The Total Synthesis of (±)-Boonein

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The first synthesis of the iridoid monoterpene lactone boonein (**1**) has been achieved, in seven steps, from the bicyclo-octenone (**5**).

The monoterpene lactone boonein (**1**) was recently isolated from the bark of *Alstonia boonei* De Wild (Apocynaceae), a Nigerian tree of medicinal value.[1] Furthermore, the presence of a monoterpene and of indole alkaloids in the same plant is of biogenetic interest.[2] Therefore we embarked upon a preparation of this interesting molecule and now describe the first total synthesis of (±)-boonein.

We reasoned that a tin hydride reduction of the tertiary chloride (**2**) should deliver a hydrogen atom to the planar radical intermediate on the side opposite to the OR group if the protecting group R is bulky.[3] This would give the correct relative stereochemistry for the vicinal methyl and hydroxy functions present in boonein. Additionally the δ-lactone in (**2**) is readily derived from the ketone (**3**) which in turn should be available from the known bicyclic ketone (**4**), incorporating the *cis*-fused ring junction present in the target molecule.

Thus, as shown in Scheme 1, the major isomer (**4**) of the [2+2] cycloaddition of cyclopentadiene and methylchloro-

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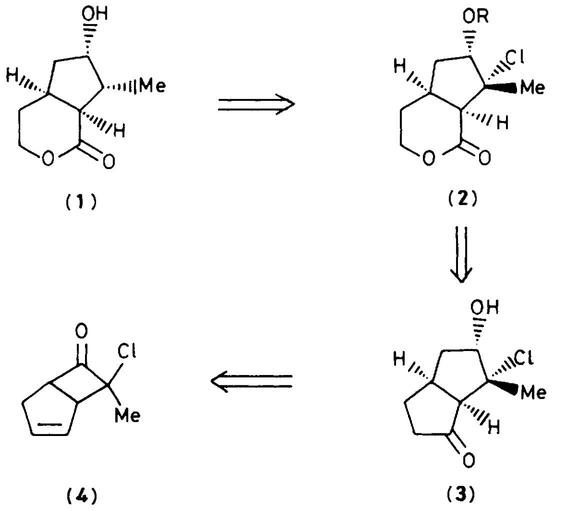
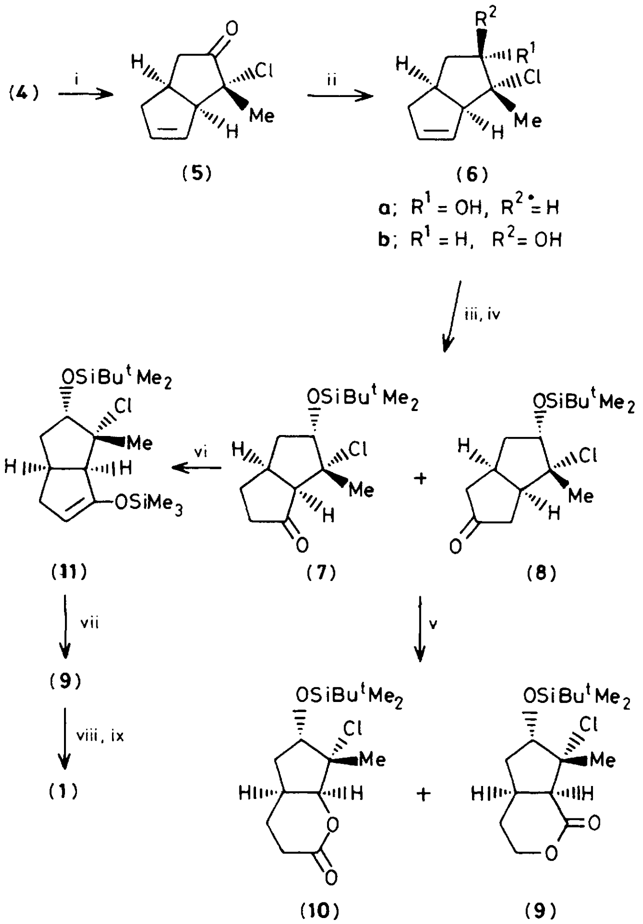


