Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron 63 (2007) 5036–5041
Tetrahedron

Total synthesis of (−)-elegansidiol by using an abnormal Beckmann fragmentation of Hajos ketone oxime as a key step

Liya Cao, Jianwei Sun, Xinyan Wang, Rui Zhu, Haijian Shi and Yuefei Hu*

Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, PR China

Received 30 January 2007; revised 20 March 2007; accepted 21 March 2007
Available online 24 March 2007

Abstract—Abnormal Beckmann fragmentation of Hajos ketone oxime regioselectively forms of a chiral 1-oxygenated 2,2-dimethyl-4-methylene-cyclohexan skeleton. Using this transformation as a key step, the total synthesis of (−)-elegansidiol, an oxygenated mono-carbocyclic sesquiterpenoid, was achieved.

1. Introduction

(−)-Elegansidiol (**1**, Chart 1) is an oxygenated mono-carbocyclic sesquiterpenoid isolated from the aerial parts of *Santolina elegans*. Its structure was first established by Barrero[1] in 1999 and the absolute configuration was determined by Monti et al.[2] in 2001. Structurally, (−)-elegansidiol is a 3-substituted chiral 2,2-dimethyl-4-methylene-cyclohexanol and many known oxygenated mono-carbocyclic terpenoids,[3–6] such as achilleol A (**2**),[3] achilleol B (**3**),[4] and farnesiferol B (**4**),[5] can be considered as its derivatives.

Since the chiral 2,2-dimethyl-4-methylene-cyclohexanol unit also is a widely used building block in other terpenoidal syntheses[7] and its construction still remains a synthetic challenge,[7,8] (−)-elegansidiol (**1**) is a very good target for total synthesis.

Two different strategies have been employed to build the skeleton of 2,2-dimethyl-4-methylene-cyclohexanol in the total synthesis of elegansidiol (**1**). The synthesis of *rac*-elegansidiol (*rac*-**1**) was accomplished by using an intramolecular epoxy-ene cyclization,[1,7f] while (−)-elegansidiol (**1**) was synthesized starting from a chiral karahana lactone.[2,9] For efficient syntheses of oxygenated mono-carbocyclic terpenoids, there remains a great need to develop more practical methods and routes. Herein, we report a new approach toward the total synthesis of enantiopure (−)-elegansidiol (**1**), in which an abnormal Beckmann fragmentation of Hajos ketone (**5**) oxime was used as a key step to construct the chiral 2,2-dimethyl-4-methylene-cyclohexanol skeleton.

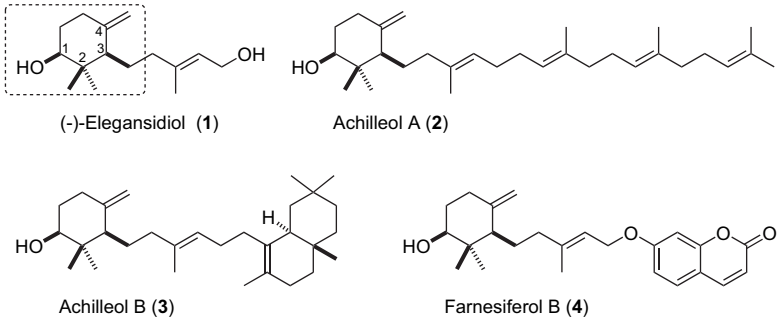


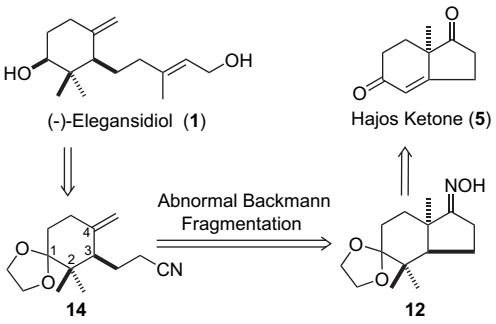
Chart 1.

Keywords: Total synthesis; (−)-Elegansidiol; Abnormal Beckmann fragmentation; Hajos ketone.
* Corresponding author. Tel.: +86 10 62795380; fax: +86 10 62771149; e-mail: yfh@mail.tsinghua.edu.cn

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.03.123

2. Results and discussion

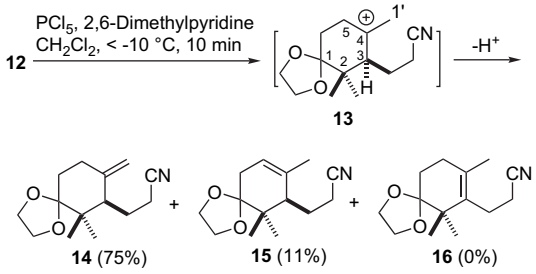
Enantiopure Hajos ketone (**5**) is a commercially available product that can also be easily prepared on a 100-g scale in the laboratory.[10] It has been employed as a versatile building block in the synthesis of many complex products,[11] in which its angular methyl group has to be an essential component in the target molecule. Thus, the application of Hajos ketone in organic synthesis has been seriously limited because no suitable method can efficiently modify or remove its angular methyl group. Recently, we have developed a novel abnormal Beckmann fragmentation procedure, which involves treatment of steroid-17-one oximes with TFA/$CH(OMe)_3$ in boiling THF for 2 h to convert the angular 18-Me into the corresponding methylene in moderate to high yields.[12] Therefore, the dimethyl derivative of Hajos ketone oxime (**12**) can be expected to give the desired 3-substituted chiral 2,2-dimethyl-4-methylene-cyclohexanone (**14**) under similar conditions. This reaction was featured in a proposed *retro*-synthetic route for (−)-elegansidiol (**1**) (Scheme 1).



