A Flexible Stereocontrolled Synthesis of β-Hydroxy-α-methyl Esters: Application to the Synthesis of Stegobiol and Serricorole

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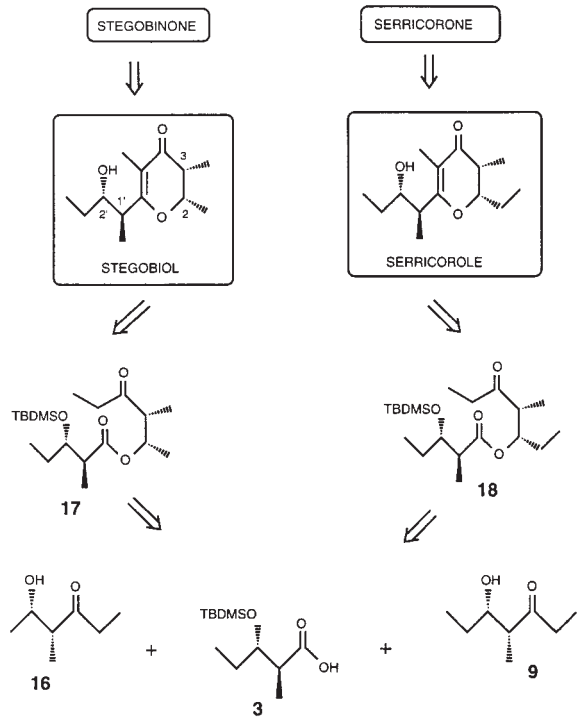
Abstract: β-Hydroxy-α-methyl esters have been obtained in a stereocontrolled manner and high enantiomeric and diastereomeric purity from commercially available methyl 3-oxopentanoate and methyl 3-oxobutanoate. The key step is the catalytic hydrogenation of the carbonyl group using (*R*)- or (*S*)-BINAP-Ru as chiral catalyst followed by asymmetric alkylation. Stegobiol and serricorole, components of the sex pheromone of the drugstore beetle, *Stegobium paniceum* (L.) and cigarette beetle, *Lasioderma serricorne* (F.), have been prepared from these chiral building blocks without the need for stoichiometric amounts of chiral auxiliaries.

Key words: catalytic chiral hydrogenation, (*R*)- and (*S*)-BINAP-Ru, asymmetric alkylation, stegobiol, serricorole

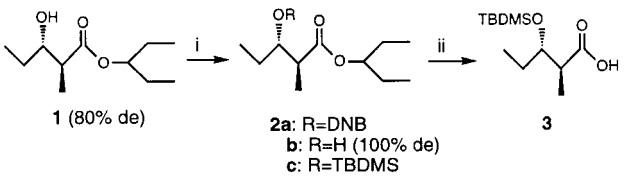
The drugstore beetle, *Stegobium paniceum*, is a devastating pest that affects stored food and crops. One of the components of the sex pheromone of this insect, stegobinone was isolated by Kuwahara et al.,[1] and the other component stegobiol was isolated by Kodama et al.[2] Stegobinone has also been reported to be the attractant of the furniture beetle, *Anobium punctatum*.[3] Chuman et al.[4] reported the isolation of serricorole and serricorone, two components of the sex pheromone produced by females of the cigarette beetle, *Lasioderma serricorne*, a serious pest that damages cured tobacco leaves and dry foodstuffs. Later, Imai et al.[5] found that this insect also uses serricorone as oviposition deterrent.

Once the exact stereochemistry of stegobiol and stegobinone was established,[6] the first asymmetric synthesis of these pheromones was achieved in 1986 by Mori et al.[7] from enantiopure hydroxy esters of microbial origin. The next synthesis via chiral boronic esters followed by aldol condensation was reported in the 1990s by Matteson et al.[8] As for serricorole, Mori,s group[9] applied the same approach used for stegobiol and Oppolzer et al.[10] used chiral sultams in an asymmetric aldol condensation to obtain the target compound.

During the course of our work on the synthesis of optically active pheromones, we recently described a stereoselective synthesis of sitophilate and sitophilure,[11] aggregation pheromones for several species of *Sitophilus* weevils, which devastate stored cereal grains. We now report the synthesis of stegobiol, stegobinone, serricorole and serricorone based on a common strategy for the preparation of the key synthetic intermediates. Retrosynthetic analysis (Scheme 1) shows an oxo ester in each case which upon disconnection leads to the three required synthetic intermediates: a protected hydroxy acid **3** with *anti*-stereochemistry, common to both pheromones, and two hydroxy ketones, **9** and **16**, with relative *syn*-configuration. The synthesis of carboxylic acid **3** (Scheme 2) started with the hydroxy ester **1**, intermediate in our synthesis of sitophi]ate, which was converted into its 3,5-dinitrobenzoate and purified by column chromatography to afford **2a** as a single diastereomer in 69% yield; deprotection yielded hydroxy ester **2b** with 100% de. After *O*-silylation (89%) and hydrolysis of the ester group (83%), pure (2*S*,3*S*)-carboxylic acid **3** was obtained (Scheme 2). The configuration at C-2 and C-3, which will turn into C-1′and C-2′, respectively, in pheromone molecules, is very important because it has been reported that the wrong stereoisomer inhibits the action of stegobinone[12] and stegobiol.[13]



Scheme 1



Reagents and conditions: i) a: 3,5-DNB acid, DCC, DMAP (69%); b: KOH 1M, THF/MeOH, 0 °C (96%); c: TBDMSCl, DMF, r.t. (89%); ii) KOH 3M, MeOH, reflux (83%).

Scheme 2

Using a similar strategy to that employed in the synthesis of sitophilure,[11] the preparation of hydroxy ketone **9** (Scheme 3) was achieved from oxo ester **4** (readily available through transesterification of commercial methyl 3-oxopentanoate). The first step, key in the synthesis, was

