Scientific Paper

CATALYTIC OXIDATIVE CLEAVAGE OF TERPENIC OLEFINS: USEFUL ROUTE TO CHIRAL POLY-FUNCTIONALISED CYCLOBUTANES AND CYCLOPROPANES

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Abstract

Catalytic oxidation of terpenic olefins (α-pinene, 2-carene and 3-carene) with RuO_4 generated in situ, produces the cyclobutane and cyclopropane isolable keto-aldehydes which evolve in prolonged reaction time to the corresponding keto-acids with excellent yields (90-100%). As these compounds can serve as building block for the synthesis of cyclobutane aminoacids and pyrethroid derivatives, the reaction affords a simple access to this class of compounds.

Key words: ruthenium, oxidation, cleavage, terpenes

Introduction

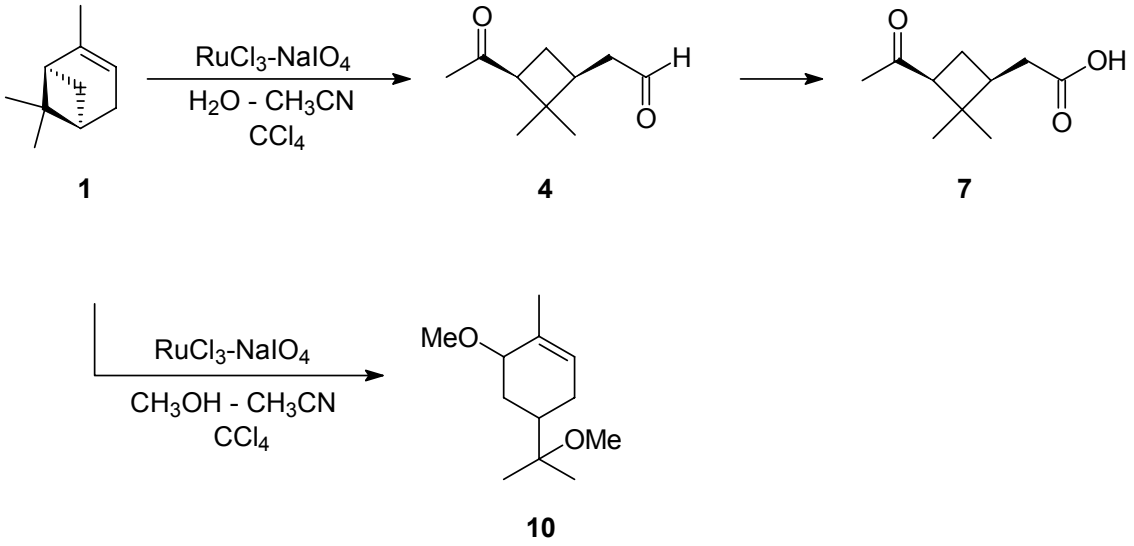
Since the discovery of highly potent pyrethroids like Deltamethrin[1] and Cypermethrin[2] there has been thorough activity in the field of synthesis of new acid compounds of the pyrethroids series. Several compounds in these families have been prepared by total synthesis[3-7] with chrysanthemic acid derivatives often serving as the ultimate source of the chirality of the cyclopropanoid systems. However, it might be argued that naturally occurring monoterpenes such as carene can be used as inexpensive source of chiral cyclopropyl-containing synthons. Homologues of these synthons have been prepared by oxidative cleavage of carene and α-pinene using the known methods based on $KMnO_4$[8-9] or ozonolysis[3-5,10-11] for example (+)-*cis* permethrimic acid[12] has been obtained from (+)-3-carene according to this method.

Ruthenium tetroxide (RuO_4) generated *in situ* under Sharpless conditions[13-16] oxidatively cleaves carbon-carbon single and double bonds[17] and is an efficient reagent

in oxidation of tertiary and secondary inactivated C-H bonds of saturated hydrocarbons.[18] Such a procedure has been used for oxidation of (–)-α-pinene, verbenone and verbenol.[19,20] However, the authors did not mention the presence of the corresponding aldehyde.

Results and discussion

We report here an application of this procedure in the oxidative cleavage of (+)-α-pinene **1**, (+)-2-carene **2**, and (+)-3-carene **3** directed towards an efficient synthesis of a series of chiral ketoaldehydes and ketoacids containing cyclobutane and cyclopropane rings. The latter can be used as potential precursors for the synthesis of cyclobutane dehydroaminoacids[19] and pyrethroid derivatives.[12]



Scheme 1

Table 1 summarises some representative results obtained with α-pinene using freshly prepared RuO_4 as catalyst and $NaIO_4$ (stoichoimetric) as oxidant. α-pinene was readily cleaved to the corresponding ketoaldehyde **4** with high selectivity (Table 1 entry 1) by quenching the reaction after 40 min (Scheme 1). Increasing the reaction time (2 h) led to further oxidation of the aldehyde into the acid **7** (entry 2) which was obtained with 96% selectivity.

