Total Synthesis of Shikalkin [(±)-Shikonin][1]

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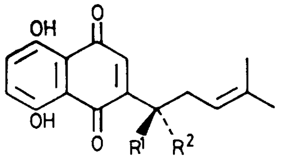
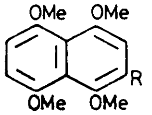
The first total syntheses of dihydroshikalkin and shikalkin were accomplished.

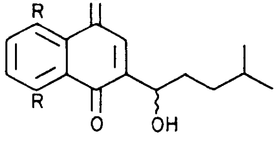
The roots of *Lithospermum erythrorhizon* Sieb. & Zucc., (violet root, Japanese name, Shikon) contain shikonin (**1a**) and its esters as purple pigments. The colouring matter of the roots of *Alkanna tinctoria* in Europe is a mixture of the enantiomeric alkannin (**1b**) and its esters.[2,3] The racemic compound of shikonin and alkannin was named shikalkin by Brockmann,[2] and we now report the first total syntheses of dihydroshikalkin (**5**) and shikalkin (**12**).



(**1a**), R^1 = OH, R^2 = H: (+)-shikonin
(**1b**), R^1 = H, R^2 = OH: (−)-alkannin



(2), R = CHO
(3), R = CH(OH)CH$_2$CH$_2$CHMe$_2$



(4), R = OMe
(5), R = OH

2-Formyl-1,4,5,8-tetramethoxynaphthalene (**2**)† (m.p. 124—125.5 °C) was prepared by the method in ref. 4 from 1,5-

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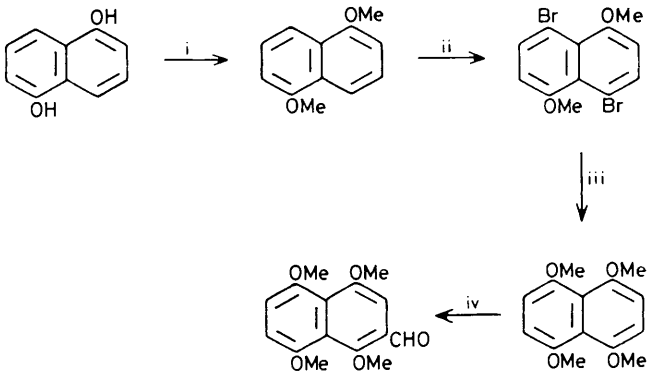
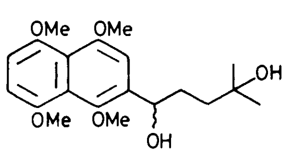
† Satisfactory elemental analyses were obtained for compounds (**2**), (**5**), (**8**), (**9**), and (**12**). Representative spectral properties of the key compounds are as follows: compound (**2**), i.r., ν_{max} (KBr): 1673 (C=O), 2845, 1067 cm^{-1} (OMe); ^{1}H n.m.r., δ(CDCl$_3$) 3.91, 3.92, 3.98, 3.99 (12H, OCH$_3$), 6.96, 7.00, 7.20 (3H, ArH), 10.56 (s, 1H, CHO); *m/z* 276 (M^+). Compound (**5**), i.r., ν_{max} (KBr): 3240 (br., OH), 1615 (C=O), and 1075 cm^{-1} (alcohol, C–O); ^{1}H n.m.r., δ(CDCl$_3$): 0.85, 0.95 (6H, CH$_3$ × 2), 2.24 [br., 1H, –CH(O*H*)–], 4.87 [t, 1H, –C*H*(OH)–], 7.14 (1H, ArH), 7.19 (2H, ArH), 12.46 and 12.58 (2H, ArOH); *m/z* 290.1143 ($C_{16}H_{18}O_5$ requires 290.1154). Compound (**8**), i.r., ν_{max} (KBr): 3300 (br., OH) and 1615 cm^{-1} (C=O); ^{1}H n.m.r., δ(CDCl$_3$) 1.28, 1.29 (6H, CH$_3$ × 2), 1.4—3.2 (m, 6H, CH$_2$ × 2, OH × 2), 4.94 [t, –C*H*(OH)–], 7.19 (3H, ArH), 12.49, and 12.59 (2H, ArOH); *m/z* 306.1079 ($C_{16}H_{18}O_6$ requires 306.1103). Compound (**9**), i.r., ν_{max} (KBr): 3410 (br., OH), 1770, 1755 (ester C=O), and 1665 cm^{-1} (quinone C=O); ^{1}H n.m.r., δ(CDCl$_3$) 1.20 (s, 6H, CH$_3$ × 2), 1.3—1.9 (m, 5H, CH$_2$ × 2, OH), 2.12 [s, 3H, –CH(OCOC*H*$_3$)–], 2.43 (s, 6H, ArOCOC*H*$_3$ × 2), 5.87 [t, 1H, –C*H*(OCOMe)–], 6.67 (1H, ArH), and 7.38 (2H, ArH); *m/z* 372 ($M^+ - 60$). Compound (**12**), i.r., ν_{max} (KBr): 3230 (br., OH), 1615 (C=O), and 1075 cm^{-1} (alcohol C–O); ^{1}H n.m.r., δ(CDCl$_3$) 1.66, 1.76 (6H, CH$_3$ × 2), 2.0—2.8 (m, 3H, CH$_2$, OH), 4.91 [t, 1H, –C*H*(OH)–], 5.20 (t, 1H, –CH=C), 7.19 (3H, ArH), 12.49, and 12.59 (2H, ArOH); *m/z* 288.0999 ($C_{16}H_{16}O_5$ requires 288.0997).

