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Radical reactions on pinene-oxide derivatives induced by Ti(III)

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ABSTRACT

A practical, brief and selective synthesis of several pinene oxide derived terpenoids can be achieved from readily available starting materials. The key step is a radical reaction promoted by titanocene chloride.

1. Introduction

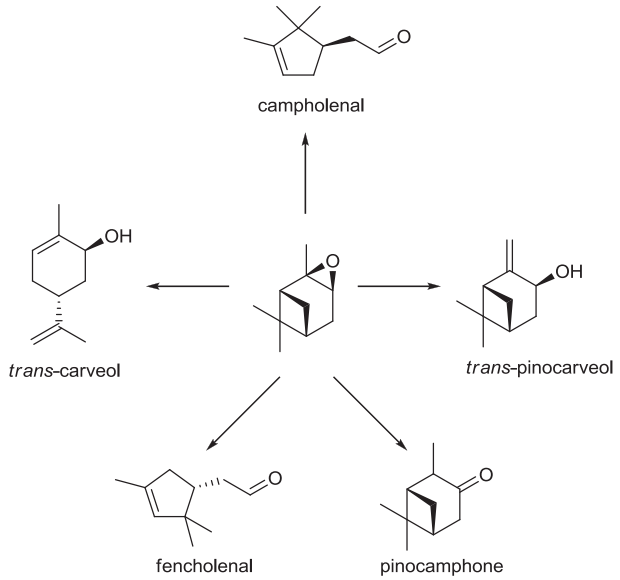
The transformation of natural products into other compounds of high added value is an activity of the chemical industry of huge economic interest. The chemical reactivity of terpenoids and steroids has been studied in depth for the synthesis of valuable compounds with low investments.[1]

In particular, monoterpenes are a vast reserve of optically active compounds that can be transformed into other products with high added value as flavours, fragrances, drugs and catalysts.

The development of new chiral ligands for asymmetric synthesis is one of the fields in which most efforts have been made in recent years. Several catalysts derived from monoterpenes, such as pulegone, β-pinene, limonene and α-pinene have shown great efficiency in enantioselective synthesis.[2]

α-Pinene, a very affordable monoterpene from the trementine essential oil, is a chiral compound, from whose oxide a large amount of valuable compounds are derived, such as campholenic aldehyde, *trans*-carveol, *trans*-sobrerol, *iso*-pinocamphone, *p*-cimene, cineol and verbenone (see Scheme 1). The rearrangement of α-pinene oxide by acids has been addressed in many classic studies in the field of terpenoid chemistry.

The regioselective oxirane ring opening, promoted by acids, leads to the formation of a carbocation, which evolves in different ways following competitive processes, such as the loss of a proton, cleavage, ring expansion, etc.



Scheme 1. Main products from pinene oxide.

Lewis acids mainly lead to cyclopentenic aldehydes, such as campholenal,[3] while Brønsted acids mainly lead to the formation of *trans*-carveol and *p*-mentane derivatives.[4]

Although most compounds generated in the acid-promoted isomerization of α-pinene oxide are of interest in the fragrance industry, pharmacy and the food industry, campholenal and *trans*-

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carveol stand out from the rest. The aldehyde is highly appreciated in the elaboration of top-brand perfumes due to its sandal-like aroma. *trans*-Carveol is the basis of the aroma of the essential orange oil; it is used as a fragrance and food preservative. Crowell et al. have discovered that it prevents breast cancer.[5] Some carveol derivatives have shown antiproliferative activity against carcinogenic prostate cells.[6]

Recently, several studies addressed to the optimization of α-pinene oxide isomerization have been developed with the objective to improve the yields of campholenic aldehyde or *trans*-carveol. In a work reported by Noyori et al.[7] a 72% yield of *trans*-carveol was achieved by reaction of α-pinene oxide with a mixture of trimethylsilyl trifluoromethanesulfonate, 2,6-lutidine and diazabicycloundecene. Unfortunately, this process does not seem adequate for large-scale use. An approach aimed at the industrial production of *trans*-carveol was developed by Motherwell et al., but with disappointing results. The authors only obtained a 45% yield of *trans*-carveol using MIPs.[8]

Better results have been achieved by Gusevskaya et al.[9] using catalytic amounts of the acid $H_3PW_{12}O_{40}$ as a promoter of the isomerization of α-pinene oxide. Using this catalyst both the polarity and the basicity of the solvent strongly influence the result of the reaction. Basic and polar solvents, such as DMF favour the formation of *trans*-carveol, and the neutral non-polar solvents, such as cyclohexane favour the formation of campholenic aldehyde.

