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SYNTHESIS OF (*S*)-MANOALIDE DIOL AND THE ABSOLUTE CONFIGURATION OF NATURAL MANOALIDE

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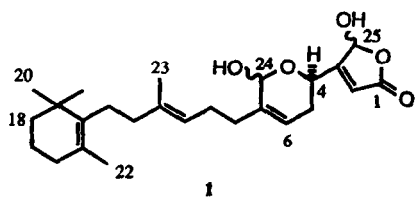
Summary: A synthesis of (*S*)-manoalide diol (**2a**) has been achieved using 2-deoxy-D-ribose as starting material to unequivocally supply the stereochemistry. Reduction of natural manoalide afforded enantiomeric manoalide diol **2b**. Thus, the absolute configuration of manoalide is *R* (as depicted in **1**).

Manoalide, a pentaprenoid isolated from the sponge *Luffariella variabilis*,[1] is a potent inhibitor of phospholipases A_2 and C, intervening by this mechanism in the arachidonic acid cascade and thereby exerting antiinflammatory activity *in vivo*.[2,3] Owing to these desirable biological effects the molecule has attracted considerable attention from which three syntheses of racemic manoalide have resulted.[4-6] Yet, little effort has been expended up to this point upon the elucidation of the chirality of the natural product. While the steric arrangements around the hemiacetal carbons C-24 and C-25 are subject to rapid tautomerization, the absolute configuration at C-4 is fixed and needed to be established. We describe here experiments which allowed us to assign *R*-stereochemistry to manoalide as depicted in **1**.

