Total Syntheses of Wyerone and Dihydrowyerone, Phytoalexins from the Broad Bean, *Vicia faba* L., using the Dianion derived from 3-(2-Furyl)-acrylic Acid

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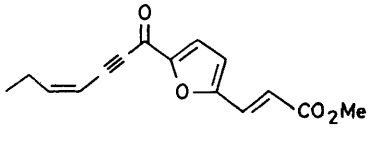
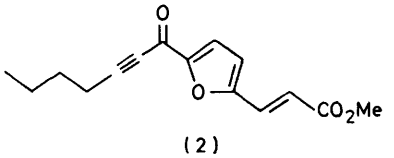
Treatment of 3-(2-furyl)acrylic acid (8) with lithium di-isopropylamide at low temperatures gives lithium 3-(5-lithio-2-furyl)acrylate (9). This has been used to prepare the broad bean metabolites wyerone (1) and dihydrowyerone (2) by condensations with (*Z*)-hept-4-en-2-ynal (13) and hept-2-ynal (11), respectively, followed by esterification and oxidation.

WYERONE (1) † is a potent antifungal compound produced by broad bean shoots (*Vicia faba* L.).[1] A reduced derivative, dihydrowyerone (2), is also present in the plants but in much smaller quantities (*ca.* 2% of the wyerone content).[1] The acid of which wyerone is the methyl ester [2] and a wyerone epoxide (3) [3] have been isolated from the same species. It has been conclusively shown [2-5] that these metabolites are either absent or



(1)



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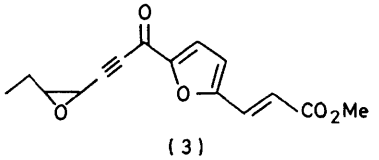

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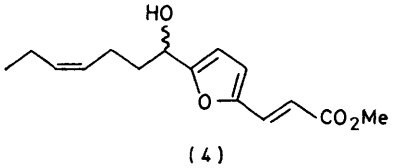
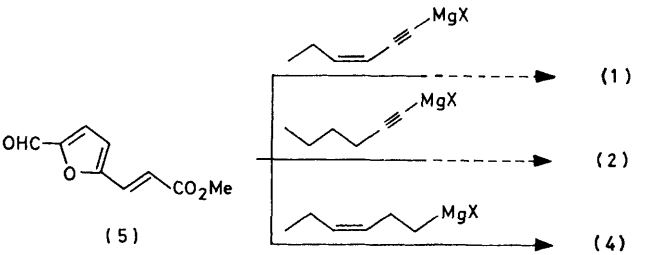


(4)

present in only very small quantities in healthy plants, and are only produced in response to fungal infection (*e.g.* by *Botrytis* species); they are thus true phytoalexins. Detoxification of these phytoalexins by fungi primarily involves reduction of both the ketone and acetylene functions; [5,6] thus (4) has been shown to be the major detoxified metabolite of wyerone.[6] Herein, we report novel syntheses of both wyerone (1) and dihydrowyerone (2).

† (*E*)-Methyl 3-{5-[(*Z*)-1-oxohept-4-en-2-ynyl]-2-furyl}prop-2-enoate.

Previous syntheses [1] of these two compounds and of the detoxified metabolite (4) [6] have, as their key step, a condensation between the appropriate Grignard reagent and methyl 3-(5-formyl-2-furyl)acrylate (5) (Scheme 1).



(5)

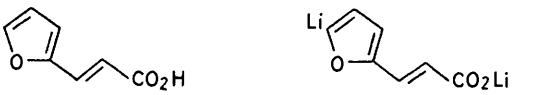
SCHEME 1

Recently,[7] we have shown that the dianionic species (6) and (7) can be obtained from the parent heterocyclic carboxylic acids, using the powerful base lithium di-isopropylamide (LDA). These intermediates can be used for the elaboration of a wide range of substituted furan- and thiophen-carboxylic acids. We were

(6) (7)