Thus, whatever method of isomerization is chosen, the reaction always affords a mixture of compounds.

Although many studies have been carried out to transform α-pinene oxide into valuable compounds by means of a highly selective process, few of them have been regarded with interest by industry. This problem still remains unsolved. Most past studies were based in ionic reactions that evolve through carbocations, contributing to their lack of selectivity.

Here we focus on the problem from a different point of view. Our strategy is based on the use of radical reactions promoted by Ti(III).[10] Our study is contrasted with that published by Volcho et al.[11] who used montmorillonite as the reagent.

2. Results and discussion

2.1. Radical reactions induced by titanocene chloride

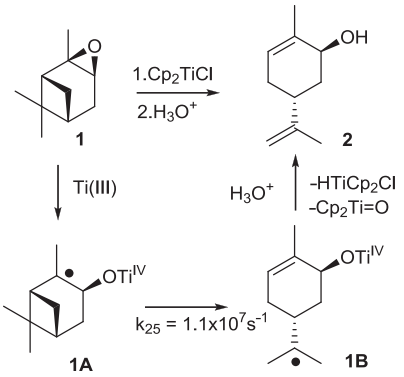
The reaction of α-pinene oxide **1**[12] with 2 equiv of Cp_2TiCl in THF leads solely to the formation of *trans*-carveol **2**[13] at an excellent 89% yield.

The reaction starts with the homolytic cleavage of the oxirane **1** induced by Ti(III), to give the radical **1A**, and evolves through a new cleavage to the radical **1B**, which loses a hydrogen atom from a methyl group, to afford the carveol **2** (Scheme 2).

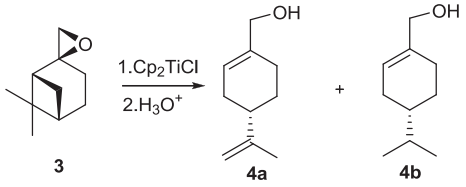
Encouraged by this result we attempted a catalytic version of the reaction using only 10% of Cp_2TiCl, and collidine hydrochloride as a source of hydrogen.[14] Unfortunately, using this method only 12% of *trans*-carveol **2** was produced, although 70% of α-pinene oxide was recovered.

The acid-mediated rearrangement of β-pinene oxide **3**[15] has been widely studied with the aim of obtaining the valuable perillalcohol **4**,[16] and perillaldehyde.[17] In our hands the reaction of β-pinene oxide **3** with Cp_2TiCl in THF led to the formation of perillalcohol **4a** in 80% yield. A small amount of the hydrogenated product phellandrol **4b**[18] was observed, probably due to adventitious water in the reaction medium. It is known that Ti(III) promotes the transference of hydrogen from water to radicals[19] (Scheme 3).

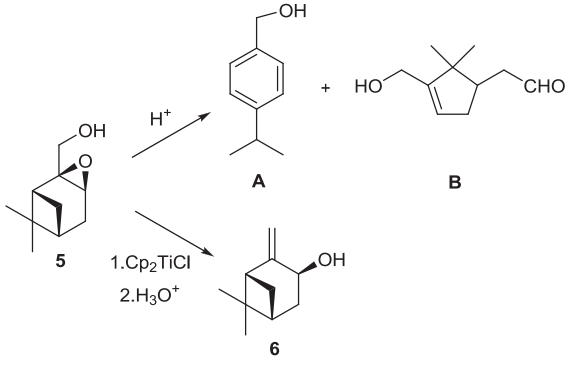
The reaction of myrtenol oxide **5** with montmorillonite was described by Volcho et al.[11] to produce a mixture of the aromatic alcohol **A** (16%) and the cyclopentenic hydroxyaldehyde **B** (27%) (Scheme 4).



Scheme 2. Reaction of α-pinene oxide with Ti(III).



Scheme 3. Reaction of β-pinene oxide with Ti(III).



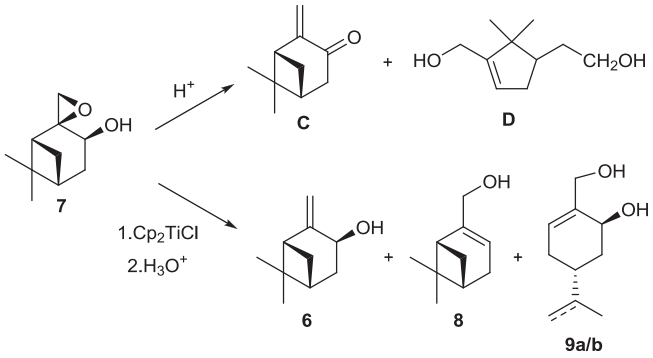
Scheme 4. Reaction of myrtenol oxide with Ti(III).

