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# Asymmetric Aldol Condensation as a Route to Polypropionate Derived Pheromones

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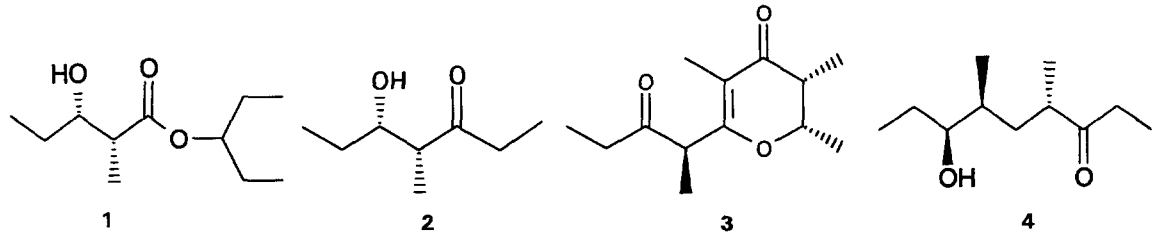
**Abstract**—The synthesis of the polypropionate-derived pheromones sitophilate (**1**) and sitophilure (**2**) are described using an asymmetric aldol condensation as the key step to adduct **6**; compound **6** was smoothly converted to the antipodes of each pheromone. This procedure can be expanded to more complicated structures with the same type of *syn* configuration such as stegobinone (**3**) and serricornin (**4**). Copyright © 1996 Elsevier Science Ltd

## Introduction

The aldol condensation has been exploited for the stereocontrolled construction of polyketide units in the synthesis of natural products over the past 20 years.[1] Advances during this time include: the development of the use of different chelating metals for the formation of enolates, the development of improved chiral auxiliaries to direct enolate face selection and improvements in the ease of handling reagents and work-up procedures. Several groups have made great improvements in these areas: Heathcock,[2] Masamune,[3] Mukaiyama,[4] Thorton[5] and Katsuki,[6] to name a few.

In particular, D.A. Evans and his group have developed a system which uses readily available enantiomerically pure amino alcohols in the preparation of oxazolidione chiral auxiliaries.[7] The work from Evans' group is quite flexible, it allows for the use of different metals for enolate formation, i.e. boron, lithium, titanium and zirconium, and is useful not only for stereoselective aldol condensations but also for displacement alkylations and Michael additions; considerable progress has been made in reagent handling and in the removal of the chiral auxiliary. For these reasons, we have chosen to pursue this line of work and have applied these systems to the formation of polypropionate derived pheromones.

Our interest in the aldol condensation as a route to polypropionate-derived pheromones came from an appreciation of the many types of biologically active, insect-produced compounds with this fundamental type of structure.[8] There is a broad range of compounds that are produced from the polyketide biosynthesis pathway that are used in chemical communication and defense.[9] With this general pattern in mind, we have set out to synthesize the antipodes of sitophilate (**1**) and sitophilure (**2**) to show the general utility of this method and to illustrate how it can be expanded to more complex structures such as stegobinone (**3**) and serricornin (**4**) (Fig. 1).




**1** (2*R*,3*S*)-Sitophilate — **2** (4*S*,5*R*)- Sitophilure — **3** (2*S*,3*R*,1'*R*)-Stegobinone — **4** (4*S*,6*S*,7*S*)-Serricornin

