Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 6264–6271
Tetrahedron

Stereoselective total synthesis of (±)-α-vetispirene, (±)-hinesol, and (±)-β-vetivone based on a Claisen rearrangement

Atsuo Nakazaki, Tomohiro Era, Yuko Numada and Susumu Kobayashi*

Faculty of Pharmaceutical Sciences, Tokyo University of Science (RIKADAI), 2641 Yamazaki, Noda-shi, Chiba 278-8510, Japan

Received 7 March 2006; revised 17 April 2006; accepted 19 April 2006
Available online 19 May 2006

Abstract—The stereoselective total syntheses of (±)-α-vetispirene, (±)-hinesol, and (±)-β-vetivone were accomplished based on a Claisen rearrangement in an alkenyl bicyclic dihydropyran system. The most striking feature of this approach is that the Claisen rearrangement of bicyclic dihydropyran proceeds stereoselectively to provide a multi-functionalized spiro[4.5]decane, which is an efficient precursor for the synthesis of the vetivane sesquiterpenes.

1. Introduction

α-Vetispirene (**1**),[1] hinesol (**2**),[2] and β-vetivone (**3**)[3] are representative members of the vetivane sesquiterpene family, which possess a spiro[4.5]decane core and a branched three-carbon unit on a cyclopentane framework (Fig. 1). Related spirocyclic terpenes such as lubimin and gleenol, substituted with an oxy-functional group at a position adjacent to the spirocyclic carbon center, have been also isolated.[4] Some of these spirocyclic terpenes exhibit interesting biological activities. Especially, (−)-**2** is a relatively specific inhibitor of H^+, K^+-ATPase and an active ingredient of cerebral circulation and metabolism improvers.[2c] Because of their unique structures and biological activities, a number of synthetic approaches to these terpenes have been reported, including intramolecular alkylations, palladium-based cyclizations, and intermolecular cycloadditions.[5,6]

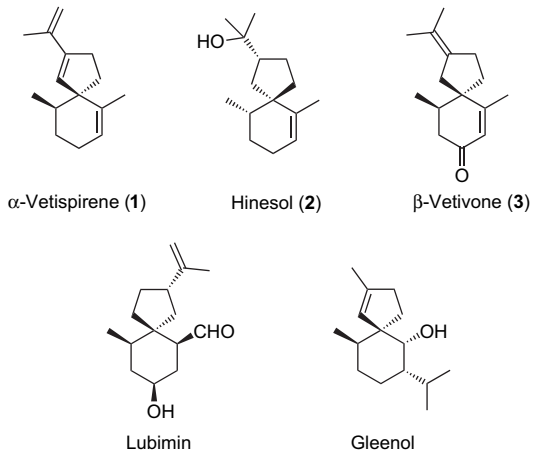
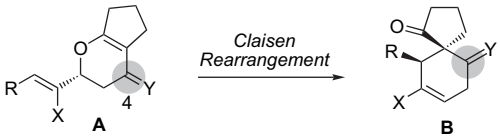


Figure 1. Terpenes with spiro[4.5]decane framework.

We have recently developed a new approach to multi-substituted spiro[4.5]decanes based on a Claisen rearrangement, in order to produce a more efficient general synthetic method for spirocyclic terpenes (Eq. 1).[7] Claisen rearrangement is one of the most reliable and efficient methods of introducing asymmetry and as such may be quite useful for the synthesis of the functionalized spiro[4.5]decane **B**.[8] The strategy involves a rearrangement of bicyclic dihydropyran **A**, substituted in the 4-position with a high-oxidation state group (Eq. 1, Y), thereby introducing a functional group at a position adjacent to the spirocyclic carbon center in **B**. By means of varying the groups R, X, and Y, this strategy could be applicable to the synthesis of multi-functionalized spirocyclic frameworks.



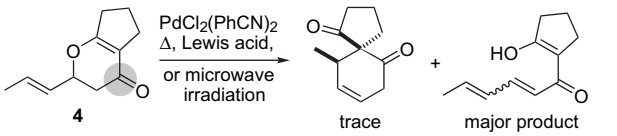
(1)

It is worth noting that the choice of the functional group Y is an important key to success in this rearrangement. Indeed, the expected rearrangement of alkenyl dihydroxypyrone (Y=O) did not proceed; instead the ring-opening product was mainly obtained (Eq. 2). On the other hand, the rearrangement of dihydropyrans, substituted in the 4-position

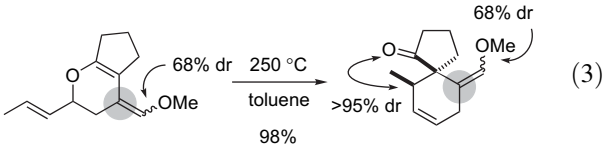
Keywords: Vetivane sesquiterpene; Spiro[4.5]decane; Claisen rearrangement.
* Corresponding author. Tel./fax: +81 4 7121 3671; e-mail: kobayash@rs.noda.tus.ac.jp

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.04.049

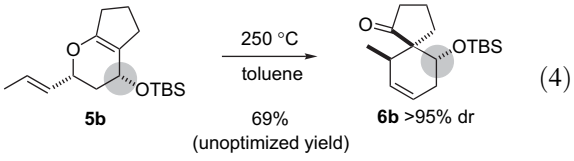
with a non-enolizable group such as a double bond or a siloxy group, proceeds in excellent yields and with high stereoselectivities (Eqs. 3 and 4).[7] This is the first report of successful Claisen rearrangement in bicyclic dihydropyran systems with a high-oxidation state functionality in the 4-position.[9]



(2)



(3)

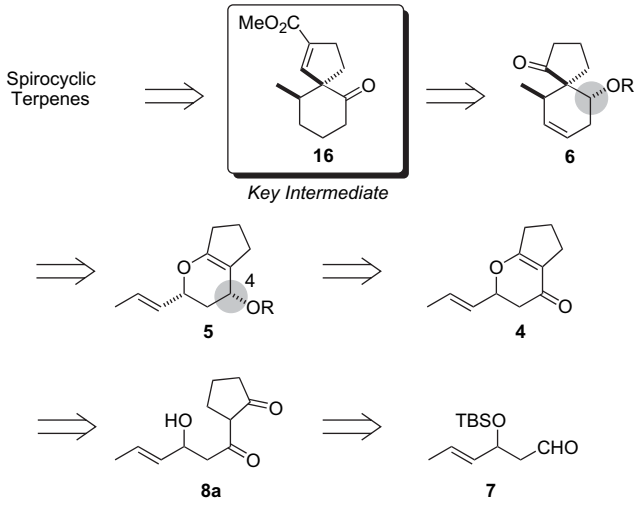


(4)

We focused our attention on the siloxy spiro[4.5]decane **6b** because this spirocycle **6b** would be a suitable precursor for the synthesis of vetivane sesquiterpenes. The present paper details optimization of the Claisen rearrangement of alkenyl bicyclic dihydropyran and the stereoselective total synthesis of (±)-α-vetispirene, (±)-hinesol, and (±)-β-vetivone.

