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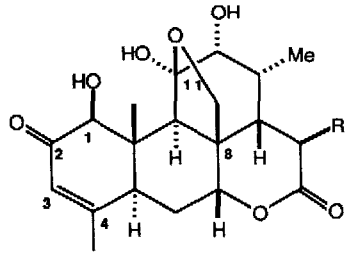
CHEMICAL TRANSFORMATIONS IN THE QUASSINOID SERIES: CONSTRUCTION OF THE C(8),C(11) BRIDGED HEMIKETAL RING SYSTEM OF CHAPARRINONE AND RELATED QUASSINOIDS

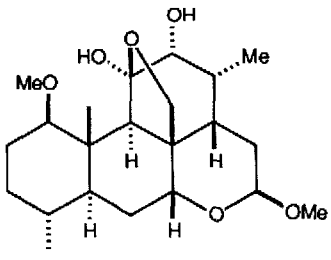
Paul A. Grieco,* David T. Parker,[1] Philip Garner and Shigeki Sasaki
Department of Chemistry, Indiana University, Bloomington, Indiana 47405

Summary: A facile five-step sequence commencing with picrasane derivative **9** has been developed for elaboration of the sensitive ring C hemiketal unit of chaparrinone [cf pentacyclic alcohol **3**].

Essential structural requirements for potent antineoplastic activity within the carbon backbone of quassinoids such as glaucarubinone (**1**) and chaparrinone (**2**) are (1) the presence in ring C of an epoxymethano bridge between C(8) and C(11), and (2) an α,β-unsaturated ketol unit in ring A.[2] To date, two reports in the literature have detailed methods for elaborating the ring A 1β-hydroxy-2-oxo-$\Delta^{3,4}$ olefin functionality.[3] In contrast no reports have appeared which address the problems associated with construction of the C(8), C(11) bridged hemiketal structural array which is common to numerous naturally occurring quassinoids. We wish to describe the synthesis of pentacyclic alcohol **3** which features a protocol for elaboration of the ring C functionality found in chaparrinone and related quassinoids.

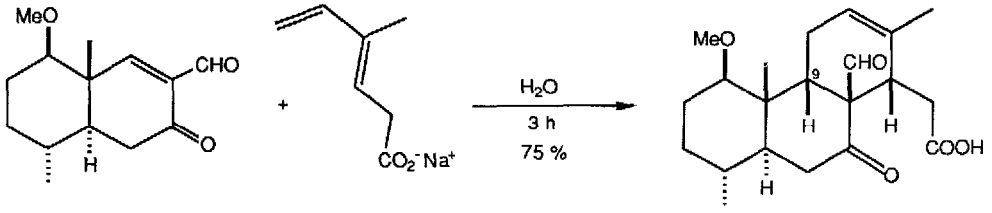


1, R = OCOC(Me)(OH)Et
2, R = H



3

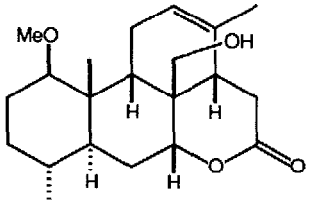
Our strategy for constructing pentacyclic alcohol **3** possessing a completely functionalized ring C commenced with tricyclic keto acid **4**[4] (cf Equation 1) which we had prepared previously in connection with our efforts to probe the scope and limitations of aqueous Diels-Alder reactions. Note that as a direct result of employing a Diels-Alder strategy, intermediate tricyclic keto acid **4** possesses the wrong configuration at C(9). However, as will be discussed below, this is of no real



(1)

4

consequence, since inversion of configuration at C(9) occurs under mild conditions, prior to deprotection of the C(8) hydroxymethyl group (vide infra). Reduction of **4** with sodium borohydride in tetrahydrofuran-water (20:1) followed by quenching with 15% hydrochloric acid furnished, in near quantitative yield, tetracyclic lactone **5**, mp 154-155°C. Reduction (i-Bu_2AlH, THF, -40°C) of the lactone carbonyl followed by exposure of the resultant lactol to a catalytic amount of concentrated hydrochloric acid in methanol gave rise to protected lactol **6**, mp 185-186°C, in 90% overall yield.



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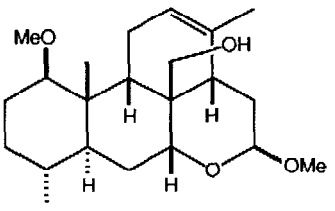
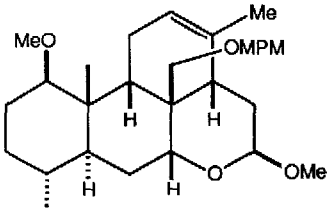


6

In order to set the stage for elaboration of the sensitive ring C funtionality, tetracyclic alcohol **6** was protected as its 4-methoxybenzyl ether **7** in 88% yield by treatment of **6** with 4-methoxybenzyl chloride and sodium hydride in tetrahydrofuran-hexamethylphosphoramide (15:1) at 70°C for 14 h. Introduction of the ring C functionality necessitated prior isomerization of the olefin in **7** from the $\Delta^{12,13}$ position to the $\Delta^{11,12}$ orientation. Thus tetracyclic olefin **7** was transformed via a straightforward four-step sequence into tetracyclic olefin **8**.[5] Exposure of olefin **8** to osmium tetroxide in pyridine followed by workup with sodium bisulfite gave rise to cis-diol **9** in 71% yield.