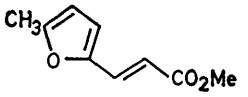
X = O or S

intrigued by the possibility of extending this work to a synthesis of wyerone (1) by using a dianionic species (9) that we hoped could be formed directly from 3-(2-furyl)-acrylic acid (8), under similar conditions to those used to generate the dianions (6) and (7). The latter species have been found to condense very efficiently with alde-



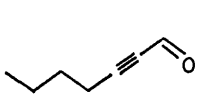
(8) (9)

hydes and ketones; [7] we therefore expected that if (9) could be formed, it would condense cleanly with the appropriate acetylenic aldehydes, resulting in brief, high-yielding syntheses of (1) and (2).



(10)

We first tested these ideas using methyl iodide as the electrophile. During our previous studies,[7] we had established that the dianions (6) and (7) could be cleanly and rapidly alkylated by this reagent. Treatment of the



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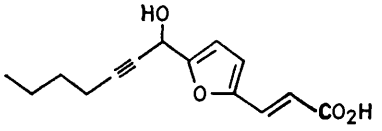
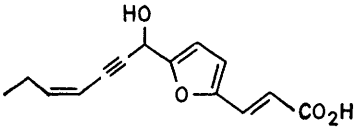


(12)

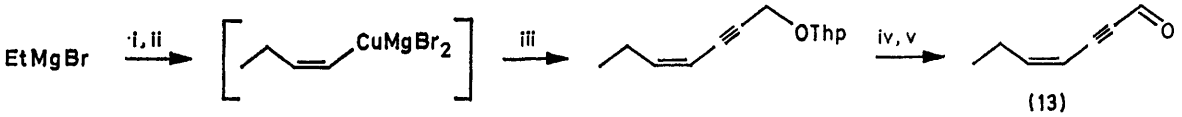
acrylic acid (8) with two equivalents of LDA in tetrahydrofuran containing hexamethylphosphoramide at −78 °C resulted in the rapid formation of a turbid, dark mixture, which was slowly decolourized on addition of methyl iodide followed by slow warming. Analysis of the product by ^{1}H n.m.r. indicated that *ca.* 50% methylation had occurred at the 5-position of the furan in structure (8), the remainder being the starting acid (8). Esterification of this mixture with diazomethane followed by preparative g.l.c. gave pure methyl 3-(5-methyl-2-furyl)acrylate (10) in 45% overall yield, together with recovered methyl 3-(2-furyl)acrylate (46%). We thus established that the dianion (9) could indeed be formed from (8), albeit to an extent of only 50%. There was no evidence that metallation had



(14)

taken place at any other site in (8). A considerable number of methods were tried in the hope of improving the extent of metallation of (8) to more than 50%. These included the use of other bases, together with the addition of co-solvents such as *N,N,N′,N′*-tetramethylethylenediamine; in our hands, none of these modifications resulted in any improvement. We therefore proceeded with the synthesis of dihydrowyerone (2) using our original conditions to generate the dianion (9). For this, we required the acetylenic aldehyde (11); this was easily obtained by the condensation of hex-1-ynylmagnesium bromide with triethyl orthoformate,[8] followed by acid hydrolysis. Condensation of (11) with the dianion (9) gave a product which was judged by ^{1}H n.m.r. to contain *ca.* 40% of the required hydroxy-acid (12), the remainder being starting acid (8). This mixture was not further purified but was immediately esterified with diazomethane and oxidised with manganese dioxide. Chromatography of the resulting mixture then gave pure dihydrowyerone (2), identical with the previously synthesised material.[1]

We then turned to the synthesis of wyerone (1) itself, for which we required (*Z*)-hept-4-en-2-ynal (13). This was prepared by the route outlined in Scheme 2. The methodology used for the construction of the (*Z*)-en-yne unit was that recently developed by Normant's group.[9] We confirm the complete stereoselectivity of this approach [we were unable to detect any of the *E*-isomers of (13) or its precursors by ^{1}H n.m.r. or g.l.c. analysis]; in our hands, the overall yield from this reaction was 55%. Condensation between the dianion (9) and the aldehyde (13) proceeded as expected to give the desired hydroxy-acid (14) in *ca.* 35% yield together with recovered acid (8). Immediate esterification using diazomethane, and oxidation over manganese dioxide



