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ELABORATION OF THE CARBON SKELETON OF QUASSINOIDS
SYNTHESIS OF (1β,9β)-1-HYDROXYPICRAS-12-EN-16-ONE

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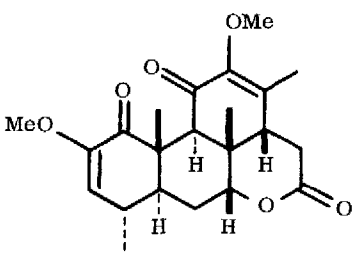
Summary The synthesis of (1β,9β)-1-hydroxypicras-12-en-16-one (2) which possesses the tetracyclic carbon framework of quassinoids (e.g., quassin) has been achieved via a remarkable Diels-Alder reaction.

The chemistry of quassinoids[2] dates back to the isolation of quassin 1 from Quassia amara during the late thirties.[3] Despite considerable effort to establish the structure and stereochemistry of quassin, it was nearly twenty-five years before its full stereochemistry was assigned.[4] The oxygen functionality



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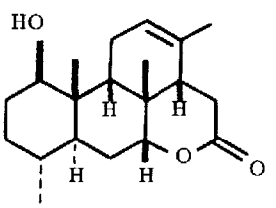

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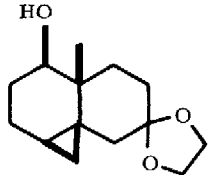
present in quassin coupled with its complex stereochemical arrangement of carbon atoms has been responsible for the limited number of synthetic studies.[5] Despite the presence of seven chiral centers in 1 only the configurations at C(5), C(7), C(8), and C(10) need be addressed during the early stages of the synthesis. Structure elucidation studies by Valenta[3] have shown that the stereochemistry at C(4), C(9), and C(14) can, if necessary, be established during the final stages of the synthesis since these centers are in their most stable configuration

We wish to describe below a Diels-Alder strategy for the construction of (1β,9β)-1-hydroxypicras-12-en-16-one (2) which possesses the complete carbon framework of quassin. With the exception of the configuration at C(9) the approach provides directly six of the seven chiral centers found in quassin.

The key intermediate dienophile 6, mp 37-38°C, was prepared in 51% overall yield via a six-step sequence from the known decalol 3.[6] Methylation [NaH, THF, MeI, Bu_4NI, reflux] of decalol 3 followed by treatment with 70% perchloric acid in methylene chloride [0°C (1 h) → 25°C (3 h)] provided enone 4 [IR (CCl_4) 1673, 1610 cm^{-1}; NMR ($CDCl_3$) δ 5.78 (d, 1H, J=1.8 Hz), 1.09 (d, 3H, J=6.5 Hz)] in 71% yield. During acid treatment simultaneous cleavage of the ketal and the cyclopropane ring was observed[7] along with equilibration at C(4) [quassin numbering].[8] Generation of the kinetic enolate of 4 and addition of methyl iodide gave the corresponding C(8) methylated enone which was subjected directly to treatment with lithium in liquid ammonia. Decalone 5, mp 51-52°C, was obtained in 77% yield from 4. Regioselective bromination [$C_6H_5N(CH_3)_3Br_3$, THF] of ketone 5 followed by dehydrobromination [LiBr, Li_2CO_3, DMF, 140°C] generated enone 6 [IR (CCl_4) 1670 cm^{-1}; NMR ($CDCl_3$) δ 7.03 (q, 1H, J=1.5 Hz), 1.75 (d, 3H, J=1.5 Hz) in 93% yield as a crystalline substance.



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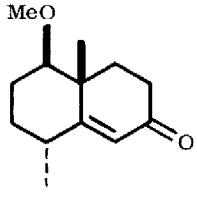

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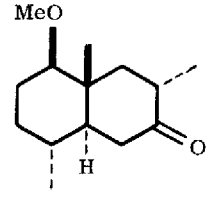

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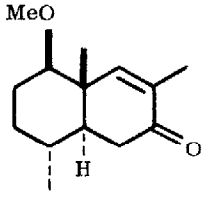
In a remarkable reaction, treatment of a benzene solution of enone 6 containing 0.25 equiv of aluminum chloride and a catalytic amount (0.02 equiv) of 4,4-thiobis-(6-tert-butyl-3-methylphenol) with excess diene (7)[10] at ambient temperature for ca. 30 h gave (40% yield based on isolated crystalline material) as the sole Diels-Alder product tricyclic ketone 8, mp 87-88°C.



