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SYNTHESIS OF (±)-CABENEGRINS A-I AND A-II

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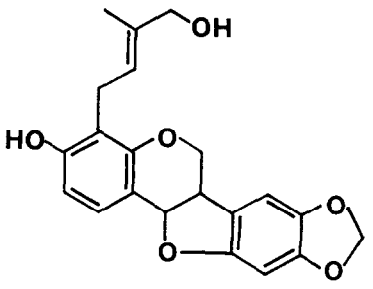
Summary (±)-Cabenegrins A-I and A-II, the potent antidotes against snake venoms, have been synthesized from maakiain(9) and 2-carbomethoxy-3-benzyl maakiain(20)

In the preceding paper[1], Nakanishi and coworkers have reported the isolation and the structural elucidation of cabenegrins A-I(1) and A-II(2) which show potent antidote activity against snake venoms In view of this unique activity, we have carried out the synthesis of these compounds which are available in only limited quantities from an as yet unidentified plant extract

Since both cabenegrins A-I and A-II have a maakiain skeleton with an isoprenyl side chain at C-4 or C-2, introduction of these side chains is a crucial step in the synthesis. As described below, Claisen rearrangement was used for introduction of the cabenegrin A-I side chain, while a Wittig reaction on the aldehyde group of 22 gave the cabenegrin A-II side chain.

Cyclization of propargyl ether 3 (derived from resorcinol by monopropargylation and subsequent benzylation) by refluxing in N,N-diethylaniline (1 5 hr) afforded 7-benzyloxy-2H-chromen(4) in 48 % yield after separation from a mixture of 4 and its regioisomeric product 5[2] This chromen 4 was then coupled with compound 7 in the presence of lithium chloropalladite in aqueous acetone according to the method developed by Inoue et al[3] The resulting benzyl maakiain 8 was hydrogenated on 5% Pd-C in acetone to give (±)-maakiain(9) in 80 % yield[4]. Refluxing of maakiain(9) with allyl bromide and K_2CO_3 in acetone gave allyl ether 10 in quantitative yield. This allyl ether 10 was regioselectively rearranged in refluxing N,N-diethylaniline to the desired compound 11[5] in 55 % yield Oxidation of 11, using the Upjohn method[6], gave the glycol 12 which was then converted to hemiacetal 13 by oxidation with sodium metaperiodate in 86 % yield The E-olefin was stereoselectively introduced by Wittig reaction on hemiacetal 13 with α-ethoxycarbonylethyl triphenylphosphorane in dimethylsulfoxide at 120° for 1 hr in 82 % yield The E-ester 14[7] was reduced by using lithium aluminum hydride in tetrahydrofuran at -40° for 1 hr to give allyl alcohol 1 in 74 % yield This allyl alcohol 1 was identical with naturally occurring cabenegrin A-I by ^{1}H-NMR, ^{13}C-NMR, IR, MS and tlc.



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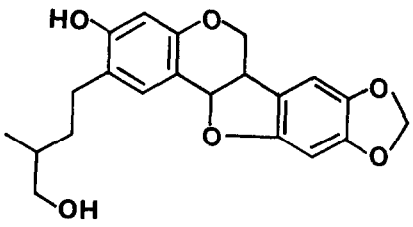

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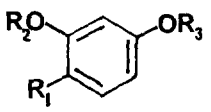
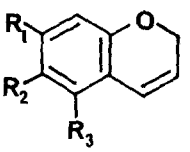
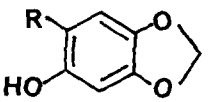
Cabenegrin A-II was also synthesized by application of Inoue's procedure to the coupling of sesamol moiety 6 and 7-benzyloxy-6-methoxycarbonyl-2H-chromen (18), the ester group of which was used for construction of the side chain at C-2.

Treatment of methyl 2,4-dihydroxybenzoate(15) with propargyl bromide and K_2CO_3 in refluxing acetone gave propargyl ether 16, which was benzylated with benzylchloride, KI and K_2CO_3 in refluxing acetone to provide 17. Cyclization of this propargyl ether 17 in refluxing N,N-diethylaniline afforded a mixture of equal amounts of the chromen derivative 18 and its regioisomer 19[8], which was readily separable by silica gel chromatography This chromen 18 was then coupled with the sesamol moiety 7 in the presence of lithium chloropalladite in aqueous acetonitrile[9] to furnish the pterocarpane derivative 20[10] in 30 % yield Reduction of ester 20 with lithium aluminum hydride in tetrahydrofuran at -20° gave alcohol 21, which was oxidized with manganese dioxide in dichloromethane (room temp., 7 hr) to provide the aldehyde 22 in 94 % yield Reaction of this aldehyde 22 and the phosphorane 23, which was prepared from 3-bromo-2-methyl propanol and triphenylphosphine and subsequent treatment with two equivalents of n-butyllithium (room temp , 2 hr) in tetrahydrofuran, afforded the E-olefin 24 in 74 % yield Hydrogenation of this olefin on 10% Pd-C gave (±)-cabenegrin A-II (2), whose physical properties were identical with a sample of naturally isolated cabenegrin A-II (100 MHz ^{1}H-NMR, IR, MS and tlc) It should be mentioned that both the natural product and synthetic specimen consisted of a diastereomeric mixture of the side chain by 360 MHz ^{1}H-NMR analysis



