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Synthesis of (±)-Palasonin

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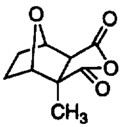
***Abstract*:** (±)-Palasonin (**1**) was prepared in nine steps from α–methoxycarbonylmaleic anhydride (**3**).

Palasonin (**1**), first isolated in 1967, is responsible for the anthelmintic activity of the seeds of the medicinal Indian tree, *Butea frondosa*.[1] Palasonin's structure, established only a year later, is strikingly similar to that of the well-known, insect-derived vesicant, cantharidin (**2**).[2] Recent observations have revealed that cantharidin plays a particularly prominent role in attracting certain male pyrochroid beetles, as well as in the mating behavior of these beetles.[3] Because of our desire to better understand the pheromonal and defensive roles played by cantharidin and cantharidin analogs in insect reproductive behavior, we set out to synthesize its closest naturally-occurring analog.



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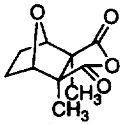

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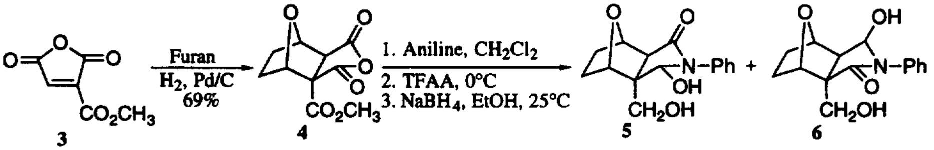
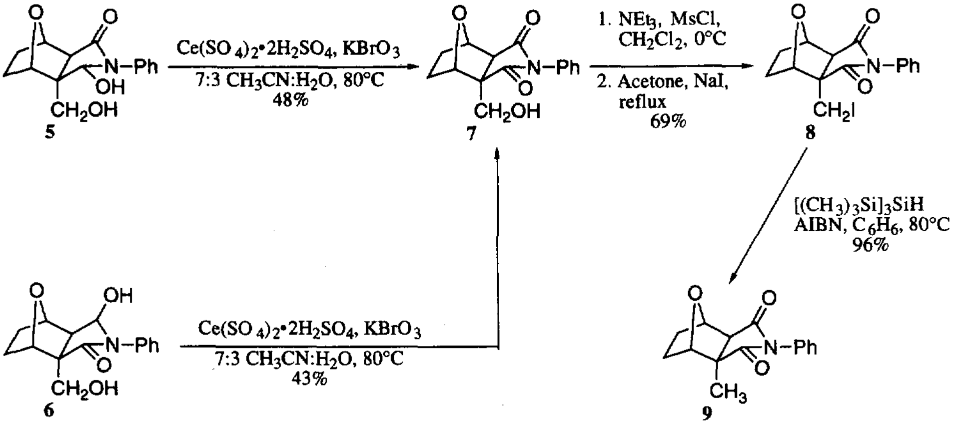
Although palasonin was both structurally and stereochemically characterized over twenty years ago, its biosynthesis remains obscure[2] and it has not, to the best of our knowledge, been synthesized. In fact, there appears to be only one attempted synthesis reported in the literature.[4] Our own approach to palasonin begins with the Diels-Alder reaction of the highly reactive dienophile, α–methoxycarbonylmaleic anhydride (**3**)[5] and furan, with concomitant *in situ* reduction of the resulting adduct to give the anhydride **4** in 69% yield. Conversion of **4** into the corresponding N-phenylimide, followed by reduction with sodium borohydride,[6] gave a mixture of **5** and **6** in 49% and 10% yield respectively from **4**.

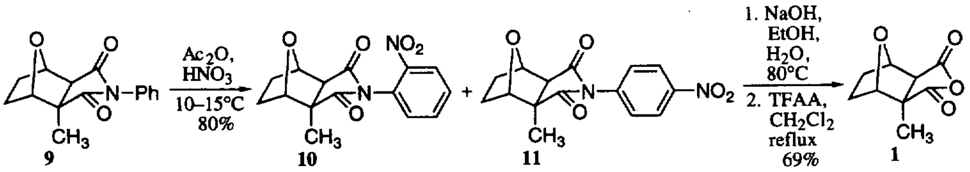


The synthesis continued with the selective oxidation of the secondary hydroxyl groups in compounds **5** and **6**. This transformation was successfully accomplished by using catalytic tetrahydrogen cerium (IV) tetrakissulfate and stoichiometric potassium bromate in aqueous acetonitrile.[7] The yields for this process were modest, with **5** being converted into the desired N-phenylimide **7** in 48% yield, while **6** was converted into **7** in 43% yield. Sodium hypochlorite in acetic acid,[8] N-bromosuccinimide (NBS) in aqueous ethylene glycol dimethyl ether,[9] DDQ in acetonitrile,[10] Fetizon's reagent, and vanadyl acetylacetonate/*tert*-butyl hydroperoxide[11] all failed to give the desired imide. Although **7** is a neopentyl alcohol, mesylation of **7** under standard conditions gave the corresponding mesylate smoothly; displacement of the mesyl group with sodium iodide gave the iodomethyl compound **8** in 69% overall yield from **7**. Radical dehalogenation of **8** then yielded the N-phenylimide **9**.[12]



Attempts to convert **9** directly into palasonin (**1**) were unsuccessful due, in part, to the vigorous conditions necessary to hydrolyze the N-phenylimide ring. In order to facilitate this hydrolysis reaction, **9** was nitrated using a mixture of nitric acid in acetic anhydride to give a 3:5 mixture of the *ortho* and *para* N-(nitrophenyl)imides **10** and **11** in 80% overall yield.[13] As anticipated, these nitrophenylimides were more readily hydrolyzed than **9** itself to yield palasonin (**1**). While attempts to remove the N-(nitrophenyl)trifluoroacetamide byproducts produced in this final step using normal or reversed phase flash chromatography or HPLC were never entirely successful, synthetic palasonin was successfully purified by preparative gas chromatography. The ^{1}H NMR and IR spectroscopic data obtained from this product were identical to those reported for the natural material.[1,2,14,15]

The elegant syntheses of cantharidin conceived of and realized by Gilbert Stork[16] and William Dauben[17] and their coworkers are achievements of great esthetic and intellectual appeal. While no comparable insight or imagination is embodied in our preparation of palasonin, the synthesis here reported does provide the opportunity to explore the possible role of this obscure natural product in the lives of insects.



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14. **1:** GC-IR 2986, 1868, 1801, 1468, 1388 , 1237, 1107, 1002 cm^{-1}; **^{1}H-NMR** δ (500 MHz, CDCl$_3$) 4.91 (d, 1H, J=5.0), 4.78 (d, 1H, J=5.0), 2.63 (s, 1H), 1.86-1.95 (m, 2H), 1.73-1.81 (m, 1H), 1.54-1.60 (m, 1H), 1.43 (s, 3H); **^{13}C-NMR** δ (100 MHz, CDCl$_3$) 175.5, 171.0, 83.3, 81.3, 56.4, 54.9, 28.2, 23.7, 16.2; **HRCI-MS:** Calcd. for $C_9H_{10}O_4$ 183.0657. Found 183.0660.

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