Scheme 1.

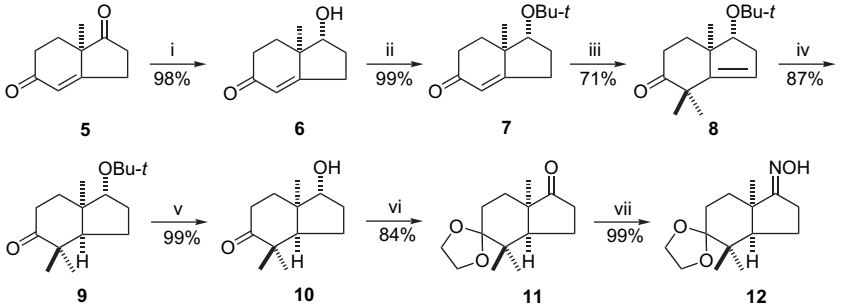
Compounds **6** and **7** were prepared according to previously reported procedures.[13] Although the preparation of compounds **8–11** has been reported in Ref. 14, our improved procedures were carried out under more convenient conditions resulting in products whose physical data differ from those in the references. By known procedures (Scheme 2),[14] the *cis*-ring fused product **9** was obtained by dimethylation of **7** followed by Pd–C catalyzed hydrogenation of **8**. After a highly efficient cleavage of *tert*-butyl ether **9** with aqueous HCl (lit.[14a] $BF_3{\cdot}Et_2O$, 100%), the ketone in product **10** was protected with ethylene glycol. Without purification, the crude ketal was oxidized by PCC in the presence of NaOAc to provide **11** in 84% yield over two steps (lit.[14a] Swern oxidation, −60 °C, 90%). When the mixture of **11**, $NH_2OH{\cdot}HCl$, and NaOAc in EtOH was refluxed for 2 h, the oxime **12** was obtained in almost quantitative yield.

Unfortunately, treatment of **12** with TFA/$CH(OMe)_3$ in boiling THF gave a mixture of three isomers (*exo*-**14**, and two inseparable *endo*-isomers **15** and **16**, Scheme 3) without any regioselectivity. Controlled experiments[15] revealed that this may result from the fact that intermediate **13** (a ring-opened intermediate of **12**) does not have a fixed conformation like that of the steroid. Thus, at high temperature, the proton elimination can occur from any of the three carbons connected to the carbonium[16] (**13**). Based on this analysis, we hypothesized that the regioselectivity of the abnormal Beckmann fragmentation of **12** may be improved by lowering the reaction temperature.



Scheme 3.

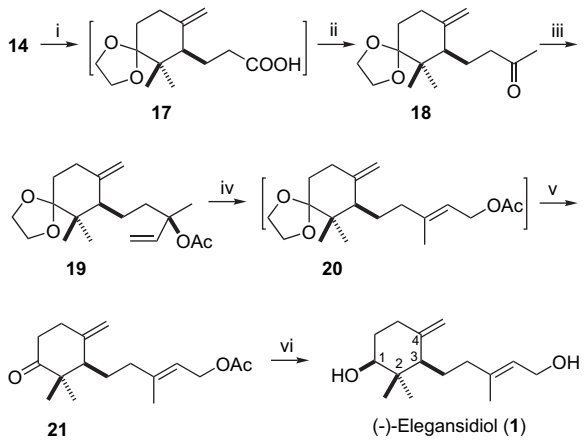
After many attempts, we found that Magnus' procedure[17] (a suspension of PCl_5 and 2,6-dimethylpyridine in Et_2O at room temperature) gave better regioselectivity providing **14** in 50% yield, but it did not work when the reaction temperature was dropped below 0 °C. By simple replacement of Et_2O with CH_2Cl_2, we obtained a transparent solution of PCl_5 and 2,6-dimethylpyridine in CH_2Cl_2. This new set of conditions was so powerful that the abnormal Beckmann fragmentation could be promoted efficiently even at −10 °C. When oxime **12** was used as a substrate, the desired isomer **14** was obtained in 75% isolated yield within 15 min at −10 °C. It was interesting to observe that the reaction at −10 °C resulted in the *endo*-isomer **15** (11%), but not the *endo*-isomer **16**. When the reaction was carried out at room temperature, both **15** and **16** were obtained in 20% and 13% yields, respectively. These temperature-controlled regioselectivities may be a result of the rigid conformation of **13** at −10 °C, which makes it difficult to form the *endo*-double bonds (for **15** and **16**). At low temperature,



Scheme 2. Reagents and conditions: (i) $NaBH_4$, EtOH, 0 °C, 30 min; (ii) $Me_2C{=}CH_2$, H_3PO_4, $BF_3.Et_2O$, CH_2Cl_2, rt, 1 h; (iii) *t*-BuOK, *t*-BuOH, MeI, rt, 45 min; (iv) H_2, Pd–C, EtOAc, rt, 30 min; (v) aq HCl, EtOH, reflux, 2 h; (vi) (a) $HOCH_2CH_2OH$, *p*-TsOH, benzene, reflux, 3 h; (b) PCC, NaOAc, CH_2Cl_2, rt, 2 h; (vii) $NH_2OH{\cdot}HCl$, NaOAc, EtOH, reflux, 2 h.

the reaction is more likely to be performed kinetically, which makes it easier to deprotonate at C1′ than C3 and C5 (Scheme 3).