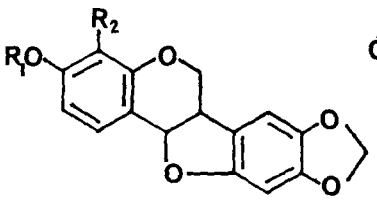


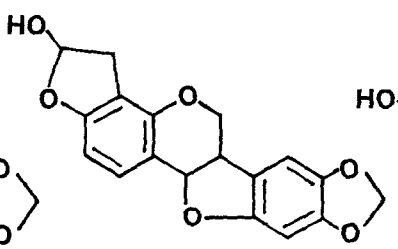


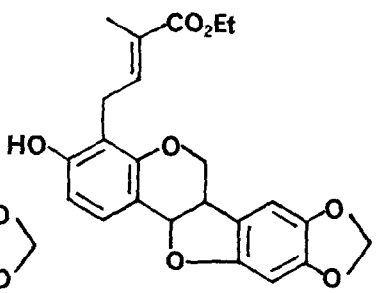
3. R_1=H, R_2=Bn, R_3=$CH_2C{\equiv}CH$
15. R_1=CO_2Me, R_2=R_3=H
16. R_1=CO_2Me, R_2=H, R_3=$CH_2C{\equiv}CH$
17 R_1=CO_2Me, R_2=Bn, R_3=$CH_2C{\equiv}CH$

4. R_1=OBn, R_2=R_3=H
5. R_1=R_2=H, R_3=OBn
18. R_1=OBn, R_2=CO_2Me, R_3=H
19. R_1=H, R_2=CO_2Me, R_3=OBn

6 R=H
7 R=HgCl



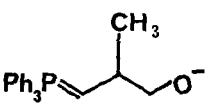




8. R_1=Bn, R_2=H
9 R_1=R_2=H
10 R_1=$CH_2CH{=}CH_2$, R_2=H
11 R_1=H, R_2=$CH_2CH{=}CH_2$
12 R_1=H, R_2=$CH_2CHOHCH_2OH$

13

14



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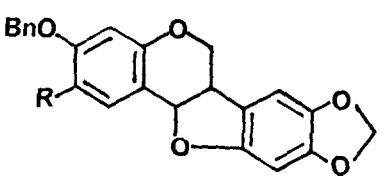
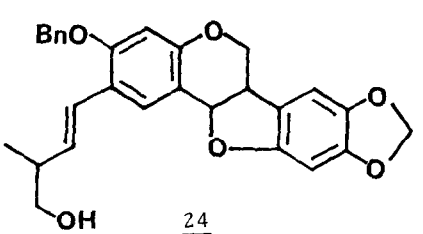


20. R=CO_2Me
21. R=CH_2OH
22. R=CHO



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References and Footnotes

1 M.Nakagawa, K Nakanishi, L.L Darko and J A Vick, preceding paper
2. J C.Breyfenbach and G J H.Rall, J Chem Soc Perkin-I, 1980, 1804
3. H Horino and N.Inoue, J Chem.Soc.Chem Comm., 1976, 500.
4 H Suginome, Bull Chem.Soc.Japan, 39, 1529 (1966) We thank Professor U Sankawa for a generous gift of natural maakiain
5 NMR($CDCl_3$, 100 MHz) 3 40-3 60(4H,m), 4.28(1H,m), 5.0-5 2(3H,m), 5 88(1H, d,J=1Hz), 5 92(1H,d,J=1Hz), 6.44(1H,s), 6 56(1H,d,J=8Hz),6 62(1H,s), 7 28 (1H,d,J=8Hz)
6. V.VanRheenen, R.C Kelly and D Y Cha, Tetra Lett , 1973 (1976).
7. NMR($CDCl_3$, 100 MHz) 1 26(3H,t,J=6Hz), 2 0(3H,bs), 3 50(4H,m), 4 14(3H,m), 5 46(1H,d,J=6Hz), 5.88(1H,d,J=1Hz), 5 92(1H,d,J=1Hz), 6 42(1H,s), 6 50(1H,d, J=8Hz), 6 72(1H,s), 7 14(1H,d,J=8Hz).
8 Cyclization of 16 gave only undesired isomeric product 19(R_1=R_3=H, R_2=CO_2Me)
9. No desired product was obtained when acetone was used for this reaction
10 NMR($CDCl_3$, 100 MHz) 3 40-3.89(2H,m), 4 28(1H,m), 5 46(1H,d,J=6Hz), 5 90 (1H,d,J=1Hz), 5 94(1H,d,J=1Hz), 6 38(1H,s), 6 49(1H,s), 7.35(5H,m), 8 04(1H, s).

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