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TETRAHEDRON: *ASYMMETRY*

Total synthesis of optically active liverwort sesquiterpenes, trifarienols A and B, using phenylethylamine as a chiral auxiliary

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Abstract

The imine of (*rac*)-2,3-dimethylcyclohexanone **10a** with (*S*)-(−)-phenylethylamine was reacted with methyl acrylate to yield methyl (1′*S*,6′*R*)-3-(1′,6′-dimethyl-2′-oxocyclohexyl)propanoate **4a** in 26% (97% ee) after hydrolysis. When (2*RS*,3*R*)-2,3-dimethylcyclohexanone **10b** was used, the same product **4b** was obtained in 59% yield (>99.5% ee) after hydrolysis. When (2*RS*,3*R*)-2,3-dimethylcyclohexanone **10b** and (*R*)-(+)-phenylethylamine were used, the reaction underwent in only 5% yield, the products being **4c**, **12**, **13**, **14**, and **15**. Thus, the reaction of **3b** with methyl acrylate is a matched case, while that of **3c** is a mismatched case. These phenomena are explained by the nonbonded interaction of methyl acrylate with chiral phenylethylamine and the methyl group at the 6′-position of the cyclohexanone ring in the transition state. The propanoate product **4b** was successfully transformed into liverwort sesquiterpene (+)-trifarienol A **1** and (−)-trifarienol B **2** in 10 steps. We have developed an HPLC method to determine the ees of 2,2-disubstituted and 2,2,3-trisubstituted cyclohexanones using the corresponding pentafluorophenyl esters.

1. Introduction

2,2-Disubstituted chiral cyclohexanones can be easily prepared using the homochiral phenylethylamine methodology developed by Pfau and d'Angelo.[1] This method is widely applied to total syntheses of natural products.[2] We have previously used this reaction with methyl propiolate to prepare α,β-unsaturated keto ester.[3] This reaction was used for 2-methylcyclopentanone and the product was converted into herbertene.[3] Trifarienols A **1** and B **2** have been found in liverworts[4] and they belong to an unusual skeleton, trifarane.[4,5] In the trifarane class, only upial[6] is known other than **1** and **2**. Recently, Huang and Forsyth have reported a total synthesis of racemic **1** and **2** by cyclization using mercury techniques.[7] We planned to synthesize these compounds as optically active forms using phenylethylamine methodologies. Vicinal dimethyl groups are usually constructed by alkylation of the thermodynamically

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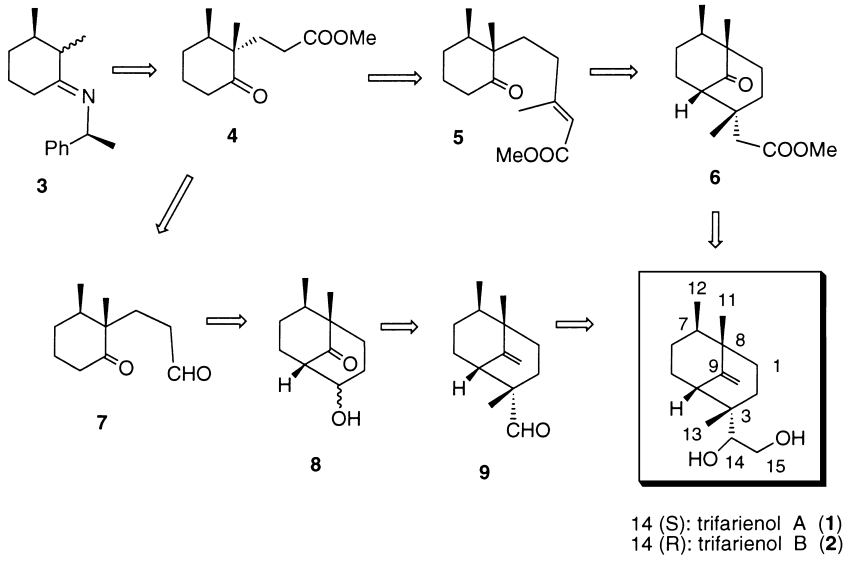
more stable enolate.[8,9] However, it is not always easy to control the stereochemistry.[9] We have studied the details of the reaction between the phenylethylimine of 2,3-dimethylcyclohexanone and methyl acrylate and found that the use of (2*RS*,3*R*)-dimethylcyclohexanone **10b** and (*S*)-(−)-phenylethylamine gives the best results. The keto aldehyde **7** derived from keto ester **4** may be cyclized into ketol **8** by aldol reaction (Scheme 1). One more carbon could be introduced after the formyl group was added. Then conversion of aldehyde **9** into trifarienols A **1** and B **2** constitutes the first total synthesis of optically-active natural products. Alternatively, intramolecular 1,4-cyclization of ester **5** into ketone **6** was unsuccessful. We now report these results in detail.



Scheme 1.

2. Results and discussion

The imine prepared from (*S*)-(−)-phenylethylamine and (*rac*)-2,3-dimethylcyclohexanone **10a** was subjected to reaction with methyl acrylate without solvent for a week. Slow reaction afforded the desired keto ester **4a** in 26% yield (from **10a**) after hydrolysis (AcOH:H_2O=9:1). The stereochemistry and conformation of **4a** were determined by careful analysis of the 600 MHz 2D NMR spectra as well as decoupling experiments. When the *sec*-methyl group was decoupled, the proton at 6′-position appeared as double doublets, which is in axial orientation. The NOEs were observed between H-6′ and H-4′α, and between Me-1′ and H-5′β, respectively, suggesting the stereochemistry as well as the conformation (Fig. 1).[10] The absolute configuration of **4** was established as shown in Fig. 1 by the CD spectrum, because the (−)-Cotton effect was observed at 297.5 nm.

