Chemoenzymatic Route to Both Enantiomers of a 1-Isopropyl-3a-methyloctahydroinden-4-one Derivative: A Synthetic Intermediate for Sesqui- and Diterpenoids

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Abstract: On the way to a chemoenzymatic synthesis of a key intermediate for sesquiterpenoids and diterpenoids, 2-methyl-2-(4-methyl-3-oxopentyl)-1,3-cyclohexanedione was reduced with the whole cells of yeast biocatalysts. *Torulaspora delbrueckii* NBRC10921 reduced a cyclic ketone of three carbonyl groups in an enantiofacially selective manner (*re*-face attack), but there was poor enantiotopic group selectivity between two carbonyl groups on the cyclohexane ring to yield a mixture of diastereomeric products. *Candida floricola* IAM13115 reduced mainly the *pro*-(*R*) carbonyl group. In contrast, the reduction proceeded in an enantiofacially poorly selective manner to give another set of diastereomeric products. In both cases, another carbonyl group on the side chain worked as a 'trapping arm' of the resulting secondary alcohol. The diastereomeric products were effectively separated as the '*syn*' or '*cis*' isomer exclusively exist in the intramolecular hemiacetal structure, while '*anti*' or '*trans*' isomer being an equilibrated mixture of cyclic hemiacetal and open-chain hydroxyketone (*ca*. 0.7:1). Starting separately from the enantiomerically enriched products as above, both enantiomers of the target compound, a key intermediate for terpenoids, were efficiently prepared *via* stereoselective ring closure under pinacol coupling reaction conditions. Furthermore, a daucane sesquiterpene intermediate, a hydroazulene derivative, was provided after one-carbon homologation of the six-membered ring.

Keywords: chiral building block; desymmetrization; prochiral substrate; terpenoid synthesis; whole-cell biocatalyst; yeast reduction

Introduction

Many naturally occurring sesquiterpenoids[1] as well as diterpenoids[2] have a common partial structure (**A**) as shown in Figure 1. (1*S*,6*R*,9*S*)-9-Isopropyl-6-methyl-10,12-dioxatricyclo[7.3.0.0^{1,6}]dodecane-5,11-dione (**1**, Scheme 1) and its antipode, (1*R*,6*S*,9*R*)-**1** are potentially good synthetic intermediates on account of the five-membered ring on which an isopropyl and a methyl group are located in the proper positions in a stereochemically defined manner. Toward this molecule, the stereoselective ring closure through an intramolecular pinacol coupling and subsequent protection of the resulting diol implies a simple precursor, a hydroxyketone (**B**). The regio- and stereoselctive reduction of a triketone (**2**), which would be easily prepared by Michael addition of an enolate of diketone (**3**) to the side chain in the form of an enone, is the key step, and the enzyme-catalyzed reduction of 2,2-asymmetrically disubstituted 1,3-diketones (**C**), by means of the whole cell yeast[3] is very attractive.

If we attempt to synthesize both enantiomers of **1**, the (*R*)- and (*S*)-enantiomers of hydroxyketone (**B**), at least in regard to the quaternary chiral center, are required. The whole cell-mediated reduction meets this criterion, as the multiple enzymes exist in the microbial cells, and they sometimes show opposite enantiotopic group selectivity, to give the desired (*R*)- and (*S*)-isomers simultaneously. For example, yeast-catalyzed reduction of such a diketone (**C**, R = $CH_2CH{=}CH_2$) yielded a mixture of hydroxy ketones (**D**) and (**E**);[4] however, these two products are hardly separable with conventional silica gel column chromatography. In the present study, a 'trapping arm' was introduced in the substrate molecule to facilitate the separation, by means of the formation of an intramolecular cyclic hemiacetal (**G**),[5,6] preferentially on the '*syn*' or '*cis*' diastereomer from the '*anti*' or '*trans*' open-chain hydroxyketone (**H**).

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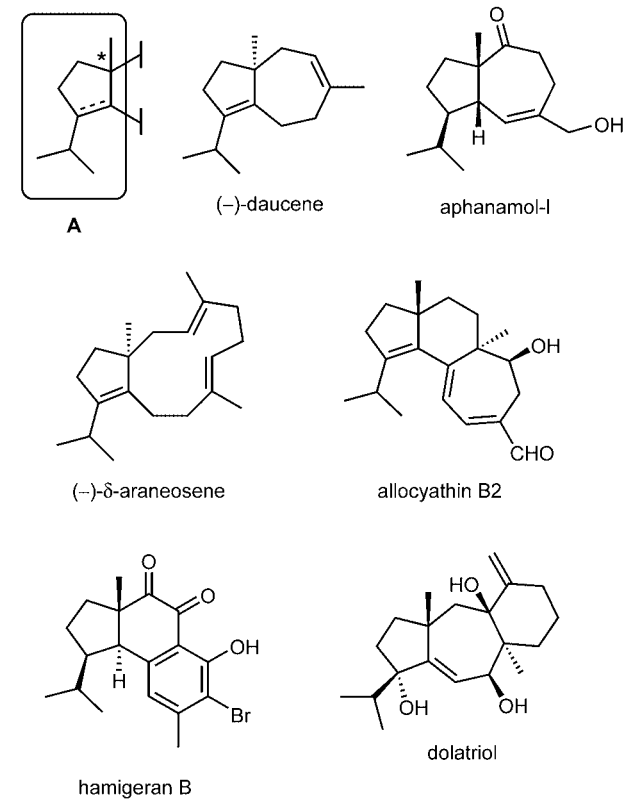
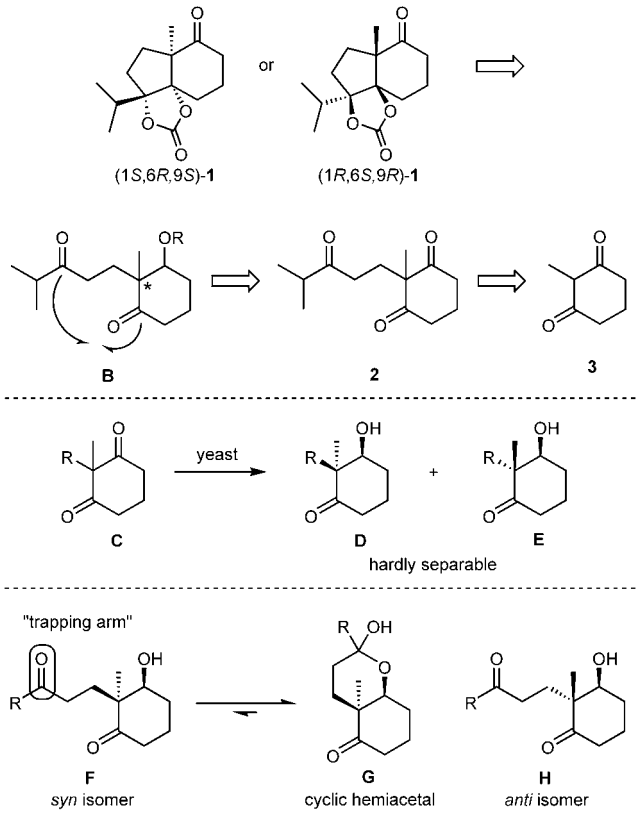


Figure 1.



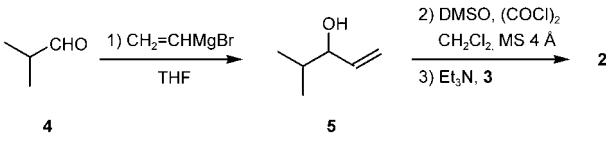
Scheme 1.

Results and Discussion

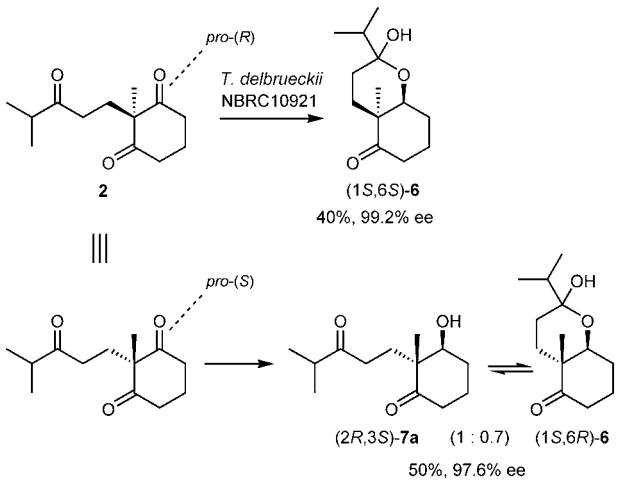
For the preparation of the substrate triketone (**2**), the Michael acceptor is isopropyl vinyl ketone. As the known procedure for generating the vinyl ketone by way of a quaternary ammonium salt[7] was a tedious multistep transformation, another route was developed as shown in Scheme 2. Isobutyl aldehyde was treated with vinylmagnesium bromide to give a volatile allylic alcohol **5**. The partially purified **5** was oxidized under Swern conditions to give an enone.[8] The crude solution of enone was treated with diketone **3** in the presence of triethylamine to give **2** in total 70% yield from **3**.