2. Results and discussion

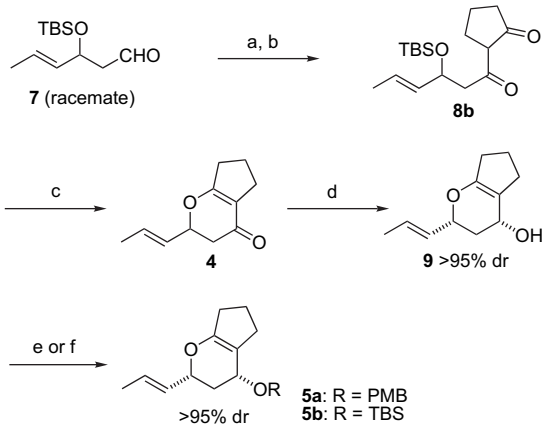
Our retrosynthetic analysis for the stereoselective synthesis of vetivane sesquiterpenes is outlined in Scheme 1. As shown, access to these spirocyclic terpenes was envisioned from a key intermediate **16**, which would be converted from spiro[4.5]decane **6**. The Claisen rearrangement of 4-oxy-functionalized alkenyl dihydropyran **5** would provide **6** in a stereoselective manner. Dihydropyran **5** should be obtainable from the corresponding dihydropyrone **4**, which would be readily available from a racemic hydroxy-1,3-diketone **8a** by acid-catalyzed cyclization. In turn, synthesis of diketone **8a** was envisaged from aldehyde **7** by means of several simple manipulations. As non-racemic **7** is easily prepared in high enantiomeric excess by several ways,[10] the present strategy would be applicable to the total synthesis of the optically active vetivane sesquiterpenes.



Scheme 1. Retrosynthetic analysis.

2.1. Stereoselective synthesis of alkenyl dihydropyranes 5

Our first step was the preparation of substrate **5** according to a modified version of our procedure (Scheme 2);[7] treatment of the known aldehyde **7** (racemate)[11] with the enolate derived from cyclopentanone afforded the aldol adduct as a mixture of diastereomers. This aldol adduct was converted to 1,3-diketone **8b** by DMSO/TFAA oxidation in good yield.[12] Notably, other oxidants, such as Dess–Martin periodinane, DMSO/$(COCl)_2$, and PCC were less effective. Next, removal of the TBS group of **8b** and acid-catalyzed cyclization proceeded in a single operation by an excess of TFA to afford alkenyl dihydropyrone **4** in 85% yield. Dihydropyrone **4** thus obtained was reduced by $LiAlH_4$ to afford **9**, followed by protection of the hydroxy group to give the requisite alkenyl dihydropyran **5a** (R=PMB) or **5b** (R=TBS) as single diastereomer. The relative stereochemistry shown for **5b** was determined by the NOESY correlation.

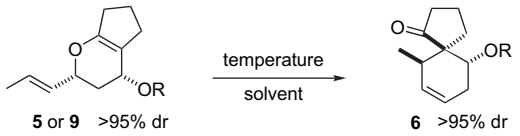


Scheme 2. Preparation of substrates **5a** and **5b** for the Claisen rearrangement. Reagents and conditions: (a) LDA, cyclopentanone, 91%; (b) DMSO, TFAA, then Et_3N, −78 °C, 87%; (c) TFA, CH_2Cl_2, 0 °C→rt, 85%; (d) $LiAlH_4$, Et_2O, 0 °C; (e) PMBCl, NaH, 57% (two steps); (f) TBSCl, imidazole, rt, 73% (two steps).

2.2. Optimization of the Claisen rearrangement

Next, we examined the construction of the spiro[4.5]decane framework by thermolytically induced Claisen rearrangement. After careful optimization, it was found that the choice of solvent, hydroxy protecting group, and temperature appears to be important for the success of this rearrangement (Table 1). The rearrangement of dihydropyran **5a** (R=PMB), in 1,2,4-trichlorobenzene (1,2,4-TCB) at 250 °C, provided a trace amount of the desired rearrangement product **6a**, along with an elimination product as the major component (entry 1). In contrast, the rearrangement of **5b**, which was protected by a bulkier group on the 4-hydroxy group, in the

Table 1. Claisen rearrangement of the alkenyl dihydropyrans



5 or **9** >95% dr **6** >95% dr

Entry	Substrate (R)	Solvent	Temperature (°C)	Product	Yield (%)
1	**5a** (PMB)	1,2,4-TCB	250	**6a**	Trace
2	**5b** (TBS)	1,2,4-TCB	250	**6b**	28
3	**5b**	Toluene	250	**6b**	87
4	**5b**	1,2,4-TCB	165	**6b**	Trace
5	**9** (H)	1,2,4-TCB	70–100	**6c**	0

same solvent, afforded rearrangement product **6b**. While this was a better result than the previous one it was still poor (28% yield, entry 2). In addition to changing the protective group, use of a less polar solvent provided much better results. Thus, alkenyl dihydropyran **5b** was heated at 250 °C in toluene to provide the desired spiro[4.5]decane **6b** in 87% yield as a single diastereomer (entry 3).[13] The rearrangement of **5b** or **9** (R=H) at lower temperature in 1,2,4-TCB afforded only elimination products; none of the desired products were obtained (entries 4 and 5).

The stereochemical assignment of **6b** was verified by NOE experiments on the tricycle, derived from **6b** in two steps [(1) $LiAlH_4$, Et_2O, 0 °C; (2) 2,2-dimethoxypropane, PPTS, CH_2Cl_2] (Fig. 2).[7] This stereochemical outcome suggests that the bicyclic dihydropyran **5b** undergoes the rearrangement through a boat-like transition state (Fig. 3).[14]

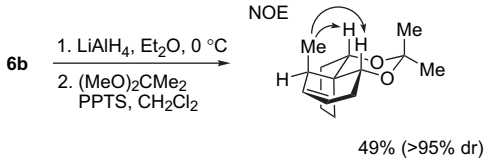


Figure 2. Stereochemical determination of **6b**.

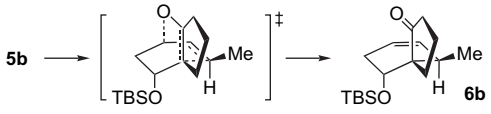
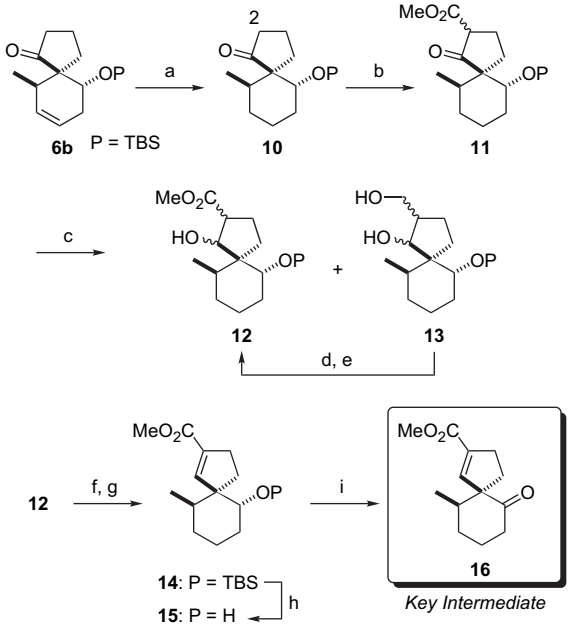


Figure 3. A possible transition state of Claisen rearrangement.