Nevertheless, when myrtenol oxide **5** was treated with Cp_2TiCl in THF only (+)-*trans*-pinocarveol **6**[20] was obtained in 90% yield.

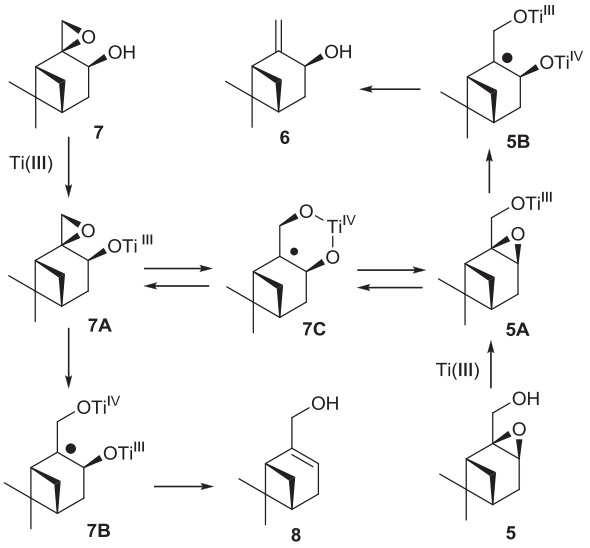
The reaction of pinocarveol oxide **7** with montmorillonite as described by Volcho et al.[11] led to a complex mixture from which pinocamphone **C** (6%) and an aldehyde analogous to campholenic aldehyde **D** could be isolated (19%) (Scheme 5).

However, pinocarveol oxide **7** with Ti(III) afforded a mixture of *trans*-pinocarveol **6** (42%), myrtenol **8** (24%) and the diols **9a**/**9b** (18%) in a ratio of 20:80. It is worth noting that while myrtenol oxide **5** afforded only the product of hydroxyl elimination, *trans*-pinocarveol **6**, the pinocarveol oxide **7** gave a mixture of four products. Although the two starting materials were isomers, the first one **5** is a primary alcohol and the last one **7** is secondary. It seems that the elimination rate depends on the type of hydroxyl group.[21] In light of the experimental data, we suggest a faster sequence from **5** to **6**, through intermediates **5A** and **5B**. From **7**, the faster sequence passes through **7A**, **7C**, **5A**, **5B** and finally **6**. The slower pathway passes through **7A**, **7B** and **8**. The equilibrium through intermediate **7C** is clearly shifted to **5A** (Scheme 6).

The reported reaction of *cis*-verbenol oxide **10** with montmorillonite by Volcho's method,[11] led to a mixture of the diol **11** (47%)

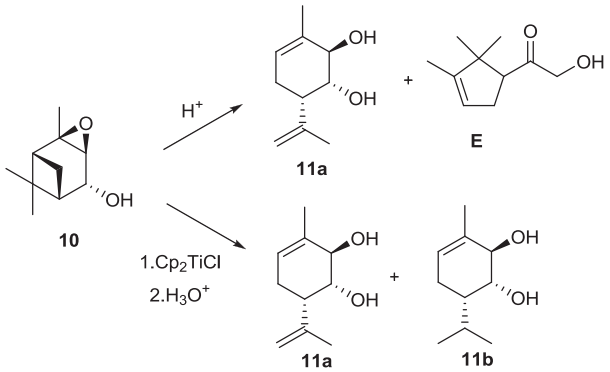


Scheme 5. Reaction of pinocarveol oxide with Ti(III).



Scheme 6. Proposed mechanism for the reaction of **7** and **5** with Ti(III).

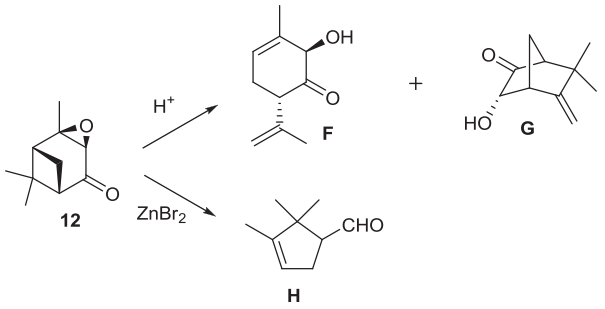
and the hydroxyketone **E** (5%). Meanwhile, treatment of **11** with Cp_2TiCl afforded a mixture of the diols 1**1a**[11] and **11b** (78%) at a ratio of 40:60 (Scheme 7).