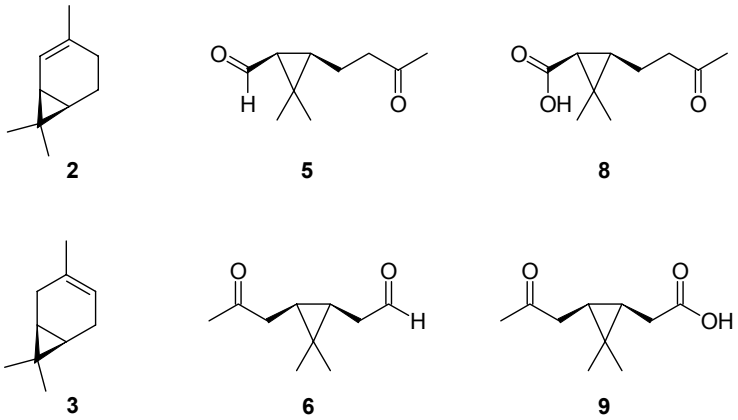
Table 1. Oxidative cleavage of (+) α-pinene[a] **1** using the system $RuCl_3$-$NaIO_4$.

Entry	Solvent	S/C[b]	Time (h)	Conversion[c] (mol %)	Selectivity[c] (%)	
					Aldehyde **4**	Acid **7**
1	CCl_4/MeCN/H_2O	50	0.7	100	100	0
2	CCl_4/MeCN/H_2O	50	2	100	4	96
3	CCl_4/H_2O	50	24	100	30	47
4	MeCN/H_2O	50	24	100	28	12
5	CCl_4/MeCN/H_2O	100	4.5	95	0	93
6	CCl_4/MeCN/H_2O	500	15	90	0	90

[a] Conditions: α-pinene = 3.16 mmol; periodic acid = 12.6 mmol; NaOH = 12.6 mmol; H_2O = 6 mL; CH_3CN = 4 mL; CCl_4 = 4 mL; Temperature =20 °C; [b] S/C = substrate/catalyst; [c] determined by GC.

An increase of the substrate/catalyst ratio (500 instead 50) led as expected to a slower reaction but interestingly high yield and selectivity into the acid were maintained at long reaction time. On the other hand modification of the reaction medium corresponding to the absence of CH_3CN or CCl_4 induced the precipitation of ruthenium tetroxide and led to poor results as total conversion was only reached after 24 h with low aldehyde and acid selectivities. Finally when water was replaced by methanol, the oxidation of α-pinene occurred via other reaction path to give the dimethoxylimonene **10** resulting from the opening of the cyclobutane ring rather than the double bond cleavage.

Under identical conditions 2- and 3-carene behave similarly (Scheme 2, Table 2) and proceeded via the isolable keto-aldehydes **5** and **6** (entries 7 and 9) which were rapidly formed and oxidised in a slower step into the acids **8** and **9** (entries 8 and 10), without opening of the cyclopropane ring.



Scheme 2

As in the case of α-pinene the acid selectivity was only slightly affected by a decrease of the catalyst/substrate ratio. On the other hand a decrease in the $NaIO_4$/substrate ratio had a very detrimental effect on both conversion and selectivity

The spectroscopic data of isolated compounds described below confirmed that the oxidative cleavage of (+)-α-pinene **1**, (+)-2-carene **2** and (+)-3-carene **3** by $RuCl_3$-$NaIO_4$ provided *cis*-poly-functionalised cycloalcanes without epimerisation.[19] The presence of one isomer was evidenced by the absorption signals for the CH_3 protons and carbons of the gem-dimethyl substitution, which shows only one set of signals both in ^1H and ^{13}C-NMR.[19] On the other hand, we have reported that the use of the same procedures for the synthesis of new poly-functionalised cyclopropanes by oxidation of dichloro- and dibromo-cyclopropan-epoxy-limonene took place without epimerisation.[21]

Table 2. Oxidative cleavage of **2** and **3** using the system $RuCl_3$-$NaIO_4$.[a]