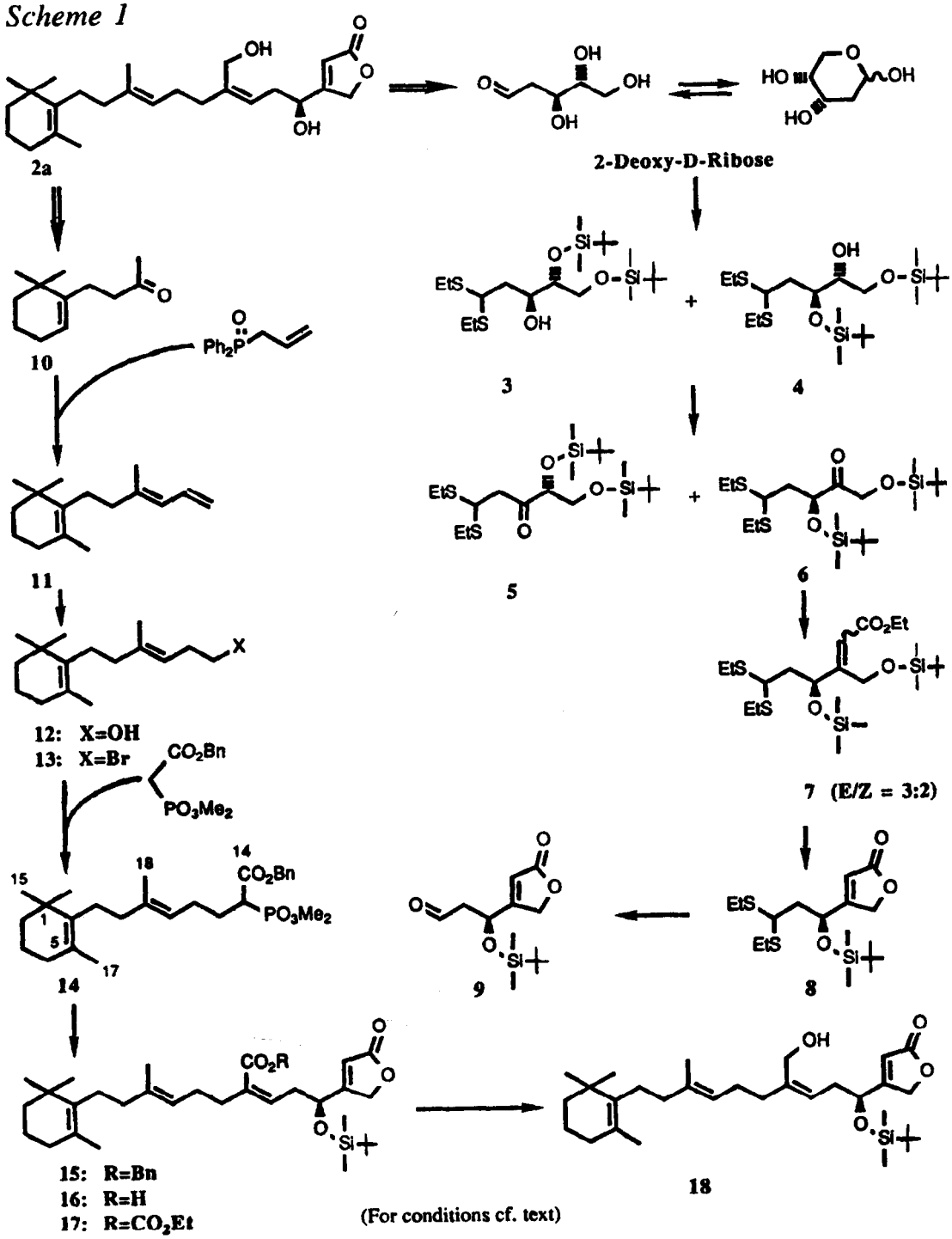


1

Manoalide had previously been reduced with sodium borohydride to "manoalide diol".[7] This molecule, depleted of tautomerizable functionalities, offered itself as target for synthesis in an enantiomerically defined form, and retrosynthetic analysis suggested that the 4*S*-isomer (**2a**) could be readily reached starting from 2-deoxy-D-ribose (Scheme 1).

Thus, 2-deoxy-D-ribose was converted to its ethyl thioacetal (92%) by treatment (at rt) in ethanethiol with a catalytic amount of $ZnCl_2$.[8] Further reaction of the resulting product with t-butyldimethylsilyl chloride (2.2 equiv.) in pyridine/CH_2Cl_2 (8d, rt) afforded after flash chromatography the two isomeric disilyl derivatives **3** and **4** (70%). The mixture of **3** and **4** was not readily separable and was therefore subjected, as is, to oxidation with DMSO/trifluoro-

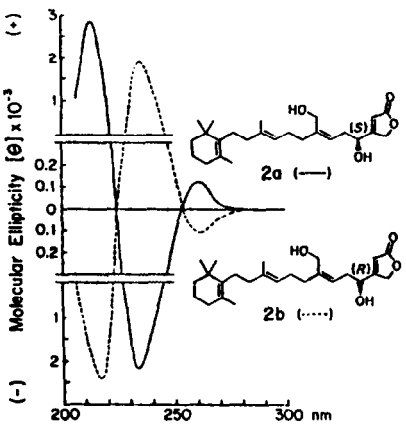
Scheme 1


2a
2-Deoxy-D-Ribose
10
3
4
11
5
6
12: X=OH
13: X=Br
7 (E/Z = 3:2)
14
9
8
15: R=Bn
16: R=H
17: R=CO2Et
18
(For conditions cf. text)

acetic anhydride in CH_2Cl_2 (-65°C to rt). Flash chromatography allowed the separation of the two ketones **5** (earlier fractions, 46.5%) and **6** (45.4%).[9] Horner-Emmons reaction of **6** with triethylphosphonoacetate Na-salt in dimethoxyethane (DME, 60 h, -20°C) afforded **7** (86%) as a mixture in which the desired *E*-isomer was predominant. Careful partial hydrolysis with 80% aq. AcOH (5h, 50°C) yielded upon chromatographic purification the lactone **8** (72.5%). Deprotection of the aldehyde function was achieved with $HgCl_2/HgO$ in 80% aq. CH_3CN (30 min, rt) to give **9** (96%).[10]

The remainder of the carbon skeleton of the target molecule was assembled starting from dihydro-β-ionone **10**,[11] which in a modified Wittig reaction with allyldiphenylphosphine oxide[12] and n-BuLi in THF/HMPA (15 min, -78°C) afforded the hydrocarbon **11**. Selective hydroboration with 9-borabicyclononane (9-BBN) in THF (2h, rt) followed by oxidative workup with 30% H_2O_2/3M NaOH (at 0°C) gave the primary alcohol **12** (18.9%), which was subsequently converted to the bromide **13** (77%) by reaction with CBr_4 and triphenylphosphine in CH_3CN (12h, rt). Alkylation of benzyl dimethyl phosphonoacetate K-salt (prepared with t-BuOK) with **13** in dry DMF (15h, rt) provided the Horner reagent **14** (69%).[13] Reaction of **14** in THF (-78°C), first with lithium diisopropylamide, then with aldehyde **9** (*vide supra*) yielded the desired *Z*-benzyl ester **15** (58.8%) together with a minor amount (15.4%) of the *E*-isomer. These were readily separable by chromatography (Chromatotron, EtOAc/cyclohexane, 2:8).

Figure 1



The benzyl ester group of **15** was cleaved by transfer hydrogenation with ammonium formate in MeOH, catalyzed by 10% Pd/C (8h, rt) to give **16** (76%). The carboxyl function of **16** was selectively reduced by first converting it to the mixed anhydride **17** with ethyl chloroformate and Et_3N in THF (1h, -10°C), and then reacting with $NaBH_4$ dissolved in DME (4h, rt) to yield after purification on a flash column the primary alcohol **18** (67.8%).

