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# TOTAL SYNTHESES OF MOKKO LACTONE, DEHYDROCOSTUS LACTONE, AND EREMANTHIN[1)]

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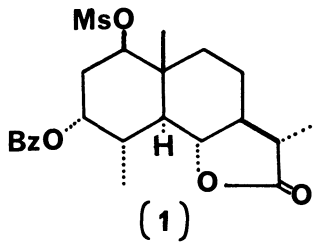
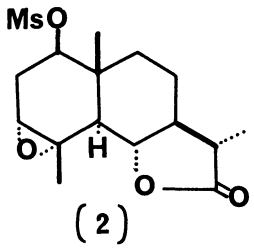
A series of guaianolides such as mokko lactone, dehydrocostus lactone, and eremanthin which posses a common structural unit in A ring have been synthesized from 1-oxoeudesm-2-eno-13,6α-lactone in 7 steps. The key step involves solvolytic rearrangement of 1β-mesyloxyeudesm-4(14)-eno-13,6α-lactone.

In the previous papers of this series[2)] we have demonstrated the utility and the generality of the approach for the syntheses of guaianolides which consists of the solvolytic rearrangement of the appropriately functionalized eudesmanolides such as compounds 1 and 2. In the present paper we want to report the successful results of the application of an analogous approach to the syntheses of a series of guaianolides such as mokko lactone (dihydrodehydrocostus lactone) (3), dehydrocostus lactone (4), and eremanthin (vanillosmin) (5) which posses a common structural unit in A ring.

Mokko lactone (3) and dehydrocostus lactone (4) were originally isolated from costus root (mokko),[3)] a plant which is used for medicinal purpose. Subsequent reports from various laboratories[4,5)] led to the acceptance of the structure 3 for mokko lactone and the structure 4 for dehydrocostus lactone.



(1)

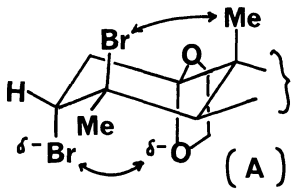


(2)

Eremanthin (5) was isolated from the hartwood oils of Eremanthus elaeagnus and Vanillosmopsis erythroppa[6,7)] and the structure was proposed as shown in the structure 5. It is interesting that eremanthin shows strong prophylatic action against the human parasite Schistosoma mansoni.

