Pergamon

Tetrahedron Letters, Vol. 37, No. 16, pp. 2699-2702, 1996

0040-4039/96 $15.00 + 0.00

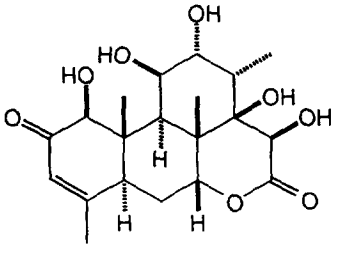
S0040-4039(96)00340-1

SYNTHETIC STUDIES ON HIGHLY OXYGENATED QUASSINOIDS: TOTAL SYNTHESIS OF (±)-14β,15β-DIHYDROXYKLAINEANONE

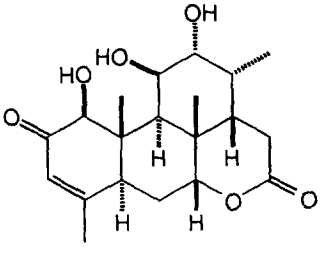
Paul A. Grieco,* Scott D. Cowen and Farahnaz Mohammadi
Department of Chemistry, Indiana University, Bloomington, Indiana 47405

Abstract: The total synthesis of the highly oxygenated quassinoid, 14β,15β-dihydroxyklaineanone has been achieved thus confirming the structural assignment which was based on spectroscopic data. Copyright © 1996 Elsevier Science Ltd

Examination of the extracts of *Eurycoma longifolia* Jack, a slender small tree indigenous to Southeast Asia which has played a major role in folk medicine, led to the isolation and characterization *via* spectral methods of a new quassinoid, 14β,15β-dihyroxyklaineanone (**1**).[1] The structural similarities between **1** and the



1

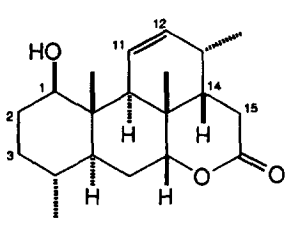


2

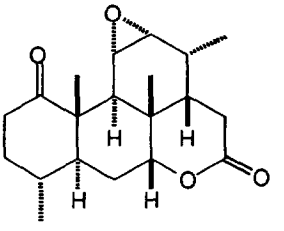
closely related quassinoid, klaineanone (**2**), suggested that the protocols developed in conjunction with the total synthesis of **2**[2] for the introduction of the ring A 1β-hydroxy-2-oxo-$\Delta^{3,4}$ olefin unit and the ring C *trans*-diaxial arrangement of the hydroxyl groups, might be applicable to a total synthesis of 14β,15β-dihydroxyklaineanone. Unfortunately our efforts to employ and/or adapt the chemistry previously employed in conjunction with the synthesis of klaineanone failed, in part, because of the presence of the vicinal diol array at C(14) and C(15). We detail below the total synthesis of (±)-14β,15β-dihydroxyklaineanone which confirms the structural assignment put forth by Itokawa and coworkers.[1]

The synthesis of **1** commences with the known tetracyclic lactone **3**[2b] which possesses all the carbon atoms of 14β,15β-hydroxyklaineanone. Transformation of **3** into **1** requires elaboration of the 1β-hydroxy-2-oxo-$\Delta^{3,4}$ olefin functionality and introduction of four additional hydroxyl groups at C(11), C(12), C(14) and C(15). The sequence of events leading to the total synthesis of **1** proved to be critical.

Attention was initially focussed on introduction of the C(11), C(12) *trans*-vicinal diol unit. Epoxidation (MCPBA, $NaHCO_3$, CH_2Cl_2, 0°C, 3.0 h) of **3** followed by oxidation (PCC, NaOAc, CH_2Cl_2, 0°C→RT, 2.0 h) of the C(1) alcohol gave rise (63% overall yield) to tetracyclic keto epoxide **4**, mp 216-218°C, which upon exposure (5.0 h) to 15% sulfuric acid in tetrahydrofuran at 50°C afforded crystalline keto diol **5**, mp 250-252°C, in 77% isolated yield.

