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SYNTHETIC STUDIES ON QUASSINOIDS· TOTAL SYNTHESIS OF (±)-GLAUCARUBOLONE AND (±)-HOLACANTHONE

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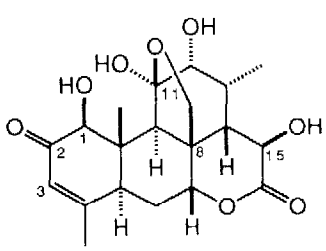
Summary: The first total synthesis of (±)-glaucarubolone (**1**) and (±)-holacanthone (**2**) is detailed which commences with tetracyclic alcohol **3**.

Since the isolation and characterization of glaucarubolone **1** by Polonsky[1] in 1965 and holacanthone **2** by Wall and Wani in 1970,[2] only limited quantities of **1** and **2** have been made available from plant species.[3] Attention has been focussed on quassinoids such as glaucarubolone and holacanthone, in part, because they display potent antileukemic activity.[4] Despite the isolation of glaucarubolone over a quarter of a century ago, synthetic efforts in this area have been plagued, over the years, by the incompatibility of existing methods for elaborating the complex array of functional groups located on the picrasane skeleton of **1**. We detail below the first synthesis of (±)-glaucarubolone (**1**) and (±)-holacanthone (**2**).



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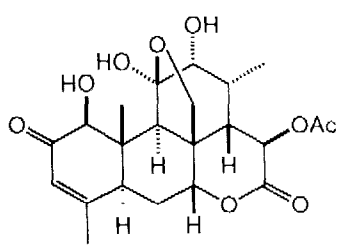

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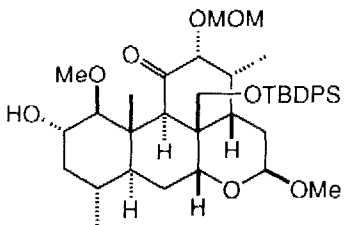
The synthesis of glaucarubolone commences with the known tetracyclic alcohol **3** which we had prepared in conjunction with a synthesis of chaparrinone.[5] The transformation of **3** into glaucarubolone requires: (a) incorporation of a 2-oxo-$\Delta^{3,4}$ olefin unit into ring A, (b) elaboration of the C(8),C(11)

bridged hemiketal structural array in ring C, and (c) introduction of a C(15) β-hydroxyl group into the eventual ring D δ-lactone. Toward this end, alcohol **3** was subjected to oxidation with 2.0 equiv of the Dess-Martin periodinane reagent[6] (methylene chloride, 1.0 h) which gave rise to crystalline tetracyclic diketone **4**,[7] mp 198.5-199.5°C, in near quantitative yield. Prior to introduction of the $\Delta^{3,4}$ olefin into ring A, incorporation of the C(15) hydroxyl group proved to be necessary. Thus, the protected lactol in **4** was hydrolyzed [THF·10% HCl (5:4), 24 h] and the resulting lactol was dehydrated [$POCl_3$



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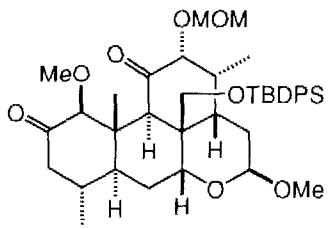

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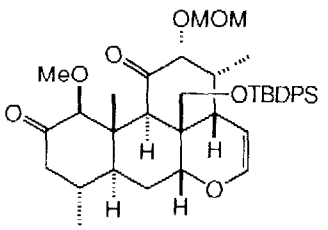

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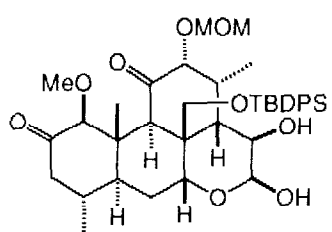
(2.0 equiv), pyr, 80°C, 1 h] giving rise to dihydropyran **5**, mp 202-204°C, in 96% yield. Osmylation [OsO_4 (1.2 equiv), pyr, 0°C, 1 h, $NaHSO_3$ (2 h)] of **5** afforded in near quantitative yield hydroxylated lactols **6**, mp 229.0-230.5°C, and **7**, mp 258-260°C, in a ratio of ca. 6:1. Exposure of **6** to 5% hydrochloric acid-tetrahydrofuran (1:2) resulted in a 2:3 equilibrium mixture of **6** and **7** which could be readily separated and reequilibrated. Attempts to oxidize **6** and **7** using conventional conditions (MnO_2, $CHCl_3$; Fetizon reagent,