**Figure 1.** Structures of compounds **1**, **2**, **3** and **4**.

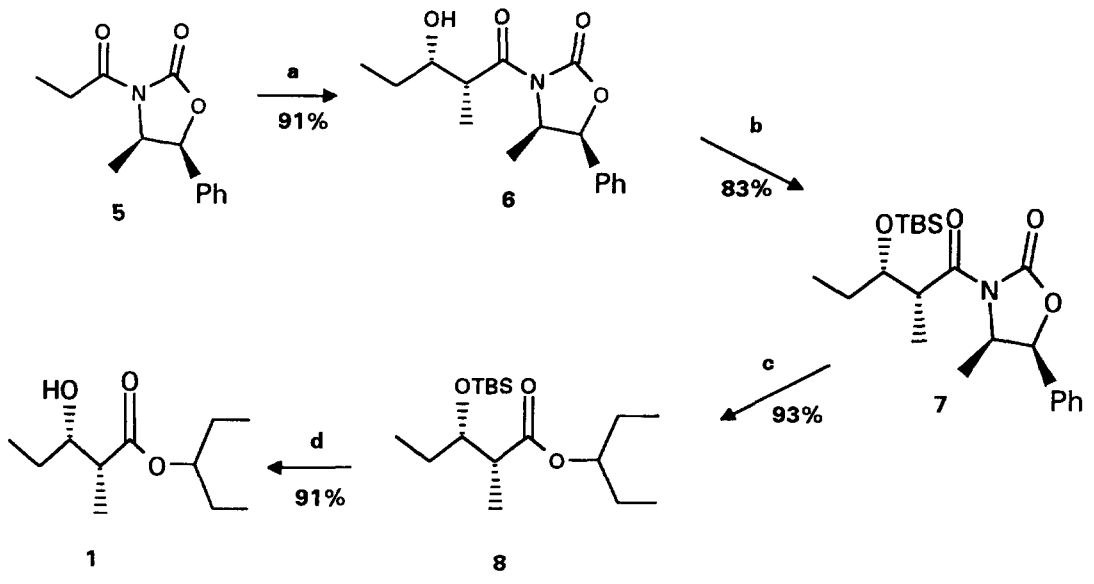
## Results and Discussion

### Sitophilate (Scheme 1)

Following the procedure of Evans,[10] the chiral imide **5** was transformed into the (*Z*)-boron enolate using di-*n*-butylboryltriflate and triethyl amine. The enolate reacted smoothly with propionaldehyde (−78 °C); the

Key words: Sitophilate, sitophilure, aldol condensation, pheromone, oxazolidinone.

†At this time further evaluation of optical purity was not pursued due to the amount of data already in the literature.

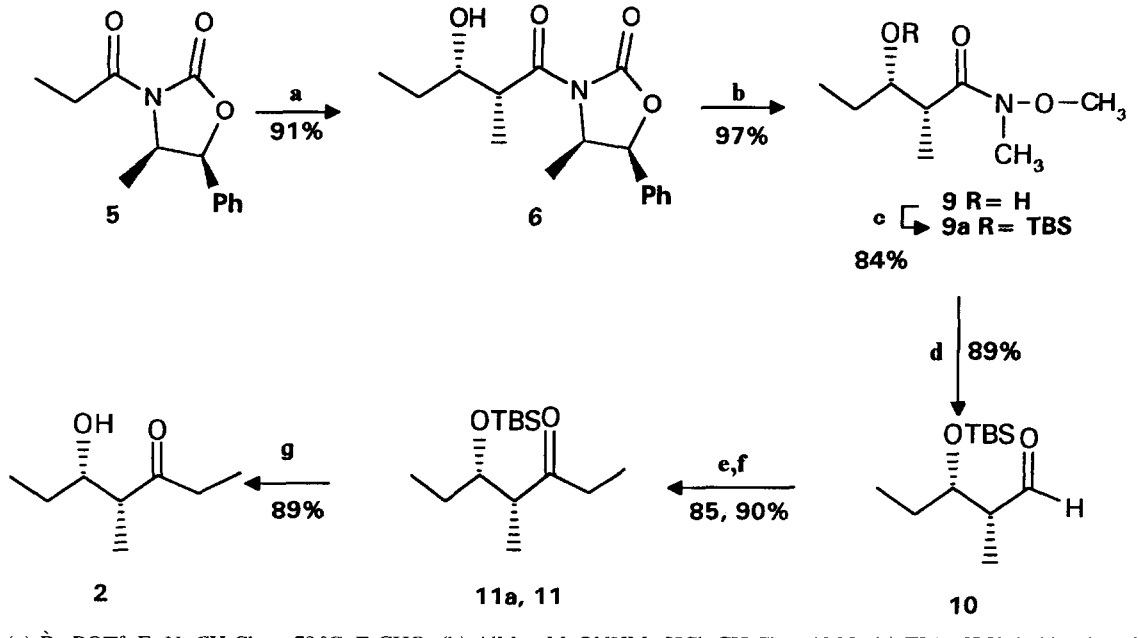



**Scheme 1.** (a) $Bu_2BOTf$, $Et_3N$, $CH_2Cl_2$, −78 °C, EtCHO; (b) TBDMSCl, imidazol, DMF, 25 °C; (c) $LiOCH(Et)_2$, THF, 0 °C; (d) tetrabutylammonium fluoride, THF, 25 °C.

aldol adduct **6** was isolated by oxidative work up (91%). Analysis by $^1H$ and $^{13}C$ NMR indicated a stereoselectivity of >97%, as reasoned by the limits of NMR detection. Flash chromatography insured 99% chemical purity of the noncrystalline product **6**. Protection of the secondary hydroxyl was carried out with *tert*-butyldimethylsilyl chloride (85%). Transesterfication of the imide **7** by treatment with lithium 3-pentoxide (made from butyl lithium in a ratio of 1:1 3-pentoxide:3-pentanol $[(CH_3CH_2)_2$ CHOLi: $(CH_3CH_2)_2CHOH)]$; 93% proved a reliable method for the removal of the chiral auxiliary while conveniently providing the correct ester.[11] (Our results confirmed Evans' work that no measurable epimerization took place.) Removal of the TBS group with tetrabutylammonium fluoride afforded the antipode of sitophilate (**1**) (91%; 64% overall yield and 94% ee based on the reported rotation of +4.1).[12,†]

## Sitophilure (Scheme 2)

Transamination of the aldol adduct (**6**) using trimethyl aluminum and *N,O*-dimethylhydroxylamine hydrochloride, according to the conditions of Evans,[13] gave the *N*-methyl, *N*-methoxy amide (**9**) (97%); the