(13)

SCHEME 2 *Reagents*: i, CuBr,Me_2S; ii, HC≡CH; iii, IC≡CCH_2OThp, TMEDA; iv, *p*-$MeC_6H_4SO_3H$, MeOH; v, MnO_2

followed by chromatography and crystallisation, gave pure wyerone (1), identical with the natural material.[1]

EXPERIMENTAL

For general details, see ref. 7.

Hept-2-ynal.—1,1-Diethoxyhept-2-yne was prepared from hex-1-yne and triethyl orthoformate, according to the procedure reported.[8]

A solution of 1,1-diethoxyhept-2-yne (4.6 g) in tetrahydrofuran (60 ml) was treated with 10% hydrochloric acid (60 ml), and the resulting solution stirred at room temperature for 4 h, then diluted with water (40 ml) and extracted with ether (3 × 80 ml). The combined extracts were washed with saturated brine then dried and distilled to give the *aldehyde* (11) (2.2 g, 80%) as a colourless oil, b.p. 64—66 °C at 15 mmHg (lit.,[10] 64 °C at 15 mmHg), τ 0.84 (CHO), 7.58 br, t, *J* 7 Hz, CH_2C:), 8.20—8.70 (m, 4 H), and 9.05 (br, t, *J* 7 Hz CH_3).

Generation of the Dianion (9) *from* 3-(2-*Furyl*)*acrylic Acid* (8); *General Procedure.*—*Methyl* 3-(5-*methyl*-2-*furyl*)*acrylate* (10). A solution of 3-(2-furyl)acrylic acid[11] (0.41 g, 3 mmol) in dry tetrahydrofuran (1.5 ml) containing hexamethylphosphoramide (2 ml; freshly distilled from CaH_2) was added dropwise *via* a syringe to a stirred solution of lithium di-isopropylamide [6 mmol; prepared from Bu^nLi (3.8 ml of a 1.6 M-solution in hexane) and di-isopropylamine (0.84 ml)] in tetrahydrofuran (20 ml) cooled, under nitrogen, to −78 °C. The resulting purple suspension was stirred at −78 °C for 0.5 h, then treated with methyl iodide (0.5 g;

freshly distilled from P_2O_5) and allowed to warm slowly to room temperature during 1 h. The mixture was then partitioned between water (30 ml) and ether (30 ml). The aqueous layer was acidified with concentrated hydrochloric acid and extracted with ether (3 × 10 ml). The combined extracts were washed with saturated brine (20 ml) then dried and evaporated. The residue was treated with ethereal diazomethane and the esterified product purified by preparative g.l.c. (Pye 105 chromatograph; 15 ft × ⅜ in 3% OV 225 on a Gas Chrom Q column at 200 °C) to give *methyl* 3-(*5-methyl-2-furyl*)*acrylate* (10) (0.22 g) (eluted second) as a colourless oil, $\nu_{max.}$ (film) 1 725 and 1 645 cm^{-1}; τ 2.61 (d, *J* 16 Hz, C*H*:CHCO$_2$Me), 3.49 (d, *J* 3 Hz, furyl 3-H), 3.77 (d, *J* 16 Hz, CH:C*H*CO$_2$Me), 3.92 (d, *J* 3 Hz, furyl 4-H), 6.23 (CO_2Me), and 7.68 (furyl 5-CH_3); M^+ 166 (Found: C, 65.4; H, 6.3. $C_9H_{10}O_3$ requires C, 65.0; H, 6.1%), and methyl 3-(2-furyl)acrylate (0.23 g) (eluted first), τ 2.49 (d, *J* 1.5 Hz, furyl 5-H), 2.52 (d, *J* 16 Hz, C*H*:CHCO$_2$Me), 3.37 (d, *J* 3 Hz, furyl 3-H), 3.53 (dd, *J* 3 and 1.5 Hz, furyl 4-H), 3.68 (d, *J* 16 Hz, CH:C*H*·CO$_2$Me), and 6.23 (CO_2Me).