In this reaction a considerable amount of **10a** (37%) was recovered. This disappointingly low yield should be mainly due to the fact that a half amount of **3a** does not give **4a** (maximum yield 50%).[11] Therefore, we next prepared (2*RS*,3*R*)-2,3-dimethylcyclohexanone **10b** from (−)-pulegone in two steps.[12] Then the similar reaction was carried out to isolate keto ester **4b** in 59% yield from **10b** after hydrolysis. Both the diastereomer excess and enantiomer excess were determined by HPLC and GC techniques applied to the corresponding pentafluorophenyl ester **11** derived from **4**. When ester **11a** was analyzed by GC (DB-17), the main peak was detected at 25.5 min with the small one at 24.7 min corresponding to the

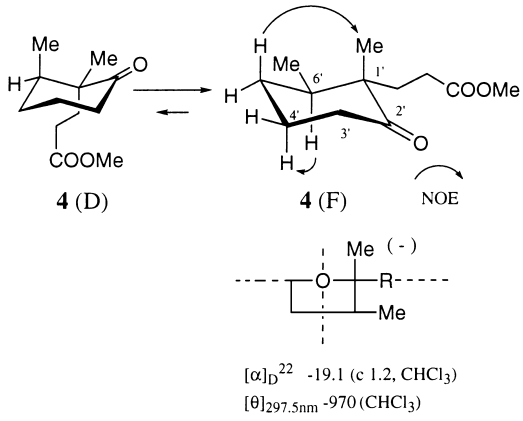
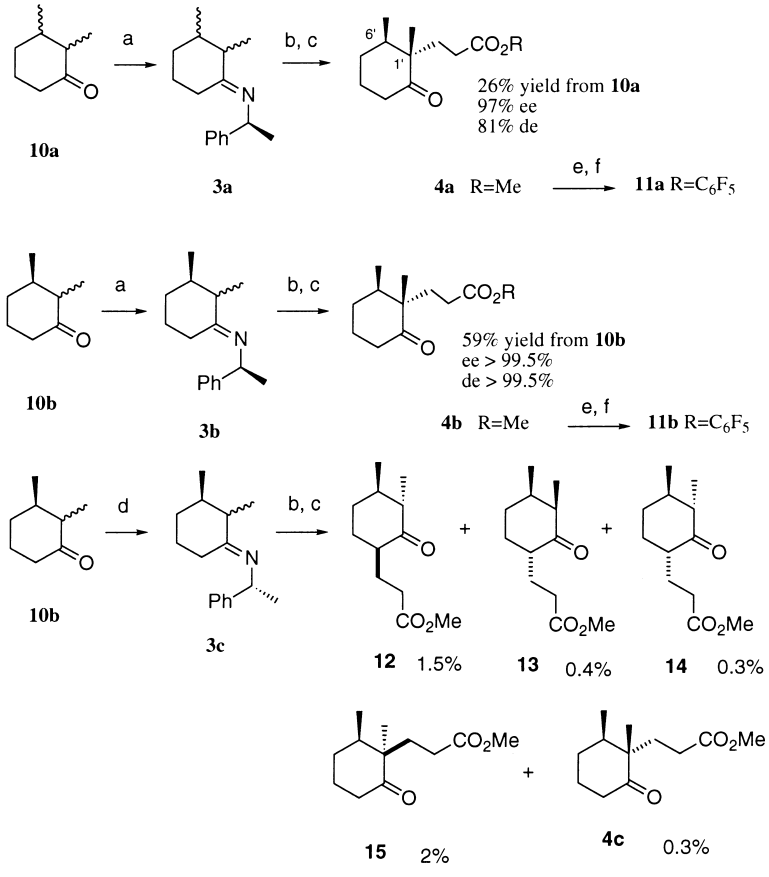


Figure 1. The configuration, conformation and absolute configuration of **4**

diastereoisomers, being 81% de. In the case of HPLC (Chiralcel OD-H), three peaks were detected (peak 1: 7.2 min; peak 2: 8.4 min; peak 3: 10.4 min), the fastest moving one (peak 1) being the enantiomer of **11a**, (1′*R*,6′*S*)-isomer, the second (peak 2) (1′*S*,6′*R*)-isomer **11a**, and the third (peak 3) the mixture of diastereoisomers, (1′*S*,6′*S*)- and (1′*R*,6′*R*)-isomers, being calculated as 97% ee.[13] However, **11b** displayed only one peak in the GC at 25.5 min, being >99.5% de. The HPLC analysis of **11b** showed only one peak of (1′*S*,6′*R*)-isomer at 8.4 min, being >99.5% ee.[13] This combination of the GC and HPLC is very effective to determine both de and ee. The phenyl ester, unlike the pentafluorophenyl ester, did not give a good separation. Use of the pentafluorophenyl ester is essential and this method can also be applied to determine the ee of methyl 3-(1′-methyl-2′-oxo-cyclohexyl)propanoate.[14]

When the imine prepared from (*R*)-(+)-phenylethylamine and **10b** was treated with methyl acrylate, conversion was very low and the isolated products were **4c** (0.3%), **12** (1.5%), **13** (0.4%), **14** (0.3%), and **15** (2%), respectively. This is a mismatched case and the transition state disfavored the desired addition reaction (Scheme 2), which was indicated by the calculation.[15] The reaction of **3b** with methyl acrylate should be a matched case. These phenomena are explained by the nonbonded interaction of methyl acrylate with the chiral phenylethylamine and the methyl group at the 6′-position of the cyclohexanone ring in the transition state.[15]

The keto ester **4b** with high enantiomeric excess was reduced ($LiAlH_4$) and reoxidized (DMSO, oxalyl chloride) to keto aldehyde **7** in 91% yield (Scheme 3). Intramolecular aldol cyclization was induced by 5% KOH in MeOH to afford a mixture of ketol **8a** and **8b** (1:1) in 67% yield. The stereochemistry at the 3-position of compound **8** was tentatively assigned. Because this position is later oxidized into ketone, the synthesis was carried out without separation of the diastereoisomers. Although the olefination of the carbonyl group was unsuccessful with the Wittig reagent ($Ph_3P{=}CH_2$), the Tebbe reagent[16] afforded the desired olefin **16** (**16a**:**16b**=1:1) in 71% yield. The Swern oxidation of **16** gave the ketone **17** as a single isomer. The Horner–Emmons olefination of **17** and separation of the isomers (by HPLC) gave **20E** as the major product (*E*:*Z*=81:19), whose spectral data was compared with those of Huang and Forsyth.[7] The ^1H NMR spectrum of **20E** corresponded to the major peaks of that of Huang and Forsyth.[7] We could isolate **20E** as a single isomer by HPLC and this constitutes the formal total synthesis of trifarienols A and B.[7] We have further developed our synthetic route to complete the synthesis of optically active trifarienols A and B. The Wittig reaction with $Ph_3P{=}CHOMe$ followed by hydrolysis yielded aldehyde **18** as a mixture of two diastereoisomers (α:β=1:1.5). Hydrolysis of the Wittig product was somewhat complicated and the yield was not good, presumably due to decomposition of the aldehyde produced. Methylation using *t*-BuOK and MeI gave the desired one-carbon homologated aldehyde **9** as a result of attack from the less hindered side of the molecule. The β orientation of the methyl group was established by the NOE between