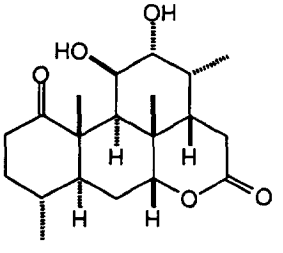


3

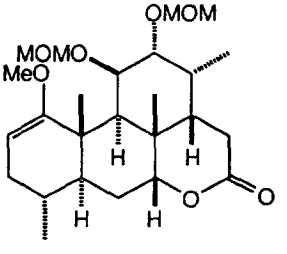


4

Our strategy dictated that the stereochemistry of the eventual C(1) hydroxyl group be set while incorporating oxygen into the C(2) position *via* hydroboration (cf enol ether **6**) prior to introduction of the 14β,15β-diol unit. Toward this end, the C(11), C(12) hydroxyl groups were protected [MOMCl (30 equiv), *i*-Pr_2NEt (20 equiv), $ClCH_2CH_2Cl$, 45°C, 24 h, 84%] as their methoxymethyl ethers. Selective enolate formation [LiHMDS, THF:HMPA (3:1), -78C, 1 h] and subsequent trapping with dimethylsulfate (-78°C→0°C, 30 min) generated enol ether **6** in 71% overall yield. Hydroboration [BH_3·THF (3.0 equiv), -30°C, 1 h; NaOH, H_2O_2] of enol ether **6** gave rise (69%) to tetracyclic alcohol **7**.

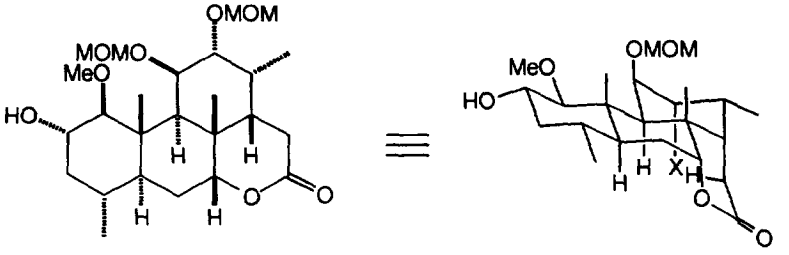


5



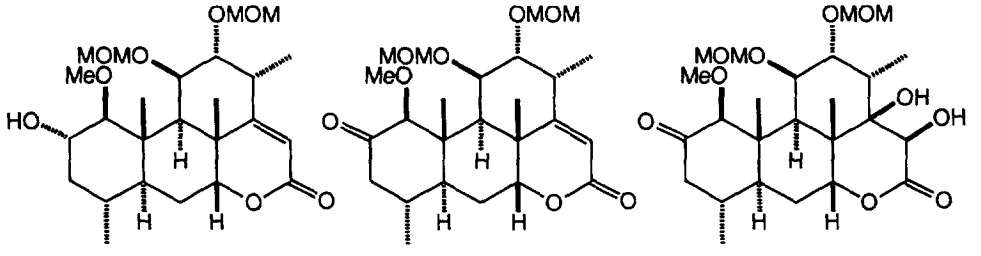
6

Elaboration of the 14β,15β vicinal diol unit necessitated prior introduction of unsaturation into δ-lactone **7**. Attempts to deprotonate **7** with excess lithium diisopropylamide in tetrahydrofuran-hexamethylphosphoramide (10:1) at temperatures below 0°C followed by addition of phenyl selenenyl chloride led only to recovered **7**. The inability to deprotonate lactone **7** stems from the fact that the C(15) axial hydrogen is very hindered. Fortunately, deprotonation at ambient temperature, followed by cooling to -78°C and



7 X=OMOM

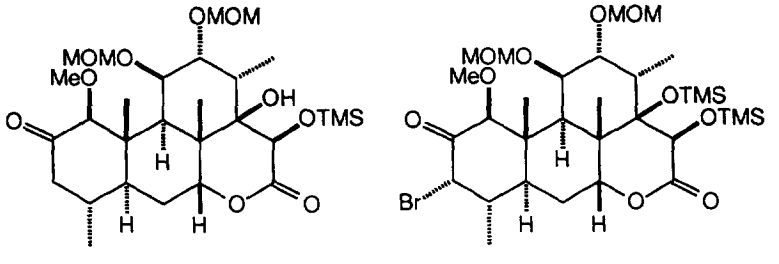
addition of phenyl selenenyl chloride with warming to ambient temperature provided the corresponding phenyl selenide which was directly treated (4.5 h) with hydrogen peroxide in tetrahydrofuran-pyridine (15:1) affording