On the occasion of the whole cell-mediated reduction of **2**, introduction of a sterically bulky isopropyl group greatly affected the stereoselectivity, in comparison to the methyl and ethyl groups,[6,9] although the substituent is located apart from the quaternary carbon atom. So far, in the case of substrates with methyl and ethyl groups, the *Torulaspora delbrueckii* NBRC10921-catalyzed reaction had yielded a single hemiacetal isomer in a good enantiotopic group-selective manner: the *pro*-(*R*) carbonyl group was reduced. In the case of **2**, the enantiotopic group selectivity was very low, and the product seemed a complex mixture, due to the reduction of *pro*-(*S*) carbonyl group. Silica gel TLC analysis indicated a stable component with an R_f value (0.6, hexane-EtOAc = 1:1), which was a nearly pure hemiacetal [(1*S*,6*S*)-**6**] in 40% yield (99.2% ee). Another component showed a broad band on TLC with a long tailing (R_f = 0.5–0.3) and this was an equilibrated mixture (*ca.* 0.7:1) of another hemiacetal [(1*S*,6*R*)-**6**] and a hydroxy ketone [(2*R*,3*S*)-**7a**] in 51% yield (97.6% ee) as shown in Scheme 3. The relative and absolute configurations as well as the stereochemical purity are discussed later. In this case, the introduction of the 'trapping arm' worked very effectively on the separation, by virtue of the difference in intramolecular hemiacetal formation[10] between diastereomers, as expected at the initial event.

When we changed the microorganism to another strain, *Candida floricola* IAM13115, a contrasting sense of stereoselection was observed. The diastereomeric profile of the resulting products was very different from that of the example shown in the previous case. This strain contains a similar enzyme to give hemiacetal [(1*S*,6*S*)-**6**] in 68% yield (94.4% ee), but the action on the *pro*-(*S*) carbonyl group was negligibly low. On the other hand, another enzyme reduces the *pro*-(*R*) car-



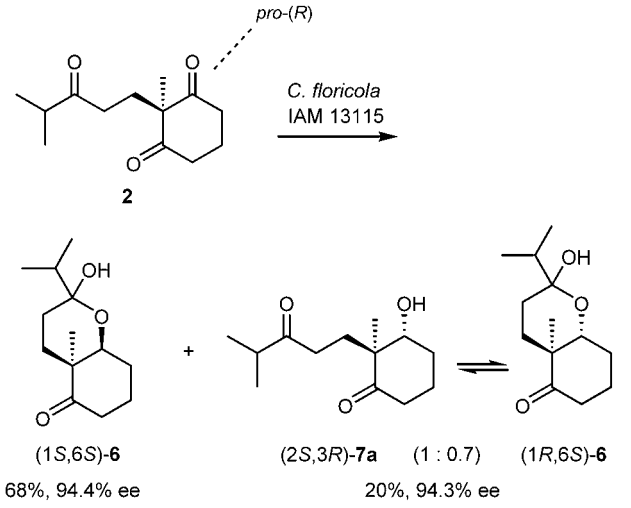
Scheme 2.



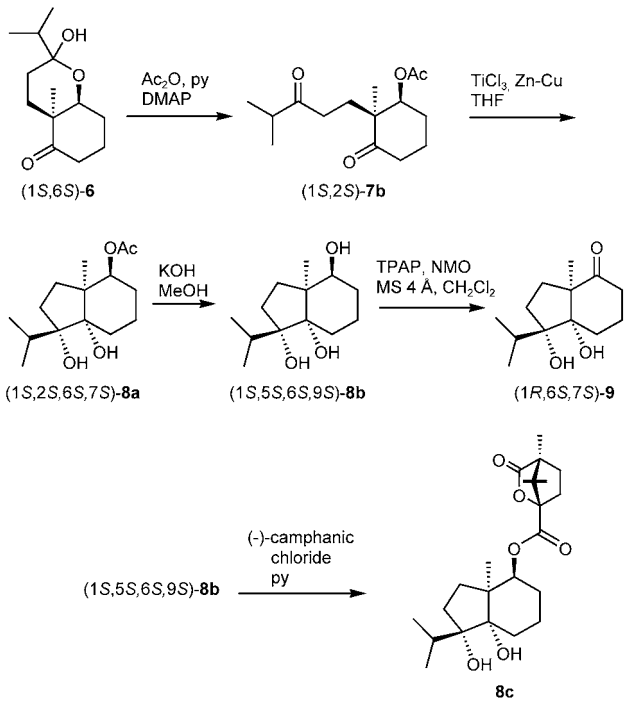
Scheme 3.

bonyl group, however, the reduction proceeds in the opposite enantiofacially selective manner, to give another diastereomeric product, an equilibrated mixture of hemiacetal (1*R*,6*S*)-**6** and hydroxy ketone [(2*S*,3*R*)-**7a**] in 20% yield (94.3% ee) as shown in Scheme 4.

The hemiacetal [(1*S*,6*S*)-**6**] provided by *T. delbrueckii* was submitted to acetylation to provide an acetoxy ketone [(1*S*,2*S*)-**7b**] with a concomitant ring-opening reaction. The pinacol coupling reaction with $TiCl_3$/Zn-Cu in THF[11] proceeded in a completely stereoselective manner to give a diol [(1*S*,2*S*,6*S*,7*S*)-**8a**]. An attempt for the further deoxygenation toward an olefin from diol under forced McMurry conditions[12] only resulted in a complex mixture of the products, as such an olefinic product was unstable even on silica gel TLC. The hydrolysis of the acetate and the subsequent oxidation of the secondary alcohol gave a bicyclic ketone [(1*R*,6*S*,7*S*)-**9**], which was analyzed by HPLC with a chiral stationary phase (ChiralCel OD) to be 99.2% ee (Scheme 5). By virtue



Scheme 4.



Scheme 5.

of the crystalline nature of the intermediate **8a**, its ee was easily raised to 100% by a single recrystallization (mp 129.5–130.0 °C).

In the same manner, the cyclic hemiacetal [(1*S*,6*S*)-**6**] prepared by *C. floricola*-mediated reduction was derived to (1*R*,6*S*,7*S*)-**9** with 94.0% ee, and the enhancement of its ee was also successful. The total relative and absolute configurations of **8b** were confirmed by the X-ray crystallographic analysis of the corresponding (−)-camphanic acid ester **8c** as depicted in Figure 2.

Another chiral product, a mixture of hemiacetal [(1*S*,6*R*)-**6**] and open-chain hydroxy ketone [(2*R*,3*S*)-**7a**] prepared by the reduction with *T. delbrueckii*, was converted into (1*S*,6*R*,7*R*)-**9** (97.6% ee) in a similar manner as described above *via* (1*R*,2*S*,6*R*,7*R*)-**8a** (Scheme 6). The acetate [(1*R*,2*S*,6*R*,7*R*)-**8a**], which is in a diastereomeric relationship with (1*S*,2*S*,6*S*,7*S*)-**8a** was also crystalline, and the enantiomerically pure compound was obtained by a single recrystallization (mp 84.5–85.0 °C).

The third diastereomer of the yeast-mediated chiral product, (2*S*,3*R*)-**7a**, the open-chain hydroxy ketone prepared by the action of *C. floricola*, was equally transformed to (1*R*,6*S*,7*S*)-**9** (94.3% ee). This was converged to (1*S*,2*S*,6*S*,7*S*)-**8a**, whose ee can be raised at this stage, as described above, by $LiAlH_4$-mediated diastereoselective reduction and the subsequent acetylation of the secondary alcohol (Scheme 6).

The diol functional group of (1*S*,2*S*,6*S*,7*S*)-**8a** could be protected as the cyclic carbonate to give **10** in 86% yield. As the contiguous tertiary alcohols have poor nucleo-