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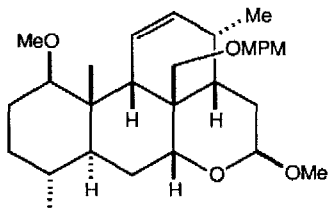

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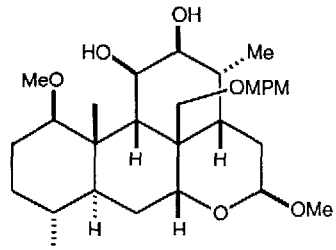
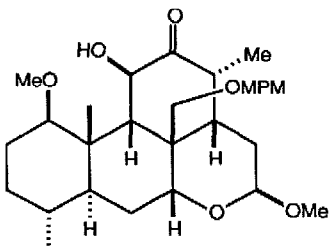


9

Elaboration of the ring C functionality of chaparrinone was successfully realized as outlined below. Swern oxidation of cis-diol **9** gave rise exclusively in 97% yield to tetracyclic ketone **10**. Base induced tautomerism-epimerization at C(9), employing sodium methoxide in DMSO-MeOH (10:1) under argon at 85°C, afforded in 86% yield picrasane derivative **11**. Removal of the p-methoxybenzyl protecting group with DDQ



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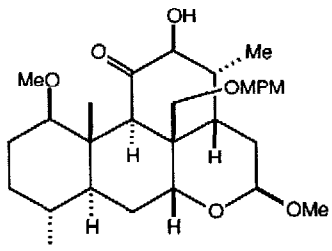

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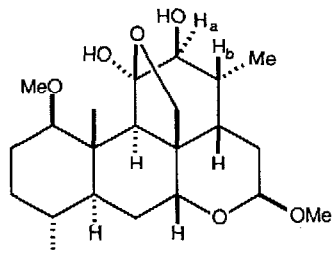
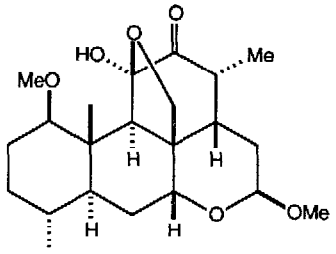


12

in methylene chloride[6] at ambient temperature provided in quantitative yield hemiketal **12**, mp 180.5-181.5°C, still possessing the C(12) hydroxyl group in the β-orientation. Examination of the ^{1}H NMR spectrum of **12** revealed H_a as a doublet with J = 10.1 Hz which is indicative of the trans-diaxial arrangement between H_a and H_b. Inversion of configuration at C(12) was realized in a straightforward fashion. Swern oxidation of alcohol **12** gave rise (70%) to pentacyclic ketone **13**, mp 204-205°C which upon reduction with diisobutylaluminum hydride in tetrahydrofuran at -23°C afforded, in 71% yield, crystalline pentacyclic alcohol **3**, mp 197-200°C. Use of sodium borohydride in methanol at 0°C provided a 1:1 mixture of alcohols **3** and **12**. The structure of **3** was unambiguously established by single crystal x-ray analysis.[7]

The C(8),C(11) bridged hemiketal unit is sensitive to base and slowly undergoes rearrangement. For example, exposure of a 0.04M solution of pentacyclic hemiketal **3** in DMSO-MeOH (9:1) under argon at 55°C to sodium methoxide gives rise after ca. 12 h to a 1:1 mixture of **3** and the rearranged C(8), C(12) bridged hemiketal compound **14**



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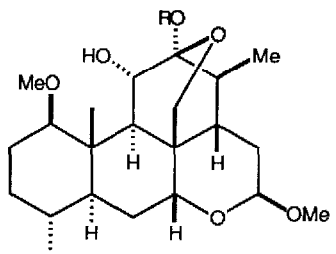

14

(R = H). Prolonged treatment affords **14** (R = H) exclusively in 66% isolated yield. Note that during the course of this rearrangement the configuration at C(13) is inverted. The structure of **14** (R = H) was unambiguously established by single crystal x-ray analysis of the crystalline TMS derivative **14** (R = TMS).[8]

The mild and efficient method detailed above for the elaboration of the sensitive C/E ring system of chaparrinone and glaucarubinone should prove exceedingly useful in quassinoid total synthesis.[9]

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4. Grieco, P.A., Garner, P.; He, Z. Tetrahedron Lett., **1983**, 24, 1897.

5. The conversion of tetracyclic olefin **7** into tetracyclic olefin **8** was performed as follows: (a) B_2H_6, THF; H_2O_2, NaOH (80%); (b) PCC, NaOAc, CH_2Cl_2 (92%); (c) $TsNHNH_2$, MeOH, THF (100%); (d) BuLi, THF (65%).

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7. Compound **3** crystallizes in space group $P2_1/a$ with cell dimensions (at -155°C) of a = 12.946(2) Å, b = 12.114(2) Å, c = 14.441(2) Å, beta = 117.84(1)°; V = 2002.46 $Å^3$, ρ calcd = 1.315 gcm^{-3} (for Z = 4). A total of 2930 reflections were measured, of which 2602 were determined to be observable, F > 2.33 σ(F). All atoms were located and refined [R(F) = 0.0514 and $R_w(F)$ = 0.0533].

8. Compound **14** (R = TMS) crystallizes in space group P1bar with cell dimensions (at -160°C) of a = 10.430(2) Å, b = 10.762(3) Å, c = 13.142(4) Å, alpha = 114.58(1)°, beta = 99.37(1)°, gamma = 71.08(1)°, V = 1268.31 $Å^3$, ρ calcd = 1.227 gcm^{-3} (for Z = 2). A total of 4070 reflections were measured, of which 3321 were determined to be observable, F > 2.33 σ (F). All atoms were located and refined [R(F) = 0.0405 and $R_w(F)$ = 0.0431].

9. This investigation was supported by the National Cancer Institute (CA 28865).

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