Scheme 2. (*S*)-(−)-1-Phenylethylamine, TsOH, PhH, reflux, 1 day; (b) CH_2=$CHCO_2Me$, rt, 7 days; (c) AcOH:H_2O (9:1), 60, 1 h; (d) (*R*)-(+)-phenylethylamine, TsOH, PhH, reflux, 1 day; (e) KOH, H_2O–MeOH; (f) EDCI, C_6F_5OH, CH_2Cl_2

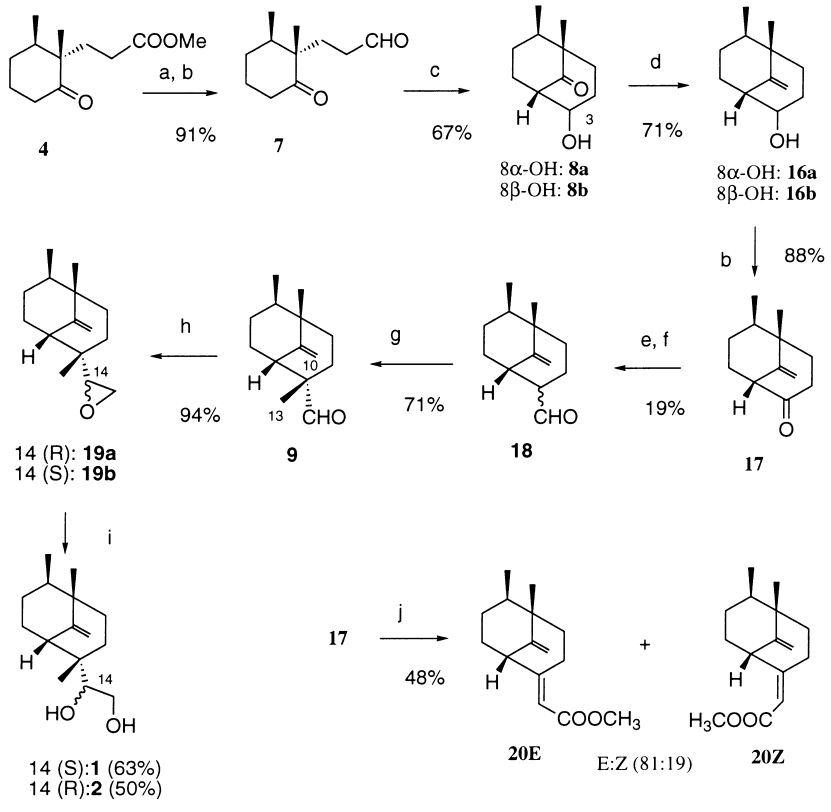
H-13 and H-10. The final steps were accomplished by epoxidation using trimethylsulfonium iodide[17] and opening of this ring into natural products. The diastereoisomers of epoxides **19a** and **19b** were separated by HPLC and the stereochemistry was determined by conversion into the natural products. The major isomer **19a** was actually transformed into (+)-trifarienol A **1** and the minor one **19b** into (−)-trifarienol B **2**. Spectral data including the specific rotations of these compounds were identical with those of the natural products.[4,18]

In summary, we have succeeded in preparation of *cis*-arranged 2,2,3-trisubstituted cyclohexanone derivative **4** in high enantiomeric excess using chiral phenylethylamine and have found that there are matched and mismatched cases in this reaction. (+)-Trifarienol A **1** and (−)-trifarienol B **2** were synthesized from **4** in 10 steps as optically active forms for the first time.

3. Experimental

3.1. General

The IR spectra were measured with a Jasco FT/IR-5300 spectrophotometer. The ^1H and ^{13}C NMR spectra were taken with a Varian Unity 200 (200 MHz), a Unity 600 (600 MHz), or a Jeol JNM GX400



Scheme 3. (a) $LiAlH_4$, Et_2O, rt, 5 h; (b) Swern oxid.; (c) 5%KOH, MeOH, rt, 3 days; (d) Tebbe reagent, rt, 1 day; (e) $Ph_3P^+CH_2OCH_3Cl^-$, *n*-BuLi, THF, reflux, 2 days; (f) 1 M HCl, THF–H_2O, rt, 1 day; (g) *t*-BuOK, MeI, THF, rt, 1.5 h; (h) $(CH_3)_3S^+I^-$, NaH, DMSO, THF; (I) $HClO_4$, THF–H_2O, rt; (j) $(MeO)_2POCH_2CO_2Me$, NaH, THF, reflux, 5 days; then HPLC

(400 MHz) spectrometer. The mass spectra, including high resolution mass spectra, were taken with a Jeol JMS AX-500 spectrometer. Chemcopak Nucleosil 50-5 (10×250 mm) was used for HPLC (Jasco pump system). For the measurement of % ee a Daicel Chiralcel OD-H (4.6×25 cm) column was used in the HPLC system. A DB-17 (0.25 mm×30 m) column was used for GC with the temperature program from 50°C to 25°C (Shimadzu GC 14B gas chromatograph with FID detector). Silica gel 60 (70–230 mesh, Merck) was used for column chromatography and silica gel 60 F_{254} plates (Merck) were used for TLC.

3.2. *Preparation of ester **4a** from racemic 2,3-dimethylcyclohexanone **10a***

(*S*)-(−)-1-Phenylethylamine (39 mL, 0.3 mol) and TsOH (4 g) were added to a solution of (*rac*)-2,3-dimethylcyclohexanone **10a** (37 g, 0.3 mol) in benzene (300 mL) and the mixture was refluxed for 24 h with the aid of a Dean–Stark water separator. The mixture was washed with water, saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated to afford an imine, which was subjected to reaction with methyl acrylate (26 mL, 0.29 mol) under ice cooling. The mixture was then stirred at rt for 7 days. Acetic acid and water (9:1, 300 mL) was added to the mixture and kept at 60°C for 1 h. The mixture was extracted with ether and the organic layer was washed with water, 1 M HCl solution, saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$), and evaporated to afford a residue. Purification by silica gel column chromatography (hexane–EtOAc, in gradient) gave ester **4a** (16.5 g, 26%, 97% ee) and 2,3-

