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SYNTHESIS AND BIOLOGICAL ACTIVITY OF A 5,6-SUBSTITUTED TELEOCIDIN

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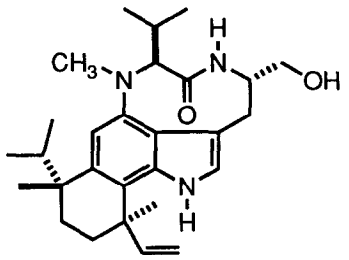
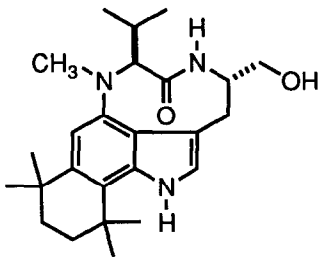
Abstract. The synthesis of 5,6-substituted teleocidin analogue **3** is reported. Reduction of oxime **7** (obtained from indole **6**) gave diastereomeric amines **8** and **9** which were cyclized to give esters **10** and **11**, respectively. Reduction of **10** yielded teleocidin analogue **3**, which displayed activity comparable to (-)-indolactam V in a standard ^{3}[H]-phorbol-dibutyrate binding assay.

The teleocidins continue to be of interest, not only as tumor promoters and activators of Protein Kinase C (**PKC**),[1,2] but also as departure points for the design of effective inhibitors. The search for inhibitors has intensified,[3] due in large part to a recent report implicating PKC in *tat* trans-activation, a process believed to be crucial for HIV infectivity.[4] One of the issues remaining to be resolved with regard to understanding the mode of action of the teleocidin tumor promoters is the function of the N-methyl group at the 4-position of the indole nucleus. In the course of preparing teleocidin **2** (an analogue of teleocidin B-4 (**1**)),[5] we became interested in the des-methyl isomeric analogue **3**. While molecular models of **3** showed severe steric crowding about the nitrogen at the 4-position, which convinced us that the N-methyl compound would be impossible to prepare, these same models showed steric interactions between the gem-dimethyl group at position 5 and the isopropyl group at position 12 that might produce a conformation of the 9-membered ring lactam similar to that found in the (N-methylated) teleocidins.[1] As very few 5-substituted and 6-substituted indolactams have been reported,[6] and since the indole needed for the synthesis of **3** was readily available, we sought to prepare the des-methyl compound **3** and evaluate it's biological activity.



1



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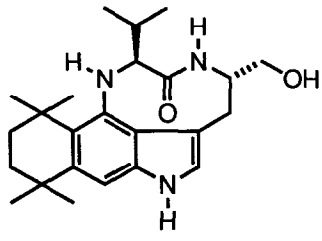

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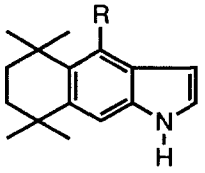
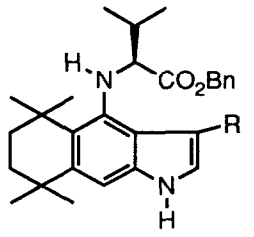
The chemistry used to prepare these compounds follows literature precedent .[5,9] Indole **4**[5] was reduced with iron in acetic acid/ethanol[7] to give the air-sensitive amino indole **5** in 66% yield.[8]

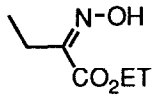
This amine was alkylated with the triflate of (*R*)-2-hydroxyvaleric acid benzyl ester[9] in refluxing dichloroethane containing 2,6-lutidine to give the N-valyl indole **6** in 63% yield.[10] Alkylation at the 3-position of indole **6** was accomplished in CH_2Cl_2/K_2CO_3 with ethyl(3-bromo-2-oximido)-propionate (Gilchrist's reagent[11]) giving oxime **7** in 50% yield.[12] Reduction of oxime **7** (Al(Hg)) furnished a 3:1 mixture of the diastereomeric amines **8** and **9** (90% total).[13] These amines were easily separated by flash chromatography, and subjected to hydrogenolysis of the benzyl ester and BOP coupling to accomplish the closure of the 9-membered rings.[5,9] Ester **10**[11] (derived from amine **8** in 55% yield) gave two conformers as displayed in the ^1H NMR, with the major conformer dominating in the ratio of 3 to 1. This ester was reduced with $LiBH_4$ in tetrahydrofuran giving alcohol **3**[12] in 90% yield, which was characterized by the presence of "twist"/"sofa" conformers[13] as evidenced in the ^1H NMR (1:1 ratio).