As shown in Scheme 4, routine alkaline hydrolysis of **14** yielded the corresponding carboxylic acid **17**. Without purification, crude acid **17** was treated with CH_3Li to give methyl ketone **18** in 77% yield (over two steps).[18] It is worthy to note that a large excess of CH_3Li lowers the yield of **18** dramatically, while 2.5 equiv of CH_3Li gave the best result. The reaction of **18** with $H_2C{=}CHMgBr$ was performed in THF at 0 °C for 1 h. For easy separation, the crude product was directly converted into the acetate **19** as a 1:1 mixture of diastereomers in 75% yield (over two steps). The acetate **19** underwent an allylic rearrangement catalyzed by $PdCl_2(MeCN)_2$ to afford compound **20** as a mixture of *trans*/*cis* isomers in the ratio of 95:5.[19] By using our procedure for deprotection of an *O*,*O*-ketal,[20] **20** was deprotected with catalytic molecular iodide to provide **21** in 80% yield (over two steps) within 5 min. Reduction of the ketone in **21** with different reducing reagents, such as $NaBH_4$, DIBAL-H or K-Selectride, showed that $NaBH_4$ gave the best stereoselectivity (1*S*/1*R*=5.7:1.0) in 80% yield, while K-Selectride gave the worst stereoselectivity (1*S*/1*R*=1.0:1.0) in 90% yield. However, when compound **21** was treated with DIBAL-H at −78 °C for 1 h, both ketone and ester were reduced in one step in 95% yield with 1*S*/1*R* in the ratio of 5.0:1.0.



Scheme 4. Reagents and conditions: (i) KOH, aq EtOH, reflux, 12 h; (ii) CH_3Li, Et_2O, 0 °C, 1 h, 77% (**14**–**18**); (iii) (a) $CH_2{=}CH_2MgBr$, THF, 0 °C, 0.5 h; (b) Ac_2O, DMAP, Et_3N, THF, reflux, 24 h, 75%; (iv) $PdCl_2(MeCN)_2$, THF, rt, 1 h; (v) I_2, acetone, rt, 5 min, 80% (**19**–**21**); (vi) DIBAL-H, CH_2Cl_2, −78 °C, 1 h, 95%.

After careful column chromatography and two successive recrystallizations, pure (−)-elegansidiol (**1**) was obtained in 70% yield. The spectral data (IR, ^1H NMR, and ^{13}C NMR) of our synthetic sample were in full agreement with those of the literature.[1,2] Our synthetic sample is a white crystalline solid with a melting point of 79.5 °C (Et_2O–Petroleum ether) and $[\alpha]_D^{25}$ −22.9 (*c* 0.2, $CHCl_3$), which are in closer agreement to the data reported by Monti et al.[2] [mp 82 °C, $[\alpha]_D^{25}$ −14.8 (*c* 1.0, $CHCl_3$)]. Thus, we agree with the conclusion suggested by Monti that the natural elegansidiol (**1**) [lit.[1] colorless oil, $[\alpha]_D^{25}$ −4.0 (*c* 0.9, $CHCl_3$)] is partially racemic.

3. Conclusion

In conclusion, we have found that the transparent solution of PCl_5 and 2,6-dimethylpyridine in CH_2Cl_2 is a powerful reagent for the abnormal Beckmann fragmentation. It promoted the fragmentation of Hajos ketone oxime derivative at −10 °C to regioselectively form a 1-oxygenated 2,2-dimethyl-4-methylene-cyclohexane skeleton smoothly. By using this transformation as a key step, the total synthesis of (−)-elegansidiol, an oxygenated mono-carbocyclic sesquiterpenoid, was achieved.

4. Experimental

4.1. General methods

All melting points were determined on a Yanaco melting point apparatus and are uncorrected. IR spectra were recorded on a Nicolet FTIR 5DX spectrometer. The ^1H NMR and ^{13}C NMR spectra were recorded on a JEOL JNM-ECA 300 spectrometer in $CDCl_3$ with TMS as internal reference. The *J* values are given in Hertz. MS was recorded on a VG-ZAB-MS spectrometer with 70 eV. Optical rotations were recorded on a Perkin-Elmer 343 polarimeter. Elementary analysis data were obtained on a Perkin-Elmer-241C apparatus. Compounds **6** and **7** were prepared according to the previously reported procedures.[13]

4.1.1. (1*R*-*cis*)-1-*tert*-Butoxy-4,4,7a-trimethyl-1,2,4,6,7,7a-hexahydro-inden-5-one (8). To a solution of metal K (6 g, 154 mmol) in anhydrous *t*-BuOH (120 mL) was added dropwise a solution of **7** (10.1 g, 50 mmol) in anhydrous *t*-BuOH (30 mL) at room temperature under nitrogen. After the mixture was stirred for 15 min, MeI (42.6 g, 300 mmol) was added dropwise. The resultant mixture was stirred for another 45 min and then was quenched with saturated aqueous NH_4Cl at 0 °C. After most of *t*-BuOH was removed in vacuum, the residue was diluted with Et_2O and washed with water. The aqueous layer was extracted with Et_2O and combined organic layers were washed with brine and dried over Na_2SO_4. Removal of solvent gave crude product, which was purified by chromatography (PE/CH_2Cl_2/EtOAc=16:4:1) to give **8** (8.9 g, 71.2%) as colorless crystals. It had mp 44.0–44.5 °C, $[\alpha]_D^{25}$ −60.7 (*c* 1.0, $CHCl_3$) [lit.[14a] enantioisomer: 40–42 °C, $[\alpha]_D^{25}$ +49 (*c* 1.0, $CHCl_3$)]. IR: ν 2975, 2935, 1710, 1470, 1362 cm^{-1}; ^1H NMR: δ 1.18 (3H, s), 1.19 (9H, s), 1.22 (3H, s), 1.28 (3H, s), 1.61–1.93 (2H, m), 2.19–2.39 (3H, m), 2.62 (1H, m), 3.77 (1H, t, *J*=8.1), 5.42 (1H, s); ^{13}C NMR: δ 17.9, 23.8, 28.1, 28.7, 33.9, 35.0, 38.2, 46.2, 48.3, 72.7, 80.8, 120.0, 154.1, 215.3; MS *m*/*z* (%): 250 (M^+, 1), 110 (60), 57 (100); Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75%; H, 10.47%. Found: C, 76.97%; H, 10.39%.

