A New Route to (−)-Cherylline *via* a Regiocontrolled Polonovski-type Reaction as the Key Step

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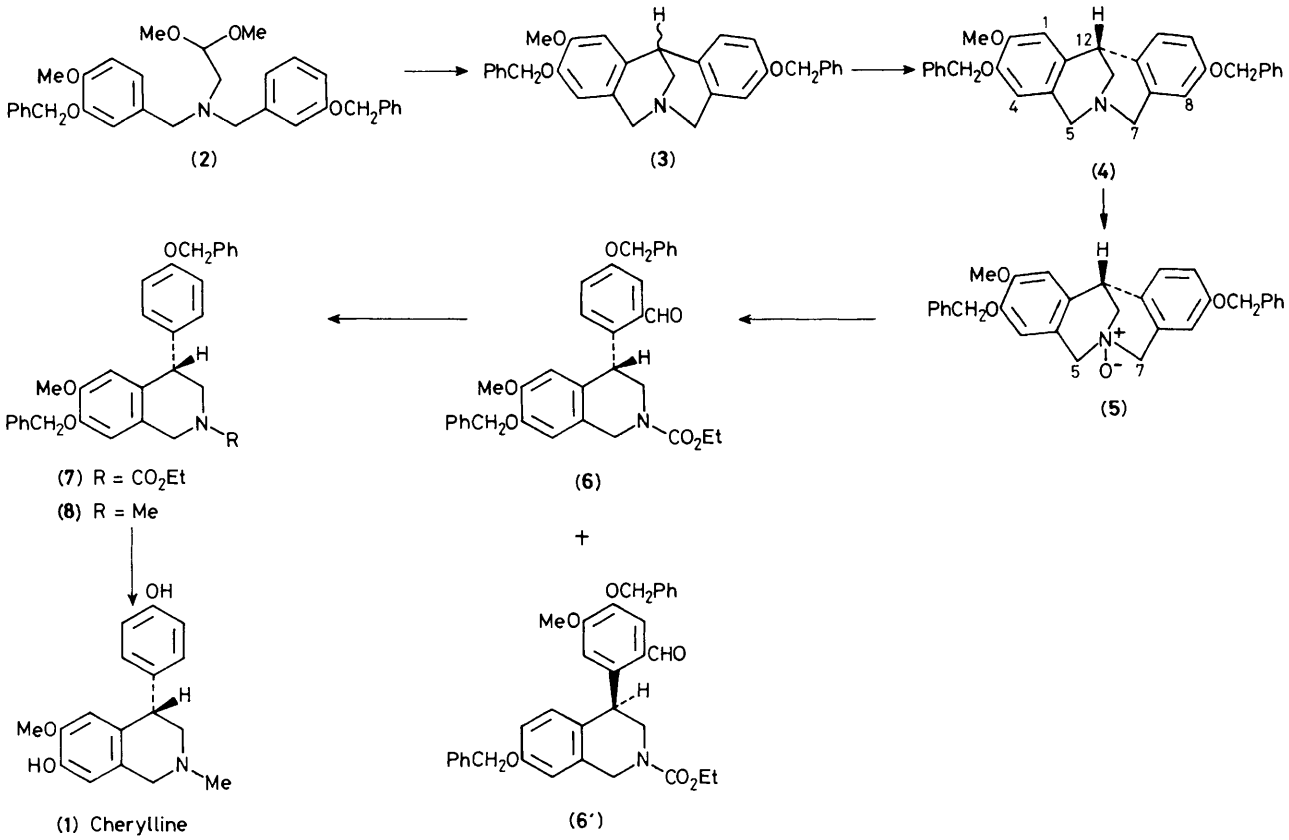
A facile and efficient synthesis of (−)-cherylline (**1**) was accomplished in 46% overall yield starting from the readily accessible (12*S*)-(−)-3,9-dibenzyloxy-2-methoxy-tetrahydro-6,12-methanodibenz[*c.f*]azocine (**4**) *via* a regiocontrolled Polonovski-type reaction as the key step.

(−)-Cherylline (**1**), isolated from several Crinum species (Amaryllidaceae),[1] has the 4-aryl-1,2,3,4-tetrahydroisoquinoline skeleton, whose pharmacological activities have recently received considerable attention.[2] While several syntheses of racemic cherylline have been reported,[3] we have applied our recently developed ring transformation[4] by using tetrahydro-6,12-methanodibenz[*c.f*]azocines in the preparation of this natural alkaloid and we now report a facile and



efficient synthesis of (**1**) starting from 3,9-dibenzyloxy-2-methoxytetrahydro-6,12-methanodibenz[*c.f*]azocine (**3**) *via* a regiocontrolled Polonovski-type reaction[5] as the key step.

