Rapid Synthesis of (±)-(*E*)- and (±)-(*Z*)-1-Amino-1-aminomethyl-2-(hydroxymethyl)cyclopropanes, Preparation of their Dichloroplatinum(II) Complexes, and Crystal Structure of a Derivative of the (±)-(*E*) Isomer

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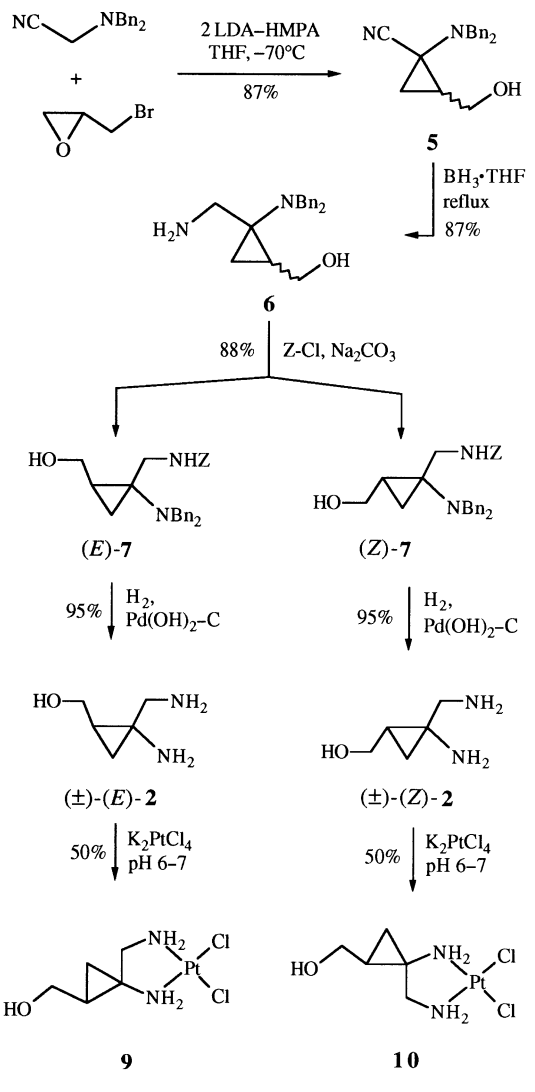
An efficient four-step synthesis of racemic *Z* and *E* forms of 1-amino-1-aminomethyl-2-(hydroxymethyl)cyclopropane is described, along with the preparation and cell-growth inhibition evaluation of the corresponding dichloroplatinum(II) complexes; the crystal structure of the synthetic intermediate (*E*)-1-[(benzyloxycarbonyl)aminomethyl]-1-dibenzylamino-2-(hydroxymethyl)cyclopropane has been determined.

Cyclopropane compounds continue to attract interest on account of their varied chemical and biological properties.[1,2] As part of our research programme dealing with the preparation of polyfunctional cyclopropanes, particularly those containing diamine functions,[15,26] we were interested in the synthesis of both diastereoisomers of the trifunctional molecule (±)-1-amino-1-aminomethyl-2-(hydroxymethyl)cyclopropane **2**. In the search for new analogues of the anticancer drug cisplatin,[16,17] the dichloroplatinum(II) complexes of **2** appeared attractive targets, since the presence of a peripheral non-metal-bound hydroxy group might be expected to improve the aqueous solubility and induce different biological activity profiles.[23,24]

The title compounds were prepared conveniently as shown in the Scheme. Double alkylation of *N*,*N*-dibenzylaminoacetonitrile with epibromohydrin gave cyclopropane **5**[10] as a mixture of diastereoisomers (60:40), which was reduced with an excesss of borane·THF to give the diamine **6**. It is noteworthy that no other products, such as those that might conceivably arise from decyanation[25] or rearrangement processes,[26] were observed. Treatment of **6** with benzyl