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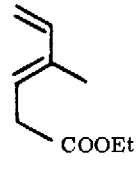

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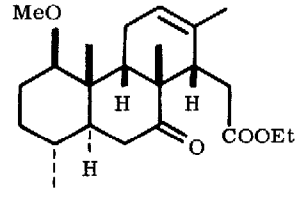

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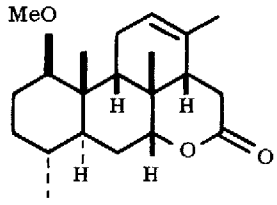
The modest yield of 8 undoubtedly stems from serious unfavorable interactions which are encountered in the endo transition state. Attempts to increase the yield of 8 by employing additional aluminum chloride (1.0 equiv) resulted in rapid and extensive polymerization of the diene Use of boron trifluoride etherate gave rise to a complex mixture of products.

Reduction of keto ester 8 with sodium borohydride in methanol proceeded in a stereospecific fashion giving rise to a single crystalline lactone (9), mp 160-161°C, in 89% yield.[11] Demethylation [ethanedithiol, $BF_3 \cdot Et_2O$, HCl, 15 h] of methyl ether 9 using a modification of the procedure by Fujita[12] afforded in 82% yield the tetracyclic hydroxy lactone 2, mp 213-214°C, which represents a versatile intermediate for further elaboration into quassinoids.



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In order to confirm the stereochemical assignments about the seven chiral centers in the above intermediates, we determined the structure of lactone 9 *via* a single-crystal x-ray analysis.[13] The molecular structure of compound 9 in Figure 1 reveals the approximate planarity of carbon atoms C(2), C(3), C(5), C(7), C(8), and C(10), chair configurations for rings A and B, and an envelope-like spacial arrangement of rings C and D.

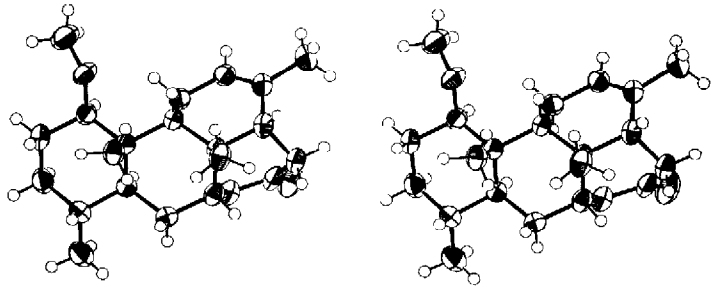

Figure 1. A stereoview of lactone 9.

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References and Notes

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7. Use of 10% hydrochloric acid in tetrahydrofuran at reflux resulted in only cleavage of the ketal.
8. The stereochemical assignment at C(4) in compound 4 was based on the fact that in 6-substituted Δ^4-3-keto steroids, the stereochemistry at C(6) can be deduced from the multiplicity of the olefinic proton at C(4). In the steroidal C(6) β-substituted series, the C(4) proton appears as a singlet (W_H = 1.5-1.8 Hz) whereas in C(6) α-substituted cases the proton is a doublet (J = 1.6-1.8 Hz).[9]
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10. Diene 7, bp 63°C/0.5 mm Hg, was prepared in 65% overall yield by condensation of triglic aldehyde with the sodium salt of triethylphosphonacetate in benzene followed by deconjugation [LDA, THF, HMPA, -78°C; HOH-HOAc] of the resultant $\alpha,\beta,\gamma,\delta$-unsaturated ester.
11. Use of absolute ethanol in place of methanol gave rise to only a 44% yield of desired lactone 9. In addition, there was obtained 3% of the lactol derived from 9 and 14% of the corresponding O-ethyl protected lactol.
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13. Crystals of racemic compound 9 are monoclinic, space group P21/n, a = 8.522(2), b = 22.773 (4), c = 10.190 (2) Å, β = 111.32 (1) deg, V = 1842.4 (6) Å^3; ρ_c = 1.20 gcm^{-3} (for Z = 4). A total of 3240 reflections were measured, of which 1713 were determined to be observable, $F_o^2 > 3\sigma(F_o^2)$. The structure was determined by routine multisolution direct methods[14] and refined to a current residual of R = 0.066. Tables of final parameters and observed and calculated structure factors will be published elsewhere.
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