2.3. Synthesis of a key intermediate 16

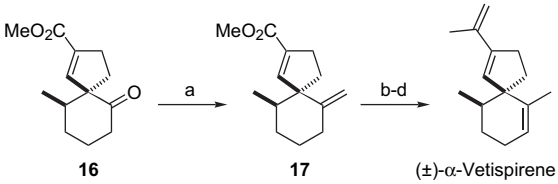
With the multi-functionalized spiro[4.5]decane framework in hand, we next synthesized **16**, a common key intermediate for the synthesis of vetivane sesquiterpenes, as shown in Scheme 3. The double bond in ketone **6b** could be saturated under 1 atm of hydrogen gas in the presence of 5% Pd on charcoal.[15] Although introduction of one-carbon unit at the C2-position of the spiro[4.5]decane framework has been achieved with difficulty,[6] exposure of ketone **10** to an excess of KH and dimethyl carbonate smoothly produced the desired keto ester **11** in good yield as a mixture of diastereomers. Next, the reduction with $NaBH_4$ was performed to give hydroxy ester **12** in moderate yield, along with the unexpected diol **13** in 20% yield. Diol **13** could be converted to hydroxy ester **12** by a two-step sequence. Chemoselective oxidation of the primary alcohol by the Merck method (TEMPO/$NaClO_2$/NaClO) to afford the corresponding carboxylic acid,[16] followed by methyl esterification (MeI, $KHCO_3$), led to **12** in 84% yield for the two steps. The hydroxy ester **12** was then mesylated and eliminated to provide the desired α,β-unsaturated ester **14**. Removal of the TBS group of **14** with an aqueous solution of hydrogen fluoride in CH_3CN, followed by Dess–Martin oxidation,[17] led to the key intermediate ketone **16**. This compound would be a versatile intermediate for the syntheses of a variety of spirocyclic terpenes.



Scheme 3. Preparation of the key intermediate **16**. Reagents and conditions: (a) Pd/C, H_2 (1 atm), EtOH; (b) KH, $(MeO)_2CO$, THF, 95 °C, 86% (two steps); (c) $NaBH_4$, MeOH, **12** 67% (based on the recovered S.M.: 74%), **13** 20%; (d) TEMPO, $NaClO_2$, NaClO; (e) MeI, $KHCO_3$, DMF, 84% (two steps); (f) MsCl, pyridine, 0 °C; (g) DBU, CH_2Cl_2, rt, 92% (two steps); (h) 48% HF aq, CH_3CN, rt; (i) Dess–Martin periodinane, CH_2Cl_2, rt, 88% (two steps).

2.4. Total synthesis of (±)-α-vetispirene

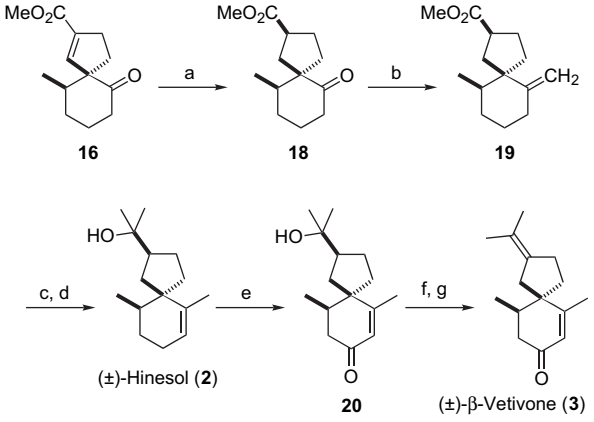
We next explored the final steps to (±)-α-vetispirene (**1**). Treatment of ketone **16** with excess MeLi, followed by acid-catalyzed dehydration with $TsOH\cdot H_2O$, led to (±)-**1**, along with inseparable byproducts. Thus, we chose an alternative stepwise route, whereby ketone **16** was first transformed into *exo*-methylene **17** under Nozaki's conditions ($TiCl_4$, CH_2I_2, and Zn) (Scheme 4).[2c,18] Acid-catalyzed isomerization of **17** provided the *endo*-isomer, which after treatment with an excess of MeLi, followed by dehydration led to (±)-α-vetispirene (**1**) in good overall yield.[19]



Scheme 4. Total synthesis of (±)-α-vetispirene (**1**). Reagents and conditions: (a) CH_2I_2, $TiCl_4$, Zn, THF–CH_2Cl_2, 72%; (b) cat. $TsOH\cdot H_2O$, PhH, reflux; (c) MeLi, THF; (d) cat. CSA, PhH, 60 °C, 87% (three steps).

2.5. Total synthesis of (±)-hinesol and (±)-β-vetivone

(±)-Hinesol (**2**) was also synthesized from the key intermediate **16** in a stereoselective manner (Scheme 5). Ketone **16** was subjected to hydrogenolysis to afford the desired ester **18** in 97% as an 87:13 mixture of separable diastereomers.[20] The keto carbonyl of **18** was converted to an *exo*-methylene group using Nozaki's conditions. Finally acid-catalyzed isomerization, to give *endo*-isomer followed by treatment with an excess of MeMgI, provided (±)-hinesol (**2**) in 90% yield for the two steps. (±)-β-Vetivone (**3**) was synthesized from (±)-hinesol by a reported procedure.[21] The regioselective allylic oxidation of (±)-hinesol (**2**) by means of CrO_3/3,5-dimethylpyrazole (3,5-DMP) afforded hinesolone **20** in moderate yield.[22] Then, treatment of **20** with acetic anhydride followed by $BF_3\cdot OEt_2$ yielded (±)-β-vetivone (**3**) contaminated with the *exo*-methylene isomer as an inseparable mixture (86:14 mixture of **3** and the *exo*-isomer) in 64% yield.[23]



Scheme 5. Total synthesis of (±)-hinesol (**2**) and (±)-β-vetivone (**3**). Reagents and conditions: (a) Pd/C, H_2 (1 atm), EtOH, 97% (87% dr), then separation; (b) CH_2I_2, $TiCl_4$, Zn, THF–CH_2Cl_2, 80%; (c) cat. TsOH·H_2O, PhH, reflux; (d) MeMgI, Et_2O, 0 °C to rt, 90% (two steps); (e) CrO_3, 3,5-DMP, CH_2Cl_2, 0 °C, 60%; (f) Ac_2O, NaOAc, 140 °C, 93%; (g) $BF_3\cdot OEt_2$, rt, 64% (based on the recovered S.M.: 84%, 86:14 mixture of **3** and the *exo*-isomer).

3. Conclusion

We were able to achieve the stereoselective total syntheses of (±)-α-vetispirene, (±)-hinesol, and (±)-β-vetivone based on a Claisen rearrangement of a functionalized alkenyl bicyclic dihydropyran system. Our strategy is unique and efficient, and could be applicable to other terpenes with a multi-functionalized spiro[4.5]decane framework. Further investigations into its application to the synthesis of optically active spirocyclic terpenes are in progress.

4. Experimental

4.1. General

All reactions sensitive to oxygen and moisture were performed in flame-dried glassware under a static argon atmosphere unless otherwise noted. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-LD400 spectrometer operating at either 400 MHz (^1H) or 100 MHz (^{13}C) or on a JEOL AL-300 spectrometer operating at either 300 MHz (^1H) or 75 MHz (^{13}C). Chemical shifts are reported in δ units and are referenced to the solvent, i.e., 7.26/77.1 for $CDCl_3$. Multiplicities are indicated as br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sept (septet), or m (multiplet). Coupling constants (J) are reported in Hertz (Hz). Infrared spectra were recorded on a Jasco FT-IR410 spectrometer. Electron impact mass spectra were performed on a HITACHI M-80B mass spectrometer. Electrospray ionization mass spectra were recorded on an Applied Biosystems API QSTAR pulsar i as high resolution, using poly(ethylene glycol) as internal standard. Thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} (Merck 1.05715.0009) plates. Flash column chromatography was performed on a PSQ100B silica gel (Fuji Silysia Co., Ltd, Japan). THF and Et_2O were purchased from Wako Pure Chemical Industries Ltd, in anhydrous grade. CH_2Cl_2 was distilled from CaH_2 immediately before use. Diisopropylamine was distilled from CaH_2 and stored over KOH pellets.

