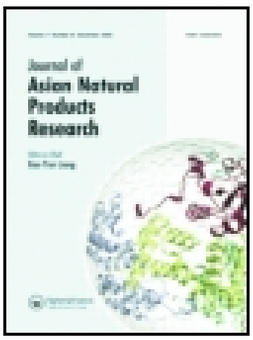

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Stereospecific synthesis of *S*-(−)-*trans*-verbenol and its antipode by inversion of sterically hindered alcohols

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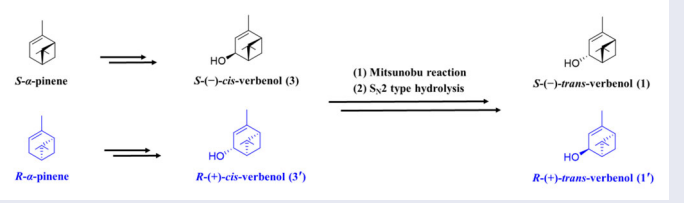
ABSTRACT

S-(−)-*trans*-Verbenol (**1**) and its antipode, *R*-(+)-*trans*-verbenol (**1′**) have been confirmed as the critical pheromone components of bark beetles. Synthesis of these two active secondary alcohols (**1** and **1′**) from commercially available starting materials *S*-α-pinene and *R*-α-pinene was reported. The key steps were mainly depended on the effective S_N2 stereo-inversion of the hydroxy group of sterically hindered alcohols (**3** and **3′**), using Mitsunobu reaction or hydrolysis of mesylate ester, alternatively. Our results provide a new and stereo-selectivity way to obtain optically active insect pheromones.



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S-(−)-trans-verbenol; *R-(+)-trans*-verbenol; sterically hindered alcohols; Mitsunobu reaction; S_N2 inversion

1. Introduction

Conifer-feeding bark beetles (Coleoptera: Scolytinae) are among the most economically important pests of conifers, which cause significant losses to pine forests worldwide [1]. It is well known that the aggregation of bark beetles is generally mediated by semichemicals released by the beetles themselves, or volatiles derived from the host trees [2].

S-(−)-*trans*-Verbenol (**1**, Figure 1(A)) and *R*-(+)-*trans*-verbenol (**1′**, Figure 1(B)) have been confirmed as the critical pheromone components of bark beetles [3,4]. Application of pheromones has become a new trend in the management of this kind of pest through mass trapping or pheromone avoidance [5]. Commonly, these two

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Figure 1. The structures of *S*-(−)-*trans*-verbenol (**1**) and *R*-(+)-*trans*-verbenol (**1′**).

monoterpenols are derived from the host monoterpene α-pinene [6]; however, natural product extraction cannot provide enough material for economical field trapping.

Presently, allylic oxidation of α-pinene is the main method to synthesize *trans*-verbenol [7]. The oxidization of α-pinene to *trans*-verbenyl acetate by use of $Pb(OAc)_4$ in benzene, followed by saponification using aqueous KOH in CH_3OH, could produce *trans*-verbenol directly [8]. However, the oxidation reaction cannot easily be scaled up, because it involves expensive reagents [$Pb(OAc)_4$], requires the use of benzene as a solvent, and has poor reproducibility and selectivity. Hence, it remains challenging to develop a versatile and efficient strategy for the total synthesis of *trans*-verbenol.