4.1.2. (1*R*)-1-*tert*-Butoxy-4,4,7a-trimethyl-octahydro-inden-5-one (9). A stirred suspension of **8** (8.9 g, 35.6 mmol) and 10% Pd–C (890 mg) in EtOAc (40 mL) was hydrogenated at atmospheric pressure and room temperature until the absorption of hydrogen ceased completely (it was carried out on an atmospheric pressure hydrogenator). Then the catalyst was filtrated off and the solvent was evaporated. Removal of the solvent gave a white solid, which was purified

by chromatography (PE/CH_2Cl_2/EtOAc=25:5:1) to give **9** (7.8 g, 87%) as white needless crystals. It had mp 75–76 °C, $[\alpha]_D^{25}$ −51.08 (*c* 0.9, $CHCl_3$) [lit.[14a] enantioisomer: 72–73 °C, $[\alpha]_D^{25}$ +64 (*c* 1.0, $CHCl_3$)]. IR: *ν* 2968, 2875, 1703, 1474, 1360 cm^{-1}; ^1H NMR: *δ* 0.96 (3H, s), 1.10 (3H, s), 1.13 (9H, s), 1.18 (3H, s), 1.20–1.50 (1H, m), 1.60–1.72 (3H, m), 1.72–1.83 (3H, m), 2.11–2.24 (1H, m), 2.45–2.55 (1H, m), 3.45–3.49 (1H, t, *J*=6.5); ^{13}C NMR: *δ* 23.5, 24.6, 26.6, 26.7, 28.6, 31.9, 32.0, 34.7, 42.1, 47.1, 54.7, 72.6, 79.3, 217.3; MS *m*/*z* (%): 252 (M^+, 9), 196 (82), 71 (57), 57 (100); Anal. Calcd for $C_{16}H_{28}O_2$: C, 76.14%; H, 11.18%. Found: C, 75.46%; H, 10.89%.

4.1.3. (1*R*)-1-Hydroxy-4,4,7a-trimethyl-octahydro-inden-5-one (10). A mixture of **9** (7.8 g, 31 mmol) and aqueous HCl (6.0 M, 10 mL) in EtOH (70 mL) was refluxed for 2 h under nitrogen. Then the mixture was neutralized with solid Na_2CO_3 at 0 °C. After evaporation of EtOH, the residue was diluted by CH_2Cl_2. Then the organic layer was washed with water, brine, and dried over Na_2SO_4. Removal of the solvent gave crude product, which was purified by chromatography (PE/EtOAc=7:3) to give pure **10** (6.1 g, quantitative yield) as a yellowish oil. $[\alpha]_D^{25}$ −29.2 (*c* 1.2, $CHCl_3$) [lit.[14a] enantioisomer: $[\alpha]_D^{25}$ +22 (*c* 1.0, $CHCl_3$)]. IR: *ν* 3447, 2961, 2932, 1705, 1455, 1385 cm^{-1}; ^1H NMR: *δ* 0.89 (3H, s), 1.21 (3H, s), 1.22 (3H, s), 1.38–1.53 (1H, m), 1.66–1.73 (2H, m), 1.73–1.91 (1H, m), 1.91–2.03 (3H, m), 2.12–2.23 (1H, m), 2.54–2.66 (1H, m), 3.70–3.80 (1H, m); ^{13}C NMR: *δ* 23.2, 23.7, 26.8, 26.9, 31.1, 32.1, 34.5, 42.7, 47.0, 54.9, 81.1, 217.3; MS *m*/*z* (%): 196 (M^+, 16), 97 (60), 55 (51), 43 (66), 41 (100); Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43%; H, 10.27%. Found: C, 73.85%; H, 10.22%.

4.1.4. (7a*R*-*cis*)-5,5-Ethylenedioxy-4,4,7a-trimethyl-octahydro-inden-1-one (11). A mixture of **10** (2.1 g, 10.7 mmol), ethylene glycol (5 mL), and *p*-TsOH (100 mg) in benzene (80 mL) was refluxed with a Dean–Stark apparatus. Two hours later, it was quenched with saturated aqueous $NaHCO_3$. The resultant mixture was extracted with EtOAc and worked up as usual to give a yellow oil, which was used in the next step without further purification.

To a suspension of PCC (3.24 g, 15.1 mmol) and anhydrous NaOAc (2.47 g, 30.1 mmol) in CH_2Cl_2 (50 mL), was added dropwise a solution of the yellow oil in CH_2Cl_2 (10 mL). After the mixture was stirred for 2 h at room temperature, it was filtrated through a pad of silica gel. Removal of the solvent gave a crude product, which was purified by a chromatography (PE/EtOAc=5:1) to give **11** (2.1 g, 84%) as white crystals. It had mp 66–68 °C, $[\alpha]_D^{25}$ −20.98 (*c* 0.4, $CHCl_3$) [lit.[14a] enantioisomer: oil, $[\alpha]_D^{25}$ +15 (*c* 1.0, $CHCl_3$)]. IR: *ν* 2973, 2929, 2888, 1733, 1461, 1400, 1373 cm^{-1}; ^1H NMR: *δ* 0.89 (3H, s), 1.11 (3H, s), 1.19 (3H, s), 1.2–2.4 (9H, m), 3.92 (4H, m); ^{13}C NMR: *δ* 20.8, 21.1, 23.6, 25.6, 26.5, 27.1, 35.6, 40.0, 47.6, 54.6, 64.3, 65.1, 112.2, 222.5; MS *m*/*z* (%): 238 (M^+, 5), 99 (100); Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56%; H, 9.30%. Found: C, 70.30%; H, 9.24%.

