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RELAY TOTAL SYNTHESIS OF GRAYANOTOXIN II

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In a previous paper we reported a partial synthesis[1] of grayanotoxin II[2] (1) from a tricyclic degradation product 2. We now describe synthesis of tricyclic diketone 3 in a racemic form and interconversion of 2 and 3 using their optically active forms. Taken together with the previous partial synthesis, the present work constitutes the first total synthesis of a grayanoid[3].

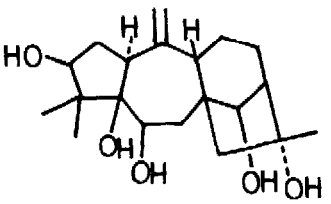
3-Oxo-4,10-dimethyl-14-methoxy-1,2,3,6,7,10-hexahydrophenanthrene 4[4] was reduced to A,B trans octahydrophenanthrene 5 (mp 141-142°) with Li-NH_3(l)-t-BuOH. Sequential hydrolysis (HI-AcOH) of methyl ether and ketalization of the hydrolytic product gave ethylene ketal 6[5,6] (mp 193-194°) in a 70% overall yield from 4. The ketal was then hydrogenated over W-7 Raney Ni in ethanol containing KOH (12 hr, 170°). An epimeric mixture (7:3 by NMR[7]) of trans-anti-trans[8]-14α(eq)- and 14β(ax)-hydroxyperhydrophenanthrene 7a 7b was obtained in a 80% yield. Pure 14α-hydroxyketone 8a[5,6] (mp 135-136°) was obtained by demasking (1N HCl-acetone) the 7a-7b mixture and by subsequent separation from 14β-hydroxyketone 8b[9]. The former compound 8a was then oxidized with DDQ in dioxane (3 day, reflux), obtaining 65% of dienone 9[5,6] (mp 134-135°; ir(nujol) 1657, 1620, 1603 cm^{-1}; NMR δ6.24, 6.99 (each 1H, d, J_{AB}=10 Hz)). UV-irradiation of 9 in acetic acid solution furnished a cleanly (80%) rearranged monoenone 10[5,6] (mp 178-180°; ir(nujol)1739, 1694, 1634 cm^{-1}; NMR δ0.89 (3H, s, CH_3-C-OAc, shielded by its endo nature)).

After conversion of 10 to 14-O-THP ether 11[6], the latter was treated with CH_3ONa-HCO_2Et in benzene (rt) to give a 85% yield of a tautomeric mixture of enone 12[5,6] (mp 157-165°;ir(nujol) 2720, 1740, 1725, 1690, 1658, 1640 cm^{-1};NMR δ9.19 (0.5H, q, J=3+1 Hz, CHO, a long rage coupling with C-1 H), 6.90 (0.5H, s, =CH-OH of enolic form)). The mixture was treated with p-TsCl-n-BuSH in pyridine (rt, 3day), and Z methylene thioether 13[6,10] (ir($CHCl_3$) 1574 cm^{-1};NMR δ6.66 (1H, s, vinylic H)) and its E isomer 14[6,10,11] (ir($CHCl_3$) 1594 cm^{-1};NMR δ7.27 (1H, s, vinylic H)) were obtained in the 45 and 30% yields, respectively. 4,4-Dimethylation of 13 was effected in HMPT-benzene (1:2) solution by means of methyl iodide (excess) in the presence of $CH_3SOCH_2^-$. 4,4-Dimethyl compound 15[6,10] (NMR δ1.02, 1.08, 1.23 (each 3H, s)) and an unwanted product, 6-monomethyl compound 16[6,10] (NMR δ1.10 (3 H, d, J=6 Hz)) were obtained in the 55 and 10% yields. n-Butylmercaptomethylene group of 15 was removed by hydrolysis with 10% KOH-ethanol (5 hr, reflux), and deacetylated ketone 17[5,10] (ir($CHCl_3$) 1746, 1681 cm^{-1}) was obtained in a 50%yield. Hydrolysis of 14-O-THP group of 17 followed by acetylation of the hydrolytic product yielded an amorphous 14-O-acetate 18[5].

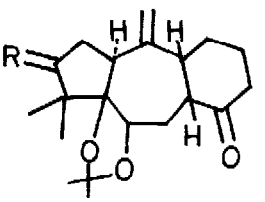
The upfield chemical shift due to C-10 methyl group of hydroazulene 18 (δ 0.92) suggested a conformation 19 for this compound. It was therefore anticipated that electrophilic attack at the 5,6 double bond of 18 would occur from the β side. In fact, treatment of 18 with OsO_4 (2 mol) in pyridine (rt, 3 day) selectively produced A,B-cis-5,6-cis-glycol 20[5,6] in a 85% yield (mp 178-179°;NMR δ1.15 (6H, s), 1.21 (3H, s), 3.76 (1H, q, J_{AX+BX}=3+10 Hz, C-6 H)). The glycol 20 was then brominated (Br_2-$CHCl_3$, rt, 3 hr) and 2β-bromoketone 21[5,6,8] was obtained (mp 119-120°;NMR δ2.92 (1H, d, J=7 Hz, C-2 H), 3.77 (1H, q, J_{AX+BX}= 3+10 Hz, C-6 H)) in a yield of 90%. Dehydrobromination of 21 with LiCl-DMF (100°, 5 hr) gave α,β-unsaturated ketone 22[5,6] in a 75% yield (mp 164-165°;ir(nujol) 1686, 1603 cm^{-1};NMR δ5.88 (1H, s);uv (EtOH) 225 nm (ε9,000)).