**Scheme 2.** (a) $Bu_2BOTf$, $Et_3N$, $CH_2Cl_2$, −78 °C; EtCHO; (b) $AlMe_3$, MeONHMe-HCl, $CH_2Cl_2$ −10 °C; (c) TBDMSCl, imidazole, DMF, 25 °C; (d) DIBAL-H, $CH_2Cl_2$, −78 °C; (e) EtMgBr, $Et_2O$, 0 °C; (f) PCC, NaOAC, $CH_2Cl_2$; (g) tetrabutylammonium fluoride, THF, 25 °C.

secondary hydroxyl group was protected as the *tert*-butyldimethylsilyl ether (84%) and reduction of protected amide **9a** with DIBAL furnished aldehyde **10** (89%). Alkylation of aldehyde **10** with excess ethylmagnesium bromide (EtMgBr) in ether ($Et_2O$) gave alcohol **11a** (85%), followed by oxidation of the secondary alcohol with pyridinium chlorochromate (PCC)[14] to afford ketone **11** (90%). Removal of the TBS group and molecular distillation gave the antipode of sitophilure (**2**) (89%; in 45% overall yield and 95–97% ee).[15,†]

The goal of this work was to demonstrate the synthetic utility of Evans' oxazolidinone chiral auxiliaries for the formation of polypropionate units by way of the aldol condensation and to develop a general method for the synthesis of polypropionate-derived pheromones. The synthesis of the enantiomerically pure antipodes of sitophilate and sitophilure are the first steps in attaining this goal. These two important compounds were synthesized using a short, relatively simple procedure with high enantiomeric purity and high overall yield. Obviously, the naturally occurring pheromones could have been made using the opposite enantiomer of the chiral auxiliary; this synthesis, however, was developed for illustrative purposes only and studies have shown that the racemates of sitophilure and sitophilate work equally well; enantiomeric purity is not essential for biological activity.[16]

We are now ready to extend to the more complicated polyketide, insect-produced semiochemicals serricornin (**4**) and stegobinone (**3**). Unlike the previous compounds, stegobinone and serricornin have a different relationship between isomeric purity and biological activity. In the case of serricornin, one stereoisomer has been shown to be inhibitory.[17] Thus, although rigorous enantiomeric purity is not essential, good control of isomeric purity is required. Furthermore, it has been shown that only a single isomer of stegobinone exhibits biological activity identical to the natural pheromone and any contamination with other stereoisomers will inhibit activity.[18] A brief retrosynthetic analysis of both stegobinone and serricornin will explain how we intend to use the compounds synthesized in this paper as intermediates for the synthesis of **3** and **4**.

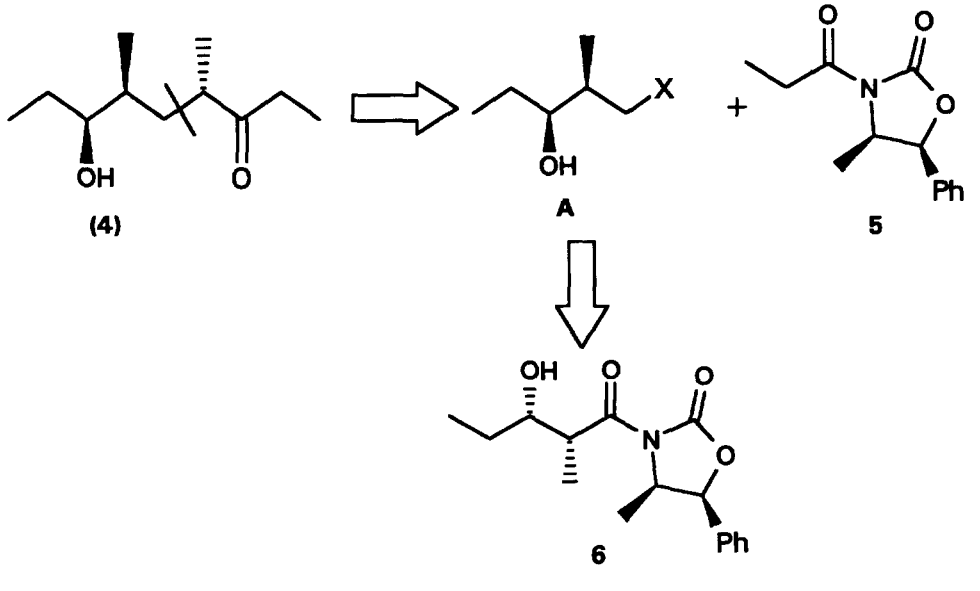
Serricornin (**4**) (Scheme 3), can be divided into two chiral subunits by detachment of the molecule between carbons 4 and 5. Piece **A** can be made from the aldol adduct **6**, which we have described here, by reductive removal of the chiral auxiliary with lithium borohydride[11] and transformation of the primary alcohol to a leaving group such as the tosylate. Coupling of this chiron with imide **5** can be carried out by a stereoselective displacement alkylation.[11] Completion of the molecule is the same as our synthesis here of sitoplilure.