4.1.5. (7a*R*,3a*S*)-5,5-Ethylenedioxy-4,4,7a-trimethyl-octahydro-inden-1-one oxime (12). The mixture of **11** (2.1 g, 8.8 mmol), $NH_2OH{\cdot}HCl$ (1.96 g, 28 mmol), and anhydrous NaOAc (3.2 g, 39 mmol) in EtOH (40 mL) was reflux for 2 h under nitrogen. After evaporation of the solvent, the residue was dissolved in H_2O (60 mL). The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with brine and dried over Na_2SO_4. Removal of the solvent gave product **12** (2.2 g, quantitative yield) as a white solid. It had mp 116–119 °C, $[\alpha]_D^{25}$ −6.76 (*c* 1.1, $CHCl_3$). IR: *ν* 3284, 2971, 2922, 2881, 1475, 1388 cm^{-1}; ^1H NMR: *δ* 0.64 (3H, s), 1.04 (3H, s), 1.23 (3H, s), 1.40–1.51 (1H, m), 1.51–1.7 (2H, m), 1.7–1.82 (1H, m), 1.82–2.01 (3H, m), 2.23–2.4 (1H, m), 2.58–2.72 (1H, m), 3.91 (4H, m), 8.69 (1H, s); ^{13}C NMR: *δ* 21.0, 23.2, 24.9, 25.0, 26.9, 27.0, 29.9, 40.5, 43.9, 55.9, 64.5, 65.0, 112.6, 171.4; MS *m*/*z* (%): 253 (M^+, 4), 99 (100), 86 (60), 41 (62); Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.37%; H, 9.15%; N, 5.53%. Found: C, 66.43%; H, 9.22%; N, 5.61%.

4.1.6. 3-[(7*R*)-6,6-Dimethyl-8-methylene-1,4-dioxa-spiro-[4,5]dec-7-yl]-propionitrile (14). To a stirred solution of PCl_5 (620 mg, 3.0 mmol) and 2,6-dimethylpyridine (0.7 mL, 7 mmol) in anhydrous CH_2Cl_2 (30 mL) was added compound **12** (500 mg, 2 mmol) dropwise in anhydrous CH_2Cl_2 (10 mL) at −10 °C under nitrogen. After stirring for 15 min, the mixture was poured into anhydrous Et_2O (100 mL). The produced white solids were filtrated off and the filtrate was washed with saturated aqueous Na_2CO_3 (50 mL), aqueous HCl (1.0 N, 50 mL), saturated aqueous Na_2CO_3 (50 mL), brine (50 mL), and dried over Na_2SO_4. Removal of the solvent gave crude product, which was purified by chromatography (PE/CH_2Cl_2/EtOAc=20:4:1) to give **14** (350 mg, 75%) as a colorless oil. $[\alpha]_D^{25}$ −18.4 (*c* 0.3, $CHCl_3$). IR: *ν* 3072, 2979, 2874, 2245, 1647, 1444, 1383 cm^{-1}; ^1H NMR: *δ* 0.89 (3H, s), 1.04 (3H, s), 1.55–1.72 (2H, m), 1.8–2.4 (7H, m), 3.8–4.0 (4H, m), 4.70 (1H, s), 4.91 (1H, s); ^{13}C NMR: *δ* 16.0, 19.5, 23.1, 24.8, 29.6, 31.5, 42.5, 53.3, 64.5, 65.2, 111.7, 111.9, 120.1, 145.5; MS *m*/*z* (%): 235 (M^+, 16), 99 (80), 86 (100), 41 (63); Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46%; H, 8.99%; N, 5.95%. Found: C, 71.32%; H, 9.22%; N, 5.67%.

4.1.7. 3-[(7*R*)-6,6,8-Trimethyl-1,4,-dioxa-spiro[4,5]dec-8-en-7-yl]-propionitrile (15). It was also obtained in 11% yield (50 mg) as a colorless oil. IR: *ν* 2977, 2879, 2243, 1732, 1383 cm^{-1}. ^1H NMR: *δ* 0.94 (s, 3H), 1.03 (s, 3H), 1.74 (s, 4H), 1.92 (s, 1H), 2.16 (s, 3H), 2.29–2.48 (m, 1H), 2.48–2.62 (m, 1H), 3.80–4.10 (m, 4H), 5.31 (s, 1H); ^{13}C NMR: *δ* 18.0, 19.4, 22.7, 24.2, 24.9, 33.9, 40.8, 50.3, 65.0, 65.3, 111.4, 120.3 (2C), 134.9; Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46%; H, 8.99%; N, 5.95%. Found: C, 71.50%; H, 9.03%; N, 5.66%.

