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The First Total Synthesis of (±)– Pygmaeocin B

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Abstract: The first 20(10→5) *abeo*–abietane diterpenoid, pygmaeocin B, was synthesised in 13 steps from catechol.

Pygmaeocins B **1** and C **2**, two novel 20(10→5) *abeo* —abietane diterpenoids were first isolated from the roots of *pygmaeopremna herbacea*, a folk medicine used in Yunnan against inflammation and malaria.[1] Their structures, as shown in figure 1, were established on the basis of spectroscopic data.

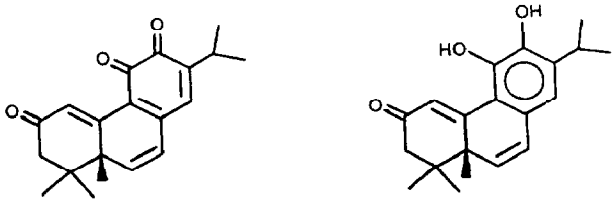
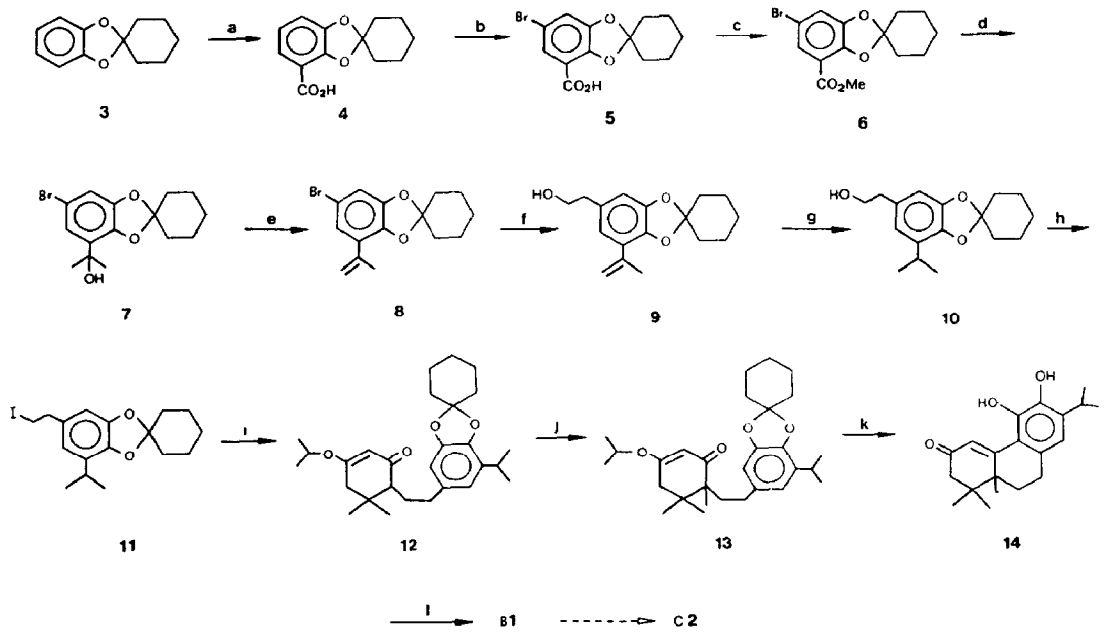


Fig. 1

Recently, a new and efficient synthetic method for constructing 2–oxygenated ring–C aromatic tricyclic diterpene was explored in our laboratory. It provided a short and convenient total synthetic route to ring–A、C polyoxygenated aromatic tricyclic diterpenes.[2] By the method, we now report the first synthesis of (±)– pygmaeocin B. In doing so, previously proposed structures of **B1** and **C2** are also further confirmed.

Lithiation of cyclohexylidene derivative of catechol **3** was done according to the literature[3] method. Subsequent carboxylation with dry ice at −78℃ produced the acid **4** in 70% yield. Bromination of **4** with bromine in acetic acid / sodium acetate[4] gave the regiospecific brominated compound **5** in excellent yield. Methyl esterification of the carboxyl group in **5** followed by treatment with excess MeMgI resulted the tertiary alcohol **7** in 90% overall yield. Dehydration of **7** in refluxing benzene with catalytic amount of toluene sulfonic acid afforded compound **8** . At −78℃, bromine–lithium exchange between compound **8** and n–butyllithium followed by successive reaction with ethylene oxide[5] afforded the alcohol **9** in 75% yield. Hydrogenation of **9** with Raney Ni furnished the saturated alcohol **10** which was converted to iodide **11** by a modified Corey's method[6].

Treatment of 3–isopropoxy–5,5–dimethyl–2–cyclohexenone with LDA in THF at –78℃ followed by alkylation with iodo **11**, produced the key intermediate **12** in 42% yield. Under the same conditions, alkylation of compound **12** with iodomethane produced compound **13** in 50% yield. Cyclodehydration of **13** with concentrated sulphuric acid in refluxing benzene afforded the cyclized compound **14**. **14** with DDQ in refluxing benzene, finally yielded (±)– pygmaeocin B1 in 78% yield. The IR, MS, ^1H and ^{13}C–NMR spectral data of synthetic (±)– pygmaeocin B are identical with those of the natural product.



a. n–BuLi, dry ice, –78℃ ; b. Br_2, CH_3CO_2Na, CH_3CO_2H; c. $(CH_3)_2SO_4$, K_2CO_3, acetone; d. MeMgI, THF; e. p–Tosa, benzene; f. n–BuLi, ethylene oxide, –78℃ ; g. H_2/ Raney Ni; h. I_2, imidazole, Ph_3P; i. LDA, 3–isopropoxy–5.5–dimethyl– 2–cyclohexenone, –78℃ ; j. LDA, iodomethane, –78℃; k. H_2SO_4, benzene; l. DDQ, benzene.

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