Scheme 7. Reaction of *cis*-verbenol oxide with Ti(III).

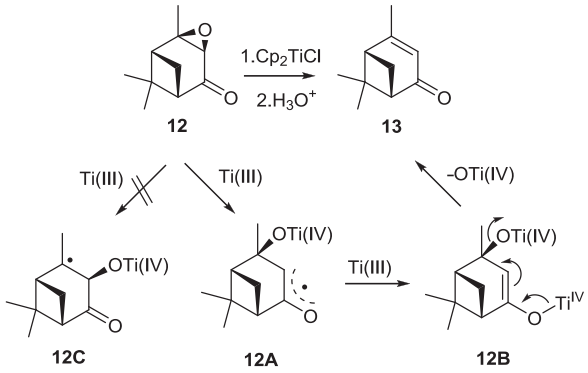
The higher proportion of the diol **11b** respect to diol **11a** should be due, in this case, to hydrogen transfer from the alcohol **11**–Ti(III) complex to the radical precursor of **11b**.[22]

Volcho's treatment of verbenone oxide **12** with montmorillonite afforded a mixture of the hydroxyketones **F** (22%) and **G** (36%).[10] With zinc bromide in benzene, only the aldehyde **H** (30%) was obtained[23] (Scheme 8).



Scheme 8. Volcho's reactions of verbenone oxide.

The reaction of verbenone oxide **12** with Ti(III) afforded only the deoxygenation product verbenone **13** (96%). This result can be rationalized in terms of the kinetic regioselective cleavage of the oxirane to afford a stabilized enol radical **12A**, which evolves through a titanium enolate **12B** to yield verbenone by the elimination of titanocene oxide. With the transformation of **12** to **13** a new deoxygenation method for α,β-epoxyketones is established (Scheme 9).

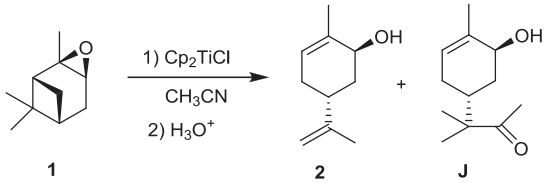


Scheme 9. Deoxygenation of verbenone oxide with Ti(III).

2.2. Tandem radical reactions

Tandem and multicomponent reactions, from the aforementioned substrates, allow the synthesis of complex molecules in a few steps, which is why attention has been paid to this issue.

In a previous study, the reaction of α-pinene oxide **1** with Cp_2TiCl and acetonitrile was investigated.[24] The products obtained were the *trans*-carveol **2**, and the hydroxyketone **J**, at a ratio of 40:60. This means that radical addition to acetonitrile is slower than cyclobutane radical cleavage and faster than hydrogen elimination. The rate constant of the cyclobutane radical cleavage in pinene derivatives calculated by the radical clock method[25] was $1.1\times10^7\ s^{-1}$ (Scheme 10).



Scheme 10. Tandem reaction of pinene oxide and acetonitrile induced by Ti(III).

In order to study the behaviour of the radical afforded by the reaction of α-pinene oxide **1** and Ti(III), we tested different additives: water, methanol, 1,4-cyclohexadiene (1,4-CHD), acrylonitrile and methyl acrylate.

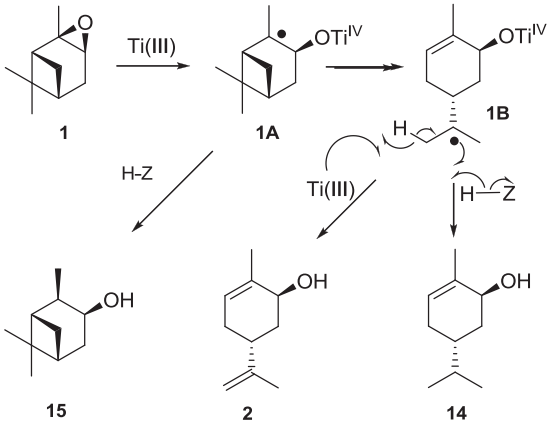
Recently water has been introduced as a source of hydrogen atoms in Ti(III)[19]-mediated radical chemistry. Also, methanol[22] and 1,4-CHD transfer hydrogen atoms in this Ti(III) chemistry. To explore the scope of the hydrogen transfer, a study of the reaction between Ti(III), α-pinene oxide and water, MeOH, and 1,4-CHD was carried out. The results are summarized in Table 1.