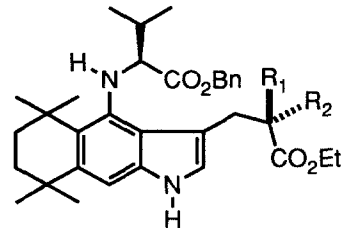


4 : R = NO_2
5 : R = NH_2

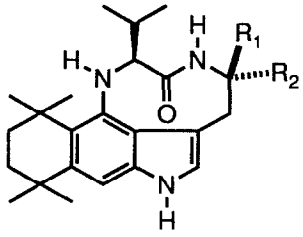


6 : R = H
7 : R =

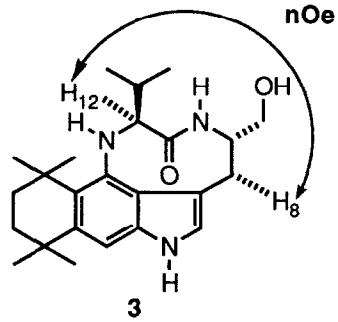




8 : R_1 = H, R_2 = NH_2
9 : R_1 = NH_2, R_2 = H



10 : R_1 = H, R_2 = CO_2Et
11 : R_1 = CO_2Et, R_2 = H
12 : R_1 = CH_2OH, R_2 = H



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As demonstrated by the teleocidins and IL-V, the methylene protons at position 8 displayed a significant nOe with the methine proton at position 12 in the ROESY spectrum. Ester **11** (derived from amine **9**), on the other hand, appeared as a single compound by ^1H NMR, and was reduced ($LiBH_4$/THF)[5] to give alcohol **12**.

Even though it lacks both substitution at the 7 position of the indole and an N-methyl group, teleocidin **3** demonstrated a level of binding to PKC comparable to that of (-)-indolactam V in a standard ^{3}[H]-PDBU assay (IC_{50} of 400nM vs 150nM for (-)-ILV; des-methyl-(-)-ILV proved inactive in this assay).[17] Accordingly, teleocidin **12** showed no binding activity at all, even at concentrations of 0.01 mM.[17] This level of potency is surprising since generally it has been assumed that the N-methyl group present in the teleocidins is required for tumor promoting activity. It is also of interest that other 5-substituted indolactams *possessing an N-methyl group*, showed reduced activity from that of (-)-ILV.[16] The above observations would seem to confirm that the stereochemistry at position 9 is the single most crucial structural aspect of these compounds, consistent with literature observations.[16] It would appear that the presence or absence of an N-methyl group and substitution at positions 5 and 6 have mixed effects on activity.

Acknowledgement. The authors thank Dr. Thomas Gadek for his assistance in obtaining 2D NMR spectra.