Retrosynthetic analysis of stegobinone (Scheme 4) starts with the hydration/regioselective ring opening between carbon 6 and the ring oxygen, which would give the selectively unprotected hydroxyl group at carbon 2 of diketone **B**. From here, disconnection between carbons 5 and 6 affords the retro product of an aldol condensation of compounds **C** and **7′** using Evans' method developed for titanium enolate condensations.[19] Compound **C** can be synthesized by way of Evans' published work using the chiral aldol adduct **D**.[10] Compound **7′** is obviously the enantiomer of **7**, as described here.

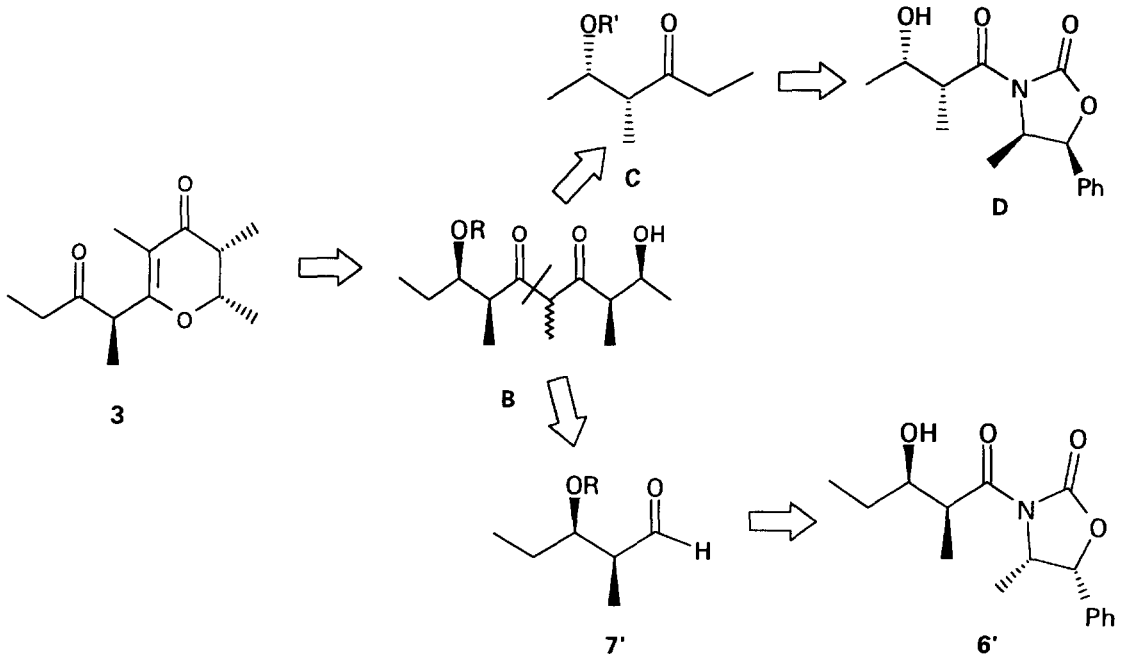
## Experimental

### General

IR were recorded on a Nicolet FT-IR 400 spectrometer. $^1H$ NMR spectra were recorded on a Bruker AM-300 (300 MHz) spectrometer, and are reported in




Scheme 3.




**Scheme 4.**

ppm from TMS on the δ scale. $^{13}C$ NMR were recorded on a Bruker AM-300 (75 MHz) spectrometer and are reported in ppm from TMS on the δ scale. Optical rotations were recorded on a Perkin–Elmer 141 polarimeter. Analytical GLC was carried out on a Hewlett Packard 5880A chromatograph with a 25 m × 0.32 mm i.d. HP-5 silica capillary column. Unless indicated otherwise, solvents and other reagents were used as received without further purification.