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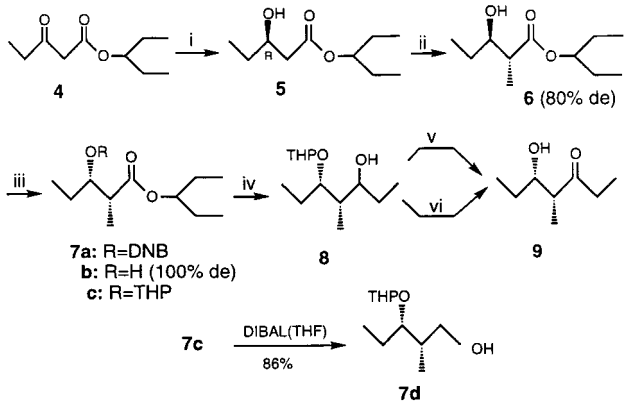
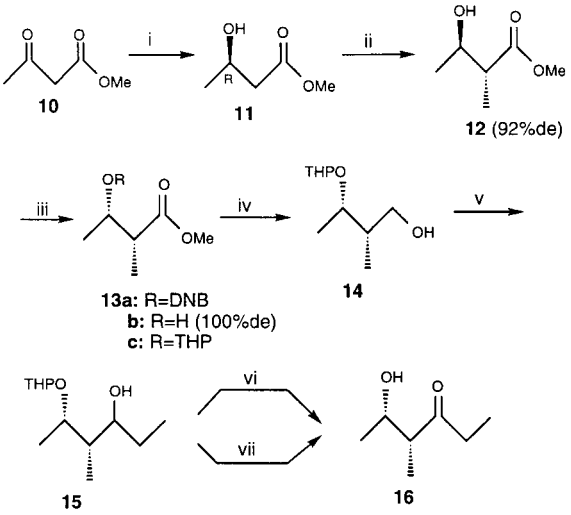
the asymmetric hydrogenation of **4** using (*R*)-BINAP-Ru as catalyst.[14] The reaction proceeded smoothly under 4 bar in a simple hydrogenation apparatus and enantiopure hydroxy ester **5** was obtained in 97% yield on 11 g scale. The enantiomeric purity (≈100% ee) was determined by chiral GC and the absolute configuration assigned by comparison of optical rotation with the enantiomer. Asymmetric alkylation afforded the *anti*-diastereoisomer **6** as the major product[15a] in almost quantitative yield. The dianion of the new hydroxy ester **5** was generated with LDA, in the presence of LiCl[15b] and using an excess of BuLi.[15c] Mitsunobu inversion[16] using 3,5-dinitrobenzoic acid, triphenylphosphine and diethyl azodicarboxylate (DEAD), afforded after purification by column chromatography, **7a** as a single diastereomer in 63% yield. Removal of the dinitrobenzoate group from **7a** yielded pure **7b**. Protection of hydroxyl group in **7b** with 3,4-dihydro-2*H*-pyran (DHP) afforded **7c** in 96% yield. Reduction of **7c** with diisobutylaluminum hydride (DIBAL) converted the ester group to the corresponding aldehyde in quantitative yield at –100 °C (as shown by GC). Due to its instability, the aldehyde was treated without further purification with ethylmagnesium bromide to give **8** in 82% yield after column chromatography. The results in Table 1 show the yield of reaction products formed, thereby revealing the role of solvent in the DIBAL reduction. Thus, for substrate **7c**, dichloromethane was the solvent of choice because when DIBAL in THF was used, only primary alcohol **7d** was detected as the reaction product. In the last step, oxidation of secondary alcohol **8** with sodium hypochlorite under mild conditions[17] yielded only the ketone **9** (69%) as the main product due to the cleavage of tetrahydropyranyl (THP) group under the acidic (HCl) workup conditions. Alternatively, Swern oxidation[18] of **8** followed by deprotection afforded **9** in a slightly higher yield (76%) (Scheme 3). However, the lower yield of the first procedure is compensated by much shorter reaction time and milder reaction conditions.



Reagents and conditions: i) H_2, (*R*)-BINAP-Ru, 4 atm, 75 °C (97%); ii) LDA,LiCl then MeI, –30 °C (>99%); iii) a) Mitsunobu (63%), b) deprot. (91%); c) DHP (96%); iv) DIBAL(CH_2Cl_2), then EtMgBr (82%); v) NaOCl, TEMPO (69%); vi) Swern oxidation, then PPTS, MeOH, reflux (76%).

Scheme 3

The third synthetic intermediate required, **16**, was obtained as shown in Scheme 4 starting from methyl 3-oxobutanoate (**10**). The sequence was similar to the previous one, but with two modifications compared to the bulkier ester **4**. First, the alkylation step yielded hydroxy ester **12** in a higher diastereomeric excess (92%) and second, when the protected ester **13c** was treated with DIBAL in dichloromethane, in contrast to that of **7c**, the corresponding primary alcohol was the main reaction product (see Table 1). Based on these results, the methyl ester **13c** was treated with $LiAlH_4$ to give the primary alcohol **14**, which was oxidized to the intermediate aldehyde, then reacted with ethylmagnesium bromide to give **15** in 73% yield. Thus in this case an additional step was required to obtain the secondary alcohol **15**. For the last step, oxidation to hydroxy ketone **16**, the results were similar to the other case.



Reagents and conditions: i) H_2, (*R*)-BINAP-Ru, 4 atm, 75 °C (97%); ii) LDA,LiCl then MeI, –30 °C (>99%); iii) a) Mitsunobu (74%), b) deprot. (85%); c) DHP (95%); iv) LAH, Et_2O, 0 °C (94%); v) Swern, then EtMgBr (73%), vi) NaOCl, TEMPO (65%); vii) Swern, then PPTS, MeOH, reflux (75%).

Scheme 4

Table 1. Reduction of Esters **7c** and **13c** with DIBAL[a]

Substrate	Solvent	Aldehyde[b,c] Yield (%)	Alcohol[b,c] Yield (%)
7c	CH_2Cl_2	100	0
7c	THF	0	100
7c	Hexane	75	25
13c	CH_2Cl_2	33	66
13c	THF	0	100

[a] 1.5 equiv at –l00 °C for 1 h.
[b] The structures of intermediate aldehyde and the *final reduction product alcohol* are not depicted in Schemes 3 and 4.
[c] Yield determined by GC.

In all cases, ^{13}C NMR was a very helpful tool to follow the course of the alkylation step and to assign the relative stereochemistry of β-hydroxy-α-methyl esters. Table 2 shows the chemical shift values for diastereomeric compounds **2b** and **7b**. There is an upfield shift of the carbons

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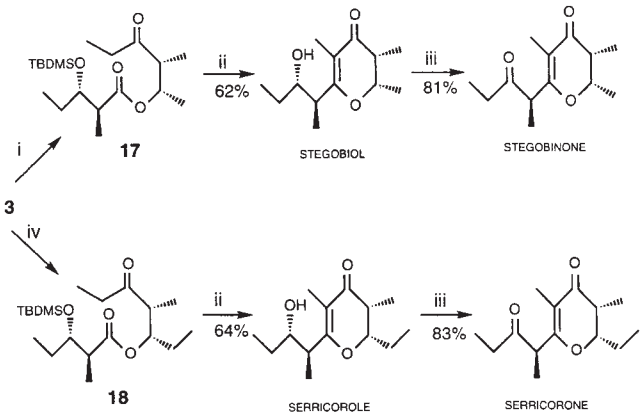
in the *syn*-isomer as compared with those of the *anti*-isomer. This shift is smaller for methine carbons than for the other two in agreement with the literature data for other β-hydroxycarbonyl compounds.[19]

Table 2. ^{13}C NMR Chemical Shift Values for Diastereomeric β-Hydroxy-α-methyl-Esters

Product	^{13}C NMR ($CDCl_3$/TMS), δ		
	CH	C–OH	CH_3
2b (*anti*)	45.11	74.68	14.69
7b (*syn*)	44.32	73.05	11.08

Once the three building blocks containing all stereocenters in the correct configuration required for the target pheromones have been obtained, we proceeded to esterify **3** with **16** and **9** to obtain the oxo esters **17** and **18**, respectively (Scheme 5). Thus, activation of carboxylic acid **3** with 2,6-dichlorobenzoyl chloride[7] and then reaction with the corresponding hydroxy ketone, furnished **17** or **18** in 83% and 86% respectively after purification by column chromatography. The next step, synthesis of the dihydropyranone ring, was accomplished by Ti-mediated cyclization.[10] After removal of TBDMS group with aqueous HF and purification, stegobiol and serricorole were obtained in 62% and 64% yield, respectively. Optical rotation values were in agreement with reported data.[8a,10a] These pheromones were easily converted to pure stegobinone and serricorone in a single oxidation step, and the analytical and spectral data were also in accord with literature.[7b,9]



Reagents and conditions: i) 2,6-dichlorobenzoyl chloride, Et_3N, then **16** and DMAP (83%); ii) $TiCl_4$, *i*-Pr_2EtN, –10 °C, then HF aq., 0 °C; iii) Swern; iv) as i) but cmpound **9** (86%).

