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# Stereocontrolled synthesis of conformationally restricted enantiopure triols and dihydroxy acids based on the norbornane framework

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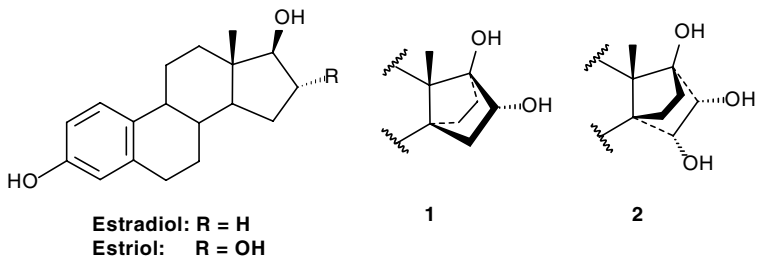
**Abstract**—The synthesis of chiral, rigid analogues of glycerol and cyclitols has been achieved by means of the stereocontrolled reduction of chiral bridgehead-substituted camphorquinones. This simple and easy procedure exclusively affords dihydroxy derivatives with a 2,3-*cis*-*exo*-configuration. The employment of different hydrides has also allowed the synthesis of enantiopure 2,3-dihydroxy carboxylic acids with high diastereoselectivity.


## 1. Introduction

Camphor or fenchone-based hydroxy derivatives are naturally occurring terpenoids with a wide range of applications as pharmaceuticals,[1] raw materials for flavour and fragance[2] or chiral auxiliaries and catalysts in asymmetric synthesis.[3] Among them, the best known is (1*R*,2*S*,3*R*)-3-hydroxyisoborneol, which has been used as a chirality transfer agent in many asymmetric processes.[4] Although reactivity of this diol has been extensively studied,[5] no effort has been made to introduce additional functional groups at the bridgehead position. In this sense, the synthesis of trihydroxy norbornane derivatives is a matter of interest because they can be considered as conformationally restricted analogues of glycerol and cyclitols,[6] and consequently, be useful not only as chiral ligands but also as centre pieces for the preparation of non-natural lipids,[7] chiral dendrimers[8] or biologically active compounds[9] among others. For example, 1,2-diol and 1,2,3-norbornanetriol moieties are located in the steroid hormone analogues **1** and **2** similar to estradiol[10] and estriol[11] (see Fig. 1), and it has been found that the bicyclic ring plays a relevant role in the oral estrogenicity.[12]

Furthermore, the replacement of one hydroxy group of the molecule by a carboxylic acid gives place to cyclic hydroxy acids; some of them, such as quinic acid or




**Estradiol: R = H**
**Estriol: R = OH**

**1** **2**

**Figure 1.** Steroid hormones estradiol and estriol, and their synthetic 14,17-ethano bridge analogues **1** and **2**.

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shikimic acid, are natural products widely used as chiral building blocks for the synthesis of pharmaceuticals.[13]

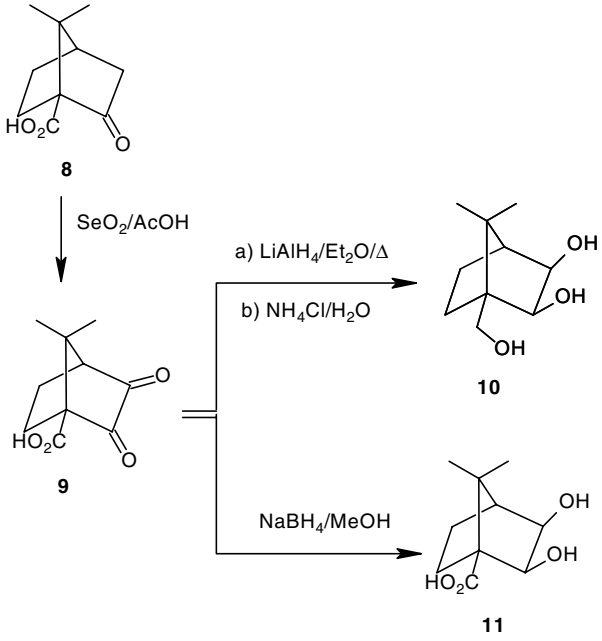
## 2. Results and discussion

The synthesis of the title compounds has been achieved using properly bridgehead-substituted 2,3-camphorquinones. These compounds have been the subject of numerous studies on their chiroptical properties[14] and used as photosensitisers in polymerisation reactions, but only 2,3-camphorquinone and some C7-substituted derivatives have been reported to be used as substrates in organic synthesis procedures.[15–17] Taking into account our previous experience on the synthesis and applications of new bridgehead mono- and dihydroxy derivatives based on the norbornane framework,[18] we planned the synthesis of the vicinal norbornanetriol **7** (Scheme 1), which can be considered as a conformationally constrained glycerine analogue.[7]