Table 1
Hydrogen transfer comparison

Source of H	Equivalents	**2** (%)	**14** (%)	**2**/**14**
MeOH	10	24	61	2,5
H_2O	10	13	63	4,8
1,4-CHD	10	27	68	2,5

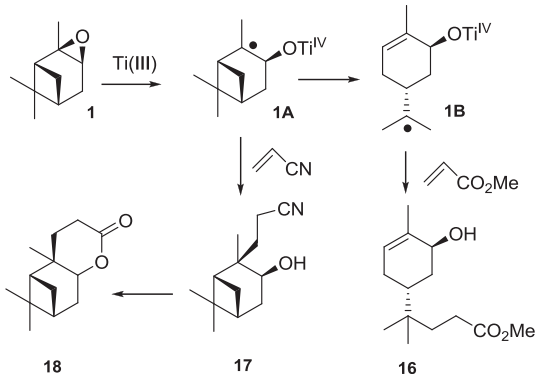
From Table 1, it may be observed that the water–titanocene complex is the best source of hydrogen. It is also observed that the transfer of hydrogen from different sources is slower than the cleavage of the cyclobutane ring; so, no neopinocampheol was obtained.

The addition of PhSH as a hydrogen source afforded a mixture of dihydro *trans*-carveol **14** (18%)[18] and neopinocampheol **15** (60%).[26] A higher rate of hydrogen transfer from PhSH to radicals than hydrogen transfer from radicals to Ti(III) was observed. The hydrogen transfer rate constant from PhSH ($k_{20}=9\times10^7\ M^{-1}\ s^{-1}$)[27] was higher than the previous hydrogen sources, and higher than cyclobutane radical cleavage (Scheme 11).



Scheme 11. Tandem reactions of pinene oxide and hydrogen donors induced by Ti(III).

The reaction with methyl acrylate afforded the hydroxyester **16** (65%). This result could be explained in terms of the homolytic cleavage of oxirane, further cyclobutane opening,[25] and trapping of the tertiary radical by the double bond of methyl acrylate. Nevertheless, the reaction with acrylonitrile afforded exclusively the nitrile **17** (74%) by trapping of the radical **1A**. The subsequent work-up in aqueous-acid media led to the formation of lactone **18** exclusively. It is clear from the latter reactions that the rate constant for radical acrylate addition is lower than cyclobutane radical cleavage in pinene namely,[25] $k=1.1\times10^7\ s^{-1}$ and higher for acrylonitrile. It is also worth noting the absolute stereoselectivity of acrylonitrile addition to radical **1A**. The kinetic regioselectivity and the total stereoselectivity observed could find application in organic synthesis (Scheme 12).



Scheme 12. Tandem reaction of pinene oxide and methyl acrylate or acrylonitrile induced by Ti(III).

3. Conclusion

The radical reactions of pinene-oxide derivatives induced by titanocene chloride selectively afford a series of valuable compounds, such as *trans*-carveol **2**, perilla alcohol **5**, (+)-*trans*-pinocarveol **7**, menthane diol **12** and verbenone **14**. It has been observed that radical primary hydroxyl elimination is faster than the secondary one, as shown by the relative behaviour of myrtenol oxide **6** and pinocarveol oxide **8** against Ti(III). The deoxygenation reaction of verbenone oxide, promoted by Ti(III) in a selective manner is noteworthy. Throughout this work we observed that reactions of titanocene chloride with pinene-oxide compounds afforded completely different results from those obtained with acidic reagents, and noted the radical character of those reactions. The kinetic regioselective addition of radical, arising from α-pinene oxide and Ti(III), to hydrogen transfer agents, methyl acrylate and acrylonitrile is also worthy of mention.

4. Experimental section

4.1. General methods

Melting points are uncorrected. ^{1}H NMR spectra were measured at either 200 or 400 MHz and ^{13}C NMR were measured at 50 or 100 MHz in $CDCl_3$ and referenced to TMS (^{1}H) or solvent (^{13}C), except where indicated otherwise. IR spectra were recorded for neat samples on NaCl plates, unless otherwise stated. Standard mass spectrometry data were acquired using a GC–MS system in EI mode with a maximum *m*/*z* range of 600. When required, all solvents and reagents were purified by standard techniques: tetrahydrofuran (THF) was purified by distillation from sodium and benzophenone ketyl and degassed before use. All reactions were conducted under a positive pressure of argon, utilizing standard bench-top techniques for the handling of air-sensitive materials. Chromatographic separations were carried out under pressure on silica gel using flash-column techniques on Merck silica gel 60 (0.040–0.063 mm). The yields reported are for chromatographically pure isolated products unless otherwise stated.