Scheme 5

In summary, the method reported here provides a highly stereoselective route to β-hydroxy-α-methyl esters and derivatives, an alternative to asymmetric aldol condensation. As illustrated in Scheme 6, this procedure allows versatile access to any of the four stereoisomers in a predictable way and high enantio- and diastereomeric purity. The key step is catalytic asymmetric hydrogenation using (*R*)- or (*S*)-BINAP which lead to (*R*)- or (*S*)-hydroxy ester, respectively. The synthesis starts with commercially available and cheap materials and the chiral catalyst was used in a substrate/catalyst ratio of 2100, making the present method suitable to large scale preparation.

Solvents were dried by distillation from drying agents as follows: THF, Et_2O (Na-benzophenone); benzene, toluene (Na); CH_2Cl_2, hexane (P_2O_5); MeOH, EtOH (Mg).Column chromatography was performed by using 230–400 mesh silica gel. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions on a Varian Gemini 200. GC analysis was conducted in a Shimazu GC-l4B, equipped with a FID detector using He as carrier gas; capillary columns were used: TRB-1 (30 m × 0.25 mm) and β-DEX 110 (30 m × 0.25 mm). Elemental analyses were performed in a Carlo Erba EA 1108 Analyzer. IR spectra were recorded on a Nicolet 510M FT-IR as films or KBr pellets. Optical rotations were measured using a JASCO-DIP-370 polarimeter. Hydrogenations were conducted in a Parr 3911 shaker-type hydrogenation apparatus.

1-Ethylpropyl (2*S*,3*S*)-3-(3,5-Dinitrobenzoyloxy)-2-methylpentanoate (2a):
A solution of **1**[11] (6.87 g, 32 mmol), 1,3-dicyclohexylcarbodiimide (DCC) (8.65 g, 42 mmol) and 4-dimethylaminopyridine (DMAP) (0.61 g, 5 mmol) in anhyd CH_2Cl_2 (90 mL) was cooled to 0 °C and 3,5-dinitrobenzoic acid (8.92 g, 42 mmol) was added. The mixture was stirred overnight at r.t., diluted with Et_2O (180 mL) and the stirring was continued for 1 h. The solid formed was filtered and the solvent removed to yield the crude product which after column chromatography on silica gel with hexane/EtOAc (15:1) as eluent afforded 8.8 g (69%) of pure **2a** as a white solid; mp 71–73 °C; $[\alpha]_D^{24}$ +23.4 (*c* = 1, $CHCl_3$).
IR (KBr): ν = 1729 (C=O), 1551,1347 cm^{-1} (NO_2).
^1H NMR: δ = 0.69–0.82 (2 t, *J* = 7.2 Hz, 6 H), 0.92 (t, *J* = 7.4 Hz, 3 H), 1.19 (d, *J* = 7.1 Hz, 3 H), 1.47 (qnt, *J* = 7.1 Hz, 4 H), 1,64–1.94 (m, 2 H), 2.90 (qnt, *J* = 7.2 Hz, 1 H), 4.65 (qnt, *J* = 6.2 Hz, 1 H), 5.34 (dt, *J* = 7.3 and 4.4 Hz, 1 H), 9.02 (d, *J* = 2.1 Hz, 2 H), 9.11 (t, *J* = 2.1 Hz, 1 H).
^{13}C NMR: δ = 9.34, 9.64, 13.67, 24.29, 26.43, 43.21, 77.20, 78.82, 122.33*, 129.28*, 133.87*, 148.54*, 161.79*, 172.87 (* DNB).
Anal. calcd. for $C_{18}H_{24}N_2O_8$: C, 54.54; H, 6.10; N, 7.07. Found: C, 54.51; H, 6.15; N, 7.03.

1-Ethylpropyl (2*S*,3*S*)-3-Hydroxy-2-methylpentanoate (2b):
To a solution of **2a** (2.2 g, 5.6 mmol) in THF/MeOH (15 mL,1:1) was slowly added an aq solution of 1M KOH (5 mL) at 0 °C. The purple solution was stirred for 2 h and then quenched with satd aq NH_4Cl soln. The aqueous layer was extracted with Et_2O, the organic layer washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give a liquid which was purified by distillation yielding 1.1 g (96%) of **2b** as a colorless liquid; bp 96–98 °C/1 Torr; $[\alpha]_D^{21}$ +6.1 (*c* = 1.02, $CHCl_3$) {Lit[20] $[\alpha]_D^{21}$ + 6.0 (*c* = 1.04, $CHCl_3$)}.
IR (Neat): ν = 3465 (OH), 1725 cm^{-1} (C=O).
^1H NMR: δ = 0.83 (t, *J* = 7.4 Hz, 6 H), 0.93 (t, *J* = 7.4 Hz, 3 H), 1.17 (d, *J* = 7.2 Hz, 3 H), 1.31–1.63 (m, 6 H), 2.48 (qnt, *J* = 7.2 Hz, 1 H), 2.79 (d, *J* = 7 Hz, 1 H), 3.35–3.62 (m, 1 H), 4.74 (qnt, *J* = 6.2 Hz, 1 H).
^{13}C NMR: δ = 9.74, 10.05, 14.69, 26.61, 27.75, 45.11, 74.68, 76.97, 176.0.

1-Ethylpropyl (2*S*,3*S*)-3-*tert*-Butyldimethylsilyloxy-2-methylpentanoate (2c):
Imidazole (0.8 g, 12 mmol) and *tert*-butyldimethylsilyl chloride (TBDMSCl, 1.13 g, 7.5 mmol) were added to a stirred solution of **2b** (1.1 g, 5.34 mmol) in anhyd DMF (10 mL). The mixture was stirred overnight at r.t. and then poured into ice-water and extracted with Et_2O (4 × 25 mL). The Et_2O solution was washed with H_2O and brine, dried ($MgSO_4$) and concentrated. The residue was distilled to give 1.5 g (89%) of **2c** as a colorless liquid; bp 108–110 °C/1 Torr; $[\alpha]_D^{21}$ +17.2 (*c* = 1, $CHCl_3$) {Lit[20] $[\alpha]_D^{19}$ +17.3 (*c* = 1.07, CHCl3)}.
IR (Neat): ν = 1735 cm^{-1} (C=O).