A crucial step in the relay synthesis was the preparation step for A,B-trans dihydro compound of 22. This conversion was performed by using trimesitylborane[12] (10 mol)-Na (10 mol)-t-BuOH in a dry and oxygen-free THF (argon atmosphere, addition of t-BuOH at -20∿-30°, then rt, 1 day). Sequential acetonization ($HClO_4$ -acetone, rt, 1 day) of the crude reduction product and oxidation (CrO_3-pyridine,

rt, 1 day) gave rise to the formation of the desired diketone 3 (mp 208-211°;ir (nujol) 1750, 1710, 1630 cm^{-1}) in a 4.5% overall yield from 22. The racemic diketone thus obtained was identical (NMR, ir, tlc) with the optically active sample, mp 196.0-196.5°, $[\alpha]_D^{25}$ -106° (c=1, MeOH). The latter was obtained by oxidation (CrO_3-pyridine) of the known degradation product 2. Finally, the optically active diketone 3 was reverted to 2 by the following sequential procedures: i) selective ketalization at C-14 (ethylene glycol-p-TsOH-benzene, reflux, 8 hr, 80%, 23[5,6], amorphous solid;$[\alpha]_D^{25}$ -67° (c=1, MeOH)), ii) stereospecific reduction from α-face at C-3 ($NaBH_4$ in methanol, rt, 90%, 24[5], amorphous solid;$[\alpha]_D^{25}$ -15° (c=1, MeOH)), and iii) hydrolysis (2N HCl in acetone, reflux, 1 hr, quantitative).

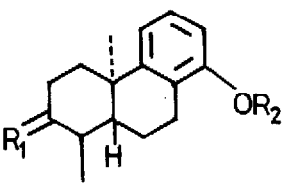


G II 1



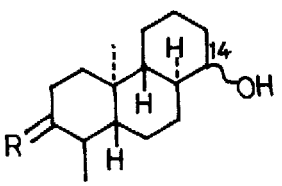
2 R =

3 R = O



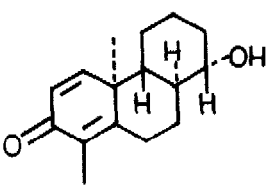
5 R_1 = O R_2 = CH_3

6 R_1 =  R_2 = H



7 R = 

8 R = O



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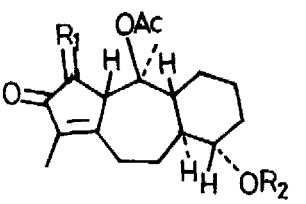
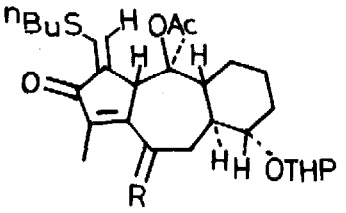


10 R_1 = H_2 R_2 = H

11 R_1 = H_2 R_2 = THP

12 R_1 = CHOH, 

R_2 = THP



13 R = H_2

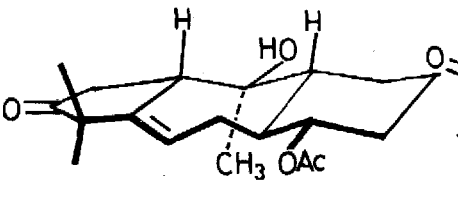
14 R = H_2 E-Mercapto-methylene compound.

16 R = 

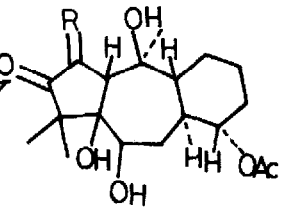
15 R_1 = CHS^nBu R_2 = THP R_3 = Ac

17 R_1 = H_2 R_2 = THP R_3 = H

18 R_1 = H_2 R_2 = Ac R_3 = H

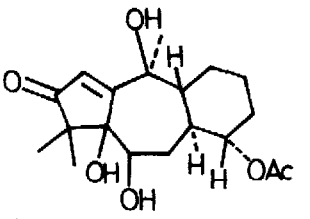


19

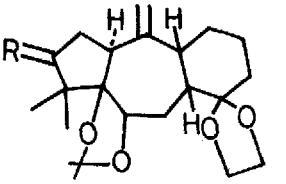


20 R = H_2

21 R = 



22



23 R = O

24 R = 

1. N. Hamanaka and T. Matsumoto, Tetrahedron Lett., 3087 (1972).
2. J. Iwasa and Y. Nakamura, Tetrahedron Lett., 3973 (1969); P. Narayanan, M. Rohrl, K. Zechmeister and W. Hoppe, Tetrahedron Lett., 3943 (1970).
3. A number of grayanoids are known. For recent examples see N. Hamanaka, A. Furusaki, H. Miyakoshi and T. Matsumoto, Chem. Lett., 779 (1972).
4. M. Shiozaki, K. Mori and M. Matsui, Agr. Biol. Chem., 36, 2539 (1972). For convenience the kauranoid numbering scheme was used.
5. Elemental composition of this compound was confirmed by combustion analyses.
6. Satisfactory ir and NMR spectral data were obtained for this intermediate.
7. All NMR spectra were taken in $CDCl_3$ solution using TMS as internal standard.
8. The structure was later fully verified by X-ray analysis of 21. The details of the X-ray analysis will be published elsewhere.
9. The 14β-hydroxyketone 8b[5,6], mp 125-126°, also was used as an intermediate for the preparation of 9. Details will be described in a full paper.
10. Most THP ethers described in the present report were amorphous and analyzed as crystalline demasked alcohols.
11. Convertible to the Z isomer by UV-irradiation.
12. S. D. Darling, O. N. Devgan and R. E. Cosgrove, J.Amer.Chem.Soc., 92, 696 (1970)