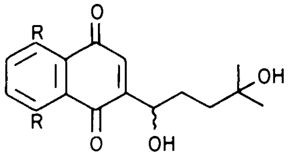


(2)

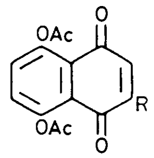
Scheme 1. i, Me_2SO_4–NaOH–MeOH, reflux, 3 h, 78%; ii, Br_2–CCl_4, 73—74 °C, 1 h, 58%; iii, MeONa, CuI–DMF–MeOH, reflux, 30 h, 84%; iv, DMF, $POCl_3$–$CHCl_3$, reflux, 10 h, 99%. DMF = *N*,*N*-dimethyl formamide.



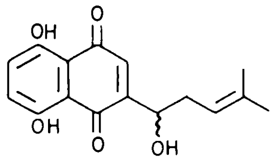
(6)



(7), R = OMe
(8), R = OH



(9), R = $CH(OAc)CH_2CH_2C(OH)Me_2$
(10), R = $CH(OAc)CH_2CH{=}CMe_2$
(11), R = $CH(OAc)CH_2CH_2C(Me){=}CH_2$



(12)

dihydroxynaphthalene in 33% overall yield (Scheme 1). Treating the aldehyde (**2**) with isopentylmagnesium bromide gave the alcohol (**3**) (92%) which could be oxidised to the 1,4-naphthoquinone (**4**) (69%) using ammonium cerium(IV) nitrate (CAN).[5] Further demethylation of (**4**) by silver oxide (AgO)–nitric acid[6] gave the dihydroshikalkin (**5**)† (28%, m.p. 79.5—81.5 °C).

In the total synthesis of shikalkin the aldehyde (**2**) was treated with the Grignard reagent of 1-bromobutan-3-one ethylene acetal[7] to yield an acetal which was easily converted into the corresponding ketone by acid hydrolysis. This ketone, in the usual Grignard reaction with methyl iodide, gave the diol (**6**) (69%), which was oxidised to the 1,4-naphthoquinone (**7**) (85%) using CAN as above. Further demethylation of the quinone (**7**) with silver oxide–nitric acid gave the key intermediate tetraol (**8**)† (27%, m.p. 151—152 °C).

Acetylation of (**8**) with acetic anhydride in pyridine led to the triacetate (**9**)† (91%, m.p. 156—158 °C), whose tertiary alcohol group remained free.

Dehydration of the remaining hydroxy group in (**9**) by thionyl chloride in pyridine at −38 °C for 7 min formed triacetylshikalkin (**10**), and the vinylidene isomer (**11**) in a 3:1 ratio (46%). They were separated by silica gel chromatography. Saponification of (**10**) with 1 M sodium hydroxide, and acidification with acetic acid gave crude crystals of shikalkin (**12**). After repeated purification by chromatography and recrystallization, a pure sample of (±)-shikonin† (37%, m.p. 146—148 °C, lit.[8] 148 °C) was obtained. The i.r., n.m.r., mass, and u.v. spectra agreed well with those of an authentic sample of shikonin.

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