**(4*R*,5*S*,2′*R*,3′*S*)-5-(2′-Methyl-3′-hydroxypentanoyl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one (6).** To a cooled (−78 °C), stirred solution of 5.0 g (22.0 mmol) of imide **5** in $CH_2Cl_2$ (30 mL) was added 26.4 mL (26.8 mmol) of a 1.0 M solution of di-*n*-butylboryltriflate over a 1 min period to produce a heterogeneous mixture. After 5 min, 3.98 mL (26.8 mmol) of triethyl amine was added over a 5 min period to produce a light tan solution. The reaction temperature was maintained at −78 °C for 30 min and then allowed to slowly warm to 0 °C and held for 1 h. The solution was recooled (−78 °C) and 3.17 mL (44.0 mmol) of freshly distilled propionaldehyde was added in one portion. The reaction temperature was held at −78 °C for 45 min, allowed to rise to 0 °C and maintained at this temperature for 1 h. The reaction mixture was quenched by the addition of 30 mL of phosphate buffer solution (pH 7), poured into a 500 mL flask containing 60 mL of MeOH cooled to 0 °C and treated with a solution of 30 mL of a 30% aq $H_2O_2$ in 75 mL of MeOH for 1 h. The organic solvents were removed in vacuo, 75 mL of 10% $NaHCO_3$ was added and the resulting solution extracted with $CH_2Cl_2$ (3 × 150 mL). The combined organic layers were dried over anhydrous $Na_2SO_4$, filtered and concentrated to a colorless oil. Flash chromatography (250 g silica gel, 40% EtOAc/hexane) afforded 5.81 g (91% yield) of **6** as a colorless oil. IR ($CDCl_3$): 3525, 3050, 3010, 2960, 2920, 2855, 1780, 1710, 1369, 1335, 1225, 1200 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.45–7.25 (m, 5H aromatic H), 5.66 (d, 1H, $C_{5'}$-H), 4.75 (qn, 1H, $C_{4'}$—H), 3.85 (m, 1H, $C_2$—H), 3.80 (dd, 1H, $C_3$—H), 2.92 (s, 1H, OH), 2.65–1.39 (m, 2H, $C_4$—$CH_2$), 1.22 (d, 3H, $C_2$—$CH_3$), 0.97 (t, 3H, $C_5$—$CH_3$), 0.87 (d, 3H, $C_{4'}$—$CH_3$); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 177.14, 152.47, 133.09, 128.66, 128.57, 125.48, 78.78, 72.97, 54.63, 41.74, 26.74, 14.18, 10.24, 10.09. $[\alpha]_D$ + 29.0 °(*c* 1.62 in $CDCl_3$).

**(4*R*,5*S*,2′*R*,3′*S*)-5-(2′-Methyl-3′-(dimethyl-*tert*-butylsiloxy)pentanoyl)-4-methyl-5-phenyl-1,3-oxazolidin-2-one (7).** To a stirred solution of 3 g (10.3 mmol) of **6** in DMF (15 mL) were added 1.32 g (20.6 mmol) of imidazole and 1.95 g (13.0 mmol) of *tert*-butyldimethylsilyl chloride. After 18 h at 25 °C, the reaction mixture was added to 20% $CH_2Cl_2$:hexane (200 mL) and successively washed with 10% aq $NaHSO_3$ (50 mL) and water (2 × 50 mL). The organic layer was dried over anhydrous $Na_2SO_4$, filtered, concentrated in vacuo and distilled (85–90 °C at 0.5 torr) to yield 4.3 g (85% yield) of **7** as a colorless oil. IR ($CDCl_3$): 3060, 3010, 2950, 2920, 2850, 1780, 1710, 1350, 1200, 1040 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.47–7.26 (m, 5H aromatic-H), 5.63 (d, 1H, $C_{5'}$—H), 4.70 (qn, 1H, $C_{4'}$—H), 3.97 (q, 1H, $C_3$—H), 3.87 (q, 1H, $C_2$—H), 1.65–1.50 (m, 2H, $C_4$—H), 1.16 (d, 3H, $C_{4'}$—$CH_3$), 0.91 (t, 3H, $C_2$-$CH_3$), 0.89 [s, 9H, $C(CH_3)_3$], 0.89 (d, 3H, $C_2$—$CH_3$), 0.05 [d, 6H, $Si(CH_3)_2$]. $^{13}C$ NMR (75 MHz $CDCl_3$): δ 175.20, 152.71, 133.23, 128.69, 125.59, 78.85, 73.94, 55.32, 42.40, 28.17, 25.80, 18.05, 14.17, 11.33, 9.34, −4.14, −4.83. $[\alpha]_D$ + 10.53° (*c* 1.33 in $CDCl_3$).

**1-Ethypropyl-(2*R*,3*S*)-2-methyl-3-(dimethyl-*tert*-butylsiloxy)pentanoate (8).** To a cooled (0 °C), magnetically

stirred solution of 0.45 g (5.13 mmol) of 3-pentanol in THF (5 mL) was added 1.64 mL (4.1 mmol) of a 2.5 M solution of *n*-butyllithium in hexane. The reaction temperature was maintained at 0 °C for 15 min; this solution was then added to a cooled (0 °C) solution of 1.0 g (2.05 mmol) of **7** in THF (15 mL). The reaction temperature was held at 0 °C for 3.5 h, added to water (70 mL) and extracted with $CH_2Cl_2$ (3 × 100 mL). The combined organic fractions were dried over anhydrous $Na_2SO_4$, filtered and concentrated in vacuo yielding 0.73 g (93% yield). IR ($CDCl_3$): 2975, 2940, 2870, 2835, 1720, 1460, 1255, 1110, 1060 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ 4.73 [qn, 1H, $CH(CH_2CH_3)_2$, 3.86 (q, 1H, $C_3$—CH), 2.55 (qn, 1H, $C_2$—$CH_2$), 1.55 (m, 6H, $CH_2$s), 1.15 (d, 3H, $C_4$—$CH_3$), 0.91 (t, 6H, $CH_2CH_3$), 0.89 [s, 9H, $C(CH_3)_3$], 0.85 (t, 3H, $C_5$-$CH_3$), 0.05 [s, 6H, $Si(CH_3)_2$]. $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 175.0, 76.50, 74.12, 44.60, 27.70, 26.44, 26.08, 25.70, 17.96, 13.18, 9.32, 8.59, −4.45, −4.73. $[\alpha]_D$ +4.7° (*c* 1.0 in $CDCl_3$).