Compound (**3**), prepared in 70% yield by the acid-catalysed double-cyclization (conc. HCl : acetone = 2:5)[6] of the corresponding dibenzylaminoacetaldehyde dimethyl acetal (**2**), was resolved using *O,O'*-dibenzoyl-L-(+)-tartaric acid into (12*S*)-(−)-(**3**) *i.e.* (**4**) {yield 89%; m.p. 151—153 °C; $[\alpha]_D^{24}$ −21° (*c* 0.8, $CHCl_3$)}.† Thus resolved optically pure (**4**) was oxidized with *m*-chloroperbenzoic acid to give quantitatively the *N*-oxide (**5**) (m.p. 191—193 °C), which was subjected to our Polonovski-type reaction[5] (Bu^tOK in hot Bu^tOH in a sealed tube, followed by the reaction with $ClCO_2Et$) to afford the tetrahydroisoquinoline aldehyde (**6**) {*m/z* 551 (M^+); ^1H n.m.r. δ($CDCl_3$) 3.70 (3H, s), 5.10 (2H, s), 5.15 (2H, s), 10.24 (1H, s); ν(neat) 1690 cm^{-1}; $[\alpha]_D^{23}$ +20° (*c* 0.61, $CHCl_3$)} in 64% yield *via* regioselective C(7)–N scission [the undesired C(5)–N scission product (**6'**) was present in only 8% yield]. The formyl group of (**6**) was removed[7] with $RhCl(Ph_3P)_3$ in refluxing toluene to furnish (**7**) {yield 84%; *m/z* 523 (M^+); ^1H n.m.r. δ($CDCl_3$) no aldehyde-H; $[\alpha]_D^{23}$ +32° (*c* 0.5, $CHCl_3$)}, which was subsequently reduced with $LiAlH_4$ in tetrahydrofuran to give *O,O*-dibenzylcherylline (**8**)‡ in 86% yield. Debenzylation of (**8**) with conc. HCl in EtOH afforded (−)-cherylline (**1**) {yield 96%; m.p. 217—218 °C; $[\alpha]_D^{21}$ −70° (*c* 0.1, MeOH); *m/z* 285 (M^+), 242, 225, 211; ^1H n.m.r. δ($[^2H_6]$acetone) 2.31 (3H, s), 2.48 (1H, dd, *J* 11.0 and 8.0 Hz), 2.82 (1H, dd, *J* 11.0 and 6.0 Hz), 3.49 (2H, s), 3.61 (3H, s), 4.05 (1H, dd, *J* 8.0 and 6.0 Hz), 6.39 (1H, s), 6.57 (1H, s), 6.75 (2H, d, *J* 9.0 Hz), 7.05 (2H, d, *J* 9.0 Hz); ν(KBr) cm^{-1} 3540, 1610, 1590, 1515, 1460}, whose physical and spectroscopic properties were identical with those reported previously.[8]

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† The optical purity was confirmed by the comparison of ^1H n.m.r. spectra using optically active shift reagent Eu(hfc)$_3$ [hfc = 3-(heptafluoropropylhydroxymethylene)-(+)-campharato].

‡ *Spectroscopic data* (**8**): m.p. 103—105 °C; $[\alpha]_D^{23}$ +5.8° (*c* 0.1, $CHCl_3$); *m/z* 465 (M^+), 422, 374, 331; ^1H n.m.r. δ($CDCl_3$) 2.37 (3H, s), 2.47 (1H, dd, *J* 11.0 and 8.0 Hz), 2.96 (1H, dd, *J* 11.0 and 6.0 Hz), 3.54 (2H, br. s), 3.65 (3H, s), 4.16 (1H, dd, *J* 8.0 and 6.0 Hz), 5.05 (2H, s), 5.12 (2H, s), 6.39 (1H, s), 6.59 (1H, s), 6.92 (2H, d, *J* 9.0 Hz), 7.11 (2H, d, *J* 9.0 Hz), 7.20—7.55 (10H, m); ν(KBr) cm^{-1} 1600, 1580, 1505, 1455: for similar results on racemic *O,O*-dibenzylcherylline, see; T. Kametani, K. Takahashi, and C. V. Loc, *Tetrahedron*, 1975, **31**, 235.

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