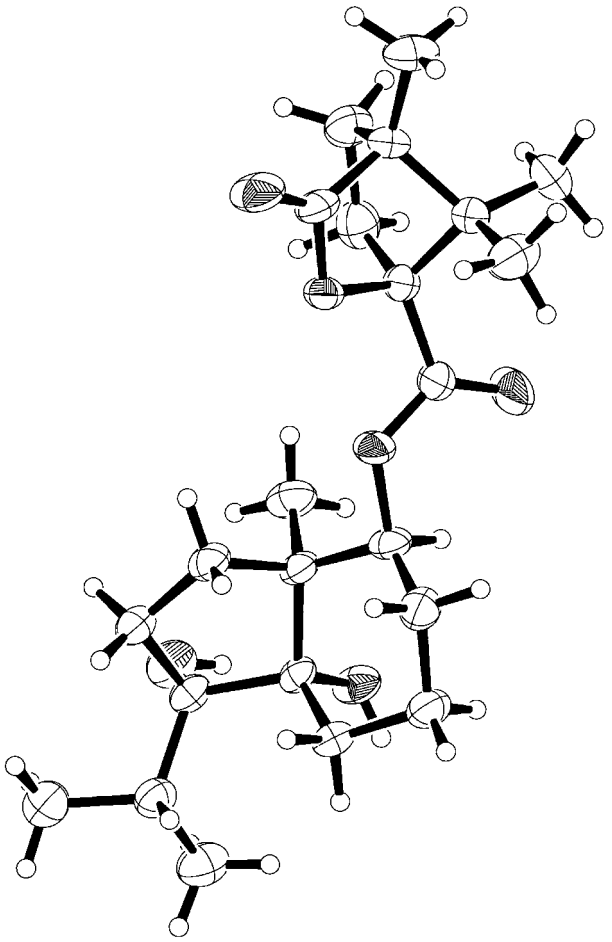
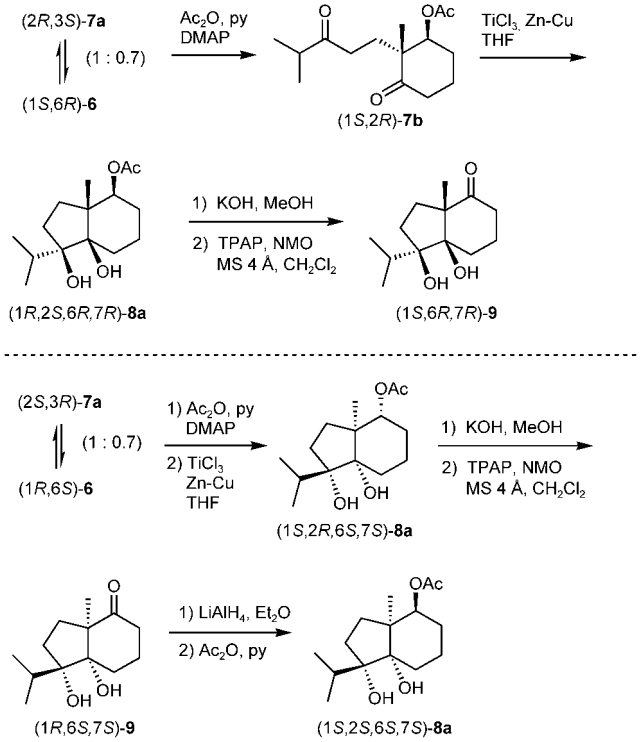
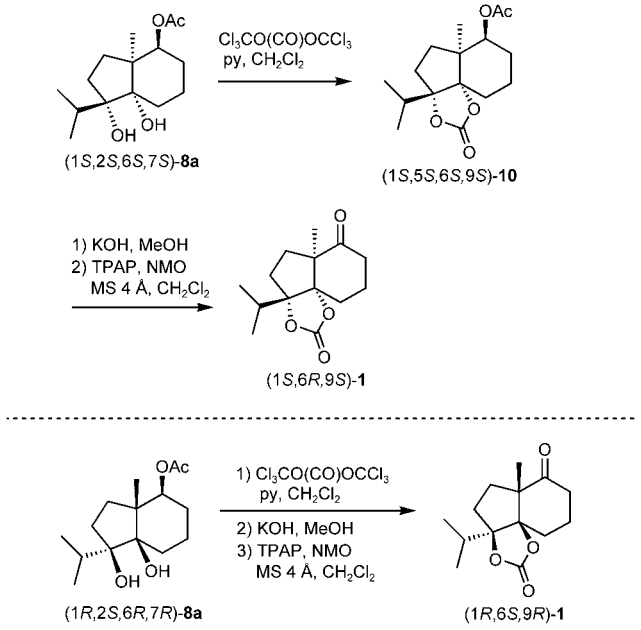


Figure 2.



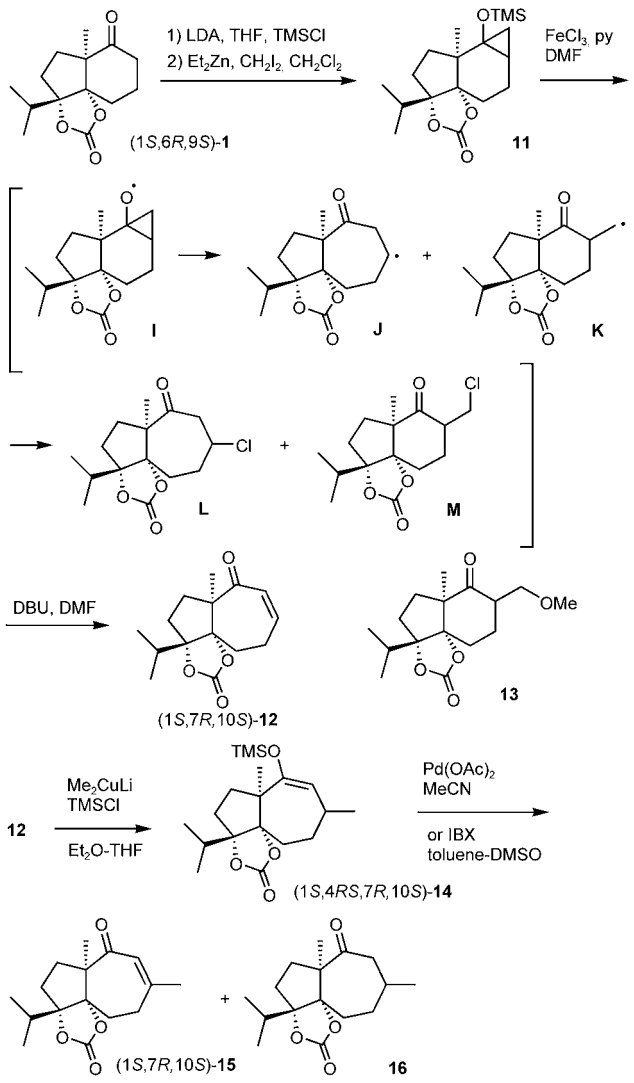
Scheme 6.



Scheme 7.

philicity and are very unstable under acidic conditions, both diacylation and protection with acetonide failed. Then the acetyl group in **10** was selectively hydrolyzed and followed by oxidation of the resulted secondary alcohol to give (1*S*,6*R*,9*S*)-**1** in 87% yield in two steps (Scheme 7). In a similar manner (1*R*,2*S*,6*R*,7*R*)-**8a** was protected, and the subsequent transformations afforded (1*R*,6S,9*R*)-**1** in 84% yield in three steps. The diol moiety in (1*S*,2*S*,6*S*,7*S*)-**8a** was very sterically hindered so that the cyclic carbonate formation was much slower than that of (1*R*,2*S*,6*R*,7*R*)-**8a**. An attempt at cyclic carbonate formation of the less sterically hindered ketone **9** resulted in a lower yield, due to the labile properties of **9** under basic conditions.

Towards daucane sesquiterpenes, the homologation reaction of a six-membered cyclic ketone was elaborated. Due to the highly congested space around the ketone carbonyl group itself as well as the adjacent methylene group, many kinds of nucleophilic and/or electrophilic substitution reactions failed. The enol silyl ether of (1*S*,6*R*,9*S*)-**1** was reacted with zinc carbenoid generated from Et_2Zn/CH_2I_2[13] to give an unstable cyclopropane derivative **11**. The cyclopropane ring was cleaved in a homolytic fashion (**I**–**J**–**L**) by Fe(III),[14] to give the ring-expanded enone [(1*S*,7*R*,10*S*)-**12**] in 42% yield from **1**, followed by the treatment with DBU (Scheme 8). A possible way to the side product which would lower the yield is the undesired primary radical formation (**I**–**K**–**M**), to result in a six-membered ring



Scheme 8.

exomethylene compound. This side reaction was confirmed by the detection of a methanol Michael adduct **13** by way of the enone, under the conditions of NaOAc in methanol, instead of DBU in DMF, was applied as the base treatment.

Finally, the 1,4-addition of Me_2CuLi to the enone **12** and the subsequent trapping as a silyl ether provided **14**. Pd(0)-catalyzed oxidation[15] of silyl ether gave an enone [(1*S*,7*R*,10*S*)-**15**], bearing the complete carbon skeleton of daucane sesquiterpenes and the stereochemically defined methyl group at the angular position, in 21% yield. A by-product, saturated ketone **16** (44%), could be recycled to the silyl ether **14** again. The oxidation of **14** with IBX[16] slightly improved the yield of **15** (25%) with the formation of **16** (25%). The selective formation of **15** (67%) became successful by means of DDQ[17] oxidation.

Conclusion

Yeast-catalyzed asymmetric reduction of cyclic ketones could provide new chiral starting materials for natural product synthesis. The 'trapping arm' worked very well as an internal tether, in the practical sense, to separate the resulting otherwise inseparable diastereomeric products. In addition, we were able to find some interesting aspects of the reductive enzymes, both depending upon the structure of the substrates, and the sort of yeast strain. The resulting products were converted to bicyclic terpenoid intermediates by an intramolecular pinacol coupling reaction.

