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A chromium-free synthesis of enantiopure 5-oxoborneol

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syntheses.

ARTICLE INFO

ABSTRACT

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Enantiopure (-)-5-oxoborneol was obtained in 35% overall yield in two steps, starting from readily avail-

able (-)-bornyl acetate and using oxone[®] as a safe and inexpensive oxidant. The reported procedure

avoids the use of large excess of noxious chromium(VI), which was required by the so far reported

Terpenes are a natural-occurring source of inexpensive enantiopure starting material for the preparation of many important chemicals, such as chiral auxiliaries, pharmaceuticals, pesticides, cosmetics, and fragrances. A key step for practical applications is the introduction in well-defined positions of further functional groups in the skeleton of the molecule. These transformations are not always trivial, especially considering the oxidation of saturated carbons,¹ which often results with unpredictable results.

Our research, aimed at the synthesis of enantiomerically pure cyclotrimers,² is based on the availability of enantiomerically pure 5-oxoborneol **2**, which has also been employed for the synthesis of drugs,³ functionalized polymers,⁴ fragrances,⁵ chemical–physical studies⁶, and as a substrate for biological transformations.⁷ This compound has always been prepared by oxidation of (–)-bornyl acetate with a large excess of chromium(VI) oxide in different solvents,⁸ affording (–)-5-oxobornyl acetate **1**, which is hydrolyzed under basic conditions (Scheme 1). In order to avoid the use of large amounts of noxious and environmentally hazardous chromium(VI) (Table 1, entries 1 and 2), an alternative procedure was studied upon screening a number of oxidation procedures for (–)-bornyl acetate, which are herein described.

The first oxidant tested was the inexpensive and environmentally friendly *N*-hydroxyphthalimide (NHPI), which is known to promote oxidation of unactivated alkanes under very mild conditions.⁹ This reagent left bornyl acetate unaltered, and the introduction of additives (e.g., cobalt(II)¹⁰ or TBABr¹¹) did not change the

* Corresponding author. *E-mail address:* fabrisfa@unive.it (F. Fabris). of ing, and it afforded very low and erratic yields of 5-oxobornyl acetate **1** (Table 1, entry 5). Slightly better results were obtained with *tert*-butyl hydroperoxide,¹⁵ which was slowly added to the reagent as an 80% solution in di-*tert*-butylperoxide/water (3:2), causing evolution of heat, n-



final outcome (Table 1, entry 3). Although ruthenium(VIII) cannot

be considered a safe reagent, its use in catalytic amounts consider-

ably reduces the risk and the environmental impact.¹² In this case,

a proper co-oxidant (unreactive with the substrate or the products)

and a suitable solvent system (to stabilize intermediates) are required. Many oxidants were tested, among them, gaseous ozone¹³

was considered the most convenient, because its excess, as well as

its by-products, can be easily removed from the reaction mixture.

Disappointedly, when the stream of O_2/O_3 passed through the

reaction mixture, it removed the volatile ruthenium(VIII) oxide,

relatively safe by-products (water in the case of hydrogen perox-

ide), and effectively promote the formation of Ru(VIII) in the catalytic cycle.¹² Hydrogen peroxide¹⁴ was mostly converted into

oxygen in the presence of RuCl₃, as witnessed by copious foam-

Peroxides are a convenient class of oxidants, which produce

leaving the starting material unchanged (Table 1, entry 4).

Scheme 1. Common procedure for the preparation of 5-oxoborneol 2.

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Entry	Oxidant	Ox. Eq.	Catalyst	Cat. Eq.	Solvent	Temp	Time	Yield
1	CrO ₃	2.9	_	-	Ac ₂ O/AcOH	25 °C	170 h	32-42% ¹²
2	CrO ₃	5.6	-	-	AcOH	140 °C	5 h	15-35% ¹²
3	02	(1.0 bar)	NHPI	0.10	AcOH	100 °C	18 h	-
4	O ₃	(0.1 bar)	RuCl ₃	0.05	AcOH/H ₂ O	25 °C	6 h	-
5	H_2O_2	20	RuCl ₃	0.05	AcOH/AcOEt	50 °C	4 h	0–3% ^a
6	t-BuOOH	40	RuCl ₃	0.05	$(t-BuO)_2/t-H_2O$	70 °C	2 h	4% ^a
7	$Ca(ClO)_2$	2.0	RuCl ₃	0.02	MeCN/AcOH/H ₂ O	60 °C	24 h	8% ^a
8	NaIO ₄	1.8	RuCl ₃	0.02	MeCN/AcOH/H ₂ O	60 °C	45 h	19% ^b
9	Oxone®	3.5	RuCl ₃	0.01	MeCN/AcOH/H ₂ O	25 °C	4 h	35% ^c

 Table 1

 Reagents and yields for the oxidation of bornyl acetate to afford 5-oxobornyl acetate 1

^a Nonisolated yield (GC). ^b Isolated yield

^b Isolated yield.

^c Isolated yield after the hydrolysis of acetate.

which serves to distill the *tert*-butanol, produced along the reaction. The conversion of bornyl acetate ceased after the addition of nearly 40 equiv of *tert*-BuOOH, affording complex mixtures of products, in which **1** was detected in modest amounts (Table 1, entry 6).