dimethylcyclohexanone (14 g, 37%); **4a**; oil: $[\alpha]_D^{20.5}$ −6.2 (*c* 1.04, $CHCl_3$); CD $[\theta]_{300nm}$ −410 ($CHCl_3$); $\Delta\varepsilon$=−0.13; FT-IR 1740, 1700 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 0.93 (3H, d, *J*=6.8 Hz), 1.02 (3H, s), 1.60 (1H, m), 1.67 (1H, m), 1.76 (1H, m), 1.80 (1H, m), 1.84 (1H, m), 1.95 (1H, m), 2.01 (1H, ddd, *J*=14, 11.2, 5.2 Hz), 2.22 (1H, ddd, *J*=12.9, 11.2, 5.1 Hz), 2.31 (1H, m), 2.33 (1H, ddd, *J*=12.9, 11.2, 5.1 Hz), 2.43 (1H, ddd, *J*=14.3, 10.7, 5.9 Hz), 3.67 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$): δ 15.3 (CH_3), 18.4 (CH_3), 24.4 (CH_2), 28.9 (CH_2), 29.1 (CH_2), 30.4 (CH_2), 38.1 (CH_2), 38.4 (CH), 51.2 (C), 51.4 (CH_3), 174.1 (C), 215.0 (C); MS *m/z* 212 (M^+), 197, 181, 168, 153, 139, 126 (base), 111, 96, 83, 69, 55, 41; HRMS found *m/z* 212.1436; calcd for $C_{12}H_{20}O_3$ 212.1413.

3.3. Preparation of ester *4b* from (2RS,3R)-2,3-dimethylcyclohexanone *10b*

The imine was similarly prepared from (2*RS*,3*R*)-2,3-dimethylcyclohexanone **10b** (18.4 g, 0,15 mol), (*S*)-(−)-1-phenylethylamine (23 mL, 0.17 mol), and TsOH (2 g) in benzene (200 mL), followed by Michael addition to methyl acrylate (15.8 mL, 0.17 mol). Workup and purification as described before afforded ester **4b** (18.3 g, 59%, >99.5% ee); $[\alpha]_D^{22}$ −19.1 (*c* 1.2, $CHCl_3$); CD $[\theta]_{297.5nm}$ −970 ($CHCl_3$); $\Delta\varepsilon$=−0.29.

3.4. Reaction of imine *3c*, prepared from (2RS,3R)-2,3-dimethylcyclohexanone *10b* and (R)-(+)-1-phenylethylamine, with methyl acrylate

The imine **3c** was similarly prepared from (2*RS*,3*R*)-2,3-dimethylcyclohexanone **10b** (1.4 g, 11.1 mmol), (*R*)-(+)-1-phenylethylamine (1.5 mL, 11.1 mmol), and TsOH (140 mg) in benzene (15 mL), followed by Michael addition to methyl acrylate (1 mL, 11.1 mmol). Workup and purification as described before in combination of HPLC afforded ester **4c** (7.1 mg, 0.3%), **12** (35 mg, 1.5%), **13** (9.4 mg, 0.4%), **14** (7.1 mg, 0.3%), and **15** (47 mg, 2%).

12; oil: $[\alpha]_D^{20}$ +56.7 (*c* 1.04, $CHCl_3$); CD $[\theta]_{295nm}$ +5300 ($CHCl_3$) $\Delta\varepsilon$=+1.6; FT-IR 1740, 1705 cm^{-1}; ^1H NMR (600 MHz, C_6D_6) δ 0.70 (3H, d, *J*=6.6 Hz), 0.98 (3H, d, *J*=6.6 Hz), 1.10 (1H, m), 1.18 (1H, m), 1.26 (1H, m), 1.32 (1H, m), 1.43 (1H, m), 1.50 (1H, m), 1.90 (1H, m), 1.93 (1H, m), 2.10 (1H, m), 2.11 (1H, m), 2.24 (1H, m), 3.37 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.4 (CH_3), 20.4 (CH_3), 26.2 (CH_2), 28.7 (CH_2), 29.9 (CH_2), 31.9 (CH_2), 40.0 (CH), 48.1 (CH), 49.1 (CH), 51.6 (CH_3), 173.5 (C), 215.6 (C); MS *m/z* 212 (M^+), 180 (base), 165, 152, 126, 111, 95, 83, 69, 55; HRMS found *m/z* 212.1393; calcd for $C_{12}H_{20}O_3$ 212.1422.

13; oil: $[\alpha]_D^{21}$ −43.5 (*c* 0.54, $CHCl_3$); CD $[\theta]_{295nm}$ −3300 ($CHCl_3$); $\Delta\varepsilon$=−1.0; FT-IR 1740, 1710 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 0.92 (3H, d, *J*=6.9 Hz), 1.02 (3H, d, *J*=7.4 Hz), 1.37 (1H, ddd, *J*=13, 11, 4.1 Hz), 1.57 (1H, m), 1.61 (1H, m), 1.67 (1H, dq, *J*=13, 4.1 Hz), 2.01 (1H, m), 2.03 (1H, m), 2.05 (1H, m), 2.32 (1H, ddd, *J*=15.9, 8.2, 6.8 Hz), 2.37 (1H, ddd, *J*=15.9, 8.5, 6.6 Hz), 2.46 (1H, m), 2.52 (1H, ddd, *J*=12, 7.1, 4.9 Hz), 3.66 (3H, s); MS *m/z* 212 (M^+), 180 (base), 165, 152, 138, 126, 111, 95, 83, 69, 55; HRMS found *m/z* 212.1426; calcd for $C_{12}H_{20}O_3$ 212.1412.

14; oil: $[\alpha]_D^{21}$+6.4 (*c* 0.95, $CHCl_3$); CD $[\theta]_{299nm}$ +1100 ($CHCl_3$); $\Delta\varepsilon$=+0.32; FT-IR 1740, 1705 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.01 (3H, d, *J*=6.3 Hz), 1.05 (3H, d, *J*=6.3 Hz), 1.34 (1H, ddd, *J*=13, 13, 3.7 Hz), 1.45 (1H, m), 1.50 (1H, m), 1.53 (1H, m), 1.83 (1H, dq, *J*=13.5, 3.3 Hz), 2.04 (1H, m), 2.06 (1H, m), 2.08 (1H, m), 2.32 (1H, ddd, *J*=16, 8, 6.5 Hz), 2.35 (1H, m), 2.41 (1H, ddd, *J*=16, 8, 6.5 Hz), 3.66 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) 11.9 (CH_3), 20.8 (CH_3), 24.9 (CH_2), 31.8 (CH_2), 33.7 (CH_2),34.6 (CH_2), 42.4 (CH), 49.3 (CH), 51.6 (CH_3), 52.1 (CH), 173.9 (C), 213.0 (C); MS *m/z* 212 (M^+), 180 (base), 165, 152, 138, 126, 111, 95, 83, 69, 55; HRMS found *m/z* 212.1412; calcd for $C_{12}H_{20}O_3$ 212.1412.