Experimental Section

All mps are uncorrected. IR spectra were measured as films for oils or KBr disks of solids on a Jasco FT/IR-410 spectrometer. ^{1}H NMR spectra were measured in $CDCl_3$ at 270 MHz on a Jeol JNM EX-270 or at 400 MHz on a Jeol JNM GX-400 spectrometer. High resolution mass spectra were recorded on a Jeol JMS-700 spectrometer. HPLC data were recorded on Jasco PU-2080 and MD-2010 liquid chromatographs. Optical rotation values were recorded on a Jasco DIP 360 polarimeter. Merck silica gel 60 F_{254} thin-layer plates (1.05744, 0.5 mm thickness) and silica gel 60 (spherical and neutral; 100–210 μm, 37560–79) from Kanto Chemical Co., were used for preparative thin-layer chromatography and column chromatography, respectively. Peptone and yeast extract were purchased from Kyokuto Pharmaceutical Co., for the cultivation of microorganism.

T. delbruekii NBRC10921 is available from the Biological Resources to the Biological Resource Center (NBRC), Independent Administrative Institution the National Institute of Technology and Evaluation (NITE), 2-5-8, Kazusakamatari, Kisarazu, Chiba 292-0818, Japan. *C. floricola* IAM13115 is available from Institute of Applied Microbiology Culture Collection; Institute of Molecular and Cellular Biosciences, University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113-0032, Japan.

2-Methyl-2-(4-methyl-3-oxopentyl)-1,3-cyclohexanedione (2)

The preparation of allylic alcohol and the subsequent treatment were according to a slightly modified procedure reported before.[18] To a solution of vinylmagnesium bromide (1.0 mol/L in THF, 115 mL, 0.115 mol) was added isobutylaldehyde (**4**, 8.65 g, 0.120 mol) dropwise at 0 °C and the mixture was stirred for 3 h at 0 °C. The reaction was quenched by the addition of saturated aqueous ammonium chloride solution and the mixture was extracted with ether. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and partially concentrated under vacuum to a volume of *ca.* 20 mL. To the resultant solution of **5** was added molecular sieves 4 Å (7.3 g) and the mixture was stirred for 1 h at room temperature. Separately, a mixture of dichloromethane (120 mL), oxalyl chloride (12 mL, 0.132 mol), and DMSO (20 mL) was prepared at −78 °C, and the above solution of **5**, which was further diluted

with dichloromethane (30 mL), was slowly added. The mixture was stirred for 6 h at −78 °C. Then triethylamine (65 mL, 0.466 mol) was added, and the mixture was gradually allowed to warm to room temperature during 1 h. To the crude solution of enone was added diketone (**3**, 15.47 g, 0.123 mol) was added and the mixture was stirred for 12 h. The reaction was quenched by the addition of saturated aqueous ammonium chloride solution and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was charged on a silica gel column (300 g), and eluted with hexane/ethyl acetate (3/1) to give pure fractions. Combination with the further isolated material from repeated chromatography of the fraction of a mixture with some impurities afforded **2** as a colorless oil; yield: 19.70 g (71% based on **3**); IR: ν_{max} = 1710, 1695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.06 (d, *J* = 6.8 Hz, 6 H), 1.24 (s, 3 H), 1.83–1.94 (m, 1 H), 2.01–2.11 (m, 1 H), 2.05 (t, *J* = 7.3 Hz, 2 H), 2.36 (t, *J* = 7.3 Hz, 3 H), 2.54 (q, *J* = 6.8 Hz, 1 H), 2.58–2.66 (m, 2 H), 2.71–2.79 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.5, 18.0, 19.5, 29.7, 34.8, 37.5, 40.7, 64.2, 209.5, 212.9; anal. calcd. for $C_{11}H_{16}O_3$: C 69.61, H 8.99; found: C 69.59, H 8.94.

Reduction of 2 with *T. delbrueckii* NBRC10921

The wet cells of *T. delbrueckii* NBRC10921 (0.6 g) incubated according to the reported procedure[6] were re-suspended in a reaction medium [containing glucose (0.5 g), phosphate buffer (0.1 M, pH 6.5), total volume of 10 mL] in a test tube (21 mm × 20 cm), together with **2** (101.5 mg, 0.453 mmol) and shaken on a reciprocal shaker (250 cpm) for 24 h at 30 °C. The reaction mixture was filtered through a Celite pad and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was charged on a silica gel column (10 g). Elution with hexane/ethyl acetate (7/1 to 3/1) afforded (1*S*,6*S*)-**6** and a mixture of (2*R*,3*S*)-**7a** and (1*S*,6*R*)-**6**.

(1*S*,6*S*)-3-Hydroxy-3-isopropyl-6-methyl-2-oxabicyclo[4.4.0]decan-7-one (6): yield: 39.9 mg (39%). Recrystallization from hexane/diethyl ether gave an analytical sample of (1*S*,6*S*)-**6** as needles; mp 94.0–95.0 °C; $[\alpha]_D^{20}$: −92.0° (*c* 1.07, EtOH); IR: ν_{max} = 3514, 1700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 7.3 Hz, 3 H), 0.91 (d, *J* = 7.3 Hz, 3 H), 0.93–1.00 (m, 1 H), 1.13 (s, 3 H), 1.41–1.67 (m, 5 H), 1.84 (s, 2 H), 1.99–2.28 (m, 4 H), 2.40–2.59 (m, 1 H), 4.20 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.4, 16.8, 21.4, 24.3, 26.3, 26.5, 27.4, 37.9, 39.1, 47.5, 75.2, 98.7, 214.4; anal. calcd. for $C_{13}H_{22}O_3$: C 68.99, H 9.80; found: C 68.96, H 9.68.

A mixture of (2*R*,3*S*)-3-hydroxy-2-(4-oxopentyl)-2-methylcyclohexanone (7a) and (1*S*,6*R*)-6: yield: 52.2 mg (51%) as a colorless oil; nearly no optical rotation; IR: ν_{max} = 3465, 1704, 1074 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.96–1.15 (m, 9 H), 1.47–2.06 (m, 7 H), 2.16–2.72 (m, 4 H), 3.09 (s, 0.59 H), 3.51 (d, *J* = 8.7 Hz, 0.59 H), 3.94 (dd, *J* = 4.3, 11.7 Hz, 0.41 H). This was revealed to an equilibrated mixture of (2*R*,3*S*)-**7a** and (1*S*,6*R*)-**6** as judged from the signals of δ = 3.09, 3.51, and 3.94. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.1, 16.2, 16.8, 18.3, 18.4, 20.3, 20.8, 25.3, 26.0, 26.2, 27.3, 27.9, 35.6, 36.4, 36.5, 37.4, 38.8, 40.8, 48.3, 54.8, 73.0, 73.3, 98.3, 213.9, 214.1, 216.3.

Pre-Incubation of *C. floricola* IAM13115

A small portion of yeast cells of *C. floricola* IAM13115 grown on the agar-plate culture was aseptically inoculated to a glucose medium [containing glucose (5.0 g), peptone (2.0 g), yeast extract (0.5 g), KH_2PO_4 (0.3 g), K_2HPO_4 (0.2 g), at pH 6.5, total volume 100 mL] in a 500-mL baffled Erlenmeyer cultivating flask with two internal projections and then shaken on a gyro-rotary shaker (180 rpm) for 2 days at 30 °C. The wet cells were harvested by centrifugation (3,000 rpm) and washed with phosphate buffer (0.1 M, pH 6.5). The weight of combined wet cells was *ca.* 2.7 g from 100 mL of the broth.

Reduction of 2 with *C. floricola* IAM13115

The combined wet cells of *C. floricola* IAM13115 (2.0 g) incubated as described above were re-suspended in a reaction medium [containing glucose (0.5 g), phosphate buffer (0.1 M, pH 7.5), total volume of 10 mL] in a test tube (21 mm × 20 cm), together with **2** (104.6 mg, 0.466 mmol) and shaken on a reciprocal shaker (250 cpm) for 24 h at 30 °C. The reaction mixture was filtered through a Celite pad and extracted with ethyl acetate. The filter cake was further extracted with acetone. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified as described before to give (1*S*,6*S*)-**6** (yield: 71.5 mg, 68%) and a mixture of (2*S*,3*R*)-**7a** and (1*R*,6*S*)-**6** (yield: 21.0 mg, 20%).

(1*S*,6*S*)-6: Its spectral data were identical with those described above. Recrystallization from hexane/diethyl ether gave an analytical sample; mp 93.0–93.5 °C; $[\alpha]_D^{20}$: −90.2° (*c* 1.03, EtOH); anal. calcd. for $C_{13}H_{22}O_3$: C 68.99, H 9.80; found: C 69.00, H 9.75.

A mixture of (2*S*,3*R*)-7a and (1*R*,6*S*)-6: nearly no optical rotation; its spectral data were identical with those of the antipodal mixture obtained by the incubation with *T. delbrueckii* as described above.