Condensation between the Dianion (9) *and Hept-2-ynal.—Dihydrowyerone* (2). The dianion (9) was prepared from 3-(2-furyl)acrylic acid (0.41 g) exactly as described in the general procedure, and treated with hept-2-ynal (0.33 g, 3 mmol). The mixture was stirred at −78 °C for 0.25 h, then allowed to reach room temperature during 1 h, and diluted with water (15 ml). The aqueous mixture was washed with ether (1 × 10 ml) then acidified with aqueous 10% citric acid and extracted with ether (2 × 15 ml). The combined extracts were washed with saturated brine (20 ml) then dried and evaporated to leave a solid residue (0.43 g), which contained *ca.* 40% of the desired product (12), as judged by ^1H n.m.r. analysis. The solid was treated with an excess of ethereal diazomethane at 10 °C for 1 h. Evaporation gave a viscous oil which was dissolved in dry methylene chloride (20 ml) and treated with manganese dioxide (5 g). The suspension was vigorously stirred for 3.5 h, then filtered and evaporated. Chromatography of the residue on silica gel eluted with methylene chloride then gave methyl 3-(2-furyl)acrylate (0.18 g), followed by *dihydrowyerone* (2), which crystallised from n-hexane as small prisms (0.1 g), m.p. 79—80 °C (lit.,[1] 80—80.5 °C); $\lambda_{max.}$ (EtOH) 341 and 235 nm; $\nu_{max.}$ (CCl_4) 2 220, 1 730, and 1 643 cm^{-1}; τ 2.50 (d, *J* 16 Hz, C*H*:CH·CO$_2$Me), 2.69 (d, *J* 3.5 Hz, furyl 3-H), 3.26 (d, *J* 3.5 Hz, furyl 4-H), 3.39 (d, *J* 16 Hz, CH:C*H*·CO$_2$Me), 6.18 (CO_2Me), 7.50 (t, *J* 7 Hz, CH_2·C:), 8.20—8.49 (m, 2 × CH_2), and 9.02 (t, *J* 7 Hz, C*H*$_3$·CH$_2$); *m/z* 260 (45%), 229 (23), 179 (5), and 151 (100) (Found: C, 69.0; H, 6.1. $C_{15}H_{16}O_4$ requires C, 69.2; H, 6.2%). These data are indistinguishable from those recorded for dihydrowyerone.[1]

(Z)-*Hept-4-en-2-ynal* (13).—The tetrahydropyranyl ether of (*Z*)-hept-4-en-2-yn-1-ol was prepared from ethylmagnesium bromide, acetylene, and 1-iodo-3-(tetrahydropyran-2-yloxy)propyne exactly as described by Commerçon *et al.*[9] (Scheme 2), in *ca.* 55% yield. The crude ether[12] showed τ, 4.15 (dt, *J* 11 and 8 Hz, CH_2·C*H*:CH), 4.61 (dt, *J* 11 and *ca.* 1 Hz, CH_2·CH:C*H*), 5.21br (O·CH·O), 5.77 (d, *J* 2 Hz, :C·CH_2O), 6.1—6.6 (m, O·CH_2), 7.72 (dquint, *J* 8 and *ca.* 1 Hz, CH_3·C*H*$_2$·CH:), 8.2—8.6 (m, 3 × CH_2), and 9.00 (t, *J* 8 Hz, C*H*$_3$·CH_2). The crude ether (0.8 g) was stirred at room temperature in methanol (15 ml) containing toluene-*p*-sulphonic acid (20 mg) for 16 h, and the solution was diluted with water (15 ml) and extracted with ether (3 × 15 ml). The combined extracts were washed with brine then dried and evaporated. Bulb-to-bulb distillation of the residue at 0.3 mmHg (oven temperature 60 °C) gave (*Z*)-hept-4-en-2-yn-1-ol[12] (0.31 g) as a colourless oil, $\nu_{max.}$ (film) 2 210 cm^{-1} τ 4.14 (dt, *J* 11 and 8 Hz, CH_2C*H*:CH), 4.61 (dt, *J* 11 and *ca.* 1 Hz, CH_2·CH:C*H*), 5.69 (C*H*$_2$OH), 7.72 (dquint, *J* 8 and *ca.* 1 Hz, CH_3·CH_2), and 9.02 (t, *J* 8 Hz, C*H*$_3$·CH_2).