4.1.1. 1,3-Diketone 8b. To the solution of diisopropylamine (0.982 mL, 7.05 mmol) in THF (14 mL) was added a solution of *n*-BuLi (4.6 mL of 1.52 M solution in hexane, 7.05 mmol) at 0 °C, then the resulting mixture was stirred at that temperature for 30 min and cooled to −78 °C. To this mixture was added cyclopentanone (0.567 mL, 6.41 mmol) at −78 °C, then this mixture was stirred at that temperature for 1 h. To this mixture was added a solution of aldehyde **7** (732 mg, 3.21 mmol) in THF (6 mL) at −78 °C, then this mixture was stirred at that temperature for 1 h 20 min. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted two times with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. Purification by silica-gel column chromatography (hexane/EtOAc=95:5→90:10→80:20) gave 908 mg (91% yield, a mixture of diastereomers by ^1H NMR analysis) of the aldol adduct: R_f 0.64, 0.52 (hexane/EtOAc=75:25); ^1H NMR (400 MHz, $CDCl_3$) δ 5.64–5.32 (m, 2H), 4.47–4.18 (m, 2H), 3.36 (br s, 0.8H), 3.21 (br s, 0.2H), 2.25 (br dd, J=16.3, 7.3 Hz, 1H), 2.13–1.95 (m, 4H), 1.76–1.59 (m, 7H), 0.851 (s, 6.3H), 0.840 (s, 2.7H), 0.0378 (s, 3H), 0.01 (s, 3H); IR (neat, cm^{-1}) 3504, 1726; HR-ESIMS calcd for $C_{17}H_{32}O_3NaSi$: 335.2018, found: 335.2018. To the solution of DMSO (1.24 mL, 17.4 mmol) in CH_2Cl_2 (10 mL) was added $(CF_3CO)_2O$ (1.21 mL, 8.72 mmol) at −78 °C, then the resulting mixture was stirred at that temperature for 40 min. To this mixture was added a solution of the aldol adduct (908 mg, 2.91 mmol) in CH_2Cl_2 (10 mL) at −78 °C, then this mixture was stirred at that temperature for 40 min. To this mixture was added Et_3N (3.65 mL, 26.2 mmol) at −78 °C, then this mixture was stirred at that temperature for 40 min. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted two times with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. Purification by silica-gel column chromatography (hexane/EtOAc=90:10) gave 820 mg of 1,3-diketone **8b** (91% yield, a mixture of diastereomers by ^1H NMR analysis): R_f 0.81 (hexane/EtOAc=75:25); ^1H NMR (400 MHz, $CDCl_3$) δ 13.6 (br s, 0.5H), 5.68–5.56 (m, 1H), 5.49–5.35

(m, 1H), 4.62–4.48 (m, 1H), 2.65–2.20 (m, 7H), 1.90–1.85 (m, 1.5H), 1.68–1.64 (m, 3H), 0.842 (s, 6.3H), 0.836 (s, 2.7H), 0.0311 (s, 0.6H), 0.0220 (s, 0.6H), 0.0085 (s, 0.6H), 0.001 (s, 2.7H), −0.014 (s, 1.5H); IR (neat, cm^{-1}) 1712, 1662, 1617; HR-ESIMS calcd for $C_{17}H_{30}O_3NaSi$: 333.1856, found: 333.1869.

4.1.2. Dihydropyrone 4. To a solution of 1,3-diketone **8b** (7.80 g, 25.1 mmol) in CH_2Cl_2 (200 mL) was added CF_3COOH (7.8 mL, 101.0 mmol) via a dropping funnel at 0 °C, then the resulting mixture was stirred at that temperature for 15 min. This mixture was warmed to rt and stirred at that temperature for 3 h. The reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted two times with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by silica-gel column chromatography (hexane/EtOAc=95:5→83:17) gave 3.779 g (85% yield) of dihydropyrone **4**: R_f 0.38 (hexane/EtOAc=75:25); ^1H NMR (300 MHz, $CDCl_3$) δ 5.88 (ddq, J=15.4, 0.72, 6.4 Hz, 1H), 5.66 (ddq, J=15.4, 7.2, 1.5 Hz, 1H), 4.88 (ddd, J=12.5, 7.2, 4.3 Hz, 1H), 2.60–2.50 (m, 5H), 2.41 (dd, J=16.9, 4.1 Hz, 1H), 1.92 (quint, J=7.5 Hz, 2H), 1.77 (ddd, J=6.4, 1.5, 0.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.7, 178.4, 131.4, 127.8, 114.0, 81.6, 40.9, 32.7, 25.4, 19.1, 17.7; IR (neat, cm^{-1}) 1779, 1666, 1613, 1426, 1154, 965; HR-EIMS calcd for $C_{11}H_{14}O_2$: 178.0994, found: 178.0987.

4.1.3. Dihydropyran 5b. To a solution of dihydropyrone **4** (153 mg, 0.859 mmol) in dry Et_2O was added $LiAlH_4$ (41 mg, 1.08 mmol) at 0 °C, then the resulting mixture was stirred for 25 min at that temperature. The reaction mixture was quenched with $Na_2SO_4\cdot 10H_2O$, and allowed to warm to rt. To this mixture was added hexane and dry Na_2SO_4, then stirred for 10 min. The resulting mixture was filtrated, and concentrated under reduced pressure to afford crude alcohol **9**. To a solution of crude alcohol **9** and imidazole (94 mg, 1.37 mmol) in CH_2Cl_2 (6 mL) was added TBSCl (194 mg, 1.29 mmol) at 0 °C, then the resulting mixture was allowed to warm to rt and stirred for 1.5 h at that temperature. The reaction was poured into a cold saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted two times with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. Purification by silica-gel column chromatography (hexane/EtOAc=98:2→96:4) gave 184 mg (73% yield for the two steps, >95% dr by ^1H NMR analysis) of dihydropyran **5b** as a colorless clear oil. The relative stereochemistry was established by the NOESY correlation between α-oxymethyne protons: R_f 0.56 (hexane/EtOAc=90:10); ^1H NMR (300 MHz, $CDCl_3$) δ 5.70 (dq, J=15.3, 6.2 Hz, 1H), 5.55 (dd, J=15.3, 7.3 Hz, 1H), 4.38–4.27 (m, 2H), 2.42–2.08 (m, 5H), 1.94 (ddd, J=13.4, 6.5, 2.2 Hz, 1H), 1.81–1.72 (m, 2H), 1.63 (d, J=6.2 Hz, 3H), 0.815 (s, 9H), 0.00 (s, 3H), −0.0104 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.0, 130.4, 129.0, 110.6, 77.4, 64.7, 38.8, 31.4, 28.9, 25.8, 19.9, 18.2, 17.7, −4.6, −4.9; IR (neat, cm^{-1}) 1686; HR-ESIMS calcd for $C_{17}H_{30}O_2NaSi$: 317.1907, found: 317.1897.