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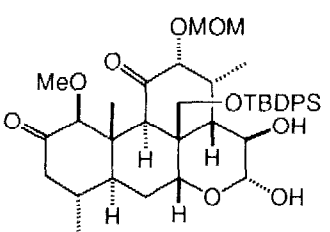

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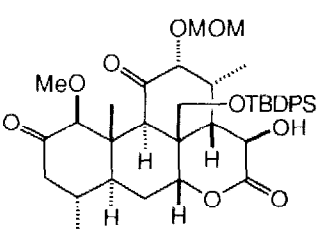

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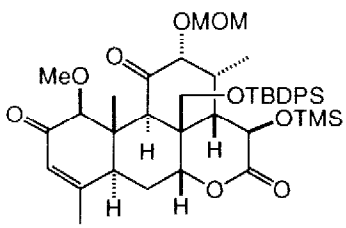
Ag_2O, CH_3CN, Swern) led to either cleavage products or recovered starting material. However, oxidation of **7** with 1.2 equiv of the Dess-Martin periodinane reagent (CH_2Cl_2, 1.5 h) afforded δ-lactone **8**, mp 212.5-214.0°C, in 75% yield along with 22% of recovered starting material.[8]

Completion of the synthesis of glaucarubolone was realized via a six-step sequence Protection (Et_3N, DMAP, TMSCl, CH_2Cl_2, 82%) of the C(15) hydroxyl of **8** as its trimethylsilyl ether followed by bromination [(i) LiHMDS, THF, TMSCl, -78°C → RT, (ii) NBS, 92%] and dehydrobromination (Li_2CO_3, DMF, LiBr, 120°C 45 min, 93%) provided crystalline tetracyclic enone **9**, mp 162-163°C Cleavage (10% HCl, THF, 30 min) of the C(15) O-silyl ether in **9** generated in quantitative yield tetracyclic alcohol **10**, mp 232-233°C, which upon exposure to excess boron tribromide [-78°C (45 min) → -43°C (1 h)] provided tetracylic triol **11**, mp 203-205°C, in 67% isolated yield Brief treatment (20 min) of **11** with tetra-n-butylammonium fluoride in tetrahydrofuran gave way in 92% yield to crystalline glaucarubolone, mp 266 5-268 0°C, whose spectral data (^{1}H NMR, IR, and MS) were identical with those of an authentic sample of **1** kindly provided by the National Cancer Institute



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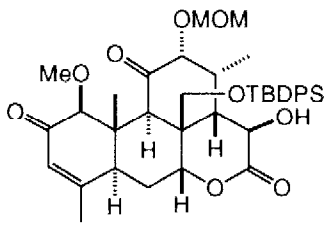

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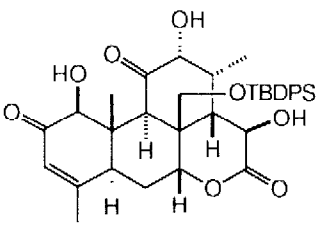

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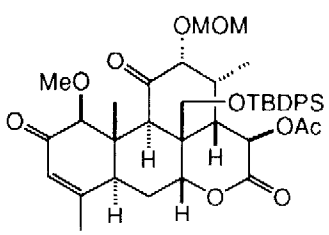
The synthesis of (±)-holacanthone was realized via a three-step sequence starting with tetracylic alcohol **10** Acetylation (AcCl, DMAP, pyr, CH_2Cl_2) of **10** provided in quantitative yield acetate **12**, mp 252-253°C, which upon exposure to excess boron tribromide in methylene chloride [78°C (1 h) → 43°C (1 5 h)] gave diol **13**, mp 233-235°C, in 46% yield. Cleavage (TBAF, THF, 15 min) of the tert-



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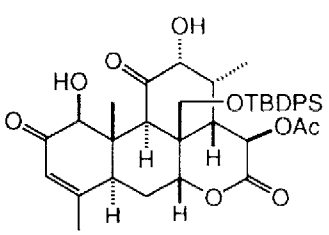

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butyldiphenylsilyl ether afforded (78%) racemic holacanthone, mp 253-254°C whose spectral properties (^{1}H NMR, IR) were identical with those recorded in the literature for natural holacanthone [3]

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7. All new compounds have been fully characterized by IR, ^{1}H NMR, ^{13}C NMR, MS, and C,H combustion analysis.

8 Similar oxidation of **6** with the Dess-Martin reagent led only to cleavage products

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