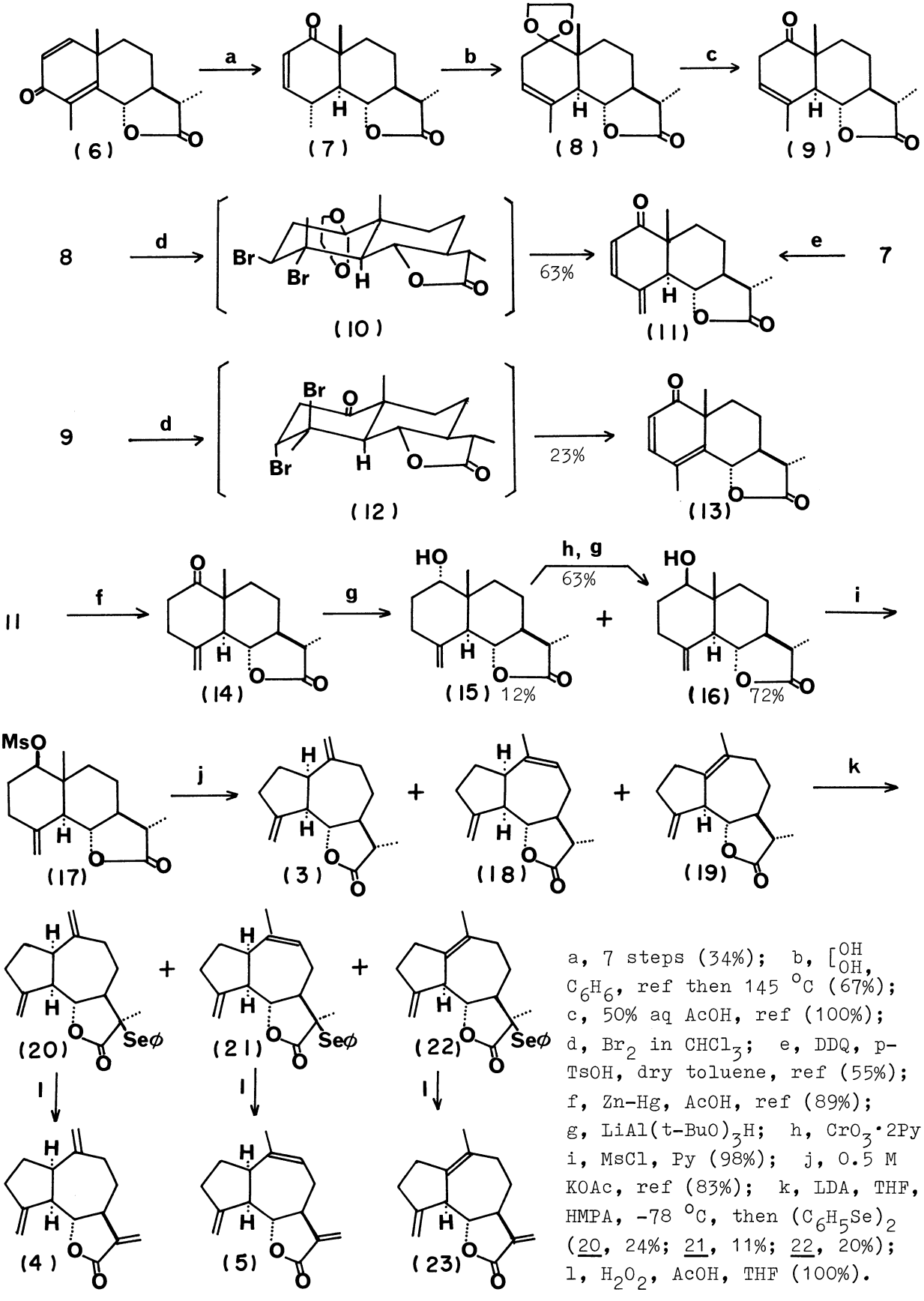
The starting material is the α,β-unsaturated ketone (7), which can be prepared from α-santonin (6) in 34% yield in 7 steps.[8)] A mixture of 7, ethylene glycol, and p-toluenesulfonic acid in dry benzene was refluxed for 24 h using a water separator, benzene was removed, and the residue was heated at 145 °C for 15 min to give the desired acetal (8) in 67% yield. Treatment of 8 with boiling 50% aqueous acetic acid gave a β,γ-unsaturated ketone (9) in quantitative yield. Treatment of 9 with bromine gave the undesirable endocyclic dienone (13), mp 145 °C, exclusively by spontaneous dehydrobromination. The formation

of this product can be rationalized by the trans eliminations of two molar hydrogen bromides from the intermediate (12) (diaxial 3α,4β-dibromide), which is formed by the normal trans-diaxial addition of bromine to the double bond. On the contrary treatment of 8 with bromine gave the desired exocyclic dienone (11), mp 140 °C, by spontaneous dehydrobromination and deacetalization in 63% yield. This reaction can be rationalized by the trans eliminations of two molar hydrogen bromides from the intermediate (10) (diequatorial 3β,4α-dibromide), which is presumably formed by the diaxial-to-dieqatorial rearrangement[9] of the 3α,4β-diaxial bromide (A) in which two serious 1,3-diaxial interactions exist as depicted in the structure A. The desired exocyclic dienone (11) was prepared by the alternative procedure. Dehydrogenation of 7 with DDQ in the presence of p-toluenesulfonic acid gave 11 in 55% yield. Treatment of 11 with zinc amalgam in refluxing acetic acid gave a γ,δ-unsaturated ketone (14) [mp 155 °C; IR (KBr): 1710 $cm^{-1}$; NMR ($CDCl_3$): δ 5.06 (1H, m) and 5.18 (1H, m)] in 89% yield. Reduction of 14 with lithium aluminium tri-t-butoxyhydride gave the desired β-alcohol (16) [NMR ($CDCl_3$): δ 3.48 (1H, dd, J=4.8 and 10.5 Hz)] in 72% yield and the corresponding α-alcohol (15) in 12% yield. The latter was further converted to 16 by Collins oxidation and successive reduction of the resulting 14 with lithium aluminium tri-t-butoxyhydride in 63% yield. Mesylation of 16 with mesyl chloride in pyridine at room temperature gave a mesylate (17) [NMR ($CDCl_3$): δ 3.01 (3H, s) and 4.54 (1H, dd, J=5.1 and 11.0 Hz)] in 98% yield.