**1-Ethylpropyl-(2*R*,3*S*)-2-methyl-3-hydroxypentanoate (1).** To a solution of 0.31 g (0.79 mmol) of ester **8** in 20 mL of anhydrous THF was added 0.21 g (0.79 mmol) of tetrabutylammonium fluoride. The resulting solution was stirred for 30 h before it was diluted with 50 mL of $Et_2O$. The mixture was washed with a 30 mL portion of satd aq $NH_4Cl$ solution, brine, dried over $Na_2SO_4$, filtered and concentrated. Purification by molecular distillation (bp 82 °C at 3 torr) yielded 0.20 g (91% yield) of product. IR ($CDCl_3$): 3450, 2970, 2945, 1715, 1700, 1460, 1260, 1195, 1110 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ 4.80 (m, 1H, $C_1$—CH), 3.81 (m, 1H, $C_3$—CH), 2.55 (dq, 1H, $C_2$—CH), 1.68–1.5 (m, 6H, $CH_2$), 1.9 (d, 3H, $C_2$-$CH_3$), 0.98 (t, 3H, $C_5$—$CH_3$), 0.87 (t, 6H, 2-$CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 176.16, 76.99, 73.28, 44.17, 26.74, 26.45, 26.40, 10.76, 10.34, 9.56, 9.51. $[\alpha]_D$ +3.86° (*c* 0.85 in $CDCl_3$).

**(3*S*,2*R*)-3-Hydroxy-*N*-methoxy-*N*,2-dimethylpentaneamide (9).** To a cooled (−10 °C) suspension of 1.25 g (12.9 mmol) of *N,O*-dimethylhydroxyamine hydrochloride in 50 mL of anhydrous $CH_2Cl_2$ was added 6.5 mL (12.9 mmol) of 2.0 M trimethylaluminium in toluene solution (much gas evolved). After the addition was complete, the cooling bath was removed and the solution was stirred at room temperature for 30 min. The solution was recooled to −20 °C and 1.0 g (4.3 mmol) of (**6**) in 50 mL of anhydrous $CH_2Cl_2$ was added. The cloudy reaction mixture was stirred for 3 h at −10 °C. The reaction was quenched by the addition of 20 mL of a 1.0 N aqueous tartaric acid solution. After stirring for 1 h, the layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (2 × 50 mL). The combined organic phases were dried over $Na_2SO_4$, filtered and concentrated. Flash chromatography (20 g silica gel), $R_f$ 0.35 in 30% EtOAc:hexane yielded 0.71 g of amide **9** (94% yield). IR ($CDCl_3$): 3490, 2960, 2925, 2875, 1780, 1640, 1460, 1420, 1010 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ 4.10 (m, 1H, $C_3$—CH), 3.70 (s, 3H, —$NOCH_3$), 3.55 (s, 1H, —OH), 3.20 (s, 3H, —N—$CH_3$), 2.90 (m, 1H, $C_2$—$CH_3$), 1.65–1.50 (m, 2H, $C_4$—$CH_2$), 1.16 (d, 3H, $C_2$—$CH_3$), 0.96 (t, 3H, $C_5$—$CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 172.26, 73.04, 61.30, 38.29, 26.75, 10.18, 9.96. $[\alpha]_D$ +13.6° (*c* 0.5 in $CDCl_3$).

**(3*S*,2*R*)-3-*tert*-Butyldimethylsiloxy-*N*-methoxy-*N*,2-dimethylpentaneamide (9a).** To a stirred solution of 0.56 g (3.2 mmol) of **9** in DMF (5 mL) was added 0.41 g (6.4 mmol) of imidizole and 0.60 g (4.0 mmol) of *tert*-butyldimethylsilyl chloride. After 18 h at 23 °C, the reaction mixture was added to a 20% $CH_2Cl_2$:hexane solution (50 mL) and successively washed with 10% aqueous $NaHSO_3$ (20 mL) and water (2 × 20 mL). The organic layer was dried over anhydrous $Na_2SO_4$, filtered and concentrated. Molecular distillation (bp 110–115 °C at 0.5 torr) afforded 0.78 g of amide **10a** (84% yield). IR ($CDCl_3$): 2955, 2940, 2820, 2800, 2250, 1760, 1650, 1210, 1000 $cm^{-1}$. $^1$ H NMR (300 MHz, $CDCl_3$): δ 3.87 (m, 1H, $C_3$—H), 3.66 (s, 3H, —NO—$CH_3$), 3.15 (s, 3H, —N—$CH_3$), 1.60–1.40 (m, 2H, $C_4$—$CH_2$), 1.13 (d, 3H, $C_2$—$CH_3$), 0.89 [s, 9H, (C—$CH_3)_3$], 0.88 (t, 3H, $C_3$—$CH_3$), 0.05 [s, 6H, Si—$(CH_3)_2$]. $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 177.0, 74.25, 61.29, 40.11. 28.15, 25.90, 25.70, 18.12, 14.48, −4.25, −4.51. $[\alpha]_D$ +4.58° (*c* 1.1 in $CDCl_3$).