References

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8. **(5)**: mp. 186-187°C (CH_2Cl_2/hexane); ^{1}H NMR δ8.19(brs, 1H, ArNHCH=), 7.08(t, J=3Hz, 1H, ArNHCH), 6.42(s, 1H, Ar), 6.39(dd, J=2Hz, 1H, ArCH=CH), 3.78(brs, 2H, exch., $ArNH_2$), 1.75(m, complex, 2H, $ArC(CH_3)_2CH_2$), 1.68(m, complex, 2H, $ArC(CH_3)_2CH_2$), 1.44(s, 6H, $ArC(CH_3)_2$), 1.29(s, 6H, $ArC(CH_3)_2$); Anal. ($C_{16}H_{22}N_2$) C, H, N.
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10. **(6)**: ^{1}H NMR δ8.20(brs, 1H, NH), 7.27(m, 5H, ArH), 7.04(t, J=3Hz, 1H, ArNHCH=), 6.43(m, 1H, NCH=), 6.25(s, 1H, ArH), 5.16(B part, ABqd, J=1, 12Hz, 1H, $ArCH_2$), 5.07(B part, ABq, J=12Hz, 1H, $ArCH_2$), 4.02(d, J=6Hz, 1H, HNCH(ipr)), 4.04(t, J=6Hz, 1H, CH(ipr)CO_2Bn), 2.19(sextet, J=6Hz, 1H, $CH(CH_3)_2$), 1.68(m, complex, 4H, $CH_2CH_2(CH_3)_2$), 1.42(s, 6H, $C(CH_3)_2$), 1.28(s, 3H, $C(CH_3)_2$), 1.23(s, 3H, $C(CH_3)_2$), 1.09(dd, J=1.5, 6Hz, 3H, $CH(CH_3)_2$), 1.03(dd, J=1.5, 6Hz, 3H, $CH(CH_3)_2$); high res MS ($C_{28}H_{36}N_2O_2$) 432.2776; found 432.2811.
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12. **(7)**: ^{1}H NMR δ9.38(brs, 1H, exch., NOH), 7.94(brs, 1H, not exch., ArNHCH=C), 7.22(m, 5H, CH_2ArH), 6.86(d, J=1Hz, 1H, ArNHCH=), 6.15(s, 1H, ArH), 5.48(br s, 1H, exch., ArNHCH(ipr)), 5.05(ABq, J=12Hz, 2H, CH_2Ar), 4.34(B part, ABq, J=12Hz, 1H, $CH_2C(=NOH)CO_2Et$), 4.18(ABq, J=6Hz, OCH_2CH_3), 4.12(A part, ABq, J=12Hz, 1H, $CH_2C(=NOH)CO_2Et$), 3.82(d, J=6Hz, 1H,

NCH(ipr)CO_2Bn), 2.10(sextet, J=6Hz, 1H, CH$(CH_3)_2$), 1.62(m, complex, 2H, C$(CH_3)_2$CH_2), 1.54(m, complex, 2H, C$(CH_3)_2$CH_2), 1.31(s, 6H, C$(CH_3)_2$), 1.20(t, J=6Hz, 3H, CH_3CH_2O), 1.17(s, 3H, $(CH_3)_2$C), 1.10(s, 3H, C$(CH_3)_2$), 1.05(d, J=6Hz, 3H, CH$(CH_3)_2$), 0.95(d, J=6Hz, 3H, CH$(CH_3)_2$); high res MS($C_{31}H_{43}N_3O_5$) 561.3202, found 561.3200.

13. **(8)**: mp 100-102°C: ^{1}H NMR δ8.05(s, 1H, NH), 7.28(m, complex, 5H, ArH), 6.87(d, J=2.5Hz, ArNHCH=), 6.20(br s, 1H, exch., NH), 5.12(ABq, J=12Hz, 2H, CH_2Bn), 4.22(ABqd, J=3, 6Hz, 2H, OCH_2CH_3), 3.98(m, 1H, NHCH(ipr)CO_2Bn), 3.86(dd, J=3, 9Hz, 1H, H_2NCHCO_2Et), 3.47(B part, ABqd, J=3, 15Hz, 1H, CH_2CH(NH_2)CO_2Et), 3.00(A part, ABqd, J=9, 15Hz, 1H, CH_2(NH_2)CO_2Et), 2.22(sextet, J=6Hz, 1H, CH$(CH_3)_2$), 1.71(m, 2H, C$(CH_3)_2$CH_2), 1.66(m, C$(CH_3)_2$CH_2), 1.43(s, 6H, C$(CH_3)_2$), 1.28(s, 3H, C$(CH_3)_2$), overlapping 1.28(t, J=6Hz, 3H, OCH_2CH_3), 1.20(s, 3H, C$(CH_3)_2$), 1.12(d, J=6Hz, 3H, CH$(CH_3)_2$), 1.05(d, J=6Hz, 3H, CH$(CH_3)_2$); Anal ($C_{33}H_{45}N_3O_4$) C, H, N.