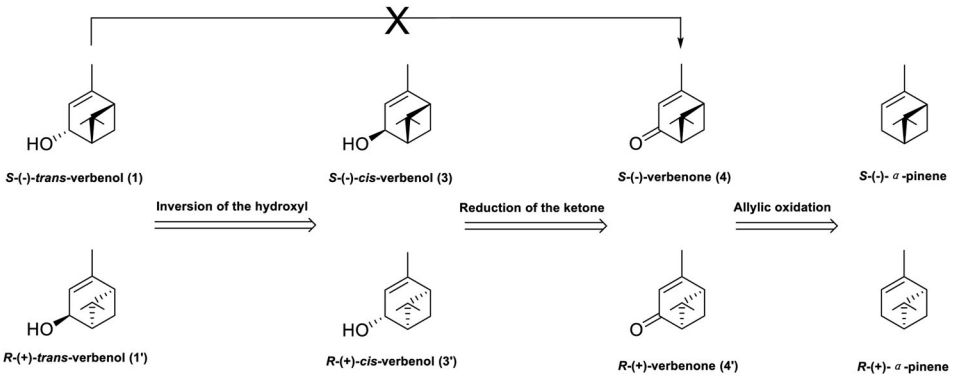
As a part of our project to obtain optically active insect pheromones, two alternative methods of S_N2 inversion were performed to realize the synthesis of *S*-(−)-*trans*-verbenol (**1**) and *R*-(+)-*trans*-verbenol (**1′**) in high chemical and optical yields.

2. Results and discussion

The retrosynthetic analysis is shown in Scheme 1 (A and B), which involves the use of α-pinene (*S* and *R* configurations) as the chirons for the construction of the stereogenic centers of target compounds (**1** and **1′**). Normally, secondary alcohols can be prepared via reduction of the corresponding ketone. However, due to steric effects, there are few stereoselective reductants that could realize the reduction of verbenone (**4** or **4′**) to obtain the *trans* products (**1** or **1′**). While, the *cis* products (**3** or **3′**) could be obtained easily by the reduction of verbenone (**4** or **4′**). Therefore, some effective methods should be designed to realize the stereo-inversion of the hydroxy group of *cis*-verbenol (**3** or **3′**), so that the optically pure *trans*-verbenol (**1** or **1′**) can be prepared.

According to our synthetic plan, the synthesis of *S*-(−)-*trans*-verbenol (**1**) began with the preparation of *S*-(−)-verbenone (**4**), which could be produced from *S*-α-pinene by allylic oxidation using manganese (III) acetate as the catalyst (Scheme 2) [9]. The preparation of *S*-(−)-*cis*-verbenol (**3**) by reducing *S*-(−)-verbenone (**4**) with $(i\text{-Bu})_2AlH$ in CH_2Cl_2 at −70°C resulted in higher yields and stereoselectivity [10].

Currently, optically active secondary alcohols can be prepared from the corresponding racemic esters in high chemical and optical yields, mainly by a combination of enzymatic hydrolysis and chemical transformation [11–13]. In order to realize stereo-inversion of the hydroxy group of *S*-(−)-*cis*-verbenol (**3**), Mitsunobu reaction,



Scheme 1. The retrosynthetic analysis of *S*-(−)-*trans*-verbenol (**1**) and *R*-(+)-*trans*-verbenol (**1′**).

as well as hydrolysis of the mesyl ester, was carried out, respectively (Scheme 2). *S*-(−)-*cis*-Verbenol (**3**) was subjected to Mitsunobu reaction by using 4-nitrobenzoic acid, PPh_3, and diethyl azodicarboxylate, which furnished *S*-(−)-*trans*-verbenyl 4-nitrobenzoate (**2a**) with an inverted configuration. $LiAlH_4$ reduction of the benzoate (**2a**) provided *S*-(−)-*trans*-verbenol (**1**) (85.5% yield based on **3**). The optical purity of **1** was determined by GC analysis (96.2% ee). As an alternative to Mitsunobu reaction, the utilization of an S_N2 type hydrolysis of a mesylate ester (**2b**) was also examined. *S*-(−)-*trans*-verbenol (**1**) with 93% ee was obtained in 80% yield by mesylation followed by hydrolysis under neutral condition (85°C in the presence of $CaCO_3$).

R-(+)-*trans*-verbenol (**1′**) (Mitsunobu reaction condition, 85.6% yield, 95% ee; hydrolysis of mesyl ester, 78% yield, 91%ee.) was synthesized, using *R*-α-pinene as the starting material as well (Scheme 3).