15; oil: $[\alpha]_D^{21}$ −91.6 (*c* 0.86, $CHCl_3$); CD $[\theta]_{302nm}$ −1700 ($CHCl_3$); $\Delta\varepsilon$=−0.52; FT-IR 1740, 1705 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.99 (3H, d, *J*=6.3 Hz), 1.06 (3H, s), 1.65–1.73 (5H, m), 1.93 (1H, ddd, *J*=16.5, 12, 4.5 Hz), 1.99 (1H, m), 2.12 (1H, ddd, *J*=14, 12, 4.6 Hz), 2.22 (1H, ddd, *J*=16, 12, 4.6 Hz), 2.31 (1H, dt, J=14, 4.6 Hz), 2.44 (1H, ddd, *J*=14, 12, 6 Hz), 3.66 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.6 (CH_3), 19.3 (CH_3), 25.6 (CH_3), 26.9 (CH_2), 28.7 (CH_2), 29.1 (CH_2), 38.4 (CH), 43.4 (CH), 51.6 (CH_3), 51.6 (C), 174.1 (C), 215.5 (C); MS *m/z* 212 (M^+), 197, 181, 152, 139, 126 (base), 111, 96, 83, 69, 55; HRMS found *m/z* 212.1390; calcd for $C_{12}H_{20}O_3$ 212.1412.

*3.5. General procedure for preparation of pentafluorophenyl ester **11***

Methyl ester **4** was treated with 10% KOH in MeOH at rt for 30 min and MeOH was then removed. The mixture was extracted with ether and the aqueous layer was acidified with 1 M HCl to pH=1. The solution was extracted with ether and the organic layer was dried ($MgSO_4$) and evaporated to afford an acid. A solution of the acid in CH_2Cl_2 was treated with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide–HCl and pentafluorophenol at rt overnight. More CH_2Cl_2 was added and the organic layer was washed with 1 M HCl, 1 M NaOH solution, and brine. Silica gel column chromatography afforded pentafluorophenyl ester, which was analyzed with HPLC (Chiralcel OD-H, hexane:*i*-PrOH=98.5:1.5).

Pentafluorophenyl ester **11b**; oil: $[\alpha]_D^{20}$ −19.0 (*c* 0.88, $CHCl_3$); CD $[\theta]_{302nm}$ −190 ($CHCl_3$); $\Delta\varepsilon$=−0.06; FT-IR 1790, 1705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (3H, d, *J*=6.4 Hz), 1.09 (3H, s), 1.67 (2H, m), 1.75 (1H, m), 1.84 (1H, m), 1.89 (1H, m), 1.99 (1H, m), 2.13 (1H, ddd, *J*=16.1, 10.7, 5.4 Hz), 2.31 (1H, dt, *J*=13.7, 4.2 Hz), 2.50 (1H, m), 2.62 (1H, ddd, *J*=16.6, 10.6, 5.4 Hz), 2.70 (1H, ddd, *J*=16.6, 10.6, 5.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 15.4, 18.3, 24.9, 28.6, 29.2, 29.7, 29.9, 38.2, 38.7, 51.3, 169.9, 215.1; MS (CI) *m/z* 365 $(M+H)^+$, 347, 267, 181 (base), 163, 111, 99; CI-HRMS found *m/z* 365.1168 $(M+H)^+$; calcd for $C_{17}H_{18}O_3F_5$ 365.1176.

*3.6. Preparation of [1′S,6′R]-3-(1′,6′-dimethyl-2′-oxocyclohexyl)propanal **7***

A solution of keto ester **4** (17.6 g, 83 mmol) in dry ether (500 mL) was reduced with $LiAlH_4$ (16 g, 42 mmol) at rt for 5 h. Excess reagent was decomposed by ethyl acetate, and water (17 mL), 15% NaOH solution (17 mL) and water (51 mL) were added, successively. After filtration, the solvent was evaporated to give diol (18 g), which was used in the next step without purification. A solution of diol (18 g) in CH_2Cl_2 (600 mL) was oxidized with oxalyl chloride (24 mL, 0.28 mol) and dimethyl sulfoxide (42 mL, 0.59 mol) at −60 to −50°C for 15 min, followed by Et_3N (168 mL, 1.2 mol). Usual workup afforded a residue (21 g), which was purified by silica gel column chromatography (hexane–EtOAc, in gradient) to give aldehyde **7** (13.8 g, 91%); oil; FT-IR 1740, 1720 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.93 (3H, d, *J*=6.6 Hz), 1.04 (3H, s), 1.55–1.85 (5H, m), 1.9–2.1 (2H, m), 2.2–2.6 (4H, m), 9.78 (1H, t, *J*=1.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.3 (CH_3), 18.6 (CH_3), 24.7 (CH_2), 27.3 (CH_2), 29.1 (CH_2), 38.2 (CH_2), 38.5 (CH), 39.3 (CH_2), 51.2 (C), 202.3 (CH), 215.3 (C); MS (CI) *m/z* 183 $(M+H)^+$ (base), 165, 147, 137, 126, 101, 95, 85, 71, 55; CI-HRMS found *m/z* 183.1394 $(M+H)^+$; calcd for $C_{11}H_{19}O_2$ 183.1385.

*3.7. Preparation of [1S,2R,5S,6S]-1,2-dimethylbicyclo[3.3.1]nonan-6-ol-9-one **8a** and [1S,2R,5S,6R]-1,2-dimethylbicyclo[3.3.1]nonan-6-ol-9-one **8b***

Aldehyde **7** (6.9 g, 38 mmol) was treated with 5% KOH in MeOH at rt for 3 days. The solvent was evaporated and the mixture was extracted with ether. The organic layer was washed with 1 M HCl and brine, dried ($MgSO_4$), and evaporated to afford a residue (6.8 g). The residue was purified by silica gel

column chromatography (hexane–EtOAc, in gradient) to give a mixture of ketol **8a** and **8b** (4.6 g, 1:1, 67%), a part of which was separated by HPLC (Nucleosil 50-5, hexane:EtOAc=4:1) into each isomer for characterization; α-isomer **8a**; oil; FT-IR 3400, 1710 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.91 (3H, d, *J*=7.2 Hz), 0.95 (3H, s), 1.3–1.6 (2H, m), 1.9–2.2 (5H, m), 2.2–2.5 (2H, m), 2.61 (1H, t, *J*=5.3 Hz), 4.03 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 18.1 (CH_3), 21.4 (CH_3), 22.9 (CH_2), 29.1 (CH_2), 30.5 (CH_2), 36.8 (CH_2), 44.8 (CH), 49.0 (C), 54.5 (CH), 73.6 (CH), 219.0 (C); MS *m/z* 182 (M^+), 167, 138, 125 (base), 109, 97, 81, 69, 55; HRMS found *m/z* 182.1311; calcd for $C_{11}H_{18}O_2$ 182.1307.