Scheme

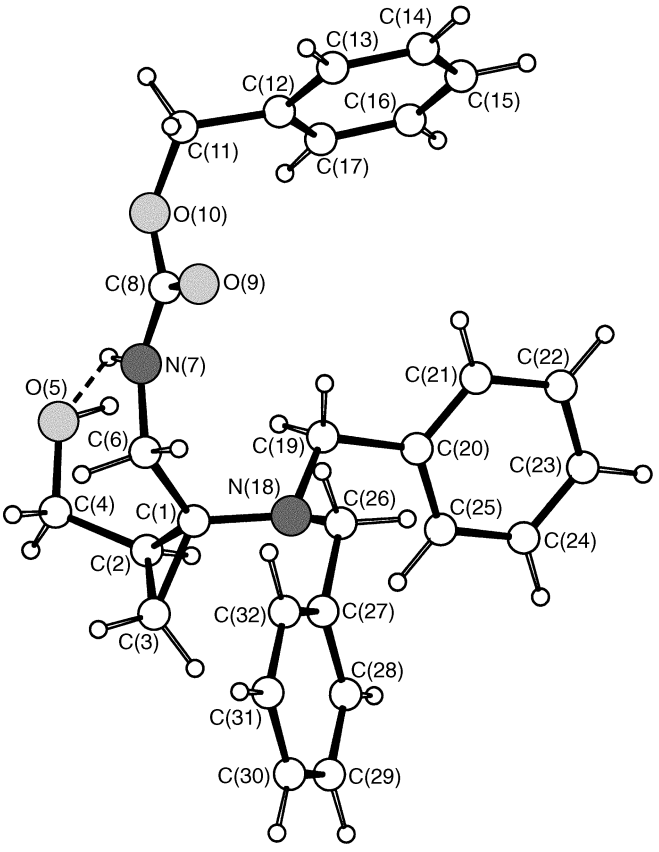


Fig. 1 X-Ray structure of compound (*E*)-**7**

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chloroformate led to the carbamate **7** whose low polarity facilitated separation of *Z* and *E* diastereoisomeric forms by flash chromatography. Each isomer of **7** was completely deprotected by hydrogenolysis to give the title compounds as hygroscopic oils. Each of the four steps in this sequence proceeded in high yield.

Surprisingly, several attempts to transform the hydroxy group of (*Z*)-**7** or (*E*)-**7** into a halide or phosphate ester function met with failure, although it was possible to obtain the corresponding acetates by reaction with acetic anhydride. There was no obvious reason for the unusual lack of reactivity of the primary alcohol, but it was interesting to observe the existence of an intramolecular hydrogen bond between the carbamate hydrogen atom and the hydroxy group oxygen atom in the crystal structure of (*E*)-**7** (Fig. 1), a phenomenon which could conceivably diminish the reactivity of the alcohol function.

The dichloroplatinum(II) complexes **9** and **10** were prepared by reaction of the appropriate isomer of **2** with potassium tetrachloroplatinate. The expected *cis*-N_2Cl_2 square-planar platinum ligand set was confirmed by the ^{195}Pt NMR resonances at around -2200 ppm,[27] thus confirming that the hydroxy function was not metal-bound. The *in vitro* cell-growth inhibition activities of **9** and **10** were evaluated as IC_{50} values on L1210 (murine leukaemia) cells, and were found to be 32 μM and >50 μM respectively. Both compounds were thus at least an order of magnitude less potent than cisplatin ($IC_{50} = 1.6$ μM).

Crystal Data for (E)-**7**.—$C_{27}H_{30}N_2O_3$, $M_r = 430.55$, orthorhombic, space group *Pbca*, $Z = 8$, $a = 8.383(6)$, $b = 13.146(9)$, $c = 44.094(20)$ Å, $V = 4859.3$ Å^3, $d_c = 1.18$ g cm^{-3}, $F(000) = 1840$, λ(CuKα) = 1.5418 Å, $\mu = 0.57$ mm^{-1}. Experimental data were collected on a Nonius CAD-4 diffractometer using graphite-monochromated CuKα radiation. The structure was solved by direct methods and the final *R* value was 0.065 ($R_w = 0.079$). Estimated standard deviations for geometrical parameters involving non-hydrogen atoms lie within the following ranges: bond lengths, 0.007–0.021 Å; bond angles, 0.4–1.3°.

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References: 30

Schemes: 2

Tables 1–5: Fractional atomic coordinates for non-H atoms, fractional atomic coordinates for H atoms, anisotropic thermal parameters, bond lengths and angles and selected torsion angles

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