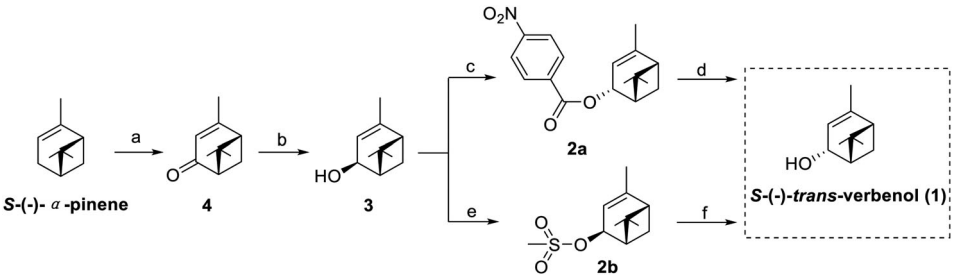
Both *S*-(−)-*trans*-verbenol (**1**) and *R*-(+)-*trans*-verbenol (**1′**) can be prepared in high chemical and optical yields from these two alternative methods of S_N2 inversion. Considering the facts that the chemical and optical yield from Mitsunobu inversion was better compared with the results obtained via mesylation. The former is preferable to finish the stereo-inversion of sterically hindered alcohols, while there are possibilities of side reactions such as elimination or S_N1 reaction during the hydrolysis of mesylate.

In conclusion, we have successfully synthesized *S*-(−)-*trans*-verbenol (**1**) and its antipode (**1′**) in excellent optical yields, using *S*-(−)-α-pinene and *R*-(+)-α-pinene as the starting materials. The stereo-inversion of the hydroxy group was realized efficiently by Mitsunobu inversion, or hydrolysis of mesylate ester. Our results are highly beneficial for preventing and controlling bark beetles in an economical and environmentally benign way.

3. Experimental

3.1. General experimental procedures

All the commercially available reagents were used without further purification. Column chromatography was performed on silica gel (200–300 mesh), and TLC



Scheme 2. The synthesis of *S*-(−)-*trans*-verbenol (**1**): (a) $Mn(OAc)_3{\cdot}2H_2O$, TBHP, O_2; (b) $(i\text{-}Bu)_2AlH$, CH_2Cl_2, −70°C in an argon, 2 h; (c) 4-nitrobenzoic acid, PPh_3, DEAD, dry THF, 0°C to room temperature (14 h), 40 °C (3 h); (d) $LiAlH_4$, dry THF, 0°C to room temperature (4 h); (e) methanesulfonic anhydride, Et_3N, CH_2Cl_2, −20°C (2 h); (f) $CaCO_3$, H_2O, 85°C (4 h).

inspections were performed on silica gel GF-254 plates (Qingdao Haiyang Chemical Co., Ltd, Qingdao, China). The NMR spectra were recorded on a Bruker NMR spectrometer (Bruker, Fällanden, Switzerland) in $CDCl_3$ (^1H at 500 MHz and ^{13}C at 125 MHz) using tetramethylsilane (TMS) as the internal standard. The purities of the synthesized compounds were estimated by gas chromatography (GC), which was performed on an Agilent 7890 A (Agilent Technologies, Wilmington, DE, USA). The column used was CYCLOSIL-B with 30 m × 0.25 mm i.d., 0.25 μm (Agilent Technologies). The chemical analysis was carried out using an Agilent GC coupled with a mass spectrometry system (TRACE GC 2000). The GC system was equipped with a DB-5 ms column (30 m × 0.25 mm × 0.25 μm, Agilent Technologies).