The oxides **3**, **5**, **7**, **10** and **12** were obtained following the methods described by Volcho.[11,23] α-Pinene oxide **1** was acquired from Sigma–Aldrich.

The following known compounds were isolated as pure samples and showed NMR spectra matching those reported previously: **2**,[13] **4a**,[18] **6**,[20] **8**,[11] **13**[11] and **15**.[26]

4.2. General procedure 1 (GP1)

Reaction of epoxides with Cp_2TiCl. A mixture of Cp_2TiCl_2 (2.20 mmol) and granulated Zn (6.60 equiv) in strictly

deoxygenated THF (10 mL) was stirred at room temperature until the red solution turned green. In a separate flask, the epoxy compound (1 mmol) was dissolved in strictly deoxygenated THF (10 mL). The green Ti(III) solution was slowly added via cannula to the epoxide solution. After 30 min, an excess of saturated NaH_2PO_4 was added, and the mixture was stirred for 20 min. The mixture was filtered to remove insoluble titanium salts. The product was extracted into ether, and the combined organic layers were washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and filtered. After removal of the solvent, the crude product was purified by flash chromatography.

4.3. General procedure 2 (GP2)

Reaction of epoxides and additives with Cp_2TiCl. A mixture of Cp_2TiCl_2 (2.20 mmol) and granulated Zn (6.60 equiv) in strictly deoxygenated THF (10 mL) was stirred at room temperature until the red solution turned green. In a separate flask, the epoxy compound (1 mmol) and the additive (10 mmol) were dissolved in strictly deoxygenated THF (10 mL). The green Ti(III) solution was slowly added via cannula to the epoxide and nitrile solution. After 30 min, an excess of saturated NaH_2PO_4 was added, and the mixture was stirred for 45 min. The mixture was filtered to remove insoluble titanium salts. The product was extracted into ether, and the combined organic layers were washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and filtered. After removal of the solvent, the crude product was purified by flash chromatography.

4.4. Reaction of α-pinene oxide 1 with Cp_2TiCl

According to GP1, reaction of **1** (100 mg, 0.66 mmol) with Cp_2TiCl followed by flash chromatography (hexane/diethyl ether 8:2) furnished *trans*-carveol **2** $[\alpha]_D^{20}$ −190.0 ($CHCl_3$, *c* 14 mg/mL) (89 mg, 89%).

4.5. Reaction of β-pinene oxide 3 with Cp_2TiCl

According to GP1, reaction of **3** (125 mg, 0.82 mmol) with Cp_2TiCl followed by flash chromatography (hexane/diethyl ether 7:3) furnished *perillylalcohol* **4a** $[\alpha]_D^{20}$ −88.0 (MeOH, *c* 12 mg/mL) (99 mg, 80%). A small amount of phellandrol **4b** was observed.

4.6. Reaction of myrtenol oxide 5 with Cp_2TiCl

According to GP1, reaction of **5** (100 mg, 0.60 mmol) with Cp_2TiCl followed by flash chromatography (hexane/diethyl ether 85:15) furnished (+)-*trans*-pinocarveol **6** $[\alpha]_D^{20}$ +53.1 ($CHCl_3$, *c* 8 mg/mL) (86 mg, 90%).

4.7. Reaction of pinocarveol oxide 7 with Cp_2TiCl

According to GP1, reaction of **7** (100 mg, 0.60 mmol) with Cp_2TiCl followed by flash chromatography furnished: (hexane/diethyl ether 85:15): (+)-*trans*-pinocarveol **6** (38 mg, 42%), (hexane/diethyl ether 85:15): myrtenol **8** (22 mg, 24%) and with (hexane/diethyl ether 1:1): a mixture of (1*S*,5*R*)-2-(hydroxymethyl)-5-(prop-1-en-2-yl)cyclohex-2-enol **9a** and (1*S*,5*R*)-2-(hydroxymethyl)-5-isopropylcyclohex-2-enol **9b** (2:8, 16 mg, 18%). IR, *ν* (liquid film) 3364, 2935, 1455, 1128, 999 cm^{-1}; ^1H NMR (200 MHz $CDCl_3$) *δ*: 0.89 (d, *J*=6.7 Hz, 3H), 0.92 (3d, *J*=6.7 Hz, 3H), 1.2–2.3 (m, 11H), 4.21 (m, 4H), 4.32 (br s, 1H), 4.36 (br s, 1H), 4.74 (br s, 1H), 4.76 (br s, 1H), 5.87 (br s, 2H) ppm; ^{13}C NMR (50 MHz $CDCl_3$) *δ*: 19.42 (CH_3), 19.58 (CH_3), 23.39 (CH_3), 26.35 (CH_2), 28.80 (CH_2), 31.85 (CH), 33.89 (CH), 34.06 (CH), 35.23 (CH_2), 36.11 (CH), 66.61 (CH), 66.80 (CH), 67.22 ($2CH_2$), 109.23 (CH_2), 129.65 (CH), 130,02 (CH), 136.99 (C), 137.11 (C), 148.79 (C) ppm.