4.1.4. Spiro[4.5]decane 6b. Degassed solutions of **5b** (47 mg, >95% dr) in dry toluene (1.7 mL) were heated at 250 °C for 14 h in sealed tubes. The resulting mixtures were cooled to rt, and concentrated. Purification by silica-gel column chromatography (hexane/EtOAc=100/1) gave 40 mg (87% yield, >95% dr by ^1H NMR analysis) of **6b** as a colorless clear oil. Multigram-scale synthesis (4.839 g, 250 °C, 12 h) was also performed to afford 3.623 g of **6b** (75% yield, >95% dr by ^1H NMR analysis). The stereochemical assignment to **6b** was verified by the NOE experiments on the tricycle.[7] R_f 0.51 (hexane/EtOAc=90:10); ^1H NMR (400 MHz, $CDCl_3$) δ 5.52–5.40 (m, 2H), 4.13 (dd, J=9.5, 6.1 Hz, 1H), 2.27–2.20 (m, 4H), 2.06–1.87 (m, 3H), 1.81–1.62 (m, 2H), 0.892 (d, J=7.4 Hz, 3H), 0.777 (s, 9H), 0.00 (s, 3H), −0.0281 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.5, 131.1, 123.1, 66.0, 56.4, 40.0, 37.2, 33.2, 29.1, 25.8, 18.7, 17.9, 17.6, −4.1, −5.3; IR (neat, cm^{-1}) 1734; HR-ESIMS calcd for $C_{17}H_{30}O_2NaSi$: 317.1907, found: 317.1903.

4.1.5. Keto ester 11. To a solution of spiro[4.5]decane **6b** (3.456 g, 11.7 mmol) in EtOH (234 mL) was added 10% Pd/charcoal (2.49 g) under argon atmosphere. The argon atmosphere was replaced by H_2 from a double balloon, the reaction mixture was stirred at rt for 5 h. After the H_2 atmosphere was replaced by argon, the resulting mixture was filtrated through a pad of Celite, and the solvent was concentrated to give 3.529 g of crude **10** (quantitative yield, >95% dr by ^1H NMR analysis) as a colorless clear oil: R_f 0.51 (hexane/EtOAc=90:10); ^1H NMR (400 MHz, $CDCl_3$) δ 3.97 (dd, J=9.8, 4.2 Hz, 1H), 2.34–2.20 (m, 2H), 2.12–2.02 (m, 1H), 1.93–1.73 (m, 5H), 1.61–1.25 (m, 5H), 0.910 (d, J=7.3 Hz, 3H), 0.831 (s, 9H), 0.0310 (s, 3H), −0.0044 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 221.3, 68.9, 57.7, 39.7, 33.5, 31.7, 30.0, 28.8, 25.8, 19.1, 19.0, 18.0, 15.4, −4.1, −5.1; IR (neat, cm^{-1}) 1733; HR-ESIMS calcd for $C_{17}H_{32}O_2NaSi$: 319.2069, found: 319.2083. To a suspension of KH (4.83 g, 60 wt % in mineral oil, 72.3 mmol) in THF (68 mL) was added a solution of crude ketone **10** in THF (50 mL) and dimethyl carbonate (9.92 mL, 118 mmol) at rt. The resulting mixture was heated at 95 °C, and stirred at that temperature for 9 h 15 min. The resulting mixture was cooled to rt, and the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted two times with Et_2O. The combined organic layer was dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. Purification by silica-gel column chromatography (hexane/EtOAc=20:1) gave 3.591 g of keto ester **11** (86% yield for the two steps, a mixture of diastereomers by ^1H NMR analysis) as a pink oil: R_f 0.47, 0.41 (hexane/EtOAc=10:1); ^1H NMR (400 MHz, $CDCl_3$) δ 4.03–4.00 (m, 1H), 3.733 (s, 1.35H), 3.730 (s, 1.65H), 3.27 (t, J=2.5 Hz, 0.45H), 3.07 (t, J=2.4 Hz, 0.55H), 2.34–1.24 (m, 11H), 0.907 (d, J=7.3 Hz, 1.65H), 0.886 (d, J=7.3 Hz, 1.35H), 0.859 (s, 4.05H), 0.823 (s, 4.95H), 0.0464 (s, 1.65H), 0.0409 (s, 1.35H), 0.0342 (s, 1.65H), 0.0134 (s, 1.35H); IR (neat, cm^{-1}) 1753, 1727; HR-ESIMS calcd for $C_{19}H_{34}O_4NaSi$: 377.2124, found: 377.2141.

4.1.6. Hydroxy ketone 12. To a solution of keto ester **11** (50 mg, 0.141 mmol) in dry MeOH (1.4 mL) was added $NaBH_4$ (53 mg, 1.41 mmol) at 0 °C, then the resulting mixture was stirred at that temperature for 35 min. The reaction mixture was quenched with an aqueous solution of NH_4Cl. The aqueous layer was extracted two times with Et_2O. The combined organic layer was dried over Na_2SO_4, filtrated,

and concentrated under reduced pressure. Purification by silica-gel column chromatography (hexane/EtOAc=10:1) gave 35 mg of hydroxy ketone **12** (67% yield, a mixture of diastereomers by ^{1}H NMR analysis) and 9 mg of diol **13** (20% yield, a mixture of diastereomers by ^{1}H NMR analysis). Hydroxy ketone **12**: R_f 0.25, 0.20; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.11–4.07 (m, 1H), 3.91 (t, J=9.5 Hz, 1H), 3.712 (s, 0.9H), 3.706 (s, 2.1H), 2.88–2.78 (m, 1H), 2.41 (br d, J=9.5 Hz, 1H), 2.14–2.02 (m, 1H), 1.95–1.26 (m, 10H), 1.13 (d, J=7.3 Hz, 2.1H), 1.05 (d, J=7.1 Hz, 0.9H), 0.902 (s, 6.3H), 0.886 (s, 2.7H), 0.113 (s, 2.1H), 0.110 (s, 2.1H), 0.0537 (s, 0.9H), 0.0495 (s, 0.9H); HR-ESIMS calcd for $C_{19}H_{36}O_4NaSi$: 379.2275, found: 379.2272. Diol **13**: R_f 0.13, 0.063 (hexane/EtOAc=10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.08 (dd, J=11.5, 4.2 Hz, 1H), 3.87–3.42 (m, 4H), 2.59 (br d, J=11.2 Hz, 1H), 2.28–1.26 (m, 12H), 1.15 (d, J=7.3 Hz, 1.8H), 1.05 (d, J=7.6 Hz, 1.2H), 0.904 (s, 3.6H), 0.894 (s, 5.4H), 0.120 (s, 1.2H), 0.117 (s, 1.2H), 0.055 (s, 1.8H), 0.051 (s, 1.8H); HR-ESIMS calcd for $C_{18}H_{36}O_3NaSi$: 351.2325, found: 351.2317.

4.1.7. α,β-Unsaturated ester 14. To a solution of **12** (1.39 g, 3.90 mmol) in pyridine (40 mL) was added MsCl (2.7 mL, 35.1 mmol) at 0 °C, then the resulting mixture was stirred at that temperature for 15 h 40 min. The reaction mixture was quenched with H_2O. The aqueous layer was extracted two times with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4, filtrated, and concentrated under reduced pressure to give the crude mesylate. To a solution of the crude mesylate in CH_2Cl_2 (66.5 mL) was added DBU (5.0 mL, 33.00 mmol) at rt. After stirring for 2 h, the resulting mixture was concentrated under reduced pressure. Purification by silica-gel column chromatography (hexane/EtOAc=20:1) gave 1.227 g of α,β-unsaturated ester **14** (93% yield for the two steps, >95% dr by ^{1}H NMR analysis) as a colorless clear oil: R_f 0.63 (hexane/EtOAc=90:10); ^{1}H NMR (400 MHz, C_6D_6) δ 6.77 (t, J=2.0 Hz, 1H), 3.52–3.51 (m, 1H), 3.47 (s, 3H), 2.69 (dddd, J=16.8, 9.5, 5.1, 2.0 Hz, 1H), 2.61 (dddd, J=16.8, 8.6, 6.4, 2.0 Hz, 1H), 2.00 (ddd, J=13.5, 9.5, 6.1 Hz, 1H), 1.94–1.85 (m, 1H), 1.70 (ddd, J=13.5, 9.0, 5.0 Hz, 2H), 1.48–1.30 (m, 4H), 1.06–0.898 (m, 1H), 0.966 (s, 9H), 0.752 (d, J=6.8 Hz, 3H), 0.0079 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 165.2, 145.8, 137.9, 73.8, 60.2, 51.0, 35.5, 32.6, 31.4, 31.4, 31.4, 26.1, 20.3, 18.3, 16.7, −4.1, −5.0; IR (neat, cm^{-1}) 1712, 1635; HR-ESIMS calcd for $C_{19}H_{34}O_3NaSi$: 361.2169, found: 361.2172.