8 9 10

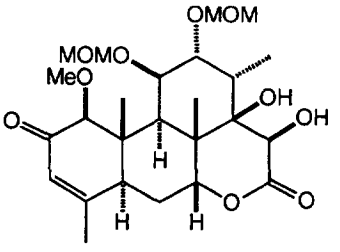
unsaturated lactone **8**, in 90% overall yield. Prior to osmylation of the $\Delta^{14,15}$ olefin, the C(2) hydroxyl was oxidized [PCC (4.0 equiv), NaOAc (3.5 equiv), CH_2Cl_2, 4 Å mol sieves, 3 h] giving rise to crystalline ketone **9**, mp 187-189°C, in 91% yield. Treatment of **9** with 1.05 equiv of osmium tetroxide in pyridine at 0°C for 6 h followed by the standard workup with sodium bisulfite generated diol **10**, mp 212-214°C, in 94% yield.

Completion of the total synthesis of **1** required introduction of the $\Delta^{3,4}$ olefin and cleavage of all protecting groups. Toward this end the C(15) hydroxyl group was selectively protected (TMSCl, Et_3N, CH_2Cl_2, 8 h, 89%) and the resultant ketone **11** was treated at -78°C with excess lithium hexamethyldisilazane, followed by sequential addition of excess trimethylsilyl chloride at 0°C and N-bromosuccinimide. The resultant

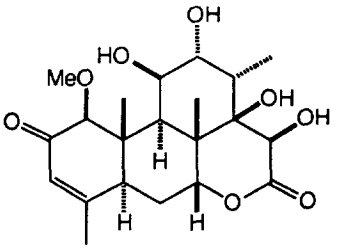


11 12

bromo ketone **12** upon treatment with tetra-*n*-butylammonium fluoride in tetrahydrofuran at 0°C for 2 h underwent desilylation, as well as dehydrobromination,[3] giving rise to **13**, mp 205.0-205.5°C, in 95% yield. Exposure (35 min) of **13** to 10 equiv of anhydrous aluminum chloride and 10 equiv of sodium iodide in acetonitrile-methylene chloride (2:1) at 0°C afforded **14** in 90% yield. Brief treatment (30 min) of **14** with boron tribromide (15 equiv) at -50°C for 1 h followed by workup at ambient temperature with a saturated



13



14

sodium potassium tartrate solution[4] (30 min) generated (40%) racemic 14β,15β-dihydroxyklaineanone, mp 221-223 (dec), whose spectral properties were identical with those of an authentic sample kindly provided by Professor Hideji Itokawa of the Tokyo College of Pharmacy. The synthesis of **1** thus confirms the structural assignment put forth by Itokawa and coworkers in 1990.

Acknowledgment: This investigation was supported by Public Health Service Research Grant CA 28865 from the National Cancer Institute. We are grateful to Professor Itokawa for providing us with an authentic sample of **1**.

References

1. Morita, H.; Kishi, E.; Takeya, K.; Itokawa, H.; Tanaka, O., *Chem. Lett.* **1990**, 749-752.
2. (a) Grieco, P.A.; Parker, D.T.; Nargund, R.P., *J. Am. Chem. Soc.* **1988**, *110*, 5568-5569. (b) Grieco, P.A.; Nargund, R.P., Parker, D.T., *J. Am. Chem. Soc.* **1989**, *111*, 6287-6294.
3. For the use of tetra-*n*-butylammonium fluoride in the dehydrobromination of similar systems see: Moher, E.D.; Collins, J.L.; Grieco, P.A., *J. Am. Chem. Soc.* **1992**, *114*, 2764-2765. Grieco, P.A.; Piñeiro-Nuñez, M.M., *J. Am. Chem. Soc.* **1994**, *116*, 7606-7615.
4. Use of a saturated sodium potassium tartrate solution in the work-up of the demethylation reaction employing boron tribromide proved critical. In its absence no product could be isolated, presumably because the 14β,15β-diol unit of **1** sequesters the boron as a mixed borate ester which does not fall apart upon exposure to aqueous sodium bicarbonate.

(*Received in USA* 6 *February* 1996; *accepted* 21 *February* 1996)