β-Isomer **8b**; oil; FT-IR 3400, 1710 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (3H, d, *J*=7.2 Hz), 0.97 (3H, s), 1.38 (1H, m), 1.6–2.2 (7H, m), 2.3–2.5 (2H, m), 4.33 (1H, br d, *J*=3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 17.4 (CH_3), 21.7 (CH_3), 26.4 (CH_2), 27.4 (CH_2), 29.6 (CH_2), 37.8 (CH_2), 44.9 (CH), 49.6 (C), 54.5 (CH), 77.0 (CH), 219.0 (C); MS *m/z* 182 (M^+), 167, 149, 138, 125 (base), 109, 97, 81, 69, 55; HRMS found *m/z* 182.1300; calcd for $C_{11}H_{18}O_2$ 182.1307.

*3.8. Preparation of [1*R*,2*S*,5*S*,6*R*]-5,6-dimethyl-9-methylenebicyclo[3.3.1]nonan-2-ol **16a** and [1*R*,2*R*,5*S*,6*R*]-5,6-dimethyl-9-methylenebicyclo[3.3.1]nonan-2-ol **16b***

A solution of keto alcohol **8** (87 mg, 0.48 mmol) in dry THF (15 mL) was treated with the Tebbe reagent (0.5 M, 2.9 mL, 1.5 mmol) at rt for 4 h. Ether (50 mL) and 10% NaOH aqueous solution (2 mL) were added. The mixture was extracted with ether and the organic layer was washed with brine. Evaporation of the solvent after drying ($MgSO_4$) afforded a residue, which was purified by silica gel column chromatography (hexane–EtOAc, in gradient) to give a mixture of olefin **16a** and **16b** (61 mg, 71%); oil; FT-IR 3300, 1650 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.86 (d, *J*=6.8 Hz), 0.87 (d, *J*=6.8 Hz), 0.93 (s), 0.97 (s), 3.86 (m), 4.60 (d, *J*=1.8 Hz), 4.78 (d, *J*=1.8 Hz), 4.86 (d, *J*=1.8 Hz), 4.94 (d, *J*=1.8 Hz); MS *m/z* 180 (M^+), 162, 147, 136, 123 (base), 105, 93, 81, 67, 55, 41; HRMS found *m/z* 180.1518; calcd for $C_{12}H_{20}O$ 180.1514.

*3.9. Preparation of [1*R*,5*S*,6*R*]-5,6-dimethyl-9-methylenebicyclo[3.3.1]nonan-2-one **17***

A solution of alcohol **16** (1.7 g, 9.4 mmol) in CH_2Cl_2 (150 mL) was oxidized with dimethyl sulfoxide (4.7 mL, 66 mmol) and oxalyl chloride (2.5 mL, 28 mmol) at −60 to −50°C for 15 min, followed by Et_3N (20 mL, 140 mmol). Usual workup and purification by silica gel column chromatography (hexane–EtOAc, in gradient) afforded ketone **17** (1.5 g, 88%); oil; $[\alpha]_D^{22}$ +121 (*c* 0.78, $CHCl_3$); CD $[\theta]_{306nm}$ +6870 ($CHCl_3$); Δε=+2.1; FT-IR 1730, 1660 cm^{-1}; ^1H NMR (200 MHz, $CHCl_3$) δ 0.91 (3H, d, *J*=7.0 Hz), 1.23 (3H, s), 1.36 (1H, m), 1.82 (6H, m), 2.45 (2H, m), 2.99 (1H, br t, *J*=3.0), 4.78 (1H, d, *J*=1.2 Hz), 4.94 (1H, d, *J*=1.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.4 (CH_3), 25.8 (CH_3), 27.4 (CH_2), 27.8 (CH_2), 35.1 (CH_2), 39.4 (CH_2), 39.9 (C), 42.1 (CH), 56.5 (CH), 109.0 (CH_2), 149.3 (C), 216.0 (C); MS *m/z* 178 (M^+, base), 163, 136, 123, 107, 93, 79, 67, 55; HRMS found *m/z* 178.1349; calcd for $C_{12}H_{18}O$ 178.1358.

*3.10. Preparation of [1*S*,2*R*,5*S*]-6-formyl-1,2-dimethyl-9-methylenebicyclo[3.3.1]nonane **18***

A solution of ketone **17** (610 mg, 3.4 mmol) in dry THF (80 mL) was treated with the ylide prepared from methoxymethyltriphenylphosphonium chloride (9 g, 34 mmol) and *n*-BuLi (1.6 M, 21 mL, 34 mmol) under reflux for 5 days. Water was added and the solvent was evaporated. The mixture was extracted with ether and the organic layer was washed with brine, dried ($MgSO_4$), and evaporated to afford an olefin (1.2 g). The olefin was treated with 1 M HCl in THF (40 mL) overnight. The

mixture was extracted with ether and the organic layer was washed with sat. $NaHCO_3$ solution and brine, dried ($MgSO_4$), and evaporated to give a residue. The residue was purified by silica gel column chromatography (hexane–EtOAc, in gradient) to give aldehyde **18** (119 mg, 19%); oil; FT-IR 1720, 1640 cm^{-1}; ^1H NMR (200 MHz, $CHCl_3$) β-isomer; δ 0.85 (3H, d, *J*=6.8 Hz), 0.92 (3H, s), 1.2–2.4 (8H, m), 2.45 (1H, m), 2.4 (1H, m), 2.9 (1H, br s), 4.58 (1H, d, *J*=1.6 Hz), 4.86 (1H, d, *J*=1.6 Hz), 9.58 (1H, s); α-isomer; δ 0.85 (3H, d, *J*=6.8 Hz), 0.96 (3H, s), 1.2–2.4 (8H, m), 2.45 (1H, m), 2.6 (1H, m), 2.9 (1H, br s), 4.60 (1H, d, *J*=1.8 Hz), 4.94 (1H, d, *J*=1.8 Hz), 9.73 (1H, s); MS *m/z* 192 $(M)^+$, 177, 163, 149, 135, 121, 107 (base), 93, 81; HRMS found *m/z* 192.1532; calcd for $C_{13}H_{20}O$ 192.1515.