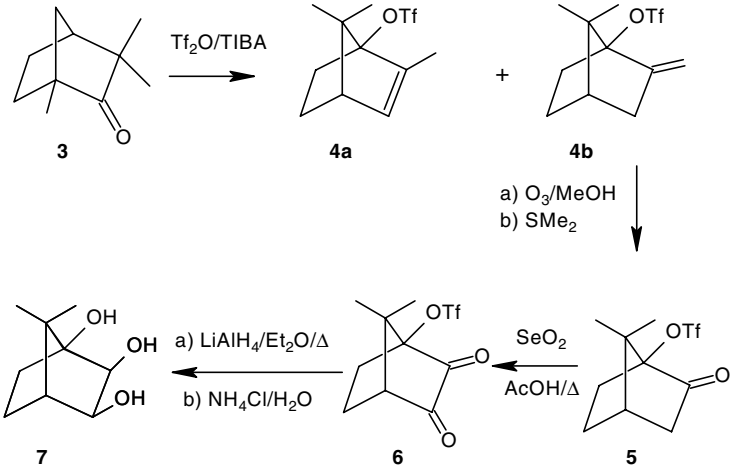
For this purpose, we proposed (1*R*)-7,7-dimethyl-1-triflyloxy-2,3-norbornanequinone **6** as the precursor, which could be obtained through a three-step synthetic route starting from commercially available (1*R*)-fenchone **3**.[19] As shown in Scheme 1, the reaction of 2-norbornanone **3** with trifluoromethanesulfonic anhydride ($Tf_2O$) and triisobutylamine (TIBA) afforded, through a Wagner–Meerwein rearrangement and proton elimination, a mixture of bridgehead triflates **4a** and **4b** that were easily separated by column chromatography.[19a] Ozonolysis of triflate **4b** in MeOH/−78 °C, followed by treatment with $Me_2S$, yielded ketone **5**,[19b] which was heated with selenium dioxide in refluxing acetic acid to obtain (1*R*)-7,7-dimethyl-1-triflyloxy-2,3-norbornanoquinone **6**. The total reduction of all functional groups with $LiAlH_4$ afforded the desired (1*R*,2*S*,3*S*)-7,7-dimethylbicyclo-[2.2.1]heptano-1,2,3-triol **7** with 63% overall yield in four steps.

The replacement of the triflyloxy group with a carboxylic acid group in the starting quinone allows the insertion of a methylene unit at the bridgehead position to give a more flexible norbornanetriol. As shown in Scheme 2, the reaction of commercially available (+)-ketopinic acid **8** with selenium dioxide in refluxing acetic acid yielded quinone **9**, which was treated with two hydrides with different ease of reduction. The most powerful $LiAlH_4$ gave, after refluxing in diethyl ether, (1*R*,2*S*,3*R*)-3,10-dihydroxyisoborneol **10** with 77% yield. Additionally, reaction of quinone **9** with the less reactive hydride, $NaBH_4$ in MeOH, allowed us to obtain a different kind of compound, such as 2,3-dihydroxy-1-norbornanecarboxylic acid **11** with 73% yield.

Owing to the high number of polar hydroxy groups in the structure, all compounds are quite soluble in water, and were extracted continuously (24 h) in diethyl ether or dichloromethane after hydrolysis of the reaction mixture. Two-dimensional NMR techniques (HMQC,




**Scheme 2.** Synthesis an hydride reduction of 1-carboxyquinone **8**.




**Scheme 1.** Total synthesis of chiral glycerol-analogue norbornanetriol **7** from (1*R*)-fenchone.

HMBC, NOESY and COSY) were used for the structural elucidation of C2 and C3 stereogenic centres, whose configuration was determined in all the cases to be exclusively 2,3-*exo*.

## 3. Conclusions

In conclusion, we have demonstrated that the hydride reduction of bridgehead-substituted canforquinones takes place with high stereocontrol to give 2,3-*exo*-derivatives; therefore, it constitutes a convenient and simple procedure to obtain interesting chiral polyhydroxylated norbornane derivatives with potential applications in asymmetric synthesis and biological studies.