4.1.8. 3-[(7*R*)-6,6-Dimethyl-8-methylene-1,4-dioxa-spiro[4,5]dec-7-yl]butan-2-one (18). A solution of **14** (1.81 g, 7.7 mmol) and KOH (5 g, 89 mmol) in H_2O (15 mL) and EtOH (20 mL) was refluxed for 12 h under nitrogen. Then it was acidified with aqueous HCl (1.0 M, 50 mL) at 0 °C. The mixture was extracted with CH_2Cl_2 and combined organic layers were washed with brine and dried over Na_2SO_4. Removal of the solvent gave crude product **17** (quantitative yield) as a yellow oil, which was used in the next step without further purification.

A stirred solution of **17** in dry ether (120 mL) was treated with CH_3Li (1.6 M THF solution, 13 mL, 20.8 mmol) at 0 °C under nitrogen. After another 1 h, it was quenched with saturated aqueous NH_4Cl. The mixture was extracted with ether and combined layers were washed with brine and dried over Na_2SO_4. Removal of the solvent gave crude product, which was purified by chromatography (PE/EtOAc=5:1) to give **18** (1.5 g, 77%) as a colorless oil. $[\alpha]_D^{25}$ −10.4 (*c* 1.0, $CHCl_3$). IR: *ν* 2953, 2880, 1716, 1642, 1445, 1359 cm^{-1}; ^1H NMR: *δ* 0.83 (3H, s), 1.00 (3H, s), 1.55–1.75 (2H, m), 1.75–1.95 (3H, m), 2.11 (3H, s), 2.11–2.19 (1H, m), 2.20–2.32 (2H, m), 2.38–2.52 (1H, m), 3.8–4.0 (4H, m), 4.56 (1H, s), 4.84 (1H, s); ^{13}C NMR: *δ* 19.3, 20.4, 23.9, 30.0, 30.8, 31.9, 42.9, 43.1, 52.7, 64.6, 65.2, 110.0, 112.3, 147.2, 209.4; MS *m/z* (%): 252 (M^+, 21), 209 (75), 99 (55), 43 (100); Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39%; H, 9.59%. Found: C, 71.50%; H, 9.65%.

4.1.9. Acetic acid 1-[2-[(7*R*)-6,6-dimethyl-8-methylene-1,4-dioxa-spiro[4,5]dec-7-yl]-ethyl]-1-methyl-allyl ester (19). To a stirred solution of **18** (1.17 g, 4.64 mmol) in dry THF (40 mL) was added dropwise vinylmagnesium bromide (1.0 M THF solution, 6 mL, 6 mmol) at 0 °C under nitrogen. After another 1 h, it was quenched with saturated aqueous NH_4Cl. Then the mixture was poured into water and extracted with ether. The combined organic layers were washed with brine and dried over Na_2SO_4. Removal of the solvent gave the crude allylic alcohols as a yellow oil, which was used in the next step without further purification.

The mixture of allylic alcohol, Ac_2O (7 mL), DMAP (400 mg), and Et_3N (20 mL) in THF (60 mL) was refluxed for 24 h. Then the reaction mixture was diluted with Et_2O at room temperature. The resultant mixture was washed with aqueous HCl (1.0 M), saturated aqueous $NaHCO_3$, brine, and dried over Na_2SO_4. Removal of the solvent gave crude product, which was purified by chromatography (PE/EtOAc=10:1) to give a diastereomeric mixture **19** in the ratio of 1:1 (970 mg, 75%) as a yellow oil. IR: *ν* 3083, 2977, 2879, 1736, 1646, 1446, 1368 cm^{-1}; ^1H NMR (major isomer): *δ* 0.84 (s, 3H), 0.98 (s, 3H), 1.45–1.51 (m, 2H), 1.52 (s, 3H), 1.58–1.61 (m, 3H), 1.60–1.97 (m, 2H), 2.01 (s, 3H), 2.04–2.30 (m, 2H), 3.83–4.00 (m, 4H), 4.60 (s, 1H), 4.84 (s, 1H), 5.01 (d, 1H, *J*=11.0), 5.03 (d, 1H, *J*=17.5), 5.97 (dd, 1H, *J*=17.5, 11.0); ^{13}C NMR (major isomer): *δ* 19.1, 19.8, 22.2, 23.2, 23.46 (1*R* or 1*S*), 23.57 (1*R* or 1*S*), 31.4, 31.9, 39.13 (*R* or *S*), 39.22 (*R* or *S*), 43.4, 52.7, 64.6, 65.1, 83.20 (*R* or *S*), 83.30 (*R* or *S*), 109.4, 112.4, 112.9, 141.93 (*R* or *S*), 142.05 (*R* or *S*), 147.3, 169.9; Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.77%; H, 9.38%. Found: C, 70.81%; H, 9.57%.

4.1.10. Acetic acid (2*E*)-5-((1*R*)-2,2-dimethyl-6-methylene-3-oxo-cyclohexyl)-3-methylpent-2-enyl ester (21). The mixture of **19** (800 mg, 2.48 mmol) and $PdCl_2(MeCN)_2$ (80 mg) in dry THF (15 mL) was stirred for 1 h at room temperature under nitrogen. Then the reaction mixture was diluted with ether and was filtrated through a pad of silica gel. Removal of the solvent gave crude product **20** as a yellow oil, which was utilized for the next step without further purification.