4.8. Reaction of *cis*-verbenol oxide 10 with Cp_2TiCl

According to GP1, reaction of **10** (50 mg, 0.30 mmol) with Cp_2TiCl followed by flash chromatography (hexane/diethyl ether 1:1) furnished a mixture of (1*R*,2*R*,6*S*)-3-methyl-6-(prop-1-en-2-yl)cyclohex-3-ene-1,2-diol **11a** and (1*R*,2*R*,6*S*)-6-isopropyl-3-methylcyclohex-3-ene-1,2-diol **11b** (4:6, 78 mg, 78%). IR, *ν* (liquid film) 3362, 2938, 1447, 1132, 997 cm^{-1}; ^1H NMR (200 MHz $CDCl_3$) *δ*: 0.95 (d, *J*=6.0 Hz, 3H), 0.99 (d, *J*=6.0 Hz, 3H), 1.0–2.5 (m, 7H), 1.81 (s, 6H), 1.83 (s, 3H), 3.82 (br s, 2H), 3.92 (br s, 1H), 4.00 (br s, 1H), 4.87 (br s, 1H), 4.99 (br s, 1H), 5.66 (br s, 2H) ppm; ^{13}C NMR (50 MHz $CDCl_3$) *δ*: 20.65(CH_3), 20.74 ($2CH_3$), 21.00 (CH_3), 22.57 (CH_3), 24.52 (CH_2), 25.31 (CH_2), 28.70 (CH), 38.89 (CH), 39.81 (CH), 70.81 (CH), 71.17 (CH), 71.94 (CH), 72.72 (CH), 111.57 (CH_2), 125.29 (CH), 126.01 (CH), 131.56 (C), 131.64 (C), 145.65 (C) ppm.

4.9. Reaction of verbenone oxide 12 with Cp_2TiCl

According to GP1, reaction of **12** (100 mg, 0.60 mmol) with Cp_2TiCl followed by flash chromatography (hexane/diethyl ether 1:1) furnished verbenone **13** (96 mg, 96%).

4.10. Reaction of α-pinene oxide 1 with Cp_2TiCl/MeOH

According to GP2, reaction of **1** (99 mg, 0.66 mmol) and MeOH (0.27 mL, 6.60 mmol) with Cp_2TiCl followed by flash chromatography (hexane/diethyl ether 7:3) furnished a mixture of (1*S*,5*R*)-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-enol **2** (24 mg, 24%) and (1*S*,5*R*)-5-isopropyl-2-methylcyclohex-2-enol **14** (61 mg, 61%).

4.11. Reaction of α-pinene oxide 1 with Cp_2TiCl/H_2O

According to GP2, reaction of **1** (100 mg, 0.66 mmol) and H_2O (0.12 mL, 6.60 mmol) with Cp_2TiCl followed by flash chromatography (hexane/diethyl ether 7:3) furnished a mixture of (1*S*,5*R*)-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-enol **2** (13 mg, 13%) and (1*S*,5*R*)-5-isopropyl-2-methylcyclohex-2-enol **14** (63 mg, 63%).

4.12. Reaction of α-pinene oxide 1 with Cp_2TiCl/1,4-CHD

According to GP2, reaction of **1** (100 mg, 0.66 mmol) and 1,4-Cyclohexadiene (0.63 mL, 6.60 mmol) with Cp_2TiCl followed by flash chromatography (hexane/diethyl ether 7:3) furnished a mixture of (1*S*,5*R*)-2-methyl-5-(prop-1-en-2-yl)cyclohex-2-enol **2** (27 mg, 27%) and (1*S*,5*R*)-5-isopropyl-2-methylcyclohex-2-enol **14** (68 mg, 68%).