(1) (2) (3) (4)

ketene[4] was ring expanded to the bicyclo-octenone (5)‡ in 77% yield by treatment with diazomethane.[5] Reduction of the ketone function gave a 98% mixture of two easily separated alcohols (6), with $LiAlH_4$ giving the most favourable ratio (1.8 : 1) for (6a).§ Protection of the free hydroxy function as the t-butyldimethylsilyl ether (100%) was followed by treatment with borane : tetrahydrofuran (THF) complex and oxidation of the intermediate alkylborane to the ketone (7)‡ in 69% yield along with 16% of the unwanted isomeric ketone (8).¶ The chlorine atom β to the ketone function did not exert much influence on the Baeyer–Villiger reaction. The required lactone (9) was formed as a minor product (20%) alongside the isomeric lactone (10). This problem was overcome by formation and ozonolysis of the *O*-silylated enolate (11) to give, after a reductive work-up, the δ-lactone (9) as the only non-polar product. || Tin hydride reduction proceeded as we had hoped with delivery of a hydrogen atom to the less hindered α-face of the molecule to form, after desilylation, (±)-boonein in 65% yield. The sample thus obtained was identical both chromatographically and spectroscopically‡ with an authentic sample of boonein. Therefore we have converted the ketone (5) into (±)-boonein in seven steps and in an unoptimised yield of 8%.

The rôle of the chlorine atom in this synthetic pathway is crucial. First this atom directs the regiochemistry of the ring expansion reaction (4) → (5); secondly the C–Cl dipole ensures that the hydride reducing agent preferentially attacks from the opposite face of the molecule (5) → (6). While disappointing in its effect on the Baeyer–Villiger ring expansion of the ketone (7), the chlorine atom is readily removed in the penultimate step to give the key radical.



(5) (6) a; R^1 = OH, R^2 = H b; R^1 = H, R^2 = OH (11) (7) (8) (9) (1) (10) (9)

Scheme 1. *Reagents:* i, CH_2N_2; ii, $LiAlH_4$; iii, Me_2SiBu^tCl, imidazole; iv, BH_3 : THF complex; v, *m*-chloroperoxybenzoic acid; vi, lithium di-isopropylamide-Me_3SiCl; vii, O_3, $NaBH_4$; viii, $Bu^n{}_3SnH$; ix, $MeCO_2H$.

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‡ All new compounds gave satisfactory spectral and analytical data. *Spectral data:* (5): $\nu_{max.}$ (thin film) 1750(C=O), 1635(C=C) cm^{-1}; $\delta(CDCl_3)$ 5.8 (2H,m,olefin), 5.5 (2H,m,olefin), 3.6 (1H,m,1-H), 3.0 (1H,m,3-H), 2.6—2.3 (2H,m,4-H), 2.3—1.8 (2H,m,6-H), and 1.6 (3H,s,Me). (7): $\nu_{max.}$ (thin film) 1733(C=O) cm^{-1}; $\delta(CDCl_3)$ 3.71 (1H,dd,*J* 8,12 Hz,7-H), 3.14 (1H,m,5-H), 2.77 (1H,d,*J* 10 Hz,1-H), 2.42—2.05 (3H,m, 3-H and 4-H), 2.04 (1H,m,6-H*endo*), 1.74 (2H,m,6-H*exo*,4-H), 1.66 (3H,s,Me), 0.94 (9H,s,Bu^t), and 0.06 (6H,s,$SiMe_2$).

§ The unwanted isomer (6b) is readily oxidised to the ketone (5) (Jones oxidation) for re-use.

¶ To date we have not examined any other hydroborating reagents in this reaction to assess if this ratio arises from steric and/or electronic effects, *cf.* ref. 6.

|| The initial conversions (7) → (9) resulted in a modest 20% yield of the required lactone. No attempt has been made to improve this yield.