The mixture of **20** and I_2 (65 mg, 0.26 mmol) in acetone (10 mL) was stirred at room temperature for 5 min. Then the reaction was quenched with 5% aqueous solution of $Na_2S_2O_3$. After the mixture was poured into water, it was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. Removal of the solvent to crude product, which was purified by chromatography (PE/EtOAc=10:1) to give **21** (550 mg, 80%) as a yellow oil. IR: *ν* 3072, 2958, 1738, 1708, 1444, 1366 cm^{-1}; ^1H NMR: *δ* 1.05 (s, 3H), 1.10–1.27 (m, 1H), 1.20 (s, 3H), 1.60–2.20 (m, 6H), 1.63 (s, 3H), 2.06 (s, 3H), 2.15–2.72 (m, 4H); ^{13}C NMR: *δ* 16.5, 21.0, 21.2 (*Z*-), 21.3 (*E*-), 25.4, 27.2, 30.6, 37.3, 37.6, 49.0, 56.0, 61.3, 113.4, 118.5, 141.8, 144.7, 171.1, 215.2; HREI MS *m/z*: 278.1894 (calcd. for $C_{17}H_{26}O_3$, 278.1882).

4.1.11. (1*S*,3*R*)-3-[(3*E*)-5-Hydroxy-3-methylpent-3-enyl]-2,2-dimethyl-4-methylenecyclohexanol (elegansidiol, 1). To a stirred solution of **21** (180 mg, 0.65 mmol) in CH_2Cl_2 was added a solution of DIBAL-H in hexane (1.0 M, 6.5 mL, 6.5 mmol) at −78 °C. One hour later, the reaction was quenched by saturated aqueous solution of NH_4Cl. The resultant mixture was extracted with CH_2Cl_2 and combined organic layers were washed with H_2O, brine, and dried over Na_2SO_4. Removal of the solvent yielded crude product, which was purified by chromatography (CH_2Cl_2/EtOAc=7:3) to give a mixture of (−)-elegansidiol (**1**) and its isomers (146 mg, 95%) as a white solid. After it was recrystallized from Et_2O–PE twice, pure elegansidiol (**1**) (108 mg, 70%) was obtained as white crystals. It had mp 79.5 °C, $[\alpha]_D^{25}$ −22.9 (*c* 0.2, $CHCl_3$) [lit.[1] oil, $[\alpha]_D^{25}$ −4.0 (*c* 0.9, $CHCl_3$); lit.[2] mp 82 °C, $[\alpha]_D^{25}$ −14.8 (*c* 1.0, $CHCl_3$)]. IR: *ν* 3566, 3292, 3078, 2939, 1647, 1024, 890 cm^{-1}; ^1H NMR: *δ* 0.74 (s, 3H), 1.04 (s, 3H), 1.12 (t, 1H, *J*=5.2, –OH, disappears after addition of D_2O), 1.34 (d, 1H, *J*=5.5, –OH, disappears after addition of D_2O), 1.44–1.60 (m, 2H), 1.60–1.67 (m, 2H), 1.69 (s, 3H), 1.78–1.92 (m, 2H), 1.93–2.09 (m, 1H), 2.09–2.21 (m, 1H), 2.30–2.40 (dt, 1H, *J*=13.1, 4.8), 3.42 (dd, 1H, *J*=9.6, 4.1, a multiplet before the addition of D_2O), 4.16 (d, 2H, *J*=6.9, a triplet before the addition of D_2O), 4.61 (s, 1H), 4.89 (s, 1H), 5.41 (t, 1H, *J*=6.9); ^{13}C NMR: *δ* 15.7, 16.3, 23.6, 25.9, 32.2, 32.8, 38.5, 40.5, 51.2, 59.4, 77.2, 108.5, 123.2, 140.2, 147.2; MS *m/z* (%): 220 (M^+−18, 4), 205 (8), 187 (8), 159 (5), 135 (10), 107 (15), 96 (26), 81 (24), 44 (13), 43 (100), 41 (93); Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58%. H, 10.99%. Found: C, 75.61%; H, 10.93%.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (20025204) and the Key Subject Foundation from Beijing Department of Education (XK100030514).

Supplementary data

^1H NMR and ^{13}C NMR spectra for products **11–12**, **14**, **18–19**, **21** and **1** were supported. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.03.123.