The foregoing alcohol (0.3 g) was stirred with manganese dioxide (2.5 g) in methylene chloride (10 ml) for 14 h. The mixture was filtered and evaporated and the residue purified by flash column chromatography[13] using methylene chloride as eluant to give the *aldehyde* (13) (0.2 g) as a colourless oil, $\nu_{max.}$ (film) 2 220, 1 680, and 1 610 cm^{-1}; τ 0.83 (CHO), 3.77 (dt, *J* 11 and 8 Hz, CH_2·C*H*:CH), 4.45 (dt, *J* 11 and *ca.* 1 Hz, CH_2·CH:C*H*), 7.63 (dquint, *J* 8 and *ca.* 1 Hz, CH_3·C*H*$_2$), and 8.96 (t, *J* 8 Hz, C*H*$_3$·CH_2), which was used directly in the next step.

Condensation of the Dianion (9) *with* (Z)-*Hept-4-en-2-ynal* (13).—*Wyerone* (1). Dianion (9) was prepared from 3-(2-furyl)acrylic acid (0.19 g) as described above, and treated with (*Z*)-hept-4-en-2-ynal (0.145 g) at −78 °C. After 0.25 h, the temperature of the mixture was allowed to rise slowly to 15 °C during 1 h. The mixture was then diluted with water, washed with ether, acidified with aqueous 10% citric acid, and extracted with ether. The combined extracts were washed with brine then dried and evaporated to leave a solid residue (0.19 g) which, by ^1H n.m.r. analysis, contained *ca.* 35% of the desired alcohol (14). The residue was immediately treated with an excess of ethereal diazomethane at 10 °C for 1 h; evaporation gave a viscous oil which was stirred with manganese dioxide (2 g) in methylene chloride (10 ml) for 14 h. The mixture was filtered and evaporated to leave a residue which was chromatographed on silica gel eluted with methylene chloride to give (i) methyl 3-(2-furyl)acrylate (80 mg) (eluted first), and (ii) *wyerone* (1), which crystallised from n-hexane as pale yellow needles (35 mg), m.p. 63—64 °C (lit.,[1] 63.5—64.5 °C); $\lambda_{max.}$ (EtOH) 352, 291, and 227 nm; $\nu_{max.}$ ($CHCl_3$) 2 200, 1 725, 1 640, and 1 610 cm^{-1}; τ(Bruker WM-250 MHz; $CDCl_3$), 2.54 (d, *J* 15.7 Hz, C*H*:CHCO$_2$Me, 2.66 (d, *J* 3.7 Hz, furyl 3-H), 3.26 (d, *J* 3.7 Hz, furyl 4-H), 3.43 (d, *J* 15.7 Hz, CH:C*H*CO$_2$Me), 3.62 (dt, *J* 10.7 and 7.5 Hz, CH_2C*H*:CH), 4.31 (dt, *J* 10.7 and 1.4 Hz, CH_2CH:C*H*), 6.18 (CO_2Me), 7.49 (dquint, *J* 7.6 and 1.4 Hz, CH_3C*H*$_2$), and 8.88 (t, *J* 7.6 Hz, C*H*$_3$·CH_2); *m/z* 258 (90%), 227 (49), 226 (67), 179 (30), and 151 (100) (Found: C, 69.9; H, 5.9. $C_{15}H_{14}O_4$ requires C, 69.8; H, 5.5%), indistinguishable from the natural material.

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