(1*S*,2*S*)-2-(4-Methyl-3-oxopentyl)-2-methyl-3-oxocyclohexyl Acetate (7b)

A mixture of (1*S*,6*S*)-**6** (4.09 g, 18 mmol), anhydrous pyridine (20 mL), acetic anhydride (10 mL), and a catalytic amount of 4-dimethylaminopyridine was stirred overnight at room temperature. The reaction mixture was poured into 1 M hydrochloric acid and extracted with ethyl acetate. The combined organic layer was washed with saturated aqueous sodium hydrogen carbonate solution and brine, dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was charged on a silica gel column (200 g). Elution with hexane/ethyl acetate (3/1) afforded (1*S*,2*S*)-**7b** as a colorless oil; yield: 4.86 g (quant.); $[\alpha]_D^{22}$: +18.9° (*c* 1.19, EtOH); IR: ν_{max} = 1739, 1712, 1236 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.08 (d, *J* = 6.1 Hz, 6 H), 1.09 (s, 3 H), 1.63–1.72 (m, 1 H), 1.76–1.84 (m, 1 H), 1.89–2.14 (m, 6 H), 2.06 (s, 3 H), 2.33–2.42 (m, 3 H), 2.51–2.62 (m, 1 H), 4.87 (dd, *J* = 3.9 Hz, 3.9 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.2, 18.3, 19.0, 20.5, 21.0, 25.6, 25.9, 34.3, 37.5, 41.0, 52.1, 78.2, 169.9, 211.9, 213.7; anal. calcd. for $C_{15}H_{24}O_4$: C 67.14, H 9.01; found: C 67.32, H 8.91.

(1*S*,2*R*)-2-(4-Methyl-3-oxopentyl)-2-methyl-3-oxocyclohexyl Acetate (7b)

In the same manner as described above, an equilibrated mixture of (2*R*,3*S*)-**7a** and (1*S*,6*R*)-**6** (6.92 g, 30.6 mmol) provided (1*S*,2*R*)-**7b** as a colorless oil; yield: 8.21 g (quant.); $[\alpha]_D^{20}$: −15.2° (*c* 0.94, EtOH); IR: ν_{max} = 1737, 1710, 1236 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.04 (s, 3 H), 1.07 (d, *J* = 6.8 Hz, 3 H), 1.08 (d, *J* = 6.8 Hz, 3 H), 1.73–2.62 (m, 11 H), 5.05 (bs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.8, 18.3, 18.3, 20.7, 21.0, 25.4, 29.2, 34.6, 37.7, 41.0, 52.0, 77.4, 169.9, 212.5, 213.3; anal. calcd. for $C_{15}H_{24}O_4$: C 67.14, H 9.01; found: C 67.24, H 8.97.

(1*S*,2*S*,6*S*,7*S*)-6,7-Dihydroxy-7-isopropyl-1-methylbicyclo[4.3.0]non-2-yl Acetate (8a)

To THF (5 mL, degassed by applying ultrasonic under vacuum three times), titanium trichloride-tris-THF complex (561 mg, 1.514 mmol) and zinc-copper couple (240 mg, 3.674 mmol) were added and the mixture was stirred under reflux under argon to give a black slurry. To this was added dropwise a solution of (1*S*,2*S*)-**7b** (0.076 mmol) in THF (1 mL) over 10 min. The resulting mixture was stirred under reflux again for 1 h. After cooling, the slurry was filtered through a Celite pad and extracted with diethyl ether. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was charged on a silica gel column (3 g). Elution with hexane/ethyl acetate (10/1 to 2/1) afforded (1*S*,2*S*,6*S*,7*S*)-**8a**; yield: 19.1 mg (93%). Recrystallization from hexane/diethyl ether gave an analytical sample of (1*S*,2*S*,6*S*,7*S*)-**8a** as needles; mp 129.5–130.0 °C; $[\alpha]_D^{22}$: +12.8° (*c* 1.01, EtOH); IR: ν_{max} = 3531, 3479, 1710, 1261 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 6.8 Hz, 3 H), 0.93 (d, *J* = 6.8 Hz, 3 H), 1.19 (s, 3 H), 1.29 (s, 3 H), 1.34–1.46 (m, 3 H), 1.59–1.92 (m, 9 H), 2.02 (s, 1 H), 2.03 (s, 3 H), 2.29 (s, 1 H), 4.75 (dd, *J* = 5.1, 11.5 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.9, 18.0, 19.6, 21.3, 21.4, 26.8, 27.0, 31.3, 33.6, 34.5, 48.6, 78.0, 83.5, 83.9, 170.9; anal. calcd. for $C_{15}H_{26}O_4$: C 66.64, H 9.69; found: C 66.75, H 9.66.

(1*R*,2*S*,6*R*,7*R*)-6,7-Dihydroxy-7-isopropyl-1-methylbicyclo[4.3.0]non-2-yl Acetate (8a)

In the similar manner as described above, (1*S*,2*R*)-**7b** (21.4 mg, 0.08 mmol) provided (1*R*,2*S*,6*R*,7*R*)-**8a** as colorless needles; yield: 20.2 mg (94%); mp 84.0–84.5 °C; $[\alpha]_D^{24}$: +11.9° (*c* 1.03, EtOH); IR: ν_{max} = 3534, 1731, 1242 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 6.4 Hz, 3 H), 0.90 (d, *J* = 6.4 Hz, 3 H), 1.22 (s, 3 H), 1.42–1.54 (m, 3 H), 1.58–1.66 (m, 1 H), 1.70–1.82 (m, 6 H), 2.07 (s, 3 H), 2.58 (s, 1 H), 2.67 (s, 3 H), 4.85 (bs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.0, 16.8, 17.9, 21.3, 22.3, 25.6, 30.7, 31.1, 33.4, 33.9, 47.0, 77.7, 82.3, 83.9, 169.9; anal. calcd. for $C_{15}H_{26}O_4$: C 66.64, H 9.69; found: C 66.60, H 9.61.

(1*S*,2*R*,6*S*,7*S*)-6,7-Dihydroxy-7-isopropyl-1-methylbicyclo[4.3.0]non-2-yl Acetate (8a)

In the similar manner as described above, an equilibrated mixture of (2*S*,3*R*)-**7a** and (1*R*,6*S*)-**6** (954 mg, 4.22 mmol) provided (1*S*,2*R*,6*S*,7*S*)-**8a** in two steps as colorless needles; yield: 877 mg (88%); mp 84.0–84.5 °C; $[\alpha]_D^{25}$: −9.3° (*c* 0.58, EtO H). Its spectral data were identical with those reported for (1*R*,2*S*,6*R*,7*R*)-**8a**; anal. calcd. for $C_{15}H_{26}O_4$: C 66.64, H 9.69; found: C 66.60, H 9.68.

(1*S*,5*S*,6*S*,9*S*)-9-Isopropyl-6-methylbicyclo[4.3.0]nonane-1,5,9-triol (8b)

Acetate (1*S*,2*S*,6*S*,7*S*)-**8a** (34.1 mg, 0.126 mmmol) was treated with a methanolic potassium hydroxide solution (10%) in the conventional manner. The reaction mixture was poured into 1 M hydrochloric acid, saturated with sodium chloride, and extracted with ethyl acetate. The combined organic layer was washed with saturated aqueous sodium hydrogen carbonate solution and brine, dried over anhydrous sodium sulfate, and concentrated under vacuum to afford (1*S*,5*S*,6*S*,9*S*)-**8b**; yield: 31.7 mg (quant.); IR: ν_{max} = 3421, 1009, 978 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 6.8 Hz, 3 H), 0.93 (d, *J* = 6.8 Hz, 3 H), 1.31–1.44 (m, 3 H), 1.35 (s, 3 H), 1.55–1.73 (m, 4 H), 1.77–1.90 (m, 4 H), 1.99 (s, 1 H), 2.04 (s, 1 H), 2.29 (s, 1 H), 3.51 (dd, *J* = 4.9, 11.7 Hz, 1 H). This was employed for the next step without further purification.

(1*S*,2*S*,6*S*,7*S*)-6,7-Dihydroxy-7-isopropyl-1-methylbicyclo[4.3.0]non-2-yl Camphanate (8c)

Triol (1*S*,5*S*,6*S*,9*S*)-**8b** (30.1 mg, 0.132 mmmol) was treated with (−)-camphanic chloride in the presence of DMAP in a conventional manner to give **8c**; yield: 54.6 mg (quant.). Recrystallization from hexane/diethyl ether gave an analytical sample of **8c** as colorless needles; mp 129.5–130.0 °C; $[\alpha]_D^{22}$: +12.6° (*c* 1.07, EtOH); IR: ν_{max} = 3531, 3500, 1760, 1724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 6.8 Hz, 3 H), 0.94 (d, *J* = 6.4 Hz, 3 H), 0.96 (s, 3 H), 1.05 (s, 3 H), 1.11 (s, 3 H), 1.21–1.52 (m, 3 H), 1.23 (s, 3 H), 1.64–2.04 (m, 11 H), 1.95 (s, 1 H), 2.36–2.43 (m, 1 H), 2.40 (s, 1 H), 4.92 (dd, *J* = 4.9, 11.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.8, 16.9, 16.9, 18.0, 19.4, 21.5, 21.5, 27.0, 27.2, 29.0, 30.6, 31.2, 33.6, 34.6, 48.6, 54.0, 54.8, 79.9, 83.6, 84.0, 91.3, 167.1, 178.3; anal. calcd. for $C_{23}H_{36}O_6$: C 67.62, H 8.88; found: C 67.35, H 8.78.