14. **(10)**: ^{1}H NMR, major conformer (ratio major/minor=3:1): δ8.18(br s, 1H, indole-ArNH), 6.93(s, 1H, ArH), 6.84(d, J=3Hz, 1H, ArNHCH=), 5.46(B part, ABq, J=12Hz, 1H, CH_2CH(NH)), 5.11(A part, ABq(d), J=3, 12Hz, 1H, CH_2CH(NH)), 4.16(m, 2H, OCH_2CH_3), 3.45(dd, J=6, 12Hz, 1H, HNCH(ipr)CO), 2.96(br s, 1H, ArNH), 2.79(d, J=12Hz, 1H, CONHCHCO_2Et), 2.25(m, complex, 1H, CH$(CH_3)_2$), 1.72(m, complex, 4H, CH_2CH_2C$(CH_3)_2$), 1.46 and 1.44(s, 3H each, C$(CH)_3)_2$), 1.37(d, J=6Hz, 3H, CH$(CH_3)_2$), 1.32(s, 6H, C$(CH_3)_2$), 1.28(t, J=6Hz, 3H, OCH_2CH_3), 0.98(d, J=6Hz, 3H, CH$(CH_3)_2$); ^{13}C NMR(major conformer) δ174.95(CO$_2$Et), 170.81(CONH), 140.28, 139.60, 136.33, 124.63, 124.18, 123.26, 118.78(Ar), 107.49, 75.54 (OCH_2CH_3), 1.13(HNCHCO_2Et), 57.80(CH_2CH(NH)CO_2Et), 37.73 and 35.07(C$(CH_3)_2$), 34.19 and 33.37(CH_2CH_2C$(CH_3)_2$), 32.10, 32.02, 28.64 and 28.56(C$(CH_3)_2$), 27.86(CH$(CH_3)_2$), 19.79 and 19.58(CH$(CH_3)_2$), 14.35(OCH_2CH_3); MS(EI) *m/e* (relative intensity, %) 439.4 (100, M^+); high res MS($C_{26}H_{37}N_3O_3$) 439.2834, found 439.2857.

15. **(3)**: mp >240°C(dec.); ^{1}H NMR twist conformer (ratio twist/sofa=1.5:1): δ8.09(br s, 1H, NH), 6.85(d, J=3Hz, 1H, NH-CH), 6.62(s, 1H, ArH), 6.38(d, J=9Hz, 1H, CONH), 5.39(br s, 1H, NHCHCH_2OH), 3.74(dd, J=4, 12Hz, 1H, CH_2OH), 3.55(m, overlapping sofa, 1H, CH_2OH), 2.93(q, overlapping sofa, J=9Hz, 2H, CH=CCH_2), 2.76(d, J=12Hz, 1H, NHCHCO), 2.27(m, overlapping sofa, 1H, $(CH_3)_2$CH), 1.65(m, 4H, $(CH_3)_2CCH_2$), 1.43(s, 3H, $(CH_3)_2$C), 1.41(s, 3H, $(CH_3)_2$C), 1.30(s, 3H, $(CH_3)_2$C), 1.26(s, 3H, (CH_3)C), 1.19(d, J=6Hz, 3H, $(CH_3)_2$CH), 1.03(d, J=6Hz, 3H, $(CH_3)_2$CH); sofa conformer: δ8.33(br s, 1H, NH), 6.96(d, J=3Hz, 1H, NH-CH), 6.93(s, 1H, ArH), 4.97(d, J=11Hz, 1H, CONH), 4.43(m, 1H, NHCHCH_2OH), 3.56(m, overlapping twist, 1H, CH_2OH), 3.46(m, overlapping twist, 1H, CH_2OH), 3.27(dd, J=3, 9Hz, 1H, CH=CCH_2), 2.98(m, overlapping twist, 1H, CH=CCH_2), 2.79(dd, J=3, 9Hz, 1H, NHCHCO), 1.71(m, overlapping twist, 1H, $(CH_3)_2CCH_2$), 1.46(s, 3H, $(CH_3)_2$C), 1.45(s, 3H, $(CH_3)_2$C), 1.36(d, J=6Hz, 3H, $(CH_3)_2$CH), 1.32(s, 3H, $(CH_3)_2$C), 1.29(s, 3H, (CH_3)C), 0.96(d, J=6Hz, 3H, $(CH_3)_2$CH); high res MS ($C_{24}H_{35}N_3O_2$) 397.2729, found 397.2730. Anal. ($C_{24}H_{35}N_3O_2$) C, H, N.

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