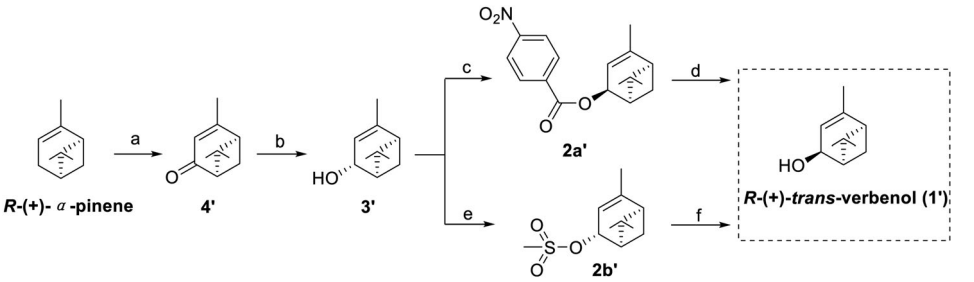
3.2. General procedure for the synthesis of verbenone (4 and 4′)

A solution of α-pinene (13.6 g, 100.0 mmol), EtOAc (40 ml), and *t*-butyl hydroperoxide (TBHP) in decane (386 mmol) was stired with 3 Å molecular sieves (25.0 g) for 30 min under nitrogen. $Mn(OAc)_3{\cdot}2H_2O$ (2.67 g, 9.97 mmol) was added. The mixture was degassed and filled with oxygen (balloon). The reaction was stirred for 48 h, diluted with 20 ml of diethyl ether, and filtered through a thin pad of Celite. The filtrate was concentrated under reduced pressure, and the residue was chromatographed over SiO_2 and eluted with hexane/EtOAc (10:1, *v/v*) to yield verbenone as a yellow oil.

S-(−)-Verbenone 4 (9.0 g, 60% yield); ^1H NMR (500 MHz, $CDCl_3$) δ: 0.99 (3H, s), 1.47 (3H, s), 1.99 (3H, d, $J = 1.5$ Hz), 2.05 (1H, d, $J = 9.5$ Hz), 2.38–2.41 (1H, m), 2.61–2.63 (1H, m), 2.76–2.80 (1H, m), 5.70–5.71 (1H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.9, 23.5, 26.5, 40.8, 49.6, 53.9, 57.5, 121.1, 170.1, 203.9.

R-(+)-Verbenone 4′ (9.3 g, 62% yield); ^1H NMR (500 MHz, $CDCl_3$) δ: 0.99 (3H, s), 1.48 (3H, s), 1.98 (3H, d, $J = 1.5$ Hz), 2.05 (1H, d, $J = 9.5$ Hz), 2.39–2.41 (1H, m), 2.62–2.64 (1H, m), 2.77–2.81 (1H, m), 5.70–5.71 (1H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.9, 23.5, 26.5, 40.8, 49.6, 54.0, 57.5, 121.1, 170.2, 204.0.

These data were consistent with the literature reports [14].



Scheme 3. The synthesis of *R*-(+)-*trans*-verbenol (**1′**): (a) $Mn(OAc)_3{\cdot}2H_2O$, TBHP, O_2; (b) $(i\text{-}Bu)_2AlH$, CH_2Cl_2, −70°C, 2 h; (c) 4-nitrobenzoic acid, PPh_3, DEAD, dry THF, 0°C to room temperature (14 h), 40 °C (3 h); (d) $LiAlH_4$, dry THF, 0°C to room temperature (4 h); (e) methanesulfonic anhydride, Et_3N, CH_2Cl_2, −20°C (2 h); (f) $CaCO_3$, H_2O, 85°C (4 h).

3.3. General procedure for the synthesis of cis-verbenol (3 and 3′)

A solution of verbenone (7.5 g, 50.0 mmol) in anhydrous CH_2Cl_2 (50 ml) was prepared, and 37.0 ml of $(i\text{-}Bu)_2AlH$ (1.5 M solution in toluene) was added dropwise at −70°C under an argon flow. The mixture was stirred for 2 h. At the same temperature, a mixture of 3.5 ml THF and 3.5 ml H_2O was added, and the stirring was continued for 0.5 h. The separated precipitate was filtered off through celite, and the organic layer was dried with Na_2SO_4 and then evaporated. The residue was chromatographed over SiO_2 and elution with hexane/EtOAc (8:1, *v/v*) to yield *cis*-verbenol as a white powder.