**(3*S*,2*R*)-3-*tert*-Butyldimethylsilyl-2-methylpentanal (10).** To a cooled (−78 °C) solution of 0.70 g of **9a** in 30 mL of anhydrous $CH_2Cl_2$ was added 4.8 mL (4.8 mmol) of DIBAL (1.0 M in toluene). The solution was stirred for 1 h before 5 mL of acetone was added to quench the reaction. The mixture was then warmed to room temperature and 5 mL of aqueous 1 N tartaric acid solution was added. The solution was stirred for 20 min, then extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic phases were dried over $Na_2SO_4$, filtered and concentrated to give 0.50 g of a clear liquid (89% yield). This product was used for the next step without purfication. $^1H$ NMR (300 MHz, $CDCl_3$): δ 9.78 (s, 1H, O=C—H), 4.07 (td, 1H, $C_3$—CH), 2.60–2.45 (m, 1H, $C_2$—CH), 1.55 (m, 2H, $C_4$—$CH_2$), 1.10 (d, 3H, $C_2$—$CH_3$), 0.95 (t, 3H, $C_5$—$CH_3$), 0.91 [s, 9H, C—$(CH_3)_3$], 0.11 (s, 3H, Si—$CH_3$), 0.08 (s, 3H, Si—$CH_3$). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 205.0,73.27, 50.70, 27.33, 25.63, 9.90, 7.43, −4.70, −4.84. $[\alpha]_D$ +5.6° (*c* 1.0 in $CDCl_3$).

**(3*RS*,4*R*,5*S*)-*tert*-Butyldimethylsilyl-4-methyl-3-heptanol (11a).** To a cooled (−78 °C) solution of 0.40 g (1.74 mmol) of aldehyde **10** in 20 mL of diethyl ether ($Et_2O$) was added 1.16 mL of ethylmagnesium bromide (3.48 mmol of a 3.0 M solution in $Et_2O$) over a 5 min period. After the addition, the cooling bath was removed and the reaction mixture was allowed to warm to room temperature; stirring was continued for 2 h. Saturated aq $NH_4Cl$ (20 mL) was added to quench the reaction. The aqueous phase was washed with 50 mL of $Et_2O$ and the combined organic phases were washed with brine, dried over $Na_2SO_4$ and concentrated. Chromatography (10 g silica gel), $R_f$ 0.20 in 10% EtOAc:hexane, afforded 0.38 g (85% yield) of a clear oil. IR ($CDCl_3$): 3510, 2950, 2900, 2865, 1255, 1065, 1045, 1000 $cm^{-1}$. $^1H$ NMR (300 MHz, $CDCl_3$): δ 3.76

(m, 1H, $C_3$—CH), 3.65 (m, 1H, $C_5$—CH), 2.87 (s, 1H, OH), 1.65–1.35 (m, 5H, $C_4$—CH and $CH_2$), 0.92 (t, 3H, $C_6$—$CH_3$), 0.90 [s, 9H, C—$(CH_3)_3$], 0.86 (d, 3H, $C_4$—$CH_3$), 0.81 (t, 3H, $C_1$—$CH_3$), 0.10 (d, 6H, Si—$CH_3$). $^{13}$C NMR (75 MHz, CDCl): δ 79.34, 77.20, 38.14, 27.94, 27.52, 25.86, 10.50, 8.87, 5.18, −3.63, −4.60. $[\alpha]_D$ +11.1° (*c* 1.8 in $CDCl_3$).

**(4*R*,5*S*,)-*tert*-Butyldimethylsilyl-4-methyl-3-heptanone (11).** At room temperature, 0.075 g (0.356 mmol) of pyridinium chlorochromate (PCC) and 0.007 g (0.069 mmol) of sodium acetate (anhydrous) were dissolved in $CH_2Cl_2$ (10 mL). To this solution, 0.060 g (0.23 mmol) of the alcohol **11a** was added. The reaction mixture was allowed to stir for 4 h, followed by the addition of 20 mL of $Et_2O$. The resulting solution was filtered through a column of florisil (10 g), dried over $Na_2SO_4$ and concentrated to give 0.053 g of a colorless oil (90 % yield). IR ($CDCl_3$): 2890, 2850, 2820, 2800, 1655, 1440, 1230, 1100, 1050 $cm^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): δ 3.48 (m, 1H, $C_5$—CH), 2.7–2.4 (m, 2H, $C_2$—$CH_2$), 1.5–1.3 (m, 2H, $C_6$—$CH_2$), 1.20 (t, 3H, $C_1$—$CH_3$), 1.05 (d, 3H, $C_4$—$CH_3$), 0.88 [s, 9H, C—$(CH_3)_3$], 0.86 (t, 3H, $C_7$—$CH_3$), 0.05 (d, 6H, Si—$CH_3$s). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 213.88, 74.89, 50.72, 35.73, 27.51, 25.88, 12.11, 9.67, 7.58, -4.32, -4.52. $[\alpha]_D$ −25.0° (*c* 1.6 in $CDCl_3$).