## 4. Experimental

### 4.1. General

$^1$H and $^{13}$C NMR spectra: Brucker AMX500 and Brucker AM300 spectrometers, with tetramethylsilane as internal standard. Capillary GC/MS: Shimadzu QP-17A (column type: TRB-1, 30 m) coupled to a Shimadzu QP-5000 Mass-spectrometer (EI, 70 eV). Melting points: Gallenkamp apparatus; values are uncorrected. Molecular rotations: Perkin–Elmer 241 spectropolarimeter. Elemental analysis: Perkin–Elmer 2400 CHN analyser. Exact mass: VG AutoSpec Mass Spectrometer. Synthesis of (1*R*)-7,7-dimethyl-2-oxobicyclo-[2.2.1]-hept-1-yl triflate **5** was achieved according to a procedure previously described by us.[19]

### 4.2. Synthesis of bridgehead 2-3-camphorquinones

In a typical procedure, 1.50 mmol of 2-norbornanone and 1.50 mmol of $SeO_2$ were heated in acetic acid (4 mL) under refluxing conditions. The reaction progress was monitored by GC or NMR until total disappearance of the starting ketone; additional amounts of $SeO_2$ (0.2 mmol) were added if necessary. Once the reaction was finished, the mixture was diluted in 30 mL of $CH_2Cl_2$, filtrated through Celites and washed with saturated $NaHCO_3$ and water (quinone **6**) or only water (quinone **9**) to eliminate the acetic acid. After drying over $MgSO_4$ and filtration, the yellow product was purified through recrystallisation.

### 4.3. (1*R*)-7,7-Dimethyl-2,3-dioxobicyclo[2.2.1]hept-1-yl trifluoromethanesulfonate 6

Following the standard procedure, 370 mg (82% yield) of the title compound were obtained. The resulting quinone was crystallised in hexane to give yellow needles. Mp 85.0–86.5 °C. $[\alpha]_D^{20} = +275.1$ (*c* 0.92, $CH_2Cl_2$). IR (KBr) *v* 2940, 1795, 1770, 1420, 1250, 1220, 1150, 1100, 1015, 935 cm$^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 2.78–2.74 (m, 1H), 2.50–2.25 (m, 2H), 2.41 (d, $J = 1.96$ Hz, 1H), 1.75–1.58 (m, 1H), 1.19 (s, 3H), 1.04 (s, 3H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 195.4, 193.4, 118.3 (q, $J = 317$ Hz), 99.5, 55.1, 44.0, 24.6, 20.7, 19.5, 16.5 ppm. MS *m/e* (% B): 139 ($M^{+\cdot}-$Tf and CO, 15), 111 (5), 95 (4), 94 (2), 83 (22), 79 (6), 69 (90), 55 (100), 41 (41). Anal. Calcd for $C_{10}H_{11}F_3O_5S$: C, 40.00; H, 3.70; S, 10.70. Found C, 40.30; H, 3.81; S, 10.76.

### 4.4. (1*S*)-7,7-Dimethyl-2,3-dioxobicyclo[2.2.1]heptane-1-carboxylic acid 9

Following the standard procedure, 255 mg (87% yield) of the title compound were obtained starting from (+)-ketopinic acid; the resulting quinone was crystallised in hexane/diethyl ether to give pure **9** as yellow needles. Mp 236.2–237.5 °C, $[\alpha]_D^{20} = +200.1$ (*c* 0.92, $CH_2Cl_2$). Experimental data agree with that previously reported for **9**:[14a] mp 236 °C. $[\alpha]_D^{20} = +204$ (*c* 0.5, $CHCl_3$).

### 4.5. Reduction of bridgehead 2,3-norbornanequinones with lithium aluminium hydride

A solution of the corresponding quinone (1.0 mmol) in absolute ether (5 mL) was added through a dropping funnel to lithium aluminium hydride (380 mg, 10 mmol) in absolute ether (20 mL) at 0 °C. The reaction was heated to reflux (8 h), cooled and carefully hydrolysed with $NH_4Cl$ solution. The aqueous mixture was continuously extracted in ether (24 h) to recover all the reaction product. After work-up, the triol can be purified by column chromatography or recrystallisation.

### 4.6. (1*R*,2*S*,3*S*)-7,7-Dimethylbicyclo[2.2.1]heptane-1,2,3-triol 7

Following the procedure described above, the reduction of quinone **6** yields, after recrystallisation in $CH_2Cl_2$ at +4 °C, 148 mg (86% yield) of the title compound as white prisms. Mp 235.2–237.0 °C. $[\alpha]_D^{20} = +16.0$ (*c* 0.99, MeOH). IR (KBr) *v* 3370, 3270, 2950, 2920, 1460, 1345, 1280, 1135, 1090, 1050 cm$^{-1}$, $^1$H NMR (300 MHz, $CD_3OD$): $\delta$ 3.85 (d, $J = 7.1$ Hz, 1 H), 3.65 (d, $J = 7.1$ Hz, 1H), 1.85–1.60 (m, 2H), 1.62 (d, $J = 4.7$ Hz, 1H), 1.20–1.04 (m, 2H), 1.14 (s, 3H), 0.92 (s, 3H) ppm. $^{13}$C NMR (75 MHz, $CD_3OD$): $\delta$ 82.4, 77.6, 75.6, 49.0, 45.7, 31.1, 23.3, 21.5, 20.5 ppm. MS *m/e* (% B): 154 ($M^{+\cdot}-H_2O$, 2), 139 (7), 136 (2), 129 (16), 128 (17), 125 (12), 111 (52), 97 (41), 95 (27), 86 (25), 83 (40), 82 (27), 71 (43), 69 (61), 67 (49), 55 (50), 43 (81), 41 (93), 29 (100). Exact Mass Calcd 172.1104. Found 172.1104.