References and notes

1. Barrero, A. F.; Alvarez-Manzaneda, E. J.; Mar Herrador, M.; Alvarez-Manzaneda, R.; Quilez, J.; Chahboun, R.; Linares, P.; Rivas, A. *Tetrahedron Lett.* **1999**, *40*, 8273–8276.
2. Audran, G.; Galano, J. M.; Monti, H. *Eur. J. Org. Chem.* **2001**, 2293–2296.
3. Barrero, A. F.; Alvarez-Manzaneda, E. J.; Alvarez-Manzaneda, R. *Tetrahedron Lett.* **1989**, *30*, 3351–3352.
4. Barrero, A. F.; Alvarez-Manzaneda, E. J.; Alvarez-Manzaneda, R.; Arseniyadis, S.; Guittet, E. *Tetrahedron* **1990**, *46*, 8161–8168.
5. Caglioti, L.; Naef, H.; Arigoni, D.; Jeger, O. *Helv. Chim. Acta* **1959**, *42*, 2557–2570.
6. (a) Amico, V. *Phytochemistry* **1995**, *39*, 1257–1279; (b) Alberto Marco, J.; Sanz-Cervera, J. F.; Morante, M. D.; Garcia-Lliso, V.; Valles-Xirau, J.; Jakupovic, J. *Phytochemistry* **1996**, *41*, 837–844.
7. (a) Yajima, A.; Saitou, F.; Sekimoto, M.; Maetoko, S.; Nukada, T.; Yabuta, G. *Tetrahedron* **2005**, *61*, 9164–9172; (b) Justicia, J.; Rosales, A.; Bunuel, E.; Oller-Lopez, J. L.; Valdivia, M.; Haidour, A.; Enrique Oltra, J.; Barrero, A. F.; Cardenas, D. J.; Cuerva, J. M. *Chem.—Eur. J.* **2004**, *10*, 1778–1788; (c) Yajima, A.; Saitou, F.; Sekimoto, M.; Maetoko, S.; Yabuta, G. *Tetrahedron Lett.* **2003**, *44*, 6915–6918; (d) Palombo, E.; Audran, G.; Monti, H. *Tetrahedron Lett.* **2003**, *44*, 6463–6464; (e) Beszant, S.; Giannini, E.; Zanoni, G.; Vidari, G. *Tetrahedron: Asymmetry* **2002**, *13*, 1245–1255; (f) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Rivas, R.; Palomino, P. L. *Tetrahedron* **2000**, *56*, 6099–6113; (g) Vidari, G.; Pazzi, N.; Lanfranchi, G.; Serra, S. *Tetrahedron Lett.* **1999**, *40*, 3067–3070; (h) Vidari, G.; Lanfranchi, G.; Masciaga, F.; Moriggi, J.-D. *Tetrahedron: Asymmetry* **1996**, *7*, 3009–3020; (i) Vidari, G.; Lanfranchi, G.; Sartori, P.; Serra, S. *Tetrahedron: Asymmetry* **1995**, *6*, 2977–2990.
8. (a) Justicia, J.; Enrique Oltra, J.; Cuerva, J. M. *J. Org. Chem.* **2005**, *70*, 8265–8272; (b) Justicia, J.; Enrique Oltra, J.; Cuerva, J. M. *Tetrahedron Lett.* **2004**, *45*, 4293–4296; (c) Justicia, J.; Enrique Oltra, J.; Cuerva, J. M. *J. Org. Chem.* **2004**, *69*, 5803–5806; (d) Xiong, Q.; Zhu, X.; Wilson, W. K.; Ganesan, A.; Matsuda, S. P. T. *J. Am. Chem. Soc.* **2003**, *125*, 9002–9003; (e) Meyer, M. M.; Xu, R.; Matsuda, S. P. T. *Org. Lett.* **2003**, *4*, 1395–1398; (f) Hasserodt, J.; Janda, K. D.; Lerner, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 40–45.
9. Audran, G.; Galano, J. M.; Monti, H. *Tetrahedron* **2000**, *56*, 7477–7481.
10. Hajos, Z. G.; Parrish, D. R. *Org. Synth.* **1984**, *63*, 26–36.
11. (a) Lepage, O.; Deslongchamps, P. *J. Org. Chem.* **2003**, *68*, 2183–2186; (b) Yang, Z.; Shannon, D.; Truong, V. L.; Deslongchams, P. *Org. Lett.* **2002**, *4*, 4693–4696; (c) Daniewsk, A. R.; Liu, W. *J. Org. Chem.* **2001**, *66*, 626–628; (d) Renneberg, D.; Pfander, H.; Leumann, G. J. *J. Org. Chem.* **2000**, *65*, 9069–9079; (e) Gool, M. V.; Zhao, X. Y.; Sabbe, K.; Vandewalle, M. *Eur. J. Org. Chem.* **1999**, 2241–2248; (f) Paquette, L. A.; Wang, T. Z.; Sivik, M. R. *J. Am. Chem. Soc.* **1994**, *116*, 2665–2666; (g) Daniewsk, A. R.; Kiegiel, J. *J. Org. Chem.* **1988**, *53*, 5534–5535; (h) Sugimura, T.; Paquette, L. A. *J. Am. Chem. Soc.* **1987**, *109*, 3017–3024.
12. (a) Wang, C.; Rath, N. P.; Covey, D. F. *Tetrahedron Lett.* **2006**, *47*, 7837–7839; (b) Wang, C.; Jiang, X.; Shi, H.; Lu, J.; Hu, Y.; Hu, H. *J. Org. Chem.* **2003**, *68*, 4579–4581.
13. (a) Rychnovsky, C. F.; Mickus, D. E. *J. Org. Chem.* **1992**, *57*, 2732–2736; (b) Micheli, R. A.; Hajos, Z. G.; Cohen, N.; Parrish, D. R.; Portland, L. A.; Sciamanna, W.; Scott, M. A.; Wehrli, P. A. *J. Org. Chem.* **1975**, *40*, 675–681.
14. (a) Arseniyadis, S.; Yashunsky, D. V.; Pereira de Freitas, R.; Dorado, M. M.; Potier, P. *Tetrahedron* **1996**, *52*, 12443–12458; (b) Arseniyadis, S.; Rodriguez, R.; Munoz Dorado, M.; Brondi Alves, R.; Ouazzani, J.; Ourisson, G. *Tetrahedron* **1994**, *50*, 8399–8426.
15. Shi, H. Ph.D. Thesis, Nanjing University, China, 2004.
16. Trost, B. M.; Fleming, I. *Comprehensive Organic Synthesis*; Pergamon: Oxford, 1991; Vol. 6, p 1066.
17. Magnus, P.; Waring, M. J.; Ollivier, C.; Lynch, V. *Tetrahedron Lett.* **2001**, *42*, 4947–4950.
18. (a) Magatti, C. V.; Kaminski, J. J.; Rothberg, I. *J. Org. Chem.* **1991**, *56*, 3102–3108; (b) Maurer, P. J.; Knudsen, C. G.; Palkowitz, A. D.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 325–332.
19. Oehlschlager, A. C.; Misher, P.; Dhami, S. *Can. J. Chem.* **1984**, *62*, 791–797.
20. Sun, J.; Dong, Y.; Cao, L.; Wang, X.; Wang, S.; Hu, Y. *J. Org. Chem.* **2004**, *69*, 8932–8934.