3.11. Preparation of [1S,2R,5R,6S]-6-formyl-1,2,6-trimethyl-9-methylenebicyclo[3.3.1]nonane 9

A solution of aldehyde **18** (61 mg, 0.32 mmol) was treated with *t*-BuOK (175 mg, 1.6 mmol) at rt for 30 min. Then MeI (0.2 mL, 3.2 mmol) was added at 0°C and the mixture was kept for 15 min at the same temperature. Water was added and the solvent was evaporated. The mixture was extracted with ether and the organic layer was washed with brine, dried ($MgSO_4$), and evaporated to afford a residue. The residue was purified by silica gel column chromatography (hexane–EtOAc, in gradient) to give aldehyde **9** (47 mg, 71%); oil; FT-IR 1730, 1645 cm^{-1}; ^1H NMR (200 MHz, $CHCl_3$) δ 0.84 (3H, d, *J*=7.2 Hz), 0.96 (3H, s), 1.03 (3H, s), 1.25 (2H, td, *J*=14.8, 7.6 Hz), 1.4–1.9 (5H, m), 2.1–2.4 (2H, m), 2.53 (1H, td, *J*=14.4, 7.2 Hz), 4.72 (1H, d, *J*=1.8 Hz), 4.88 (1H, d, *J*=1.8 Hz), 9.49 (1H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.5 (CH_3), 21.5 (CH_3), 25.7 (CH_3), 26.0 (CH_2), 27.6 (CH_2), 29.0 (CH_2), 29.9 (C), 37.6 (CH_2), 40.0 (C), 40.8 (CH), 46.4 (CH), 108.1 (CH_2), 150.6 (C), 206.9 (CH); MS *m/z* 206 $(M)^+$, 177, 163, 149, 136, 121 (base), 107, 95, 81; HRMS found *m/z* 206.1674; calcd for $C_{14}H_{22}O$ 206.1671.

3.12. Preparation of [1S,2R,5R,6S]-1,2,6-trimethyl-9-methylene-6-oxiranylbicyclo[3.3.1]nonane 19

A solution of trimethylsulfonium iodide (475 mg, 2.3 mmol) in DMSO (2 mL) was added into a mixture of NaH (90 mg, 2.3 mmol), DMSO (3 mL), and THF (4 mL) at −20°C. A solution of aldehyde **9** (47 mg, 0.23 mmol) in DMSO (2 mL) was added to this solution and the mixture was kept at 0°C for 25 min. Water was added and the solvent was evaporated. The mixture was extracted with ether and the organic layer was washed with brine, dried ($MgSO_4$), and evaporated to afford a residue. The residue was purified by silica gel column chromatography (hexane–EtOAc, in gradient) to give a mixture of epoxides **19** (47 mg, 94%), which was further separated by HPLC to afford **19a** (16.6 mg, 33%) and **19b** (5.4 mg, 11%); **19a**; oil; $[\alpha]_D^{19}$+3.1 (*c* 1.7, $CHCl_3$); FT-IR 1640 cm^{-1}; ^1H NMR (200 MHz, $CHCl_3$) δ 0.85 (3H, s), 0.87 (3H, d, *J*=6.8 Hz), 0.94 (3H, s), 1.1–1.3 (2H, m), 1.5–1.8 (4H, m), 1.9–2.1 (3H, m), 2.23 (1H, m), 2.73 (1H, dd, *J*=4.0, 4.0 Hz), 2.81 (1H, dd, *J*=4.0, 3.0 Hz), 2.90 (1H, dd, *J*=4.0, 3.0 Hz), 4.63 (1H, d, *J*=1.8 Hz), 4.80 (1H, d, *J*=1.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.8 (CH_3), 22.3 (CH_3), 25.2 (CH_2), 25.8 (CH_3), 29.7 ($CH_2\times2$), 38.1 (CH_2), 38.3 (C), 40.0 (C), 41.0 (CH), 44.8 (CH_2), 48.8 (CH), 59.1 (CH), 106.8 (CH_2), 152.6 (C); MS *m/z* 220 $(M)^+$, 189, 175, 161, 147, 133, 119, 107 (base), 93, 81, 67, 55; HRMS found *m/z* 220.1836; calcd for $C_{15}H_{24}O$ 220.1827.

19b; oil; $[\alpha]_D^{19}$ −21 (*c* 0.54, $CHCl_3$); FT-IR 1640 cm^{-1}; ^1H NMR (200 MHz, $CHCl_3$) δ 0.85 (3H, d, *J*=6.8 Hz), 0.87 (3H, s), 0.93 (3H, s), 1.21 (1H, m), 1.5–1.9 (4H, m), 1.9–2.4 (5H, m), 2.47 (1H, dd, *J*=4.0, 3.0 Hz), 2.59 (1H, dd, *J*=4.0, 4.0 Hz), 2.80 (1H, dd, *J*=4.0, 3.0 Hz), 4.61 (1H, d, *J*=1.8 Hz), 4.78 (1H, d, *J*=1.8 Hz); MS *m/z* 220 (M^+), 205, 189, 175, 161, 133, 119, 105 (base), 93, 81, 67; HRMS found *m/z* 220.1809; calcd for $C_{15}H_{24}O$ 220.1827.

3.13. Preparation of trifarienols A **1** and B **2**

Epoxide **19a** (16.6 mg, 0.076 mmol) was treated with 70% $HClO_4$ (13 mL) in THF:H_2O (3:2, 5 mL) at rt for 4 h. The mixture was extracted with ether and the organic layer was washed with brine, dried ($MgSO_4$), and evaporated to afford a residue. The residue was purified by silica gel column chromatography (hexane–EtOAc, in gradient) to give trifarienol A (**1**) (11.4 mg, 63%); mp 82–82.5°C (from hexane) [lit.[4] 59–60°C]; $[\alpha]_D^{20}$ +15 (*c* 0.57, $CHCl_3$) [lit.[4] +10.2 (*c* 0.63, $CHCl_3$]; FT-IR 3400, 1640 cm^{-1}; ^1H NMR (200 MHz, $CHCl_3$) δ 0.85 (3H, s), 0.86 (3H, d, *J*=6.8 Hz), 0.92 (3H, s), 1.1–1.3 (2H, m), 1.5–1.8 (4H, m), 1.8–2.0 (3H, m), 2.1–2.3 (3H, m), 3.55 (1H, dd, *J*=10.6, 9.4 Hz), 3.73 (1H, dd, *J*=10.6, 2.6 Hz), 3.81 (1H, dd, *J*=9.6, 2.6 Hz), 4.63 (1H, d, *J*=1.8 Hz), 4.80 (1H, d, *J*=1.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.7 (CH_3), 19.2 (CH_3), 24.6 (CH_2), 25.9 (CH_3), 29.7 (CH_2), 32.7 (CH_2), 38.5 (CH_2), 39.8 (C), 40.7 (C), 41.0 (CH), 47.0 (CH), 63.5 (CH_2), 76.8 (CH), 107.0 (CH_2), 152.7 (C); MS *m/z* 238 (M^+), 220, 207, 189, 177 (base), 161, 136, 123, 107, 95, 81, 69; HRMS found *m/z* 238.1927; calcd for $C_{15}H_{24}O$ 238.1933.