Entry	Substrate	$NaIO_4$/S	S/C	Time (h)	Conversion (%)	Aldehyde selectivity[b] (%)	Acid selectivity[b] (%)
7	3	4	50	0.7	100	95 (6)[c]	0
8	3	4	50	2	100	0	92 (9)[c]
9	2	4	50	0.7	100	98 (5)	0
10	2	4	50	2	100	0	96 (8)
11	3	3	50	48	100	75 (6)	10 (9)
12	3	2	50	48	79	49 (6)	07 (9)
13	3	1	50	48	40	18 (6)	0
14	3	4	100	4	90	0	90 (9)
15	3	4	500	16	92	0	80 (9)
16	2	4	100	4	96	0	95 (8)
17	2	4	500	16	95	0	87 (8)

[a] Conditions: substrate = 3.16 mmol, periodic acid = 12.6 mmol, NaOH = 12.6 mmol, H_2O = 6 mL, CH_3CN = 4 mL, CCl_4 = 4 mL, Temperature = 20 °C.
[b] determined by GC analysis.
[c] numbers in parentheses refer to the corresponding obtained products.

Conclusion

In conclusion, we have developed an effective and very easy way (in comparison to the known method based on ozonolysis[3-5,10-11]) to synthesise chiral poly-functionalised cycloalcanes. These products can be used, for example, in the case of cyclopropanic compounds as starting material for the synthesis of pyrethroid homologues, which constitute an upper class of pesticides with high biological

activity.[5,22-25] This method is based on the oxidative cleavage of cheap and readily available terpenes with a simple catalytic system and allows to obtain chiral ketoaldehydes or ketoacids in high yields without epimerisation.

Experimental

General

All reagents and solvent were purchased from commercial sources (Aldrich, Acros) and used as received. The reaction mixture were analysed on a Trace 2000 series chromatograph equipped with an FID detector, using silica capillary columns CPSil5CB (10 m × 0.33 mm, Chrompack).

Liquid chromatographies were performed on silica gel (Merk 60, 220-440 mesh; eluents: hexane-OAcEt). A BP5 (25 m × 0.25 mm) capillary column was used for GC/MS coupled analyses with a Saturn 2000 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Model AVANCE 300 using $CDCl_3$ as the solvent and $SiMe_3$ as the internal standard. Optical rotations were measured on a Perkin–Elmer 343 polarimeter.

General procedure for oxidative cleavage of terpenes

In a typical procedure, water (6 mL), periodic acid (2.88 g, 12.6 mmol) and NaOH (0.5 g, 12.5 mmol) were introduced in a three necked flask equipped with a magnetic stirrer bar. The mixture was stirred and cooled at 0 °C (ice bath). Then, at this temperature were successively added CCl_4 (4 mL), CH_3CN (4 mL) and $RuCl_3 \cdot 3H_2O$ (16.45 mg, 0.063 mmol). After 15 min, the substrate (0.422 g, 3.1 mmol) was added. The ice bath was removed and the reaction, conducted at room temperature, was monitored by gas chromatography of samples taken at regular time interval. At the end of the reaction, 25 mL of $CHCl_3$ were added, and the organic layer was washed, dried ($MgSO_4$), filtered on silica gel in order to remove the precipitated RuO_4 and then concentrated.

Products characterizations

(3-Acetyl-2,2-dimethyl-cyclobutyl)-acetaldehyde (4). Yield 84.6%. $[\alpha]^{20}_{D}$ +42.5 ° (*c* 1, EtOH); MS, m/z: 168 (M^+). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.75 (s, 3H), 1.25 (s, 3H),

1.80–1.90 (m, 2H), 1.95 (s, 3H), 2.3–2.4 (m, 1H), 2.45 (dd, *J* 2.19, 1.28 Hz, 2H), 2.84 (dd, *J* 12.0, 14.2 Hz, 1H), 9.64 (d, *J* 1.28 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.4 (CH_3), 22.6 (CH_2), 29.9 (CH_3), 30.1 (CH_3), 35.6 (CH), 43.1 (Cq), 44.9 (CH_2), 54.1 (CH), 201.3 (CHO), 207.3 (C=O).

2,2-Dimethyl-3-(3-oxo-butyl)-cyclopropanecarbaldehyde (5). Yield 71.5%. $[\alpha]^{20}_D$ +25.8° (*c* 1, EtOH). MS, m/z: 168 (M^+). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14–1.25 (m, 1H), 1.19 (s, 3H), 1.33 (s, 3H), 1.42–1.61 (m, 1H), 1.92–2.05 (m, 2H), 2.14 (s, 3H), 2.40–2.49 (m, 2H), 9.46 (d, *J* 4.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.9 (CH_3), 18.6 (CH_3), 28.9 (CH_3), 29.9 (CH), 30.1 (Cq), 37.0 (CH_2), 38.4 (CH), 43.4 (CH_2), 201.6 (CHO), 207.9 (C=O).