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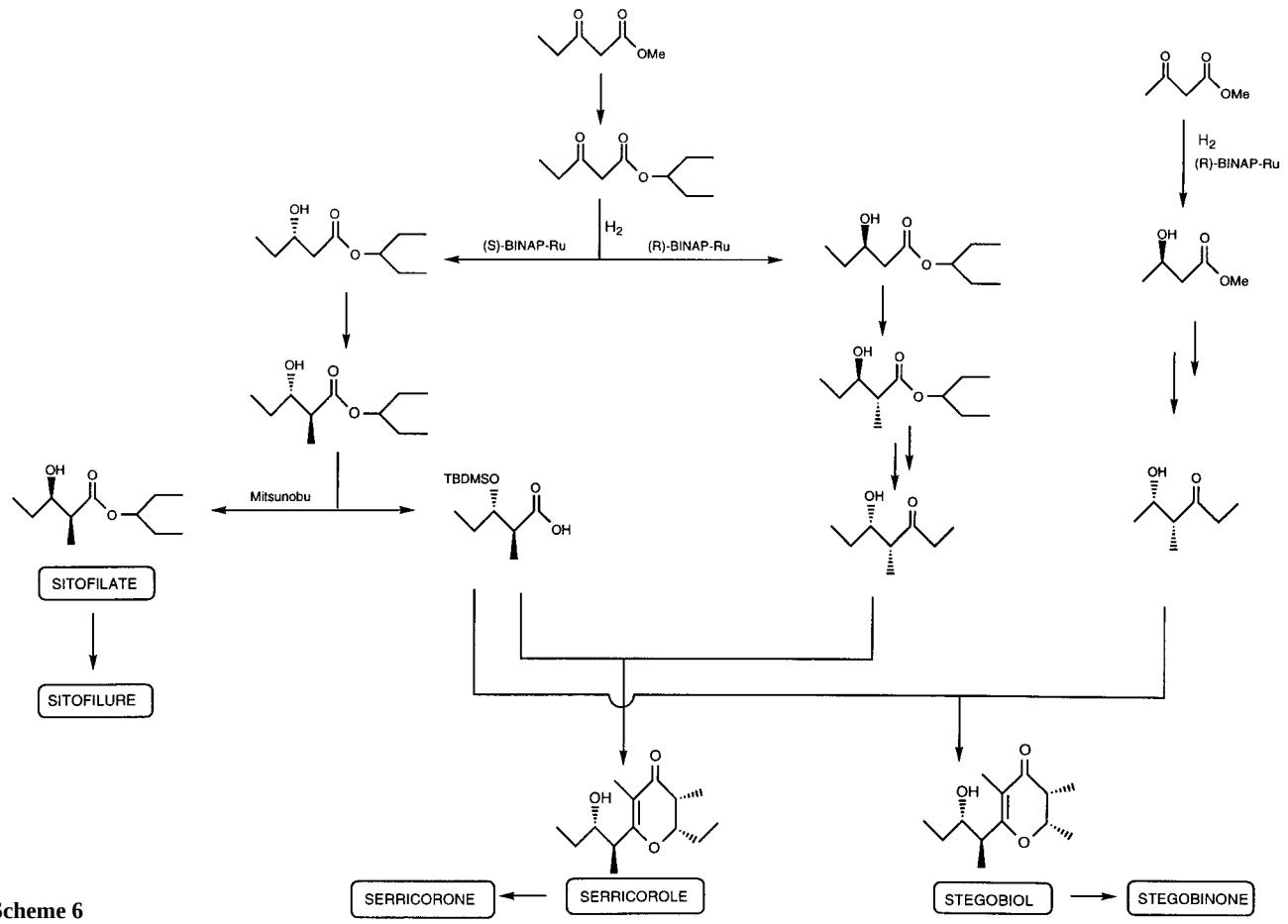

Scheme 6

^{1}H NMR: δ = 0.01 (s, 3 H), 0.02 (s, 3 H), 0.84 (s, 9H, t, J = 7.5 Hz, 9H), 1.05 (d, J = 7.3 Hz, 3 H), 1.31–1.61 (m, 4 H), 2.59 (dq, J = 7.1 and 5.7 Hz, 1 H), 3.90 (q, J = 5.5 Hz, 1 H), 4.69 (qnt, J = 6.1 Hz, 1 H).
^{13}C NMR: δ = –4.69*, –4.51*, 9.44, 9.57, 11.57, 18.10*, 25.75*, 25.85*, 26.20, 26.28, 45.34, 74.26, 76.23, 174.25 (* TBDMS).

(2*S*,3*S*)-3-tert-Butyldimethylsilyloxy-2-methylpentanoic Acid (3):
To a solution of **2c** (2.1 g, 6.6 mmol) in MeOH (30 mL) was slowly added an aq solution of 3 M KOH (9 mL) and the mixture was stirred under reflux for 36 h. The mixture was concentrated, diluted with H_2O (25 mL), and extracted with Et_2O (2×20 mL). The aqueous phase was acidified with AcOH to pH 5 and extracted with Et_2O (3 × 20 mL). Evaporation of Et_2O afforded a liquid which upon distillation yielded 1.35 g (83%) of **3**; bp 144–146 °C/1.1 Torr; $[\alpha]_D^{24}$ +13.0 (c = 1.3, $CHCl_3$) {Lit[10a] $[\alpha]D_D^{22}$ +13.08 (c = 1.36, $CHCl_3$)}.
IR (Neat): ν = 3500–2500 (OH), 1711 cm^{-1} (C=O).
^{1}H NMR: δ = 0.02 (s, 3 H), 0.04 (s, 3 H), 0.85 (s, 9H, t, J = 7.3 Hz, 3 H), 1.09 (d, J = 7.0 Hz, 3 H), 1.50 (dq, J = 7.5 and 5.3 Hz, 2 H), 2.63 (qnt, J = 6.8 Hz, 1 H), 3.87 (q, J = 6.1 Hz, 1 H), 11.6 (br s, 1 H).
^{13}C NMR: δ = –4.94*, –4.38*, 8.65, 12.41, 18.05*, 25.79*, 26.15, 44.83, 74.46, 181.01 (* TBDMS).

1-Ethylpropyl (*R*)-3-Hydroxypentanoate (5):
Following the procedure used for its enantiomer,[11] a 25 mL flask was charged with benzeneruthenium(II) chloride dimer (6.9 mg, 0.0137 mmol), (*R*)-BINAP[21] (18 mg, 0.029 mmol) and anhyd DMF (1 mL) under N_2. The resulting suspension was stirred at 100 °C for 10 min, DMF was then eliminated under vacuum yielding a reddish solid which was taken up in anhyd MeOH (10 mL). The solution was transferred to a previously degassed 250 mL Parr bottle containing **4** (11.35 g, 0.061 mol) and MeOH (20 mL). The bottle, provided with a heating mantle, was assembled in the Parr hydrogenation apparatus. After flushing several times with H_2, this was pressurized to 4 bar. The mixture was heated at 75 °C for 8 h with magnetic stirring and continuous H_2 supply. After cooling, the excess H_2 was removed and the apparatus disassembled. The orange solution was concentrated and the residue purified by distillation to afford 11.14 g (97%) of **5** as a colorless liquid. GC: capillary column: β-DEX 110, temp. 120 °C, R_t 24.52 min., single peak (determined as acetate derivative); bp 72–74 °C /0.9 Torr; $[\alpha]_D^{22}$ –26.91 (c = 0.53, $CHCl_3$).
IR (Neat): ν = 3450 (OH), 1733 cm^{-1} (C=O).
^{1}H NMR: δ = 0.77 (t, J = 7.5 Hz, 6 H), 0.85 (t, J = 7.4 Hz, 3 H), 1.30–1.57 (m, 6 H), 2.29 (dd, J = 16.1 and 8.3 Hz, 1 H), 2.41 (dd, J = 16.1 and 4.0 Hz, 1 H), 3.23 (d, J = 4.1 Hz, 1 H), 3.72–3.93 (m, 1 H), 4.69 (qnt, J = 6.2 Hz, 1 H).
^{13}C NMR: δ = 9.56, 9.81, 26.37, 29.41, 41.15, 69.30, 77.00, 172.70.