Finally, removal of the silyl protecting group with a catalytic amount of aq. HF in CH_3CN (15h, rt) afforded 4*S*-manoalide diol **2a** (82%).[14] The CD-spectrum of this material is depicted in Figure 1. A sample of natural manoalide[15] was reduced with $NaBH_4$[7] to give manoalide diol (**2b**) identical by nmr and ir with **2a**, however with a CD-spectrum (Fig. 1) which is the mirror image of that obtained with the synthetic material.[16] Thus, **2b** and manoalide have 4*R*-stereochemistry.

S-Manoalide diol, when tested for inhibition of phospholipase A_2 from human synovial fluid, had considerable activity, albeit reduced as compared to that of manoalide and the *R*-diol.[16]

References and Notes:

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9. ^{1}H NMR of **6** ($CDCl_3$): δ 0.09, 0.10 (2s, 6H each, 2 Me_2Si), 0.92, 0.93 (2s, 9H each, 2*t*-BuSi), 1.23, 1.25 (2t, 3H each, J=7.5 Hz, 2 CH_3 of SEt), 2.12 (m, 2H, 2 H-2), 2.46-2.72 (m, 4H, 2 CH_2 of SEt), 4.00 (t, 1H, J=7.5 Hz, H-1), 4.50, 4.67 (AB, 2H, J_{gem}=18.5 Hz, 2 H-5), 4.55 (t, 1H, J=6 Hz, H-3).
10. ^{1}H NMR of **9** ($CDCl_3$): δ 0.08, 0.11 (2s, 3H each, Me_2Si), 0.89 (s, 9H, *t*-BuSi), 2.78 (dd, 1H, J_{vic}=6 Hz, J_{gem}=17 Hz, one of 2 H-2), 2.86 (ddd, 1H, J_{vic}=1.5 and 6 Hz, J_{gem}=17 Hz, one of 2 H-2), 4.80 (dd, 1H, J_{vic}=1.5 Hz, J_{gem}=18 Hz, one of 2 H-5), 4.87 (d, 1H, J_{gem}=18 Hz, one of 2 H-5), 5.17 (t, 1H, J=6 Hz, H-3), 6.00 (d, 1H, J=1.5 Hz, -*CH*=), 9.78 (s, 1H, H-1).
11. We are grateful to Dr. K. Steiner, F. Hoffmann-La Roche & Co., Ltd., Basle, for a supply of this material.
12. J. Ukai, Y. Ikeda, N. Ikeda, and H. Yamamoto (1983), Tet. Lett. 24, 4029.
13. ^{1}H NMR of **14** ($CDCl_3$): δ 0.98 (s, 6H, gem di-Me), 1.42 (m, 2H, 2 H-2), 1.55 (s, 3H, Me-18), 1.56 (m, 2H, 2 H-3), 1.59 (s, 3H, Me-17), 1.90 (m, 2H, 2 H-4), 1.94-2.15 (m, 4H, 2 H-11 and 2 H-12), 2.00 (m, 4H, 2 H-7 and 2 H-8), 3.05 (ddd, 1H, J=4,11 and 23 Hz, H-13), 3.73 (d, 6H, J=11 Hz, $P(OMe)_2$), 5.07 (t, 1H, J=6 Hz, H-10), 5.18, 5.23 (AB, 2H, J=12 Hz, $CH_2Ø$), 7.30-7.41 (m, 5H, arum.).
14. ^{1}H NMR of **2a** ($CDCl_3$): δ 0.99 (s, 6H, gem di-Me), 1.41 (m, 2H, 2 H-18), 1.57 (m, 2H, 2 H-17), 1.60 (s, 3H, Me-22), 1.65 (s, 3H, Me-23), 1.90 (t, 2H, J=6.5 Hz, 2 H-16), 2.02 (m, 4H, 2 H-12 and 2 H-13), 2.10-2.25 (m, 4H, 2 H-8 and 2 H-9), 2.54 (m, 2H, 2 H-5), 4.10, 4.19 (AB, 2H, J_{gem}=11.5 Hz, 2 H-24), 4.63 (t, 1H, J=6 Hz, H-4), 4.88 (br AB of ABX, 2H, 2 H-25), 5.13 (m, 1H, H-10), 5.39 (t, 1H, J=8 Hz, H-6), 5.98 (m, 1H, H-2).

15. We are very grateful to Professor Paul Scheuer and Wesley Yoshida for providing a generous sample of natural manoalide.
16. We thank Dr. V. Toome and Mrs. Bogda Wegrzynski for CD-spectra, Mr. Gino Sasso for help with the interpretation of NMR spectra, and Dr. W. Hope for biological measurements.

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