***S*-(−)-*cis*-*Verbenol* 3** (6.99 g, 92% yield);^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.07 (3H, s), 1.34 (3H, s), 1.67–1.69 (1H, m), 1.72–1.73 (3H, m), 1.95–1.97 (1H, m), 2.27–2.29 (1H, m), 2.42–2.46 (1H, m), 4.44–4.46 (1H, m), 5.35–5.36 (1H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 22.6, 22.6, 26.8, 35.5, 38.9, 47.7, 48.1, 73.5, 119.3, 147.4.

***R*-(+)-*cis*-*Verbenol* 3′** (6.92 g, 91% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.08 (3H, s), 1.35 (3H, s), 1.70 (1H, m), 1.72–1.74 (3H, m), 1.96–1.98 (1H, m), 2.27–2.31 (1H, m), 2.43–2.46 (1H, m), 4.45–4.46 (1H, m), 5.36–5.37 (1H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 22.6, 22.6, 26.8, 35.5, 38.9, 47.7, 48.2, 73.5, 119.3, 147.3.

These data were consistent with the literature reports [15].

3.4. General procedure for the synthesis of trans-verbenyl 4-nitrobenzoate (2a and 2a′)

cis-Verbenol (3.04 g, 20.0 mmol), 4-nitrobenzoic acid (13.4 g, 80.0 mmol), and triphenylphosphine (PPh_3) (21.0 g, 80.0 mmol) were dissolved in THF (150 ml), then diethyl azodicarboxylate (13.9 g, 80.0 mmol) was added dropwise, and the reaction mixture was maintained below 10 °C. Upon completion of the addition, the mixture was stirred first at room temperature overnight (14 h) and then at 40 °C for 3 h. The reaction mixture was cooled to room temperature, diluted with 150 ml of ether and washed twice with 100 ml portions of saturated aqueous $NaHCO_3$ solution. The aqueous layers were combined and back-extracted with 100 ml of ether. The combined organic layers were dried over Na_2SO_4. Excess solvent was removed under reduced pressure. The resulting semi-solid was suspended in 40 ml of ether, and the suspension stand at room temperature

overnight. The mixture was stirred, while 20 ml of hexanes was slowly added. The resulting white solid was filtered, and the filter cake was washed with 200 ml of 50% (*v/v*) ether-hexanes. The solvent was removed under reduced pressure. The residue was chromatographed over SiO_2 and eluted with hexane/EtOAc (8:1, *v/v*) to yield *trans*-verbenyl 4-nitrobenzoate as a white powder.

***S*-(−)-*trans*-Verbenyl 4-nitrobenzoate 2**, [α] −124 ($c = 0.7$, $CHCl_3$). (5.42 g, 90% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.98 (3H, s), 1.38 (3H, s), 1.59–1.61 (1H, m), 1.78–1.79 (3H, m), 2.11–2.13 (1H, m), 2.37–2.39 (1H, m), 5.44–5.45 (1H, m), 5.61–5.63 (1H, m), 8.17–8.21 (2H, m), 8.25–8.28 (2H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ: 20.7, 22.8, 26.4, 29.6, 44.4, 46.6, 47.7, 75.7, 114.6, 123.4, 123.4, 130.6, 130.6, 136.4, 150.7, 151.6, 164.5.

***R*-(+)-*trans*-Verbenyl 4-nitrobenzoate 2′**, [α] +161 ($c = 1.0$, $CHCl_3$). (5.54 g, 92% yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.99 (3H, s), 1.39 (3H, s), 1.59–1.62 (1H, m), 1.79–1.80 (3H, m), 2.12–2.14 (1H, m), 2.38–2.40 (1H, m), 5.45–5.46 (1H, m), 5.62–5.64 (1H, m), 8.19–8.21 (2H, m), 8.26–8.28 (2H, m). ^{13}C NMR (125 MHz, $CDCl_3$): δ: 20.7, 22.8, 26.4, 29.6, 44.4, 46.6, 47.7, 75.7, 114.6, 123.4, 123.4, 130.7, 130.7, 136.4, 150.4, 151.6, 164.5.