[2,2-Dimethyl-3-(2-oxo-propyl)-cyclopropyl]-acetaldehyde (6). Yield 75.6%. $[\alpha]^{20}_D$ –5.2° (*c* 1, EtOH). MS, m/z: 168 (M^+). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (s, 3H), 0.9–1.20 (m, 2H), 1.14 (s, 3H), 2.16 (s, 3H), 2.29–2.38 (m, 4H), 9.77 (t, *J* 1.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.2 (CH_3), 17.2 (Cq), 19.5 (CH), 21.4 (CH_3), 28.5 (CH), 29.6 (CH_3), 39.4 (CH_2), 39.7 (CH_2), 201.7 (CHO), 208.1 (C=O).

(3-Acetyl-2,2-dimethyl-cyclobutyl)-acetic acid (7). Yield 85.5%. $[\alpha]^{20}_D$ +57.2° (*c* 1, EtOH). MS, m/z: 184 (M^+). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.80 (s, 3H), 1.26 (s, 3H), 1.78–1.94 (m, 2H), 1.98 (s, 3H), 2.14–2.23 (m, 1H), 2.27 (d, *J* 5.12 Hz, 2H), 2.83 (dd, *J* 9.6, 11.4 Hz, 1H), 10.5 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.1 (CH_3), 22.7 (CH_2), 29.9 (CH_3), 30.0 (CH_3), 34.7 (CH_2), 37.5 (CH), 43.1 (Cq), 53.9 (CH), 178.6 (COOH), 207.9 (C=O).

2,2-Dimethyl-3-(3-oxobutyl)-cyclopropanecarboxylic acid (8). Yield 81.4%. $[\alpha]^{20}_D$ +34.4° (*c* 1, EtOH). MS, m/z: 184 (M^+). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.12 (s, 3H), 1.17 (s, 3H), 1.15 (td, *J* 9.52, 7.1 Hz, 1H), 1.36 (d, *J* 9.52 Hz, 1H), 1.84–1.96 (m, 2H), 2.1 (s, 3H), 2.42 (td, *J* 7.1, 2.77 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1 (CH_3), 17.9 (CH_2), 27.0 (Cq), 28.3 (CH), 29.0 (CH_3), 29.8 (CH), 33.8 (CH_3), 43.3 (CH_2), 177.9 (COOH), 209.0 (C=O).

[2,2-Dimethyl-3-(2-oxo-propyl)-cyclopropyl]-acetic acid (9). Yield 88.47%. $[\alpha]^{20}_D$ –10.5° (*c* 1, EtOH). MS, m/z: 184 (M^+). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (s, 3H), 0.89 (td, *J* 9.92, 6.74 Hz, 1H), 0.92 (td, *J* 9.92, 6.7 Hz, 1H), 1.07 (s, 3H), 2.13 (s, 3H), 2.24 (d, *J* 6.74 Hz, 2H), 2.33 (dd, *J* 6.7, 2.16 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.9 (CH_3), 17.2 (Cq), 21.0 (CH), 21.4 (CH), 28.6 (CH_3), 29.6 (CH_3), 30.0 (CH_2), 39.3 (CH_2), 179.2 (COOH), 209.1 (C=O).

6-Methoxy-4-(1-methoxy-1-methyl-ethyl)-1-methyl-cyclohexane (10). This compound was prepared following the procedure described above by replacing water with methanol. Yield 56.4%. MS, m/z: 198 (M^+). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (s, 3H), 1.11 (s, 3H), 1.74 (d, *J* 1.27 Hz, 3H), 1.84–2.00 (m, 4H), 2.08 (dd, *J* 13.67, 1.91 Hz, 1H), 3.18 (s, 3H), 3.38 (s, 3H), 3.45 (t, *J* 2.36 Hz, 1H), 5.57 (dd, *J* 4.2, 1.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0 (CH_3), 22.4 (CH_3), 22.7 (CH_3), 26.8 (CH_2), 27.2 (CH_2), 34.7 (CH), 48.6 (CH_3O), 57.1 (CH_3O), 76.1(CqO), 78.0 (CH-O), 125.8 (=CH), 133.2 (=Cq).

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Povzetek

Katalitska oksidacija terpenskih olefinov (α-pinen, 2-caren in 3-caren) z RuO_4, generiranem in situ, vodi do nastanka ustreznih ciklobutan- in ciklopropan-ketoaldehidov, ki se po daljšem času pretvorijo v keto-kisline z odličnimi izkoristki (90-100%). Te spojine lahko služijo kot gradniki v sintezi ciklobutan-aminokislin in podobnih derivatov.