1-Ethylpropyl (2*R*,3*R*)-3-Hydroxy-2-methylpentanoate (6):
To a suspension of LiCl (6.78 g, 160 mmol) in anhyd THF (40 mL), was added diisopropylamine (9.5 mL, 66.4 mmol). After cooling at –78 °C, a 2.5 M solution of BuLi in hexane (26.6 mL, 66.4 mmol) was added dropwise under N_2. After stirring for 1 h at 0 °C, the LDA solution was cooled to –78 °C and compound **5** (5 g, 26.56 mmol) in THF (15 mL) was added dropwise. The mixture was then stirred at –30 °C for 2 h. Another portion of BuLi (26.6 mL, 66.4 mmol) was added at –78 °C and the mixture was allowed to react for 2 h at –30 °C. The dianion thus formed was cooled to –78 °C and MeI (8.5 mL, 133 mmol) in THF (6 mL) was added keeping the mixture at –30 °C for 1.5 d in a freezer. The reaction was quenched with satd aq NH_4Cl solution. After usual workup, 5.3 g of **6** was obtained. GC analysis showed that conversion was >99% and diastereomeric excess 80%; capillary column: TRB-1, temp. 120 °C, R_t 7.91 min (*anti*), R_t 8.07 min (*syn*).

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1-Ethylpropyl (2*R*,3*S*)-2-Methyl-3-(3,5-dinitrobenzoyloxy)pentanoate (7a):
A mixture of **6** (5.1 g, 25.8 mmol), Ph_3P (13.66 g, 51.5 mmol), and 3,5-dinitrobenzoic acid (11.05 g, 51.5 mmol) in anhyd THF (90 mL) was stirred and cooled to 0 °C under N_2. To the mixture was added dropwise DEAD (8.1 mL, 51.5 mmol) and stirred for 2 d at r.t. The reaction was monitored by observing changes in color: yellow, blue-greenish, dark blue, red, orange and finally yellow again. Hexane (60 mL) and Et_2O (20 mL) were added to the mixture, and stirring was continued for 1 h. After filtration and concentration of the filtrate in vacuo, the residue was chromatographed on silica gel. Elution with hexane/EtOAc (15:1) afforded 6.5 g (63%) of **7a** as a single diastereomer; mp 34–35 °C; $[\alpha]_D^{24}$ +6.66 (c = 1.12, $CHCl_3$) { Lit[20] $[\alpha]_D^{22}$ +6.61 (c = 1.01, $CHCl_3$)}.
IR (KBr): ν = 1730 (C=O), 1547,1341 cm^{-1} (NO_2).
^{1}H NMR: δ = 0.78 (t, *J* = 7.3 Hz, 6 H), 0.92 (t, *J* = 7.4 Hz, 3 H), 1.23 (d, *J* = 7.1 Hz, 3 H), 1.48 (qnt, *J* = 7.1 Hz, 4 H), 1.67–l.87 (m, 2 H), 2.82 (dq, *J* = 7.1 and 5.5 Hz, 1 H), 4.67 (qnt, *J* = 6.1 Hz, 1 H), 5.38 (dt, *J* = 5.7 and 5.4 Hz, 1 H), 9.05 (d, *J* = 2.1 Hz, 2 H), 9.14 (t, *J* = 2.1 Hz, 1 H).
^{13}C NMR: δ = 9.56, 9.96, 12.39, 24.94, 26.28, 42.97, 77.24, 78.42, 122.26*, 129.27*, 133.81*, 148.48*, 161.83*, 172.90 (* DNB).
Anal. calcd. for $C_{18}H_{24}N_2O_8$ C, 54.54; H, 6.10; N, 7.07. Found: C, 54.50; H, 6.14; N, 7.04.

1-Ethylpropyl (2*R*,3*S*)-3-Hydroxy-2-methylpentanoate (7b):
Removal of DNB group was done using the procedure as described for **2b**. Thus, from **7a** (7.57 g, 19.1 mmol), 3.53 g (91%) of **7b** was obtained as a single diastereomer; bp 105–107 °C/1.1 Torr; $[\alpha]_D^{24}$ +4.16 (*c* = 1.5, $CHCl_3$) {Lit[20] $[\alpha]_D^{24}$ +4.1 (*c* = 1.46, $CHCl_3$)}.
IR (Neat): ν = 3484 (OH), 1719 cm^{-1} (C =O).
^{1}H NMR: δ – 0.74 (t, *J* = 7.5 Hz, 6 H), 0.83 (t, *J* = 7.3 Hz, 3 H), 1.05 (d, *J* = 7.2 Hz, 3 H), 1.22–1.53 (m, 6 H), 2.38 (dq, *J* = 7.1 and 4.4 Hz, 1 H), 2.92 (d, *J* = 4.8 Hz, 1 H), 3.56–3.72 (m, 1 H), 4.64 (qnt, *J* = 6.2 Hz, 1 H).
^{13}C NMR: δ = 9.38, 10.17, 11.08, 26.27, 26.85, 44.32, 73.05, 76.57, 175.71.

1-Ethylpropyl (2*R*,3*S*)-3-Tetrahydropyranyloxy-2-methylpentanoate (7c):
Protection of hydroxyl group as tetrahydropyranyl ether was accomplished by reacting **7b** (1.7 g, 8.40 mmol) with DHP (1.61 mL, 16.32 mmol) in the presence of PPTS as a catalyst. Compound **7c** was obtained in 96% yield as a colorless liquid; bp 148–150 °C/1.4 Torr; $[\alpha]_D^{22}$ –14.80 (*c* = 1, $CHCl_3$).
IR (Neat): ν = 1731 cm^{-1} (C =O).
^{1}H NMR: δ = 0.60–0.85 (m, 9H), 0.93–1.10 (2 d, *J* = 7.1 Hz, 3 H), 1.23–1.73 (m, 12 H, 6 H, THP), 2.40–2.57 (m, 1 H), 3.21–3.37 (m, 1 H, THP), 3.58–3.83 (m, 2 H, 1 H, THP), 4.49 (t, *J* = 3.3 Hz, 1 H, THP), 4.58 (qnt, *J* = 6.1 Hz, 1 H).
^{13}C NMR: δ = 8.62, 9.27, 9.57, 11.68, 13.30, 19.41*, 19.65*, 23.56*, 25.24, 25.72*, 25.99, 30.65*, 30.71*, 42.45, 43.42, 62.05*, 62.37*, 75.93, 76.06, 77.54, 79.84, 96.66*, 99.08*, 174.19 (* THP).