Hypochlorites are inexpensive reagents, which are suitable for ruthenium catalyzed oxidations of alkanes.¹⁶ Calcium hypochlorite furnished crude materials containing unreacted acetyl borneol, the expected 5-oxobornyl acetate **1** and many chlorinated by-products (Table 1, entry 7). These compounds were presumably derived from the reaction of reagent and products with chlorine generated by the dismutation of hypochlorous acid (HClO) arising from the interaction of acetic acid and hypochlorite ion. Substitution of acetic acid with dichloromethane almost suppressed reactivity even at 60 °C.

Sodium periodate¹⁷ can be considered an expensive reagent, but it was tested as an oxidant in ruthenium catalyzed oxidation of bornyl acetate. The best compromise between selectivity and reactivity was found while carrying out the reaction at 60 °C for 45 h in a ternary solvent (AcOH/MeCN/H₂O) with RuCl₃ as the pre-catalyst (2 mol %), to afford a partially converted (10% unreacted bornyl acetate) mixture of camphor (25%), 2,5-bornanedione **4** (9%) and 5-oxobornyl acetate **1** (16% yield) (Table 1, entry 8).

Eventually, inexpensive and readily available oxone[®] (2KHSO₅·KHSO₄·K₂SO₄)¹⁸ afforded a complete conversion of bornyl acetate and acceptable selectivity. The reaction was best performed with 1 mol % of ruthenium and 3.5 equiv of oxone[®] and did not require external heating. Indeed, the controlled spontaneous exothermicity sufficed to lead the reaction to completion (Table 1, entry 9). Analysis of the crude mixtures (GC–MS, ¹H NMR) displayed the formation of the expected 5-oxobornyl acetate **1** (37% yield) and the isomeric 3-oxobornyl acetate **3** (10% yield), concomitantly with minor amounts of borneol and 2,5-bornanedione **4** (10% combined yields) (Scheme 2).

Since the large scale (fractional distillation or crystallization) separations of **1** from **3** proved to be not possible, the crude material of the oxidation step was directly hydrolyzed. We were pleased



Scheme 2. Ruthenium(VIII) catalyzed oxidation of (–)-bornyl acetate and hydrolysis to afford (–)-5-oxoborneol **2**.

to notice that 3-oxobornyl acetate **3** was converted into a watersoluble derivative, which could be readily separated from the desired (-)-5-oxoborneol (Scheme 2).

In conclusion, although ruthenium(VIII) oxide is not a 'green' reagent, the low amount (1 mol %) required for the reaction could compensate its toxicity, especially in consideration of the original procedures. An added advantage of the present method is the ease of separation and recovery of the desired product after saponification. The expected (–)-5-oxoborneol **2** is hence obtained in a reproducible 35% overall yield after crystallization from hot cyclohexane.

Experimental

(-)-Bornyl acetate (14 mL, 13.7 g, 70.0 mmol), a mixture of MeCN/AcOH/H₂O (1:1:1.4, 155 mL), oxone[®] (150.0 g, 244 mmol) and a 0.1 M aq solution of RuO_4^{19} (7 mL) were added in sequence in a 500 mL screw-capped Schott Duran[®] bottle. The bottle was carefully sealed and placed in a bucket²⁰ containing water at room temperature, enough to fit the level of the reaction mixture (nearly 2 L). The slurry was maintained under vigorous stirring for 4 h, during which heat and oxygen evolved and pressure increased. The end-point of the reaction was monitored by the change of color from bright yellow to light brown. The bottle was cautiously opened (dissolved oxygen in the liquid can cause foaming) and the resulting slurry was filtered, washing the inorganic salts with AcOEt (3 \times 50 mL). The aqueous layer was diluted with H₂O (100 mL) and extracted with AcOEt (3×50 mL). Combined organic washing and extracts were placed into a 1 L beaker and cautiously neutralized adding solid Na₂CO₃, then the mixture was filtered and the organic layer dried over MgSO4 and concentrated under reduced pressure. The resulting oil was dissolved in EtOH (70 mL) and KOH (3.92 g, 70.0 mmol) was added. The resulting solution was stirred at rt under Ar for 4 h. Volatile materials were removed under reduced pressure, the residue was diluted in satd aq NaCl (100 mL) and extracted with Et_2O (3 \times 50 mL). Combined organic layers were dried over MgSO4 and concentrated under reduced pressure. The residue was purified by re-crystallization from hot cyclohexane to afford 3.76 g of $2 (32\% \text{ yield})^{21}$ as pale yellow crystals, mp 235–237 °C (lit.⁸ 239–241 °C); [α]_D²² –86 (*c* 1.1, CHCl₃) (lit.⁸ -74 (c 1.6, CHCl₃)); ¹H NMR (CDCl₃, 200 MHz) δ (ppm): 4.42 (1H, ddd, J = 9.6, 3.7 and 1.8 Hz), 2.64 (1H, d, J = 18.7 Hz), 2.51 (1H, ddd, J = 14.4, 9.6 and 5.3 Hz), 2.14 (1H, d, J = 5.3 Hz), 1.91 (1H, ddd, J = 18.7 and 1.8 Hz), 1.60 (1H, br s), 1.31 (1H, dd, J = 14.4 and 3.7 Hz), 1.03 (3 H, s), 0.98 (3 H, s), 0.94 (3 H, s).

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- The solution was obtained dissolving RuCl₃·H₂O (2.25 g, 10.0 mmol) and NaIO₄ (4.28 g, 20.0 mmol) in H₂O (100 mL).
- 20. In one case we experienced a violent rupture of the bottle with splashing of the reaction mixture: the bucket was used to contain possible breaks, while water was used to remove the excess of heat produced by the reaction.
- Mother liquors of the crystallization were extracted with water and concentrated to afford 35% yield of the desired product.