A New Synthesis of the Alkaloid (±)-Colchicine

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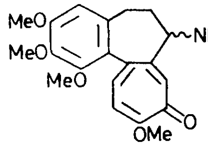
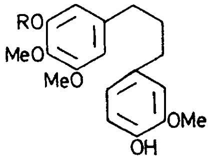
Summary The alkaloid (±)-colchicine (**1**) was synthesized by a methylene transfer reaction from the spirodienone (**3b**), followed by acid catalysed rearrangement and dehydrogenation to give deacetamido-isocolchicine (**7**).

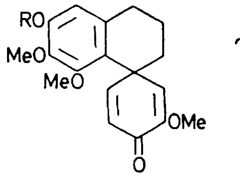
TOTAL synthesis and biosynthesis[1] of the alkaloid colchicine (**1**), a major alkaloid of the *Colchicum* species, has been extensively studied. We have previously reported that compound (**3**) could be synthesized from the corresponding 1,3-diphenylpropane (**2**)[2] by an intramolecular oxidative phenol coupling reaction with an iron-DMF complex [Fe(DMF)$_3$Cl$_2$][FeCl$_4$]. We now report a new synthesis of the alkaloid (±)-colchicine based on a hypothetical biosynthesis by Anet and Robinson[3] from the spirodienone (**3b**).



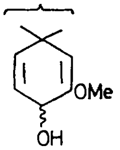
(1)



(2) a; R=H
b; R=Me



(3) a; R = H
b; R = Me



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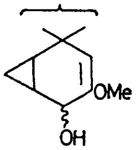

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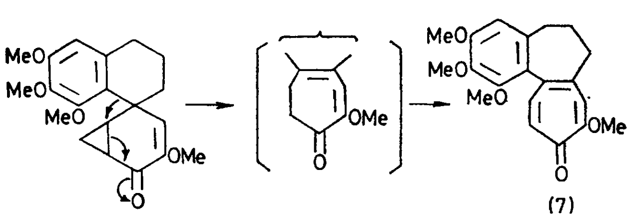
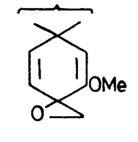


(6) (7)



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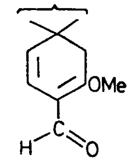
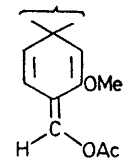


(9)



(10)

Compound (**3b**), m.p. 166—168°, was synthesized† by the oxidation of (**2a**), m.p. 102—104°, with an iron–DMF complex[2] followed by methylation with diazomethane, or was more conveniently obtained by anodic oxidation of (**2b**),[4] in 80% yield. Electrolytic oxidation of (**2b**) which was synthesized from the corresponding chalcone by catalytic hydrogenation (yield from 3,4,5-trimethoxybenzaldehyde 80%) was carried out in CH_3CN at an anode potential of 0·92—1·00 V (SCE) in the presence of HBF_4 as electrolyte for 20 min. $NaBH_4$ reduction of (**3b**) gave an epimeric mixture of (**4**) which was used for the methylene transfer reaction without purification. The Simmons-Smith reaction was carried out using an active Zn–Cu couple prepared by the method of LeGolf[5] and the resulting mixture was oxidized by Jones' reagent to give (**6**) (42%); [m.p. 163—165°, i.r. ($CHCl_3$) 1668, 1630, 1602, 1500, and 1131 cm^{-1}, n.m.r. ($CDCl_3$) δ 6·40 (s, 1H), 5·53 (s, 1H), 3·85 (s, 6H), 3·80 (s, 3H), 3·60 (s, 3H), 3·0—2·6 (2H), and 2·45—1·0 (8H)]. Compound (**6**) was treated with Ac_2O–H_2SO_4 (2 : 1) for 2 h at room temperature to give (**7**), m.p. 147—149°, (90%), which was identical with an authentic sample of desacetamidoisocolchicine. Cyclopropane ring cleavage, aryl migration, and dehydrogenation took place in one flask. Since the transformation of (**7**) to (±)-colchicine has been established by Eschenmoser,[1] the total synthesis of (±)-colchicine was completed in this step.

Reaction of (**3b**) with dimethyloxosulphonium methylide either in DMSO or in DMF[6] gave only the oxirane (**8**) (30%), m.p. 126—128°, i.r. (Nujol) 1664, 1617, 1600, and 1582 cm^{-1}. Reaction of (**3b**) with dimethylsulphonium methylide yielded an aldehyde (**9**), (90%), m.p. 143—145°, i.r. (Nujol) 1631, 1580 cm^{-1}, n.m.r. ($CDCl_3$) δ 10·25 (s, 1H), 6·40 (s, 1H), 6·33 (d, 1H, J 10 Hz), 5·4 (d, 1H, J 10 Hz), 3·85 (s, 9H), 3·80 (s, 3H), 3·28 (d, 1H, J 16 Hz), 2·62 (d, 1H, J 16 Hz), 2·80 (2H), and 2·1—1·5 (4H), which was acetylated to give (**10**), m.p. 102—105°.

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† The yield of (**3a**) from (**2a**) by oxidation with an iron–DMF complex was increased to 91% from 67% by the further purification of (**2a**).

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