(1*R*,6*S*,7*S*)-6,7-Dihydroxy-7-isopropyl-1-methylbicyclo[4.3.0]non-2-one (9)

To a solution of (1*S*,5*S*,6*S*,9*S*)-**8b** (31.7 mg, 0.139 mmol) in dichloromethane (1.5 mL) was added *N*-methylmorpholine *N*-oxide (44.3 mg, 0.378 mmol), molecular sieves 4 Å (*ca.* 50 mg), and TPAP (2.2 mg, 0.006 mmol), and the mixture was stirred for 2 h at room temperature. The mixture was concentrated under vacuum and the residue was charged on a silica gel column (3 g). Elution with hexane/ethyl acetate (3/1) afforded (1*R*,6*S*,7*S*)-**9** as colorless solid; yield: 27.6 mg (97%); IR: ν_{max} = 3539, 3437, 1687, 1188, 1012 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 6.8 Hz, 3 H), 0.99 (d, *J* = 6.8 Hz, 3 H), 1.30 (s, 3 H), 1.39–1.46 (m, 1 H), 1.55–1.68 (m, 3 H), 1.76–1.96 (m, 4 H), 1.87 (s, 1 H), 2.11–2.25 (m, 2 H), 2.30–2.38 (m, 1 H), 2.52–2.60 (m, 1 H), 2.92 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.6, 18.1, 19.0, 21.6, 31.1, 31.5,

32.8, 34.6, 35.8, 59.1, 84.9, 85.4, 216.1; HPLC analysis [column, Daicel Chiralcel OD, 0.46 cm × 25 cm; hexane/2-propanol (30/1); flow rate 1.0 mL/min, detected at 211 nm]: tR = 15.7 min for (1*S*,7a*S*)-**9**, 17.1 min for (1*R*,6*S*,7*S*)-**9**, the ee of (1*S*,6*R*,7*R*)-**9** was determined to be 99.2%.

Recrystallization from hexane/diethyl ether gave an analytical sample of (1*R*,6*S*,7*S*)-**9** as needles; mp 102.5–103.0 °C; $[\alpha]_D^{23}$: −36.0° (*c* 0.54, EtOH); anal. calcd. for $C_{13}H_{22}O_3$: C 68.99, H 9.80; found: C 66.86, H 9.74. The recrystallized sample at the stage of (1*S*,2*S*,6*S*,7*S*)-**8a** either from 99.4% (*T. delbrueckii*) or 94% ee (*C. floricola*) was revealed to be enantiomerically pure as judged from the HPLC analysis of **9** as described above.

On the other hand, the sample (1*R*,6*S*,7*S*)-**9** was 94.3% ee, prepared from (1*S*,2*R*,6*S*,7*S*)-**8a** originating from the incubation with *C. floricola*, as judged from the HPLC analysis. Recrystallization from hexane/diethyl ether gave an analytical sample of (1*R*,6*S*,7*S*)-**9** as needles; mp 102.5–103.0 °C; $[\alpha]_D^{24}$: −37.0° (*c* 1.02, EtOH). The intermediate, (1*S*,5*R*,6*S*,9*S*)-**8b** showed the following ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (d, J = 6.4 Hz, 6 H), 1.32–1.59 (m, 4 H), 1.34 (s, 3 H), 1.66–1.81 (m, 5 H), 1.86–1.97 (m, 2 H), 2.58 (s, 1 H), 3.21 (s, 1 H), 3.64 (bs, 1 H).

(1*S*,6*R*,7*R*)-6,7-Dihydroxy-7-isopropyl-1-methylbicyclo[4.3.0]non-2-one (9)

In the same manner as described for (1*R*,6*S*,7*S*)-**9**, (1*R*,2*S*,6*R*,7*R*)-**8a** (32.6 mg, 0.121 mmol) provided (1*S*,6*R*,7*R*)-**9** in two steps; yield: 20.0 mg (73%). Its spectral data were identical with those for (1*R*,6*S*,7*S*)-**9**. The ee of (1*S*,6*R*,7*R*)-**9** was determined to be 97.6% HPLC analysis as described above.

Recrystallization from hexane/diethyl ether gave an analytical sample of (1*S*,6*R*,7*R*)-**9** as needles; mp 102.5–103.0 °C; $[\alpha]_D^{24}$: +37.7° (*c* 0.62, EtOH); HR-MS (FAB$^+$): calcd. for $C_{13}H_{22}O_3$: [M + Na$^+$]: 249.1467; found: m/z = 249.1449. The recrystallized sample at the stage of (1*R*,2*S*,6*R*,7*R*)-**8a** was revealed to be enantiomerically pure as judged from the HPLC analysis of **9**.

(1*S*,2*S*,6*S*,7*S*)-6,7-Dihydroxy-7-isopropyl-1-methylbicyclo[4.3.0]non-2-yl Acetate (8a)

To a solution of the ketone (1*R*,6*S*,7*S*)-**9** (31.3 mg, 0.138 mmol), which was prepared from (1*S*,2*R*,6*S*,7*S*)-**8a** originated from the incubation with *C. floricola*, in anhydrous diethyl ether (1.5 mL) was added lithium aluminum hydride (10 mg, 0.264 mmol) at 0 °C and the mixture was stirred at room temperature. Then the reaction was quenched with an excess amount of 1 M hydrosulfuric acid the mixture was extracted several times with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was charged on a silica gel column (2 g). Elution with hexane/ethyl acetate (4/1) afforded the recovery of (1*R*,6*S*,7*S*)-**9** (9.8 mg, 31%) and (1*S*,5*S*,6*S*,9*S*)-**8b**; yield: 19.1 mg (60%). Its ^{1}H NMR was identical with that of (1*S*,5*S*,6*S*,9*S*)-**8b** as described before and easily distinguished with that of the diastereomeric (1*S*,5*R*,6*S*,9*S*)-**8b** as above.

Acetylation of this sample (18.4 mg, 0.081 mmol) in the conventional manner provided (1*S*,2*S*,6*S*,7*S*)-**8a**; yield: 20.0 mg (91%). Its spectral data were identical with those for the authentic (1*S*,2*S*,6*S*,7*S*)-**8a** as described above; mp 129.5–130.0 °C; $[\alpha]_D^{20}$: +12.5° (*c* 0.98, EtOH).

(1*S*,5*S*,6*S*,9*S*)-9-Isopropyl-6-methyl-11-oxo-10,12-dioxatricyclo[7.3.0.0^{1,6}]dodec-5-yl Acetate (10)

To a solution of (1*S*,2*S*,6*S*,7*S*)-**8a** (2.277 g, 8.424 mmol) in dichloromethane (50 mL) and pyridine (13.6 mL) was added a solution of triphosgene (12.5 g, 0.042 mmol) in dichloromethane (30 mL) at −78 °C. The reaction mixture was warmed to room temperature, then heated under reflux with stirring for 16 h. The reaction was quenched by the addition of saturated aqueous ammonium chloride solution and the mixture was extracted with ethyl acetate. The combined organic layer was washed with 1 M hydrochloric acid, saturated aqueous sodium hydrogen carbonate solution and brine, dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was charged on a silica gel column (200 g). Elution with hexane/ethyl acetate (5/1 to 3/1) afforded (1*S*,5*S*,6*S*,9*S*)-**10**; yield: 2.15 g (86%). Recrystallization from hexane/diethyl ether gave an analytical sample of (1*S*,5*S*,6*S*,9*S*)-**10** as colorless prisms; mp 85.5–86.0 °C; $[\alpha]_D^{20}$: −23.6° (*c* 0.48, EtOH); IR: ν_{max} = 1797, 1739, 1240, 1020 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (d, J = 6.8 Hz, 3 H), 1.08 (d, J = 6.4 Hz, 3 H), 1.14 (s, 3 H), 1.52–1.80 (m, 5 H), 1.86–2.14 (m, 6 H), 4.94 (dd, J = 4.4, 4.9 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.9, 17.2, 18.7, 21.5, 21.9, 24.9, 26.9, 32.2, 33.6, 33.7, 49.6, 77.2, 93.9, 99.1, 154.5, 169.7; anal. calcd. for $C_{16}H_{24}O_5$: C 64.84, H 8.16; found: C 64.96, H 8.05.