4.1.8. Ketone 16. To a solution of silyl ether **14** (43 mg, 0.128 mmol) in CH_3CN (3 mL) was added aqueous solution of HF (46–48%, 30 drops via a pipette) at rt, then the resulting mixture was stirred at that temperature for 1 h. The reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted two times with EtOAc. The combined organic layer was dried over $MgSO_4$, filtrated, and concentrated under reduced pressure to afford crude alcohol **15**: R_f 0.27 (hexane/EtOAc=75:25); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (t, J=1.9 Hz, 1H), 3.74 (s, 3H), 3.73–3.70 (m, 1H), 2.61 (dddd, J=16.9, 9.5, 5.4, 1.9 Hz, 1H), 2.56 (dddd, J=16.9, 8.8, 6.8, 1.9 Hz, 1H), 2.10 (ddd, J=13.5, 9.3, 6.9 Hz, 1H), 1.91–1.51 (m, 8H), 1.30–1.21 (m, 1H), 0.874 (d, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 146.0, 137.5, 72.3, 59.4, 51.5, 35.9, 31.1 (br s), 31.0, 30.6, 19.8, 16.2; IR (neat, cm^{-1}) 3454, 1717, 1634. To a solution of crude alcohol **15** in CH_2Cl_2 (6 mL) was added Dess–Martin periodinane (275 mg, 0.648 mmol) at rt, then the resulting mixture was stirred at that temperature for 30 min. The reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted two times with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by silica-gel column chromatography (hexane/EtOAc=85:15) gave 25 mg of ketone **16** (88% yield for the two steps, >95% dr by ^{1}H NMR analysis) as a colorless clear oil: R_f 0.41 (hexane/EtOAc=75:25); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (t, J=2.0 Hz, 1H), 3.74 (s, 3H), 2.66–2.40 (m, 5H), 2.08–2.03 (m, 1H), 1.88–1.62 (m, 5H), 0.940 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.2, 165.0, 141.2, 138.7, 69.8, 51.6, 42.8, 39.5, 30.9, 30.7, 28.6, 25.2, 16.8; IR (neat, cm^{-1}) 1713, 1630, 1299, 1260, 1213, 1154; HR-ESIMS calcd for $C_{13}H_{18}O_3Na$: 245.1148, found: 245.1144.

4.1.9. *exo*-Methylene 17. To a suspension of Zn (1.75 g, 26.8 mmol) in THF (20 mL) was added freshly distilled CH_2I_2 (1.19 mL, 14.74 mmol) at rt, then the resulting mixture was stirred at that temperature for 30 min. After the resulting mixture was cooled to 0 °C, to this mixture was added a solution of $TiCl_4$ in CH_2Cl_2 (1.0 M, 2.76 mL) at 0 °C, and stirred for 30 min. To this suspension was added a solution of **16** (318 mg, 1.42 mmol) in CH_2Cl_2 (17 mL) at rt, then the resulting mixture was stirred at that temperature for 30 min. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl, and Et_2O was added. The organic layer was washed with brine, dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. Purification by silica-gel column chromatography (hexane/EtOAc=50:1) gave 225 mg (72% yield) of **17** as a colorless clear oil: R_f 0.55 (hexane/EtOAc=90:10); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (t, J=1.8 Hz, 1H), 4.72 (br s, 1H), 4.57 (br s, 1H), 3.75 (s, 3H), 2.56 (td, J=7.6, 1.6 Hz, 2H), 2.27–2.17 (m, 2H), 2.05 (t, J=7.0 Hz, 2H), 1.82–1.43 (m, 5H), 0.916 (d, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 151.0, 148.0, 135.1, 107.8, 59.8, 51.3, 39.3, 34.7, 33.6, 30.3, 30.2, 22.8, 16.0; IR (neat, cm^{-1}) 3077, 2933, 1719, 1636; HR-ESIMS calcd for $C_{14}H_{20}O_2Na$: 243.1360, found: 243.1369.

4.1.10. (±)-α-Vetispirene (1). To a solution of *exo*-isomer **17** (10 mg) in benzene (2.5 mL) was added $TsOH\cdot H_2O$ (1.6 mg, 0.0084 mmol) at rt, then the resulting mixture was heated at 95 °C for 14 h. The resulting mixture was cooled to rt, and the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted two times with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$, filtrated, and concentrated under reduced pressure to afford 12 mg of crude *endo*-isomer. To a solution of crude *endo*-isomer in THF (2 mL) was added a solution of MeLi (0.98 M, 1 mL, 0.98 mmol) at 0 °C, then the resulting mixture was warmed to rt over 30 min. The reaction mixture was quenched with H_2O. The aqueous layer was extracted two times with Et_2O. The combined organic layer was dried over $MgSO_4$, filtrated, and concentrated under reduced pressure to afford crude *tert*-alcohol. To a solution of this *tert*-alcohol in

benzene (2 mL) was added camphorsulfonic acid (2.3 mg, 0.0099 mmol) at rt. The resulting mixture was warmed to 60 °C and stirred at that temperature for 1 h 20 min. The resulting mixture was cooled to rt, and the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted two times with hexane. The combined organic layer was washed with brine, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by silica-gel column chromatography (hexane) gave 8.6 mg of (±)-α-vetispirene (**1**) (87% yield for the three steps, >95% dr by ^1H NMR analysis) as a colorless clear oil: R_f 0.71 (hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 5.51 (br s, 1H), 5.40–5.38 (m, 1H), 4.91 (br s, 1H), 4.88 (br s, 1H), 2.60–2.46 (m, 2H), 2.09–1.93 (m, 3H), 1.94 (s, 3H), 1.83 (ddd, J=13.7, 9.0, 5.8 Hz, 1H), 1.70–1.61 (m, 2H), 1.56 (d, J=1.5 Hz, 3H), 1.46–1.38 (m, 1H), 0.859 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 140.3, 138.7, 132.7, 121.7, 112.3, 57.3, 37.8, 34.4, 32.3, 28.2, 23.8, 20.7, 19.9, 16.5; IR (neat, cm^{-1}) 3087, 2960, 1773, 1630, 1597, 1375, 1200, 1076, 881, 842, 796; HR-EIMS calcd for $C_{15}H_{22}$: 202.1721, found: 202.1717.