(A)

Solvolytic rearrangement of 17 in 0.5 M acetic acid solution of potassium acetate gave ca. 2:1:2 mixture of di-, tri-, and tetrasubstituted olefins (3, 18, and 19) in 83% yield, which showed a single spot on silica gel TLC in various solvent systems. We could separate some 3 from the mixture by a combination of column chromatography on silver nitrate impregnated silica gel and HPLC (10 μm silica gel, EtOAc-hexane 5:95). The $^1$H-NMR ($CCl_4$) and IR (neat) spectra and $[\alpha]_D$ value in chloroform were in good accordance with those of natural mokko lactone.[3] For the practical purpose, we employed the mixture in the next step without separation. When 1.5 molar equivalents of LDA and diphenyl diselenide were employed in the phenylselenenylation of this mixture, a phenylselenenyl group was introduced selectively in the endocyclic olefins (18 and 19) to give the recovered exocyclic olefin (3)[10] and the mixture of phenylselenides (21 and 22) after separation by TLC (silica gel, EtOAc-hexane 2:8). The latter mixture was further separated by HPLC (10 μm silica gel, EtOAc-hexane 5:95) to give 21 [mp 147 °C; NMR ($CDCl_3$): δ 1.53 (3H, s), 1.82 (3H, broad s), 4.13 (1H, t, J=9.6 Hz), 4.95 (1H, m), 5.13 (1H, m), 5.52 (1H, m), 7.20-7.65 (5H, m)] in 11% yield and 22 [NMR ($CDCl_3$): δ 1.52 (3H, s), 1.78 (3H, broad s), 3.18 (1H, d, J=9.8 Hz), 4.05 (1H, t, J=9.8 Hz), 5.07 (1H, m), 5.12 (1H, m), 7.20-7.65 (5H, m)] in 20% yield. The recovered 3 was further treated with 2 molar equivalents of LDA and diphenyl diselenide to give 20 [mp 135 °C; NMR ($CDCl_3$): δ 1.54 (3H, s), 4.03 (1H, t, J=9.0 Hz), 4.78 (1H, m), 4.89 (1H, m), 5.00 (1H, m), 5.12 (1H, m), 7.20-7.65 (5H, m)] in 24% yield after purification by HPLC. The oxidative syn-elimination




a, 7 steps (34%); b, [OH, OH], $C_6H_6$, ref then 145 °C (67%); c, 50% aq AcOH, ref (100%); d, $Br_2$ in $CHCl_3$; e, DDQ, p-TsOH, dry toluene, ref (55%); f, Zn-Hg, AcOH, ref (89%); g, $LiAl(t\text{-}BuO)_3H$; h, $CrO_3 \cdot 2Py$; i, MsCl, Py (98%); j, 0.5 M KOAc, ref (83%); k, LDA, THF, HMPA, -78 °C, then $(C_6H_5Se)_2$ (20, 24%; 21, 11%; 22, 20%); l, $H_2O_2$, AcOH, THF (100%).

of 20, 21, and 22 gave the corresponding α-methylene-γ-lactones (4, 5, and 23) in quantitative yields, respectively. The compounds 4 and 5 were identical with dehydrocostus lactone and eremanthin, respectively, in the comparison of $^1$H-NMR and IR spectra, $[\alpha]_D$ values in chloroform and melting points. The structure of 23 were fully supported by the $^1$H-NMR spectrum (90 MHz, $CDCl_3$) [δ 1.77 (3H, broad s), 3.30 (1H, d, J=9.8 Hz), 3.63 (1H, t, J=9.8 Hz), 5.07 (1H, m), 5.15 (1H, m), 5.34 (1H, d, J=3.0 Hz), and 6.07 (1H, d, J=3.5 Hz)]. It is interesting that the ratio of exo- and endoolefins in the products of solvolytic rearrangement is dependent on the structure of the starting material.[2)]

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10) Compound 3 separated here contains small amounts of 18 and 19.

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