The Diels–Alder Reaction of Methyl Coumalate with Isoprene

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Contrary to a reported observation, iodolactonisation of acid (**4**), an intermediate in trichothecene synthesis, produces the bicyclo[2.2.2]octane framework (**12**); selenolactonisation proceeds analogously to give (**11**).

The synthetic challenge and pronounced biological activity of the complex trichothecene mycotoxins have combined to generate intense interest in this family of compounds.[1] The employment of Diels–Alder cycloaddition between methyl coumalate (**1**) and various dienes as key steps in certain syntheses[2] and synthetic approaches[3] to these toxins prompts us to report some preliminary observations in this area.

Cycloaddition of methyl coumalate with isoprene has been reported[4] to produce the adduct (**3**) in modest yield. More recent studies,[5] employing ^{13}C n.m.r. spectroscopy, detected the additional presence of the regioisomer (**5**), with a regioisomeric ratio of 10 : 1 in favour of (**3**). As partial proof of structure, the major isomer (**3**) was reported on iodolactonisation to produce the lactone (**7**), which surprisingly did not undergo base-induced elimination of HI. It appeared attractive to modify this sequence to one of selenolactonisation,[6] and so obtain (**8**) and thence, by selenoxide *syn*-fragmentation,[7] the unsaturated dilactone (**9**), which possesses suitable ring A functionality for elaboration to T2 toxin and related trichothecenes.

In our hands, cycloaddition of methyl coumalate with an excess of isoprene (110 °C, toluene, 18 h) gave an inseparable mixture of (**3**) and (**5**) in a total yield of 15%; the regioisomeric ratio, as determined by ^{13}C n.m.r. spectroscopy, was 5 : 2. Neither yield nor ratio could be improved by use of a range[†] of Lewis acid catalysts. A major by-product proved to be the hitherto unisolated alternative Diels–Alder adduct (**10**).[‡][§] However, by employing coumaloyl chloride[8] (**2**) as dienophile

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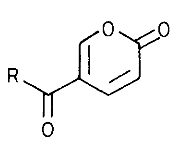
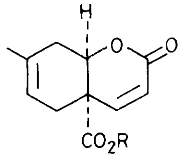
[†] TiCl$_4$, Ti(OPr^i)$_4$, or TiCl$_4$/Ti(OPr^i)$_4$ (1 : 1).

[‡] This compound was fully characterised by elemental analysis and/or mass spectrometry, and ^{1}H and ^{13}C n.m.r. spectroscopy.

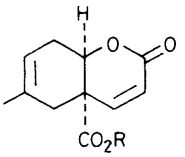
[§] Or regioisomer with isopropenyl group adjacent to ester function.



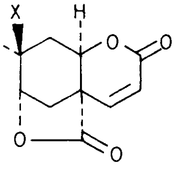
(1) R = OMe
(2) R = Cl



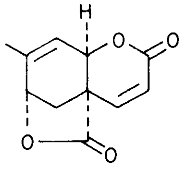
(3) R = Me
(4) R = H



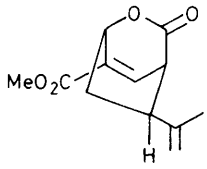
(5) R = Me
(6) R = H



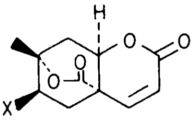
(7) X = I
(8) X = SePh



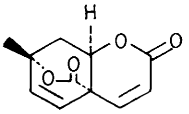
(9)



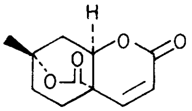
(10)



(11) X = SePh
(12) X = I



(13)



(14)

(110 °C, toluene, 48 h), followed by esterification of the product mixture (MeOH, Et_3N), the overall yield was improved to 40%, and the regioisomeric ratio to 4 : 1.

Hydrolysis of the product mixture to the corresponding acids (**4**) and (**6**), followed by selenolactonisation (PhSeCl, CH_2Cl_2), gave a mixture of lactones, from which the major component could readily be obtained pure by chromatography. The structure of this lactone was shown unambiguously to be the bicyclo[2.2.2]octane derivative‡ (**11**) by ^{13}C n.m.r. spectroscopy [δ 24.4 (q, CH_3–C), 43.6 (d, CH–Se), and 85.1 (s, C–O)], and also by its smooth oxidative elimination (H_2O_2, pyridine, CH_2Cl_2) to give the unsaturated lactone‡ (**13**) [^{13}C, δ 21.98 (q, CH_3–C), 81.1 (s, C–O), 122.6, 128.9, 137.9, and 144.2 (all d, =CH)]. Reductive cleavage[6] of (**11**) [Bu_3SnH, toluene, azoisobutyronitrile (AIBN)] gave the saturated lactone‡ (**14**). All attempts to isomerise[6]¶ selenolactone (**11**) to the expected bicyclo[3.2.1]octane derivative (**8**) were unsuccessful.

Iodolactonisation ($NaHCO_3$, I_2, KI) of the original mixture of acids gave a corresponding mixture of iodolactones. The major iodolactone possessed the structure‡ (**12**), as shown by ^{13}C n.m.r. spectroscopy [δ 22.5 (d, CH–I), 26.3 (q, CH_3–C), and 78.3 (s, C–O)], and by its reductive cleavage (Bu_3SnH, toluene, AIBN) to give a saturated lactone identical to lactone (**14**). That iodolactone (**12**) cannot be induced to undergo elimination of HI is not surprising, since there is no appropriate antiperiplanar C–H bond. No evidence could be detected for the formation of the reported iodolactone (**7**).

In conclusion, both iodo- and seleno-lactonisation of acid (**4**) give lactones arising from carboxy trapping of the more stable, more substituted carbocation, with the resulting formation of a bicyclo[2.2.2]octane framework. This framework appears to be thermodynamically stable, in contrast to other, unsubstituted cases, where a bicyclo[3.2.1]octane system, with a five-membered lactone ring, is preferred.[6]

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References

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¶ SiO_2; $BF_3 \cdot Et_2O$, CH_2Cl_2; Et_3NH^+ Cl^-, CH_2Cl_2; $AlCl_3$, CH_2Cl_2; $Ti(OPr^i)_4$, CH_2Cl_2.