### 4.7. (1*R*,2*S*,3*R*)-1-(Hydroxymethyl)-7,7-dimethylbicyclo[2.2.1]heptane-2,3-diol 10

Following the procedure described above, the reduction of quinone **9** yields, after recrystallisation in hexane/dichloromethane or hexane/diethyl ether, 143 mg (77% yield) of the title compound as white needles. Mp 275–277 °C. $[\alpha]_D^{20} = -27.7$ (*c* 1.05, MeOH). IR (KBr) *v* 3370, 2940, 2885, 1460, 1395, 1375, 1120, 1045, 1020, 990 cm$^{-1}$. $^1$H NMR (500 MHz, $CDCl_3$ with a drop of $D_2O$): $\delta$ 3.96 (d, $J = 7.0$ Hz, 1H), 3.94 (d, $J = 11.1$ Hz, 1H), 3.84 (d, $J = 7.0$ Hz, 1H), 3.76 (d, $J = 11.0$ Hz, 1H), 1.79 (d, $J = 4.7$ Hz, 1H), 1.72 (dddd, $J = 12.5$, 12.3, 4.7, 4.2 Hz, 1H), 1.46 (ddd, $J = 12.5$, 12.3, 4.2 Hz,

1H), 1.27 (s, 3H), 1.08 (ddd, $J = 12.5$, 12.0, 4.0 Hz, 1H), 1.01 (ddd, $J = 12.5$, 12.0, 4.0 Hz, 1H), 0.90 (s, 3H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$ with a drop of $D_2O$): $\delta$ 78.0, 75.7, 62.6, 52.4, 52.2, 46.6, 29.1, 23.7, 22.1, 22.0 ppm. MS *m/e* (% B): 168 ($M^{+\cdot}-H_2O$, 3), 167 (2), 154 (2), 150 (2), 137 (8), 121 (9), 111 (22), 110 (28), 95 (27), 81 (23), 79 (30), 77 (22), 69 (36), 67 (44), 55 (30), 53 (19), 43 (50), 41 (100), 39 (4). Exact Mass Calcd (for $M-H_2O$) 168.1150. Found 168.1150.

### 4.8. (1*S*,2*S*,3*R*)-2,3-Dihydroxy-7,7-dimethylbicyclo-[2.2.1]heptane-1-carboxylic acid 11

To a solution of quinone **9** (1.0 mmol) in 5 mL of methanol was added sodium borohydride in small pieces (380 mg, 10 mmol) at 0 °C. The cooled reaction was stirred for 30 min and carefully hydrolysed with water. The aqueous mixture was then washed with $CH_2Cl_2$, acidified with HCl 10% and continuously extracted with $CH_2Cl_2$ (24 h) to recover all the dihydroxy acid **11**. After drying and evaporation of the solvent, the product can be purified by recrystallisation in $CH_2Cl_2$/hexane (73% yield, white prisms). Mp 241–243 °C. $[\alpha]_D^{20} = -18.2$ (*c* 0.50, MeOH). IR (KBr) *v* 3500–2600, 3420, 2960, 1700, 1460, 1390, 1375, 1270, 1110, 1050 $cm^{-1}$. $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 4.50 (br s, 2H), 4.08 (d, $J = 6.9$ Hz, 1H), 3.98 (d, $J = 6.9$ Hz, 1H), 2.25 (td, $J = 8.4$ Hz, 4.3 Hz, 1H), 1.93 (d, $J = 4.7$ Hz, 1H), 1.90–1.80 (m, 1H), 1.35–1.25 (m, 1H), 1.33 (s, 3H), 1.10–1.00 (m, 1H), 1.07 (s, 3H) ppm. $^{13}C$ NMR (125 MHz, $CDCl_3$): $\delta$ 177.1, 77.6, 75.8, 57.5, 52.0, 50.4, 29.6, 23.7, 22.9, 21.5 ppm. Exact Mass Calcd 200.1049. Found 200.1055.

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