(2*S*,3*S*)-3-Tetrahydropyranyloxy-2-methylpentan-1-ol (7d):
A solution of **7c** (1.97 g, 6.88 mmol) in anhyd Et_2O (20 mL) was cooled to –100 °C and a 1M THF solution of DIBAL (21 mL, 21 mmol) was added dropwise. The mixture was stirred for 1 h and then MeOH (4 mL) was added. The mixture was allowed to warm to r.t. and poured into a sat. solution of Rochelle salts. After stirring for 1 h, the aqueous layer was extracted with Et_2O, the organic layer was dried ($MgSO_4$) and the solvent removed to give after distillation 1.2 g (86%) of **7d** as a colorless liquid; bp 122–124 °C/1.3 Torr; $[\alpha]_D^{24}$ +8.9 (*c* = 1, $CHCl_3$).
IR (Neat): ν = 3438 cm^{-1} (OH).
^{1}H NMR: δ = 0.68–1.00 (m, 6 H), 1.25–1.99 (m, 9 H, 6 H, THP), 3.32–3.94 (m, 6 H, 2 H, THP), 4.39–4.66 (m, 1 H, THP).
^{13}C NMR: δ = 9.83, 10.62, 10.87, 11.73, 20.13*, 21.72*, 24.02, 24.96*, 25.23 *, 25.51, 31.24*, 31.51*, 36.81, 37.68, 63.10*, 64.89*, 65.44, 65.56, 78.77, 81.43, 98.65*, 101.10* (* THP).

(4*S*,5*S*)-5-Tetrahydropyranyloxy-4-methylheptan-3-ol (8):
Following the above mentioned procedure, **7c** (2.3 g, 8 mmol) was reacted with 1M DIBAL solution in CH_2Cl_2 (12 mL, 12 mmol), and after workup, gave 1.76 g (quantitative yield by GC) of the corresponding aldhehyde that was used for the next step without further purification. To a solution of the aldehyde (1.76 g) in Et_2O (20 mL) was added dropwise a 1M solution of EtMgBr in THF (16 mL, 16 mmol) at –15 °C and the mixture was stirred for 15 min., and then quenched with aq sat. NH_4Cl solution. After workup, the liquid obtained was purified by chromatography to give 1.52 g (82%) of **8**; bp 109–111 °C/0.9 Torr; $[\alpha]_D^{22}$ –14.5 (*c* = 1.05, $CHCl_3$).
IR (Neat): ν = 3454 cm^{-1} (OH).
^{1}H NMR: δ = 0.55–0.86 (m, 9 H), 1.10–1.76 (m, 11 H, 6 H, THP), 2.95 (br s, 1 H), 3.20–3.60 (m, 3 H, 1 H, THP), 3.60–3.85 (m, 1 H, THP), 4.35–4.62 (m, 1 H, THP).

(4*R*,5*S*)-5-Hydroxy-4-methylheptan-3-one (9):
Method A: To a solution of **8** (0.65 g, 2.82 mmol) and 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO, 5 mg, 0.03 mmol) in CH_2Cl_2 (10 mL) was added a solution of KBr (36 mg, 0.3 mmol) in H_2O (1 mL). The mixture was cooled to 0 °C and vigorously stirred. Then a 1.16 M aq NaOCl solution (17 mL, 19.72 mmol, pH 9.5) was added. After 20 min., the organic phase was separated and the aqueous phase extracted with CH_2Cl_2. The organic extract was washed with 6% aq HCl (25 mL) containing KI (0.4 g) by stirring the biphasic system for 20 min. The organic phase was treated with (2 × 30 mL) of 10% aq $Na_2S_2O_3$, then with H_2O, and dried (Na_2SO_4). The residue obtained after evaporation of the solvent was purified by column chromatography (hexane/EtOAc, 10:1) to furnish 0.28 g (69%) of **9**.
GC: capillary column TRB-1, temp. 120 °C, R_t 3.32 min (single peak); bp 59–61 °C/0.9 Torr; $[\alpha]_D^{22}$ –27.2 (*c* = 1.5, Et_2O) {Lit[22]: $[\alpha]_D^{20}$ –26.7 (*c* = 1.52, Et_2O)}.
IR (Neat): ν = 3466 (OH), 1706 cm^{-1} (C=O).
^{1}H NMR: δ = 0.83 (t, *J* = 7.4 Hz, 3 H), 0.93 (t, *J* = 7.3 Hz, 3 H), 1.01 (d, *J* = 7.1 Hz, 3 H), 1.18–1.45 (m, 2 H), 2.31–2.58 (m, 3 H), 2.99 (br s, 1 H), 3.60–3.75 (m, 1 H).
^{13}C NMR: δ = 7.30, 10.05, 10.23, 26.86, 34.90, 49.53, 72.55, 216.01.
Method B: To a cooled (–70 °C) and stirred solution of oxalyl chloride (0.3 mL, 3.46 mmol) in anhyd CH_2Cl_2 (6 mL) was added dropwise a solution of DMSO (0.3 mL, 4.32 mmol) and the mixture was stirred for 20 min. Then a solution of **8** (0.4 g, 1.73 mmol) in CH_2Cl_2 (4 mL) was added dropwise. The mixture was kept for 1.5 h at –70 °C, then *i*-Pr_2EtN (1.5 mL, 8.65 mmol) was added and the stirring was continued for 20 more min. The mixture was allowed to warm to 0 °C, stirred for 20 min at this temp. and partitioned between a mixture of H_2O (20 mL) and benzene/Et_2O (4:1, 25 mL). The organic layer was washed with brine, dried ($MgSO_4$) and concentrated in vacuo to yield 0.43 g of a yellowish liquid. This was taken up in anhyd MeOH (5 mL), then pyridinium *p*-toluenesulfonate (PPTS, 0.1 g, 0.4 mmol) was added and the mixture was refluxed for 3 h. After usual workup, a liquid was obtained which upon purification by column chromatography, afforded 0.19 g (76%) of **9** as a colorless liquid and identical physical and spectroscopic data as mentioned above.

Methyl (*R*)-3-Hydroxybutanoate (11):
Prepared as described for **5** by hydrogenation of **10** (28 g, 0.24 mol) using (*R*)-BINAP (71 mg, 0.115 mmol). After workup and purification by distillation, 27.7 g (97%) of **11** was obtained; bp 34–36 °C/0.9 Torr; $[\alpha]_D^{25}$ –23.5 (neat) { Lit[14c] $[\alpha]_D^{25}$ –23.1/–23.6 (neat)}.
IR (Neat): ν = 3440 (OH), 1735 cm^{-1} (C =O).
^{1}H NMR: δ = 1.08 (d, *J* = 6.2 Hz, 3 H), 2.32 (d, *J* = 6.6 Hz, 2 H), 3.30 (br s, 1 H), 3.55 (s, 3 H), 4.05 (sext, *J* = 6.3 Hz, 1 H).
^{13}C NMR: δ = 22.38, 42.65, 51.40, 63.95, 172.65.