4.13. Reaction of α-pinene oxide 1 with Cp_2TiCl/PhSH

According to GP2, reaction of **1** (100 mg, 0.66 mmol) and PhSH (0.63 mL, 6.60 mmol) with Cp_2TiCl followed by flash chromatography (hexane/diethyl ether 7:3) furnished a mixture of (1*S*,5*R*)-5-isopropyl-2-methylcyclohex-2-enol **14** (18 mg, 18%) and neopinocampheol **15** (60 mg, 60%).

4.14. Reaction of α-pinene oxide 1 with Cp_2TiCl/methyl acrylate

According to GP2, reaction of **1** (100 mg, 0.66 mmol) and methyl acrylate (0.59 mL, 6.60 mmol) with Cp_2TiCl followed by flash chromatography (hexane/diethyl ether 7:3) furnished methyl 4-((1*R*,5*S*)-5-hydroxy-4-methylcyclohex-3-enyl)-4-methyl penta noate **16** (102 mg, 65%). $[\alpha]_D^{20}$ −15.8 ($CHCl_3$, *c* 31 mg/mL) IR, *ν*: 3404, 2940, 1728, 1445 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 0.83 (s, 6H), 1.3–2.3 (m, 9H), 1.76 (br s, 3H), 3.64 (s, 3H), 3.99 (br s, 1H), 5.54 (m, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) *δ*: 20.74 (CH_3), 24.03 (CH_3), 24.11 (CH_3),

26.59 (CH_2), 28.99 (CH_2), 32.56 (CH_2), 33.77 (C), 34.87 (CH_2), 35.24 (CH), 51.54 (CH_3), 68.79 (CH), 125.73 (CH), 134.23 (C), 174.93 (C) ppm; EIMS, *m*/*z* (relative intensity) 222 (M^+-18, 12), 191 (1), 149 (8), 133 (28), 93 (64); 74 (100), 55 (100); HRMS (ESI): calcd for $C_{14}H_{24}O_3Na$ 263.1623; found 263.1627.

4.15. Reaction of α-pinene oxide 1 with Cp_2TiCl/acrylonitrile

According to GP2, reaction of **1** (100 mg, 0.66 mmol) and methyl acrylate (0.44 mL, 6.60 mmol) with Cp_2TiCl followed by flash chromatography (hexane/diethyl ether 7:3) furnished 4-((1*R*,5*S*)-5-hydroxy-4-methylcyclohex-3-enyl)-4-methylpentane nitrile **17** (101 mg, 74%). $[\alpha]_D^{20}$ +4.8 ($CHCl_3$, *c* 9 mg/mL) IR, *ν*: 3436, 2925, 1453, 1060 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 1.03 (s, 3H), 1.07 (s, 3H), 1.25 (s, 3H), 1.0–2.6 (m, 10H), 4.24 (m, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) *δ*: 12.53 (CH_2), 24.78 (CH_3), 25.34 (CH_3), 28.56 (CH_3), 29.66 (CH_2), 32.50 (CH_2), 39.11 (CH_2), 39.55 (C), 40.60 (CH), 41.44 (C), 51.73 (CH), 72.48 (CH), 120.93 (C) ppm; EIMS, *m*/*z* (relative intensity) 177 (M^+-30, 15), 149 (100), 135 (2), 76 (14), 55 (16); HRMS (ESI): calcd for $C_{13}H_{21}NO_3Na$ 230.1515; found 230.1517. Due to the work-up in aqueous-acid media compound **17** leads to the formation of the lactone **18**. $[\alpha]_D^{20}$ −20.3 ($CHCl_3$, *c* 28 mg/mL) IR, *ν*: 3412, 2929, 1733, 1451, 1248, 1141, 1017 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ*: 0.98 (s, 3H), 1.21 (s, 3H), 1.27 (s, 3H), 1.2–2.6 (m, 10H), 4.26 (d, *J*=7.4 Hz, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) *δ*: 24.14 (CH_3), 26.10 (CH_3), 26.87 (CH_2), 27.33 (CH_2), 27.95 (CH_3), 33.40 (CH_2), 34.22 (CH_2), 38.62 (C), 39.03 (CH), 39.50 (C), 52.44 (CH), 79.79 (CH), 174.37 (C) ppm; EIMS, *m*/*z* (relative intensity) 193 (M^+-15, 5), 165 (6), 135 (12), 96 (64), 81 (41), 67 (51), 55 (100); HRMS (ESI): calcd for $C_{13}H_{20}O_2Na$ 231.1355; found 231.1346.

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Supplementary data

Experimental procedures and copies of the ^1H and ^{13}C NMR spectra for all new compounds. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.10.004. These data include MOL files and InChiKeys of the most important compounds described in this article.

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