**(4*S*,5*R*)-5-Hydroxy-4-methyl-3-heptanone (2).** To a solution of 0.050 g (0.195 mmol) of ketone **11** in anhydrous THF (10 mL) was added 0.051 g (0.195 mmol) of tetrabutylammonium flouride. The resulting solution was stirred for 18 h before being diluted with 20 mL of $Et_2O$. The mixture was washed with satd aq $NH_4Cl$ (2 × 10 mL), brine, dried over $Na_2SO_4$, filtered and concentrated. Chromatography (5 g silica gel), $R_f$ 0.20 in 10% EtOAc:hexane, afforded 0.025 g of a colorless oil (89% yield). IR ($CDCl_3$): 3450, 2980, 2950, 2890, 1710, 1460, 1410, 1250, 1150, 1100, 1030 $cm^{-1}$. $^1$H NMR (300 MHz, $CDCl_3$): δ 3.80 (m, 1H, $C_5$—CH), 3.60 (s, 1H, OH), 2.55 (m, 1H, $C_4$—CH), 1.55–1.30 (m, 4H, $CH_2$), 1.10 (d, 3H, $C_4$—$CH_3$), 1.03 (t, 3H, $C_1$—$CH_3$), 0.93 (t, 3H, $C_7$—$H_3$). $^{13}$C NMR (75 MHz, $CDCl_3$): δ 216.6, 72.6, 49.3, 35.0, 26.8, 11.5, 10.3, 9.9. $[\alpha]_D$ +26.2° (*c* 1.5 in $Et_2O$).

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## References

1. (a) Heathcock, C.H. *Science* **1981**, *214*, 395; (b) Evans, D.A.; Nelson, J.V.; Taber, T.R. *Top. Stereochem.* **1982**, *13*, 1; (c) Mukaiyama, T. *Organic Reactions*; Wiley: New York, 1982; Vol. 28, p. 203; (d) Heathcock, C.H. In *Comprehensive Carbanion Chemistry*; Burcel, E.; Durst, T. Eds.; Elsevier: Amsterdam, 1984; Part B, Ch. 4; (e) Heathcock, C.H. In *Asymmetric Synthesis*; Morrison, J.D., Ed.; Academic Press: New York, 1984, Vol. 3, Ch. 2; (f) Masamune, S.; Choy, W; Petersen, J.S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1; (g) Braun, M. *ibid.* **1987**, *26*, 24.

2. Heathcock, C. H.; Buse, C. T., Kleschrick, W.A.; Perung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066.

3. Masamune, S.; Chow, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566.

4. Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503.

5. Siegel, C.; Thornton, E. R. *J. Am. Chem. Soc.* **1989**, *111*, 5722.

6. Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1985**, *26*, 5807.

7. Evans, D. A. *Ald. Acta,* **1982**, *15*, 1.

8. Phillips, J. K.; Walgenbach, C. A.; Klein, J. A.; Burkholder, W. E.; Schmuff, N. R.; Fales, H. M. *J. Chem. Ecol.* **1985**, *11*, 1263.

9. Chuman, T.; Mochizuki, K.; Mori, M.; Kohno, M.; Kato, K.; Noguchi, M. *J. Chem. Ecol.* **1985**, *11*, 417.

10. Evans, D. A.; Dow, R. L.; Shih, T. L.; Takas, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290.

11. Evans, D. A.; Ennis, M. D.; Mather, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

12. Mori, K.; Ishikura, M. *Liebigs Ann. Chem.* **1989**, 1263.

13. Evans, D. A.; Miller, S. J.; Ennis, M. D.; Ornstein, P. L. *J. Org. Chem.* **1992**, *57*, 1067.

14. Corey, E. J.; Suggs, J. W. *Tetrahedron Lett,* **1975**, 2647.

15. Mori, K.; Ebata, T. *Tetrahedron* **1986**, *42*, 4421.

16. Philips, J. K.; Miller, S. P. F.; Andersen, J. F.; Fales, H. M.; Burkholder, W. E. *Tetrahedron Lett.* **1987**, *28*, 6145.

17. Mochizoki, K.; Chuman, T.; Mori, M.; Kohno, M.; Kato, K. *Agric. Biol. Chem.* **1984**, *48*, 2833.

18. Kodama, H.; Ono, M.; Ohnishi, A. *J. Chem. Ecol.* **1987**, *13*, 1859.

19. Evans, D. A.; Rieger, D. C.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.*, **1991**, *113*, 1047.