4.1.11. Ester 18. To a solution of α,β-unsaturated ester **16** (58 mg, 0.261 mmol) in EtOH (5.23 mL) was added 10% Pd/charcoal (56 mg) under argon atmosphere. The argon atmosphere was replaced by H_2 from a double balloon, the reaction mixture was stirred at rt for 2 h 20 min. After replaced by argon, the resulting mixture was filtrated through a pad of Celite, and the solvent was concentrated. Purification by silica-gel column chromatography (hexane/EtOAc=5:1) gave 57 mg (97% yield, 87% dr by ^1H NMR analysis) of **18**: R_f 0.32 (hexane/EtOAc=5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 3.67 (s, 3H), 2.74 (tt, J=8.7, 8.6 Hz, 1H), 2.42 (t, J=6.8 Hz, 2H), 2.34 (ddd, J=12.9, 7.6, 3.1 Hz, 1H), 2.12 (dd, J=13.7, 8.2 Hz, 1H), 1.98–1.67 (m, 7H), 1.60–1.46 (m, 2H), 0.940 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.5, 175.5, 60.6, 51.7, 44.0, 41.2, 38.3, 33.6, 33.1, 30.4, 29.1, 24.1, 16.0; IR (neat, cm^{-1}) 1735, 1704; HR-EIMS calcd for $C_{13}H_{20}O_3Na$: 247.1304, found: 247.1310.

4.1.12. (±)-Hinesol (2). To a solution of *exo*-isomer **19** (200 mg, 0.90 mmol) in benzene (45 mL) was added $TsOH\cdot H_2O$ (29.1 mg, 0.153 mmol) at rt, then the resulting mixture was heated at 95 °C for 12 h. The resulting mixture was cooled to rt, and the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted two times with CH_2Cl_2. The combined organic layer was dried over Na_2SO_4, filtrated, and concentrated under reduced pressure to afford the crude *endo*-isomer. To a solution of MeMgI (1 M, 15.7 mL) in dry Et_2O (120 mL) was added a solution of the crude *endo*-isomer in dry Et_2O (42 mL) at 0 °C, then the resulting mixture was stirred at that temperature for 30 min. The resulting mixture was allowed to warm to rt, then stirred at that temperature for 3 h. The reaction mixture was quenched with H_2O. The aqueous layer was extracted two times with Et_2O. The combined organic layer was washed with brine, dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. Purification by silica-gel column chromatography (hexane/EtOAc=15:1) gave 181 mg of (±)-hinesol (**2**) (89% yield for the two steps, >95% dr by ^1H NMR analysis) as a colorless clear oil: R_f 0.34 (hexane/EtOAc=5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 5.31 (br s, 1H), 2.00–1.90 (m, 3H), 1.79–1.25 (m, 13H), 1.20 (s, 6H), 0.922 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0, 121.7, 72.0, 51.4, 48.7, 36.7, 35.7, 33.3, 28.4, 28.0, 27.9, 27.7, 24.2, 19.9, 16.2; IR (neat, cm^{-1}) 3400, 1659; HR-ESIMS calcd for $C_{15}H_{26}ONa$: 245.1881, found: 245.1876.

4.1.13. (±)-Hinesolone (20). To a suspension of CrO_3 (360 mg, 3.60 mmol; need to dry by heating under reduced pressure just before use) in CH_2Cl_2 (5 mL) was added 3,5-dimethylpyrrazole (346 mg, 3.60 mmol) at −20 °C, then the resulting mixture was stirred at that temperature for 30 min. After allowing to warm to 0 °C, to this mixture was added a solution of **2** (40 mg, 0.180 mmol) in CH_2Cl_2 (4 mL), then the resulting mixture was stirred for 2.5 h. The resulting mixture was filtrated with a pad of Florisil. The filtrate was washed with 1 N HCl and brine. The combined organic layer was dried over Na_2SO_4, filtrated, and concentrated under reduced pressure. Purification by silica-gel column chromatography (hexane/EtOAc=2:1) gave 26 mg (60%) of **20** as a colorless needle: mp: 112.5–115.0 °C; R_f 0.13 (hexane/EtOAc=2:1); ^1H NMR (400 MHz, $CDCl_3$) δ 5.76 (s, 1H), 2.44 (dd, J=16.6, 4.2 Hz, 1H), 2.22 (dd, J=16.6, 9.8 Hz, 1H), 2.14–2.02 (m, 2H), 1.97 (s, 3H), 1.90–1.81 (m, 4H), 1.68–1.61 (m, 1H), 1.50 (dd, J=13.3, 12.3 Hz, 1H), 1.25 (s, 3H), 1.24 (s, 3H), 1.02 (d, J=6.8 Hz, 3H), 0.867 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.3, 168.2, 125.9, 71.4, 50.8, 50.3, 42.8, 37.1, 34.8, 31.7, 28.7, 28.5, 27.6, 20.8, 16.4; IR (KBr, cm^{-1}) 3410, 1653; HR-EIMS calcd for $C_{15}H_{24}O_2Na$: 259.1673, found: 259.1682.

4.1.14. (±)-β-Vetivone (3). A mixture of **20** (28 mg, 0.118 mmol) and NaOAc (19 mg, 0.236 mmol) in Ac_2O (1.18 mL) was heated to 140 °C for 2 h in a sealed tube, cooled to rt. The reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted two times with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4, filtrated, and concentrated under reduced pressure to afford a crude product. Purification by silica-gel column chromatography (hexane/EtOAc=83:17) gave 31 mg (93% yield) of the acetate as a colorless clear oil. To a solution of this acetate in Et_2O (2.19 mL) was added $BF_3\cdot OEt_2$ (0.104 mL, 0.822 mmol) at rt, then the mixture was stirred at that temperature for 6 h. The reaction mixture was quenched with a 5% aqueous solution of NaOH. The aqueous layer was extracted two times with Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. Purification by silica-gel column chromatography (hexane/EtOAc=83:17) gave 15 mg of (±)-β-Vetivone (**3**) and the inseparable *exo*-isomer [64% yield (84%: based on the recovered S.M.), **3**/*exo*-isomer=86:14 by ^1H NMR analysis] and recovered acetate (24%): R_f 0.66 (hexane/EtOAc=2:1); ^1H NMR (400 MHz, $CDCl_3$) δ 5.79 (br s, 1H), 5.76 (br s, 0.17H), 4.74 (br s, 0.34H), 2.94–1.94 (m, 9.5H), 2.66 (dd, J=16.9, 4.8 Hz, 1H), 2.54 (dd, J=12.0, 5.4 Hz, 0.17H), 1.92 (d, J=1.2 Hz, 0.5H), 1.90 (d, J=1.2 Hz, 3H), 1.76 (s, 0.5H), 1.67 (s, 3H), 1.63 (s, 3H), 1.04 (d, J=6.6 Hz, 0.5H), 0.971 (d, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.1, 167.15, 147.4, 133.8, 126.0, 122.6, 109.0, 51.1, 50.2, 47.0, 42.9, 42.9, 39.0, 38.1, 37.7, 35.4, 35.0, 32.1, 29.7, 29.4,

21.7, 21.3, 21.1, 21.0, 20.7, 16.6, 16.6; IR (KBr, cm^{-1}) 1668, 1613; HR-ESIMS calcd for $C_{15}H_{22}O_3Na$: 245.1562, found: 245.1564.

Acknowledgements

We thank Professor Istvan E. Markó (Université Catholique de Louvain) for providing the spectra of α-vetispirene. We also thank Shin-Etsu Chemical Co., Ltd, for the gift of silicone oil.