Epoxide **19b** (5.4 mg, 0.024 mmol) was similarly treated with 70% $HClO_4$ (1.2 mL) in THF:H_2O (3:2, 5 mL) at rt for 7 h to afford trifarienol B (**2**) (2.9 mg, 50%); mp. 108–109.5°C (from hexane) [lit.[4] 105–105.5°C]; $[\alpha]_D^{21}$ −3.5 (*c* 1.01, $CHCl_3$) [lit.[4] −3.6 (*c* 1.62, $CHCl_3$)]; FT-IR 3400, 1640 cm^{-1}; ^1H NMR (200 MHz, $CHCl_3$) δ 0.82 (3H, s), 0.85 (3H, d, *J*=7.0 Hz), 0.93 (3H, s), 1.2–1.3 (2H, m), 1.5–1.8 (4H, m), 1.8–2.1 (3H, m), 2.2–2.4 (3H, m), 3.51 (1H, dd, *J*=11, 9.8 Hz), 3.73 (1H, dd, *J*=11, 2.8 Hz), 3.82 (1H, dd, *J*=9.8, 2.8 Hz), 4.60 (1H, d, *J*=1.8 Hz), 4.76 (1H, d, *J*=1.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.7 (CH_3), 19.0 (CH_3), 24.5 (CH_2), 25.9 (CH_3), 29.5 (CH_2), 33.6 (CH_2), 38.3 (CH_2), 39.7 (C), 40.9 (CH, C), 48.2 (CH), 62.1 (CH_2), 78.4 (CH), 106.7 (CH_2), 152.7 (C); MS *m/z* 238 (M^+), 220, 207, 189, 177 (base), 161, 136, 123, 107, 95, 81, 69; HRMS found *m/z* 238.1913; calcd for $C_{15}H_{26}O$ 238.1933.

3.14. Preparation of unsaturated ester **20**

A solution of ketone **17** (65 mg, 0.37 mmol) in dry PhH (30 mL) was treated with trimethylphosphonoacetate (0.1 mL, 0.61 mmol) and sodium hydride (35 mg, 0.88 mmol) and the mixture was refluxed for 5 days. Water was added and the mixture was extracted with ether and the organic layer was washed with brine, dried ($MgSO_4$), and evaporated to afford a residue. The residue was purified by silica gel column chromatography (hexane–EtOAc, in gradient) to give a mixture of (*E*)- and (*Z*)-ester **20** (42 mg, 48%) (*E*:*Z*=81:19),[7] a part of which was further separated by HPLC (hexane:EtOAc, 99:1) to afford (*E*)-**20** (8.2 mg) and (*Z*)-**20** (3.5 mg); (*E*)-**20**; FT-IR 1720, 1640 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.87 (3H, d, *J*=7.0 Hz), 1.00 (3H, s), 1.3 (1H, m), 1.5–1.7 (2H, m), 1.7–2.2 (4H, m), 3.0–3.2 (3H, m), 3.67 (3H, s), 4.61(1H, d, *J*=1.4 Hz), 4.88 (1H, d, *J*=1.4 Hz), 5.66 (1H, br q, 1.5 Hz); MS *m/z* 234 (M^+, base), 219, 203, 175, 159, 145, 133, 119, 105, 91; HRMS found *m/z* 234.1631; calcd for $C_{15}H_{22}O_2$ 234.1620. (*Z*)-**20**; FT-IR 1720, 1640 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.87 (3H, d, *J*=7.0 Hz), 1.02 (3H, s), 1.28 (1H, m), 1.5–1.8 (2H, m), 1.8–2.1 (4H, m), 2.2–2.6 (2H, m), 3.68 (3H, s), 4.27 (1H, m), 4.63 (1H, d, *J*=1.8 Hz), 4.96 (1H, d, *J*=1.8 Hz), 5.64 (1H, br q, *J*=1.4 Hz); MS *m/z* 234 (M^+, base), 219, 202, 187, 175, 159, 145, 133, 119, 105, 91; HRMS found *m/z* 234.1604; calcd for $C_{15}H_{22}O_2$ 234.1620.

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10. The conformation **4(F)** is favored to **4(D)**.
11. Because **10a** is racemic, there are two diastereoisomers in imine **3a**. Only one half of **3a** could yield **4a**, while the other half remains unattached (Fig. 2).

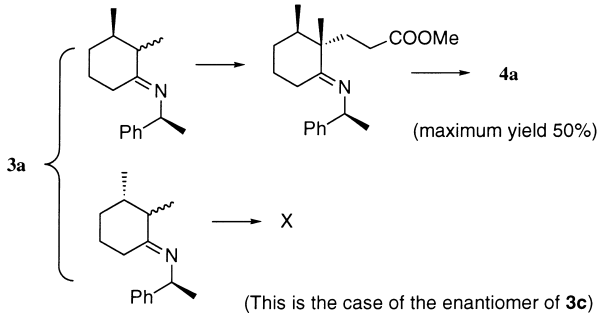

Figure 2.

12. Tori, M.; Uchida, N.; Sumida, A.; Furuta, H.; Asakawa, Y. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1513–1517.
13. Conditions for HPLC: Chiralcel OD-H (4.6 mm×250 mm), hexane:*i*PrOH=98.5:1.5, 1 mL/min.
14. Unpublished results: we have succeeded in determination of ees of several 2,2-disubstituted cyclohexanones and cyclopentanones by this methodology. Although we have reported that the ees of cyclopentanone derivatives were directly determined by chiral HPLC in Stereochemistry Abstracts in Ref. 3, this should be corresponding pentafluorophenyl esters.
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18. The melting point of the synthetic sample was ca. 20° higher than that of the natural one. This is presumably due to the fact that the natural sample includes the water in its crystal, which was indicated by the X-ray crystallography (see Ref. 4) although both crystals were made from hexane (private communication with Dr. T. Hashimoto).