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Terpenoid Chirons: Preparation and Transformations of 2-Hydroxy-1,1,4a(R),6-Tetramethyl-*Trans*-$\Delta^{5,6}$-Octalin

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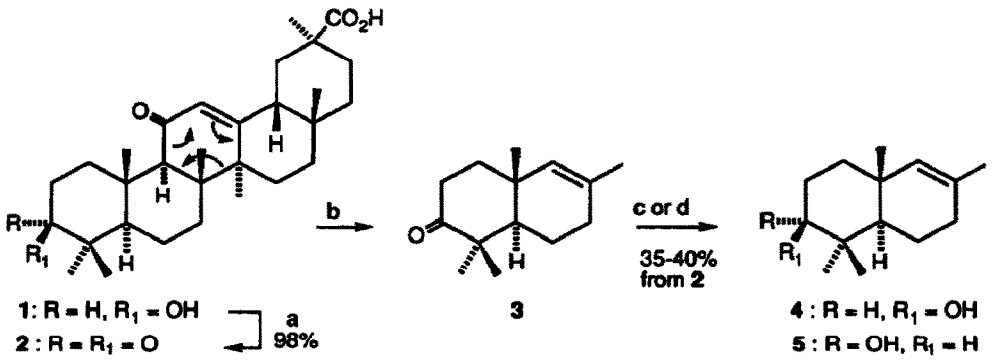
Abstract: Octalins **4** and **5** are prepared conveniently in 3 steps from commercial 18ß-glycyrrhetinic acid and converted to a variety of functionalized *trans*-AB ring chirons.

In recent years, there has been a worldwide resurgence of interest in the asymmetric total synthesis of sesquiterpenes and higher homologs.[1] This has been sustained in part by the burgeoning list of novel compounds from both marine and terrestrial sources,[2] many of which display significant biological activities. To help contend with the synthetic challenge, we have sought to devise a new generation[3] of optically active terpenoid building blocks or chirons by excision of appropriate subunits from a readily available but little utilized segment of the chiral pool, i.e., steroids.[4] Herein, we describe a convenient, multi-gram synthesis of 2α– and 2β-hydroxy-1,1,4a(R),6-tetramethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalenes **4** and **5**, respectively, and their conversion to a variety of useful AB-ring chirons.

SCHEME 1



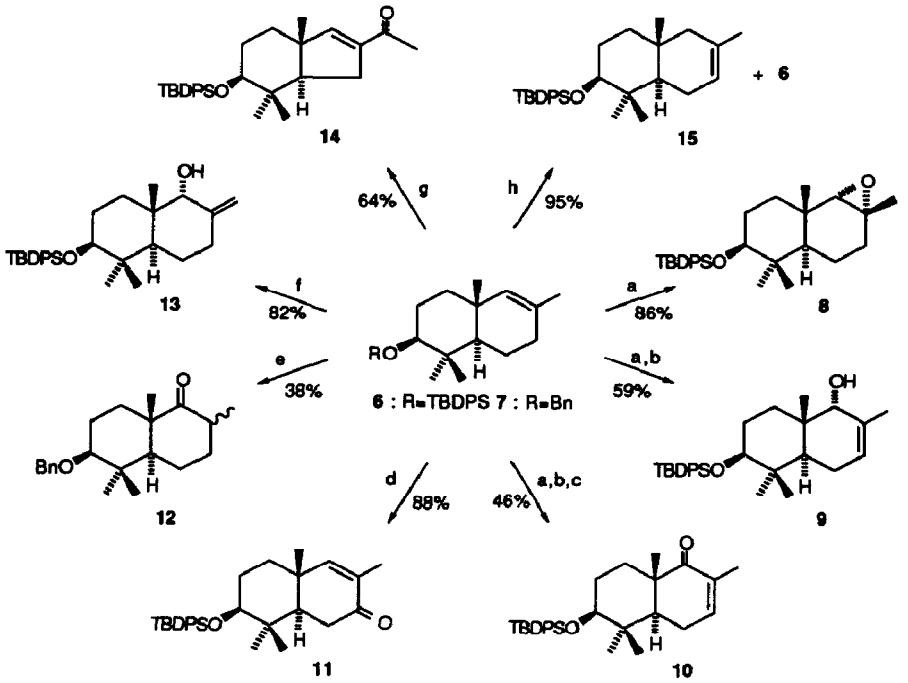
[a] CrO_3/H_2SO_4, acetone, 0°C, 1 h. [b] BMPS, 350°C, 40 mmHg, 3 h. [c] $NaBH_4$, MeOH, -78 to 0°C, 1 h. [d] $KB[CH(CH_3)C_2H_5]_3H$, THF, 0°C, 1 h.

Initially, the key octalone intermediate **3**[5,6] was obtained in poor yield by simple thermolysis of ketone **2**, which

in turn was derived from commercial 18ß-glycyrrhetinic acid 1[7] by Jones oxidation (Scheme 1). However, after extensive optimization studies, preparatively useful amounts of **3** could be generated by mixing **2** with the antioxidant 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide (BMPS) (10% w/w) and distillation from a kugelrohr or bulb-to-bulb apparatus under reduced pressure. This degradation can be envisioned as a retro-Diels-Alder reaction,[8] but is more likely a heterolytic process.[9]

Sodium borohydride reduction of the crude pyrolysate **3** led stereoselectively to ß-alcohol **4** in 35-40% overall yield from **2**. On the other hand, the α-alcohol **5** was the sole product using potassium tri-*sec*-butylborohydride (K-Selectride®). The sequence of thermolysis and hydride reduction using 40 mmoles of **2** consistently furnished over 3 g of **4** or **5**. Expensive pyrolysis equipment or high-temperature ovens were not required even on a preparative scale.

SCHEME 2



[a]3-$ClC_6H_4CO_3H$, $NaHCO_3$, CH_2Cl_2, 0°C, 0.5 h. [b]BF_3•Et_2O, THF, 0°C, 2 h. [c]MnO_2 (20 equiv), CH_2Cl_2, 50°C, 24 h. [d]pyridinium dichromate, *t*-BuOOH (90%), Celite, C_6H_6, 12 h. [e](i) BH_3, THF, 23°C, 5 h; H_2O_2/NaOH, 23°C, 4 h; (ii) PCC, CH_2Cl_2, 23°C, 2h. [f]$^1O_2$, C_5H_5N, 23°C, 24 h; $NaBH_4$, MeOH, 0°C, 2 h. [g](i) O_3, MeOH, -15°C, 15 min; $H_2NC(S)NH_2$, 23°C, 1h; (ii) K_2CO_3, MeOH, 23°C, 0.5 h; (iii) MsCl, Et_3N, CH_2Cl_2, 0°C, 10 min; (iv) DBU, CH_2Cl_2, 23°C, 8 h. [h]$RhCl_3$, EtOH, 100°C, 20 h.

The potential utility of **4** and **5** was explored by their conversion to a variety of functionalized AB ring chirons (Scheme 2, shown for **4** only). For this, the C(3)-alcohol was protected as its *tert*-butyldiphenylsilyl (TBDPS) ether **6** (TBDPS-Cl, DMAP, DMF, 50°C, 24 h, 90%) or benzyl ether **7** (Bn-Br, NaH, DMF, 23°C, 3h, 69%). Treatment of **6** with 3-chloroperbenzoic acid gave rise to epoxide **8**, free of any ß-isomer, which