References and notes

1. For the structure of **1**, see: (a) Andersen, N. H.; Falcone, M. S.; Syrdal, D. D. *Tetrahedron Lett.* **1970**, *11*, 1759–1762; For total synthesis of (±)-**1**, see: (b) Yamada, K.; Aoki, K.; Nagase, H.; Hayakawa, Y.; Hirata, Y. *Tetrahedron Lett.* **1973**, *14*, 4967–4970; (c) Caine, D.; Boucugnani, A. A.; Chao, S. T.; Dawson, J. B.; Ingwalson, P. F. *J. Org. Chem.* **1976**, *41*, 1539–1544; (d) Ibuka, T.; Hayashi, K.; Minakata, H.; Ito, Y.; Inubushi, Y. *Can. J. Chem.* **1979**, *57*, 1579–1584; (e) Yan, T.-H.; Paquette, L. A. *Tetrahedron Lett.* **1982**, *23*, 3227–3230; (f) Balme, G. *Tetrahedron Lett.* **1985**, *26*, 2309–2310.
2. For the structure and first total synthesis of (±)-**2**, see: (a) Marshall, J. A.; Brady, S. F. *J. Org. Chem.* **1970**, *35*, 4068–4077; For total synthesis of this substance, see: (b) Nyström, J.-E.; Helquist, P. *J. Org. Chem.* **1989**, *54*, 4695–4698; For first total synthesis of (−)-**2**, see: (c) Du, Y.; Lu, X. *J. Org. Chem.* **2003**, *68*, 6463–6465.
3. For the structure and first total synthesis of **3**, see: (a) Marshall, J. A.; Johnson, P. C. *J. Chem. Soc., Chem. Commun.* **1968**, 391–392; For total synthesis of this substance, see: (b) Yamada, K.; Nagase, H.; Hayakawa, Y.; Aoki, K.; Hirata, Y. *Tetrahedron Lett.* **1973**, *14*, 4963–4966; For total synthesis of (−)-**3**, see: Posner, G. H.; Hamill, T. G. *J. Org. Chem.* **1988**, *53*, 6031–6035.
4. Some biologically active spirocyclic terpenes have been isolated. For lubimin, see: (a) Murai, A.; Sato, S.; Masamune, T. *J. Chem. Soc., Chem. Commun.* **1982**, 513–514; For gleenol, see: (b) Kurvyakov, P. I.; Gatilov, Y. V.; Yu, V.; Khan, V. A.; Dubovenko, Zh. V.; Pentegova, V. A. *Khim. Prir. Soedin.* **1979**, 164–168; For axisonitrile-**3**, see: (c) Di Blasio, B.; Fattorusso, E.; Magno, S.; Mayol, L.; Pedone, C.; Santacroce, C.; Sica, D. *Tetrahedron* **1976**, *32*, 473–478; For axenol, see: (d) Barrow, C. J.; Blunt, J. W.; Munro, M. H. G. *Aust. J. Chem.* **1988**, *41*, 1755–1761.
5. For reviews on the synthesis of spirocyclic compounds, see: (a) Krapcho, A. P. *Synthesis* **1974**, 383–419; (b) Sannigrahi, M. *Tetrahedron* **1999**, *55*, 9007–9071; (c) Pradhan, R.; Patra, M.; Behera, A. K.; Mishra, B. K.; Behera, R. K. *Tetrahedron* **2006**, 779–828.
6. For a recent example of the stereoselective total synthesis of the vetivane sesquiterpenes, see: Maulide, N.; Vanherck, J.-C.; Markó, I. E. *Eur. J. Org. Chem.* **2004**, 3962–3967 and references cited therein.
7. Nakazaki, A.; Miyamoto, H.; Henmi, K.; Kobayashi, S. *Synlett* **2005**, 1417–1420.
8. For reviews on Claisen rearrangement, see: (a) Rhoads, S. J.; Raulins, N. R. *Org. React.* **1975**, *22*, 1–252; (b) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423–1452; (c) Wipf, P. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 827–873; (d) Enders, D.; Knopp, M.; Sciffers, R. *Tetrahedron: Asymmetry* **1996**, *7*, 1847–1882; (e) Ito, H.; Taguchi, T. *Chem. Soc. Rev.* **1999**, *28*, 43–50; (f) Chai, Y.; Hong, S.-P.; Lindsay, H. A.; McFarland, C.; McIntosh, M. C. *Tetrahedron* **2002**, *58*, 2905–2928; (g) Hiersemann, M.; Abraham, L. *Eur. J. Org. Chem.* **2002**, 1461–1471; (h) Martin Castro, A. M. *Chem. Rev.* **2004**, *104*, 2939–3002.
9. For examples of synthesis of spirocycles by Claisen rearrangement of bicyclic dihydropyrans without a high-oxidation state functionality in the 4-position, see: (a) Ireland, R. E.; Aristoff, P. A. *J. Org. Chem.* **1979**, *44*, 4323–4331; (b) Shishido, K.; Hiroya, K.; Fukumoto, K.; Kametani, T. *Tetrahedron Lett.* **1986**, *27*, 971–974; (c) Brugnolotti, M.; Corsico Coda, A.; Desimoni, G.; Faita, G.; Gamba Invernizzi, A.; Righetti, P. P.; Tacconi, G. *Tetrahedron* **1988**, *44*, 5229–5242; (d) Desimoni, G.; Faita, G.; Gamba, A.; Righetti, P. P.; Tacconi, G.; Toma, L. *Tetrahedron* **1990**, *46*, 2165–2178; Very recently, an example of Claisen rearrangement in 4-*hydroxy*-2-(alkenyl)dihydropyran system to afford the spirocycle by the side reaction was reported, see: (e) Morency, L.; Barriault, L. *J. Org. Chem.* **2005**, *70*, 8841–8853.
10. Paterson, I.; Wren, S. P. *J. Chem. Soc., Chem. Commun.* **1993**, 1790–1792.
11. Collins, I.; Nadin, A.; Holmes, A. B.; Long, M. E.; Man, J.; Baker, R. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2205–2215.
12. Huang, S. L.; Omura, K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 3329–3331.
13. The diluted condition was essential for obtaining **6b** in good yield (0.1 mol/L: 87% yield; 0.3 mol/L: 46% yield). Multigram-scale synthesis was also performed to afford **6b** in 75% yield as a single diastereomer.
14. Büchi, G.; Powell, J. E., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 3126–3133.
15. Longer reaction time (2 h → 3 h) caused isomerization of the methyl group in **10**. In contrast, the Crabtree catalyst, $[Ir(cod)(PCy_3)(py)]PF_6$, gave no isomerized **10** in 80% yield with >95% dr. For this catalyst, see: Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655–2661.
16. Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1999**, *64*, 2564–2566.
17. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.
18. Hibino, J.; Okazoe, T.; Takai, K.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26*, 5579–5580.
19. Similar transformation has been reported, see Refs. 1b and 6.
20. Similar stereoselectivity was observed, see Ref. 2c.
21. Yoshioka, I.; Kimura, T. *Chem. Pharm. Bull.* **1965**, *13*, 1430–1434.
22. For similar allylic oxidation, see: (a) Dauben, W. G.; Lorber, M.; Fullerton, D. S. *J. Org. Chem.* **1969**, *34*, 3587–3592; (b) Hwu, J. R.; Wetzel, J. M. *J. Org. Chem.* **1992**, *57*, 922–928; (c) Blay, G.; Cardona, L.; Collado, A. M.; García, B.; Morcillo, V.; Pedro, J. R. *J. Org. Chem.* **2004**, *69*, 7294–7302.
23. Marshall's group also obtained a mixture of the regio isomers in the ratio of 89:11, see: Marshall, J. A.; Johnson, P. C. *J. Org. Chem.* **1970**, *35*, 192–196.