(1*S*,6*R*,9*S*)-9-Isopropyl-6-methyl-10,12-dioxatricyclo[7.3.0.0^{1,6}]dodecane-5,11-dione (1)

Through the deprotection of acetate and subsequent oxidation in a similar manner as described for (1*S*,5*S*,6*S*,9*S*)-**8b** and (1*R*,6*S*,7*S*)-**9**; the cyclic carbonate (1*S*,5*S*,6*S*,9*S*)-**10** (871.3 mg, 2.94 mmol) provided (1*S*,6*R*,9*S*)-**1**; yield: 648.6 mg (87%). Recrystallization from hexane/diethyl ether gave an analytical sample of (1*S*,6*R*,9*S*)-**1** as needles; mp 118.5–119.0 °C; $[\alpha]_D^{21}$: −42.5° (*c* 1.0, EtOH); IR: ν_{max} = 1778, 1714 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 (d, J = 6.8 Hz, 3 H), 1.10 (d, J = 6.8 Hz, 3 H), 1.29 (s, 3 H), 1.31–1.48 (m, 1 H), 1.66–1.71 (m, 1 H), 1.91 (q, J = 6.8, 6.8 Hz, 3 H), 2.01–2.08 (m, 2 H), 2.14–2.37 (m, 3 H), 2.57–2.65 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.2, 18.8, 18.8, 20.7, 28.7, 30.1, 31.7, 34.5, 36.4, 61.4, 95.0, 98.5, 153.7, 210.6; anal. calcd. for $C_{14}H_{20}O_4$: C 66.65, H 7.99; found: C 66.44, H 7.97.

(1*R*,6*S*,9*R*)-9-Isopropyl-6-methyl-10,12-dioxatricyclo[7.3.0.0^{1,6}]dodecane-5,11-dione (1)

In a similar manner as described for (1*S*,2*S*,6*S*,7*S*)-**8a**, the diol moiety of (1*R*,2*S*,6*R*,7*R*)-**8a** (49.8 mg, 0.184 mmol) was protected as the cyclic carbonate to provide (1*R*,5*S*,6*R*,9*R*)-**10** as colorless oil; yield: 49.4 mg (90%); IR: ν_{max} = 1780, 1734, 1238, 1026 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.08 (d, J =

6.8 Hz, 3 H), 1.12 (d, $J=6.8$ Hz, 3 H), 1.16 (s, 3 H), 1.40–1.54 (m, 3 H), 1.58–1.66 (m, 4 H), 1.76–1.87 (m, 3 H), 1.93–2.11 (m, 3 H), 2.08 (s, 3 H), 2.19–2.25 (m, 1 H), 4.70 (dd, $J=4.4$, 11.7 Hz, 1 H). This was employed for the next step without further purification. The deprotection of acetate of (1*R*,5*S*,6*R*,9*R*)-**10** (15.2 mg, 0.051 mmol) and the subsequent oxidation as in the similar manner for (1*S*,5*S*,6*S*,9*S*)-**10** provided (1*R*,6*S*,9*R*)-**1**; yield: 12.1 mg (93%). Recrystallization from hexane/diethyl ether gave an analytical sample of (1*R*,6*S*,9*R*)-**1** as needles; mp 118.5–119.0 °C; $[\alpha]_D^{24}$: +43.0° (*c* 0.19, EtOH); anal. calcd. for $C_{14}H_{20}O_4$: C 66.65, H 7.99; found: C 66.45, H 7.98. Its IR and NMR spectra were identical with those for (1*S*,6*R*,9*S*)-**1**.

(1*S*,7*R*,10*S*)-10-Isopropyl-7-methyl-11,13-dioxatricyclo[8.3.0.0^{1,7}]tridec-4-ene-6,12-dione (12)

To an LDA solution, separately obtained by the addition of *n*-butyllithium (2.71 M in hexane, 700 μL, 1.897 mmol) to a solution of diisopropylamine (330 μL, 2.355 mmol) in THF (3.0 mL) at 0 °C, a solution of (1*S*,6*R*,9*S*)-**1** (96.5 mg, 0.382 mmol) in THF (2.0 mL) was added at −78 °C and the mixture was stirred for 30 min. Then trimethylsilyl chloride (240 μL, 1.891 mmol) was added and the mixture was further stirred at −78 °C for 2 h. The reaction was quenched by the addition of saturated aqueous sodium hydrogen carbonate solution and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and partially concentrated under vacuum. The residue was diluted with dichloromethane (8.0 mL) and diethylzinc (1.0 M in hexane, 2.0 mL, 2.0 mmol) and diiodomethane (300 μL, 3.72 mmol) were added and the mixture was stirred under reflux for 1 d. Then diethylzinc (1.0 M in hexane, 2.0 mL, 2.0 mmol) and diiodomethane (300 μL, 3.72 mmol) were further added and the mixture was stirred again under reflux for another 1 d. The reaction was quenched by the addition of saturated aqueous sodium hydrogen carbonate solution and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and partially concentrated under vacuum to give a crude cyclopropane derivative **11**; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.01 (s, 9 H), 0.27 (dd, $J=6.4$, 6.4 Hz, 1 H), 0.60–0.78 (m, 1 H), 0.73 (d, $J=6.8$ Hz, 3 H), 0.86 (d, $J=6.4$ Hz, 3 H), 1.07–1.13 (m, 1 H), 1.21–1.46 (m, 5 H), 1.27 (s, 3 H), 1.50–1.68 (m, 2 H), 1.81 (dd, $J=6.8$, 7.3 Hz, 1 H), 1.89–1.96 (m, 1 H). This was employed for the next step without further purification.

Ferric chloride (450 mg, 2.77 mmol) was dried by evacuation (at 10 mmHg) at 80 °C for 2 h. This was suspended in anhydrous DMF (2.0 mL) and pyridine (224 μL, 2.77 mmol) and the mixture was degassed by applying ultrasonics under vacuum three times. Then a solution of the above crude **11** in anhydrous DMF (2.0 mL) was added and further degassed in the same manner. The mixture was stirred at 80 °C for 30 min and then at 120 °C for 6 h. The reaction was quenched by the addition of 1 M hydrochloric acid and the mixture was extracted with diethyl ether. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and partially concentrated under vacuum. The residue was diluted again with anhydrous DMF (4.0 mL) and DBU (57 μL, 0.381 mmol) was added, and the resulting mixture was stirred at 80 °C for 1 h. The reaction was quenched by the addition of 1 M hydrochloric acid and the mixture was extracted with diethyl ether. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and partially concentrated under vacuum. The residue was charged on a silica gel column (10 g). Elution with hexane/ethyl acetate (3/1) afforded (1*S*,7*R*,10*S*)-**12**; yield: 42.9 mg (42%). Recrystallization from hexane/diethyl ether gave an analytical sample of (1*S*,7*R*,10*S*)-**12** as colorless prisms; mp 149.0–149.5 °C; $[\alpha]_D^{24}$: +43.4° (*c* 0.19, EtOH); IR: $\nu_{max}=1801$, 1671, 1259, 1026 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (d, $J=6.9$ Hz, 3 H), 1.07 (d, $J=6.6$ Hz, 3 H), 1.35 (s, 3 H), 1.46–1.59 (m, 1 H), 1.69–1.96 (m, 3 H), 2.01–2.09 (m, 1 H), 2.39–2.59 (m, 3 H), 2.72–2.84 (m, 1 H), 5.97 (dd, $J=3.3$, 11.6 Hz, 1 H), 5.94–6.00 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.6, 19.0, 23.1, 26.5, 31.4, 32.5, 32.8, 34.4, 65.2, 93.6, 100.0, 130.2, 143.6, 153.6, 203.0; anal. calcd. for $C_{15}H_{20}O_4$: C 68.16, H 7.63; found: C 68.16, H 7.54.

(1*S*,7*R*,10*S*)-10-Isopropyl-4,7-dimethyl-11,13-dioxatricyclo[8.3.0.0^{1,7}]tridec-4-ene-6,12-dione (15)

To a lithium dimethylcuprate solution, separately prepared by the addition of methyllithium (0.98 M in diethyl ether, 1.80 mL, 1.76 mmol) to a suspension of cuprous iodide (170 mg, 0.89 mmol) in diethyl ether (3.0 mL) at 0 °C, trimethylsilyl chloride (106 μL, 0.84 mmol) and a solution of (1*S*,7*R*,10*S*)-**12** (23.3 mg, 0.088 mmol) in THF (0.5 mL) were added at −78 °C and the mixture was stirred for 30 min. The reaction was quenched by the addition of saturated aqueous ammonium chloride solution and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was charged on a silica gel column (1 g). Elution with hexane/ethyl acetate (5/1) afforded (1*S*,4*RS*,7*R*,10*S*)-10-isopropyl-4,7-dimethyl-6-trimethylsilyloxy-11,13-dioxatricyclo[8.3.0.0^{1,7}]tridec-5-en-12-one (**14**) as a colorless oil; yield: 24.2 mg (78%); IR: $\nu_{max}=1710$, 1695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.19 (s, 9 H), 0.97 (d, $J=6.4$ Hz, 3 H), 1.05 (d, $J=6.8$ Hz, 3 H), 1.06 (d, $J=6.8$ Hz, 3 H), 1.24–1.43 (m, 2 H), 1.39 (s, 3 H), 1.62–1.82 (m, 5 H), 1.92–2.13 (m, 4 H), 4.66 (d, $J=5.8$ Hz, 1 H). This was employed for the next step without further purification.