Methyl (2*R*,3*R*)-3-Hydroxy-2-methylbutanoate (12):
Under the same conditions described for **6**, asymmetric alkylation of **11** (5.1 g, 43 mmol) afforded 5.7 g (quant. yield) of **12** (92% de) as shown by GC: capillary column TRB-1, temp. 80 °C, R_t 3.81 min (*anti*), R_t 3.98 min (*syn*).

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Methyl (2*R*,3*S*)-2-Methyl-3-(3,5-dinitrobenzoyloxy)butanoate (13a):
As described for compound **7a**, Mitsunobu inversion of **12** (5.7 g, 43 mmol) with Ph_3P (22.82 g, 86 mmol), 3,5-dinitrobenzoic acid (18.46 g, 86 mmol) and DEAD (13.53 mL, 86 mmol) yielded, after purification, 10.44 g (74%) of **13a** as a white solid. GC: capillary column TRB-1, temp. 250 °C, R_t 5.11 min. (single peak), mp 67–68 °C; $[\alpha]_D^{23}$ +12.9 (*c* = 1, $CHCl_3$).
IR (KBr) : ν = 1746, 1725 (C=O), 1549, 1347 cm^{-1} (NO_2).
^1H NMR: δ = 1.27 (d, *J* = 7.2 Hz, 3 H), 1.41 (d, *J* = 6.5 Hz, 3 H), 2.83 (dq, *J* = 7.1 and 5.4 Hz, 1 H), 3.69 (s, 3 H), 5.46 (dq, *J* = 6.4 and 5.4 Hz, 1 H), 9.07 (d, *J* = 2.1 Hz, 2 H), 9.17 (t, *J* = 2.1 Hz, 1 H).
^{13}C NMR: δ = 12.23, 17.30, 43.95, 51.97, 73.80, 122.20*, 129.20*, 133.80*, 148.41*, 161.45*, 173.28 (* DNB).
Anal. calcd. for $C_{13}H_{14}N_2O_8$: C, 47.86; H, 4.32; N, 8.59. Found: C, 47.87; H, 4.30; N, 8.61.

Methyl (2*R*,3*S*)-3-Hydroxy-2-methylbutanoate (13b):
To a solution of **13a** (3 g, 9.19 mmol) in THF/MeOH (25 mL, 4:1) was added a solution of KOH (0.132 g, 2 mmol) in MeOH (6 mL). After stirring the mixture for 2 h at 0 °C, usual workup and purification afforded 1.03 g (85%) of **13b**, GC: column TRB-1, temp. 80 °C, R_t 3.98 min (single peak); bp 115–117 °C/18 Torr; $[\alpha]_D^{25}$ –13.6 (*c* = 0.5, MeOH) {Lit[23] $[\alpha]_D^{25}$ –13.4 (*c* = 0.51, MeOH)}.
IR (Neat): ν = 3469 (OH), 1738 cm^{-1} (C = O).
^1H NMR δ = 0.92 (d, *J* = 2.3 Hz, 3 H), 0.95 (d, *J* = 3.2 Hz, 3 H), 2.24 (dq, *J* = 7.1 and 5.2 Hz, 1 H), 3.30 (d, *J* = 5.3 Hz, 1 H), 3.45 (s, 3 H), 3.76 (sext, *J* = 5.6 Hz, 1 H).
^{13}C NMR: δ = 11.31, 19.93, 45.77, 51.19, 67.74, 175.50.

Methyl (2*R*,3*S*)-3-Tetrahydropyranyloxy-2-methylbutanoate (13c):
As described for **7c**, DHP protection of **13b** (2 g, 15.14 mmol) yielded **13c** (3.1 g, 95%); bp 91–93°C/1 Torr; $[\alpha]_D^{22}$ +12.1 (*c* = 1, $CHCl_3$).
IR (Neat): ν = 1740 cm^{-1} (C=O).
^1H NMR: δ = 1.02 (pseudo t, *J* = 6.8 Hz, 3 H), 1.08–1.13 (2d, *J* = 2.9 Hz, 3 H), 1.26–1.73 (m, 6 H, THP), 2.41 (qnt, *J* = 6.6 Hz, 1 H), 3.24–3.44 (m, 1 H, THP), 3.54 (d, *J* = 2.2 Hz, 3 H), 3.60–3.99 (m, 2 H, 1 H, THP), 4.45–4.62 (2t, *J* = 3.2 Hz, 1 H, THP).
^{13}C NMR: δ = 12.09, 12.45, 16.79, 19.15*, 19.58, 19.71*, 25.30*, 25.37*, 30.72*, 45.21, 45.80, 51.25, 61.80*, 62.52*, 71.28, 75.42, 94.69*, 99.74*, 174.72, 174.79 (* THP).

(2*S*,3*S*)-2-Methyl-3-tetrahydropyranyloxybutan-1-ol (14):
To a cooled solution (0°C) of $LiAlH_4$ (0.6 g, 15.72 mmol) in anhyd Et_2O (20 mL) was added dropwise a solution of **13c** (1.7 g, 7.86 mmol) in Et_2O (10 ml). The mixture was stirred for 2 h at 0 °C and then H_2O was added (1 mL) followed by 1M NaOH (1 mL) and stirring was continued for 2 more hours. After filtration and washing with Et_2O, the organic layer was dried ($MgSO_4$) and evaporated yielding a liquid which upon distillation afforded 1.4 g (94%) of **14**; bp 115–117 °C/1.4 Torr; $[\alpha]_D^{22}$ +30.5 (*c* = 1, $CHCl_3$).
IR (Neat): ν = 3425 cm^{-1} (OH).
^1H NMR: δ – 0.70–0.77 (2d, *J* = 5.9Hz, 3 H), 1.0–1.14 (2d, *J* = 6.5 Hz, 3 H), 1.30–1.90 (m, 7 H, 6 H, THP), 2.99 (br s, 1 H), 3.30–3.65 (m, 3 H, 1 H, THP), 3.69–3.87 (m, 1 H, THP), 3.93 (dq, *J* = 6.5, 3.3 Hz, 1 H), 4.38–4.65 (m, 1 H, THP).
^{13}C NMR: δ – 10.47, 12.07, 15.95, 17.31, 19.80*, 20.77*, 25.17*, 25.33 *, 30.97*, 31.27*, 39.37, 39.84, 62.70*, 64.18*, 64.90, 72.32, 76.55, 97.82*, 99.11* (* THP).