These data were consistent with the literature reports [7].

3.5. General procedure for the synthesis of cis-verbenyl mesylate (2 b and 2 b′)

A solution of *cis*-verbenol (3.04 g, 20.0 mmol) in CH_2Cl_2 (30 ml) was prepared. To this solution was added triethylamine (2.73 g, 27.0 mmol) and methanesulfonic anhydride (4.00 g, 23.0 mmol) at −40°C. After stirring at −40°C for 2 h, the reaction mixture was poured into 30 ml of 1% aq. HCl and extracted with CH_2Cl_2. The organic phase was washed with water and concentrated *in vacuo* to give the crude product. The crude product was used for the next hydrolysis without purification.

3.6. General procedure for the synthesis of trans-verbenol (1 and 1′)

3.6.1. Procedure for the reduction of trans-verbenyl 4-nitrobenzoate

A solution of *trans*-verbenyl 4-nitrobenzoate (3.01 g, 10.0 mmol) was added dropwise to a suspension of $LiAlH_4$ (760 mg, 20.0 mmol) in THF (30 ml) under a N_2 atmosphere. The resulting mixture was stirred for 30 min at 0 °C and then warmed to room temperature for 4 h. Then, the mixture was cooled with an ice bath, and treated by successive dropwise addition of 0.68 ml of water and stirred for 15 min, 0.68 ml of 15% NaOH solution and stirred for 15 min, and then 2.04 ml of water and stirred for 30 min at room temperature. The dry granular precipitate was removed by filtration, the filtrate was dried over Na_2SO_4, and the solvent was evaporated. The crude material was purified by flash chromatography on silica gel using hexane-ethyl acetate (5:1 *v/v*) as the eluent to provide *trans*-verbenol (**1,** 1.37 g, 90% yield; ***1′,*** 1.41 g, 93% yield) as a yellow oil.

3.6.2. Procedure for hydrolysis of cis-verbenyl mesylate

The whole amount of the crude *cis*-verbenyl mesylate mixture obtained above was heated in 45 ml of water in the presence of $CaCO_3$ (0.40 g, 4 mmol) at 85°C over 4 h.

After neutralization with aq. $NaHCO_3$ and extraction with EtOAc, the organic phase was concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel using hexane-ethyl acetate (5:1 *v/v*) as the eluent to give *trans*-verbenol (**1,** 2.43 g, 80% yield based on **3**; ***1′,*** 2.37 g, 78% yield based on ***3′***) as a yellow oil.

S-(−)-trans-Verbenol 1, [α] −136 (*c* 0.80, $CHCl_3$), ee 93%. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 0.85 (3H, s), 1.32 (3H, s), 1.66–1.67 (1H, m), 1.70–1.71 (3H, m), 1.99–2.02 (1H, m), 2.14–2.17 (1H, m), 2.23–2.26 (1H, m), 4.24–4.26 (1H, m), 5.32–5.34 (1H, m). ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 20.4, 22.6, 26.6, 28.6, 36.1, 47.0, 48.0, 70.4, 118.8, 148.8. GC-MS (70 eV) *m/z*: 152.

R-(+)-trans-Verbenol 1′, [α] +112 (*c* 12.0, $CHCl_3$), ee 95%. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 0.85 (3H, s), 1.32 (3H, s), 1.66–1.68 (1H, m), 1.70–1.71 (3H, m), 1.99–2.02 (1H, m), 2.14–2.17 (1H, m), 2.22–2.26 (1H, m), 4.24–4.26 (1H, m), 5.32–5.34 (1H, m). ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 20.4, 22.6, 26.6, 28.6, 36.1, 47.0, 48.0, 70.4, 118.8, 148.8. GC-MS (70 eV) *m/z*: 152.

These data were consistent with the literature reports [7].

Disclosure statement

No potential conflict of interest was reported by the authors.

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