Silyl ether **14** (11.4 mg, 0.032 mmol) was diluted with anhydrous acetonitrile (1.0 mL) and palladium acetate (10 mg, 0.045 mmol) was added, and the resulting mixture was stirred under reflux overnight. The mixture was filtered through a Celite pad and the filter cake was washed with ethyl acetate. The combined filtrate and washings were concentrated under vacuum and the residue was purified on silica gel preparative TLC [10 cm × 10 cm, developed with hexane/ethyl acetate (3/2)] to provide the desired (1*S*,7*R*,10*S*)-**15** and (1*S*,4*RS*,7*R*,10*S*)-**16** as a byproduct.

(1*S*,7*R*,10*S*)-10-Isopropyl-4,7-dimethyl-11,13-dioxatricyclo[8.3.0.0^{1,7}]tridec-4-ene-6,12-dione (15): yield: 1.9 mg (21%) as colorless solid; IR: $\nu_{max}=1803$, 1666, 1254, 1030 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (d, $J=6.8$ Hz, 3 H), 1.06 (d, $J=6.4$ Hz, 3 H), 1.25–1.28 (m, 1 H), 1.32 (s, 3 H), 1.45–1.53 (m, 1 H), 1.69–1.77 (m, 1 H), 1.81–2.05 (m, 2 H), 1.93 (s, 3 H), 2.31–2.50 (m, 3 H), 2.79–2.86 (m, 1 H), 5.82 (s, 1 H). This was employed for the next step without further purification.

(*1S,4RS,7R,10S*)-10-Isopropyl-4,7-dimethyl-11,13-dioxatricyclo[8.3.0.0^{1,7}]tridecane-6,12-dione (16): yield: 3.9 mg (44%) as a diastereomeric mixture; IR: ν_{max} = 1795, 1703, 1460, 1271, 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98 (d, J = 6.8 Hz, 3 H), 1.04 (d, J = 5.9 Hz, 6 H), 1.25–1.36 (m, 2 H), 1.38 (s, 3 H), 1.62–1.78 (m, 4 H), 1.76 (dd, J = 6.4, 6.8 Hz, 1 H), 2.01–2.10 (m, 3 H), 2.22–2.30 (m, 2 H), 2.75–2.80 (m, 1 H). Its conversion to the trimethylsilyl ether (**14**) confirmed the saturated structure.

In a separate procedure, starting from enone **12** (11.1 mg, 0.042 mmol), the enol silyl ether **14** was prepared in a same manner. The crude **14** was dissolved in a mixture of DMSO (0.25 mL) and toluene (0.5 mL), IBX (24 mg, 0.086 mmol) was added and the mixture was stirred at 80 °C for 15 h. The reaction was quenched by the addition of saturated aqueous sodium hydrogen carbonate solution and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was purified with a silica gel preparative TLC [10 cm × 10 cm, developed with hexane/ethyl acetate (3/2)]. The desired enone **15** (2.9 mg, 25%) and the saturated byproduct **16** (3.0 mg, 25%) were obtained, and the spectral data were identical with those reported as above.

An Improved Oxidation with DDQ

To a stirred solution of DDQ (400 mg, 1.76 mmol) and HMDS (372 μL, 1.76 mmol) in dry benzene (2.0 mL), a solution of (1*S*,4*RS*,7*R*,10*S*)-**14** (24.2 mg, 0.069 mmol) in dry benzene (1.0 mL) was added, and the resulting mixture was heated under reflux with stirring for 30 min. The reaction was quenched by the addition of saturated aqueous sodium hydrogen carbonate solution and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated under vacuum. The residue was charged on a silica gel column (2 g) and eluted with ethyl acetate to remove most of the excess DDQ. The eluent was concentrated under vacuum, and the residue was charged again on a silica gel column (2 g). Elution with hexane/ethyl acetate (5/1) afforded (1*S*,7*R*,10*S*)-**15**; yield: 16.5 mg (86%). Recrystallization from hexane/diethyl ether gave an analytical sample as colorless needles; mp 140.0–140.5 °C; $[\alpha]_D^{20}$: +48.9° (*c* 0.18, EtOH). Its IR and ^{1}H NMR data were identical with those given above. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.7, 19.0, 23.4, 25.5, 31.4, 31.5, 32.6, 32.8, 34.0, 64.7, 93.4, 100.1, 126.8, 153.7, 155.0, 202.2; anal. calcd. for $C_{16}H_{22}O_4$: C 69.04, H 7.97; found: C 68.89, H 7.92.

X-Ray Crystal Structure Analysis of 8c

Crystal data: orthorhombic, $P2_12_12_1$, a = 11.4474(10), b = 30.547(5), c = 6.4964(10) Å, V = 2271.7(5) Å^3, Z = 4, D_x = 1.194 g cm^{-3}. A colorless needle crystal grown from hexane-Et_2O was used. The X-ray intensities were measured on a Rigaku AFC-7R four-circle diffractometer with Mo Kα irradiation. The positional and anisotropic displacement parameters of non-H atoms were refined. The hydroxy H atoms were located from difference syntheses and the other H atoms were positioned geometrically (R = 0.0433).

The absolute structure was assigned based on the known absolute configuration of (+)-camphor (2-bornanone). There are intramolecular and intermolecular O–H...O hydrogen bonds, forming molecular chains along the *a* axis. Calculations were performed using the TEXSAN crystallographic software package (Version 1.11) of Molecular Structure Corporation.

Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number CCDC-258374.

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References and Notes

[1] a) Daucene: G. V. Pigulevskii, V. I. Kovaleva, *Dokl. Acad. Nauk SSSR* **1961**, *141*, 1384–1385; b) aphanamol I: M. Nishizawa, A. Inoue, Y. Hayashi, S. Sastrapradja, S. Kosela, T. Iwashita, *J. Org. Chem.* **1984**, *49*, 3660–3662.

[2] a) Araneosene: J. Luzi, H.-J. Borschberg, *Helv. Chim. Acta* **1995**, *78*, 715–731; b) allocyatin B2: W. A. Ayer, S. P. Lee, *Can. J. Chem.* **1979**, *57*, 3332–3337; c) hamigeran B: K. D. Wellington, R. C. Cambie, P. S. Rutledge, P. R. Bergquist, *J. Nat. Prod.* **2000**, *63*, 79–85; d) dolatriol: G. R. Pettit, R. H. Ode, C. L. Herald, R. B. Von Dreele, C. Michel, *J. Am. Chem. Soc.* **1976**, *98*, 4677–4678.

[3] a) S. Servi, *Synthesis* **1990**, 1–25; b) R. Csuk, B. I. Glänzer, *Chem. Rev.* **1991**, *91*, 49–97; c) T. Sugai, *Curr. Org. Chem.* **1999**, *3*, 373–406; d) K. Fuhshuku, S. Oda, T. Sugai, *Recent Res. Devel. Org. Chem.* **2002**, *6*, 57–74; e) K. Nakamura, R. Yamanaka, T. Matsuda, T. Harada, *Tetrahedron: Asymmetry* **2003**, *14*, 2659–2681.

[4] a) D. W. Brooks, H. Mazdiyasni, P. G. Grothaus, *J. Org. Chem.* **1987**, *52*, 3223–3232; b) Z.-L. Wei, Z.-Y. Li, G.-Q. Lin, *Synthesis* **2000**, 1673–1676.

[5] W. Zhou, D. Huang, Z. Wang, *Kexue Tongbao* **1980**, *25*, 741–742.

[6] K. Fuhshuku, N. Funa, T. Akeboshi, H. Ohta, H. Hosomi, S. Ohba, T. Sugai, *J. Org. Chem.* **2000**, *65*, 129–135.

[7] C. Rochin, O. Babot, J. Dungues, F. Duboudin, *Synthesis* **1986**, 667–668.

[8] D. H. Philip, C. B. Andrew, L. N. David, *Synth. Commun.* **1991**, *21*, 2157–2163.

[9] K. Fuhshuku, M. Tomita, T. Sugai, *Adv. Synth. Catal.* **2003**, *345*, 766–774.

[10] K. Mori, H. Watanabe, *Tetrahedron* **1985**, *41*, 3423–3428.

[11] I. Ben, L. Castedo, J. M. Saá, J. A. Seijas, R. Suau, G. Tojo, *J. Org. Chem.* **1985**, *50*, 2236–2240.

[12] M. Ephritikhine, *Chem. Commun.* **1998**, 2549–2554.

[13] S. E. Denmark, J. P. Edwards, *J. Org. Chem.* **1991**, *56*, 6974–6981.
[14] Y. Ito, S. Fujii, T. Saegusa, *J. Org. Chem.* **1976**, *41*, 2073–2074.
[15] Y. Ito, T. Hirao, T. Saegusa, *J. Org. Chem.* **1978**, *43*, 1011–1013.
[16] K. C. Nicolaou, D. L. F. Gray, T. Montagnon, S. T. Harrison, *Angew. Chem. Int. Ed.* **2002**, *41*, 996–1000.
[17] I. Ryu, S. Murai, Y. Hatayama, N. Sonoda, *Tetrahedron Lett*. **1978**, 3455–3458.
[18] M. M. Midland, R. W. Koops, *J. Org. Chem.* **1990**, *55*, 5058–5065.