(4*S*,5*S*)-5-Tetrahydropyranyloxy-4-methylhexan-3-ol (15):
Swern oxidation of **14** (1.69 g, 9 mmol), using oxalyl chloride (1.76 mL, 20 mmol), DMSO (1.77 mL, 25 mmol), and *i*-Pr_2EtN (7.1 mL, 40 mmol), afforded 2.34 g of a liquid that was taken up in Et_2O (20 mL). Addition of a 1M THF soln of EtMgBr (20 mL), workup and column chromatography (hexane/EtOAc, 12:1) afforded 1.42 g (73%) of **15**; bp 127–129 °C/1.4 Torr; $[\alpha]_D^{22}$ –16.5 (*c* = 1.06, $CHCl_3$).
IR (Neat): ν = 3419 cm^{-1} (OH).
^1H NMR: δ = 0.67–0.98 (m, 6 H), 1.08–1.80 (m, 11 H, 6 H, THP), 2.90 (br s, 1 H), 3.31–3.56 (m, 2 H, 1 H, THP), 3.56–3.97 (m, 3 H, 1 H, THP), 4.44–4.79 (m, 1 H, THP).
^{13}C NMR: δ = 5.11, 6.17, 10.64, 10.73, 17.23, 19.94*, 20.41*, 25.24*, 25.38*, 27.60, 27.95, 31.10*, 31.51*, 41.59, 42.30, 62.92*, 63.58*, 75.83, 76.69, 77.44, 81.63, 95.86*, 100.56* (* THP).

(4*R*,5*S*)-5-Hydroxy-4-methylhexan-3-one (16):
Analogous to the preparation of compound **9**, oxidation of **15** was done by two different methods.
Method A: From **15** (0.25 g, 1.16 mmol), TEMPO (2 mg, 0.018 mmol), KBr (21 mg, 0.18 mmol), 1.2 M NaOCl (6.6 mL, 8 mmol), 6% HCl (20 mL), KI (0.32 g). After column chromatography, 98 mg (65%) of **16** was obtained; bp 50–52 °C/1.4 Torr; $[\alpha]_D^{21}$ –30.0 (*c* = 1.31, Et_2O) {Lit[7b] $[\alpha]_D^{21}$ –30.2 (*c* = 1.43, Et_2O)}.
IR (Neat): ν = 3423 (OH), 1708 cm^{-1} (C=O).
^1H NMR: δ – 0.95 (t, *J* = 7.2 Hz, 3 H), 1.04 (d, *J* = 7.5 Hz, 3 H), 1.05 (d, *J* = 6.0 Hz, 3 H), 2.34–2.60 (m, 3 H), 3.07 (br s, 1 H), 3.89–4.07 (m, 1 H).
^{13}C NMR: δ – 7.59, 10.60, 20.10, 35.39, 51.17, 67.44, 216.37.
Method B: From **15** (0.25 g, 1.16 mmol), oxalyl chloride (0.2 mL, 2.31 mmol), DMSO (0.2 mL, 2.88 mmol), *i*-Pr_2EtN (1 mL, 5.77 mmol), and PPTS (50 mg, 0.2 mmol), 113 mg (75%) of **16** was obtained.

(1′*S*,2′*R*)-1′,2′-Dimethyl-3′-oxopentyl (2*S*,3*S*)-3-*tert*-Butyldimethylsilyloxy-2-methylpentanoate (17):
To a mixture of 3 (0.25 g, 1 mmol) and Et_3N (0.16 mL, 1.1 mmol) in anhyd THF (8 mL) was added 2,6-dichlorobenzoyl chloride (0.15 mL, 1.1 mmol) under a N_2 atmosphere. The mixture was stirred overnight at r.t. After filtration and removal of the solvent, the residue was dissolved in anhyd benzene (6 mL). To the mixture were added a solution of **16** (0.1 g, 0.77 mmol) in anhyd benzene (2 mL) and DMAP (0.104 g, 0.85 mmol) in benzene (2 mL). The resulting mixture was stirred for 6 h at 0 °C and then overnight at r.t. lt was diluted with Et_2O (20 mL), washed with 1M HCl, H_2O, aq $NaHCO_3$, brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane/EtOAc, 50:1) to give 0.23 g (83%) of **17** as a colorless liquid.
IR (Neat): ν = 1735 (C=O, ester), 1718 cm^{-1} (C=O, ketone).
^1H NMR: δ = 0.01 (s, 3 H), 0.02 (s, 3 H), 0.83 (s, 9H, t, *J* = 7.3 Hz, 3 H), 0.90–1.20 (m, 12 H), 1.28–1.51 (m, 2 H), 2.36–2.78 (m, 4 H), 3.84 (dq, *J* = 5.9, 1.2 Hz, 1 H), 5.09 (qnt, *J* = 6.1 Hz, 1 H).
^{13}C NMR: δ = –4.68*, –4.50*, 7.66, 9.40, 11.32, 12.29, 17.72*, 25.65, 25.83*, 35.62, 45.43, 50.44, 71.00, 74.18, 173.52, 211.69 (* TBDMS).

(2*S*,3*R*)-2,3-Dihydro-6-[(1′*S*,2′*S*)-2′-hydroxy-1′-methylbutyl]-2,3,5-trimethyl-4H-pyran-4-one (Stegobiol):
A 1M soln of $TiCl_4$ in CH_2Cl_2 (3.1 mL, 3.1 mmol) was added dropwise at –78 °C to a mixture of **17** (0.22 g, 0.6 mmol) and *i*-Pr_2EtN (0.85 mL, 4.9 mmol) in CH_2Cl_2 (30 mL). The mixture was stirred at –78 °C for 1 h, then allowed to warm up to –10 °C over 2 h and stirred at that temperature for 20 h. Workup gave a liquid that was taken up in MeCN (8 mL) and treated with 40% aq HF (10 drops) The mixture was stirred at 0 °C for 10 h, diluted with Et_2O, washed with satd aq $NaHCO_3$ solution and dried ($MgSO_4$). Column chromatography on silica gel (hexane/Et_2O, 2:1) gave pure stegobiol (85 mg, 62%); oil. GC: column TRB-1, temp. 180 °C, R_t 5.19 min. (single peak). $[\alpha]_D^{23}$ –116±5 (c = 0.21, $CHCl_3$) {Lit[8a] $[\alpha]_D^{25}$ –118±7 (*c* = 0.107, $CHCl_3$)}.
IR (Neat): ν = 3432 (OH), 1661 (C=O), 1600 cm^{-1} (C=C).
^1H NMR: δ = 0.97 (t, *J* = 7.3 Hz, 3 H), 1.00 (d, *J* = 7.3 Hz, 3 H), 1.15 (d, *J* = 7.1 Hz, 3 H), 1.29 (d, *J* = 5.6 Hz, 3 H), 1.33–1.62 (m, 2 H), 1.72 (s, 3 H), 1.91 (br s, 1 H), 2.34 (dq, *J* = 7.2 and 3.5 Hz, 1 H), 2.83 (qnt, *J* = 6.9 Hz, 1 H), 3.46–3.62 (m, 1 H), 4.46 (dq, *J* = 6.6 and 3.4 Hz, 1 H).
^{13}C NMR: δ = 9.31, 9.51, 10.16, 14.81, 15.97, 28.30, 40.89, 43.71, 75.30, 76.59, 109.22, 172.60, 196.91.

(2*S*,3*R*)-2,3-Dihydro-2,3,5-trimethyl-6-[(*R*)-1′-methyl-2′-oxobutyl]-4H-pyran-4-one (Stegobinone):
Oxidation of stegobiol was done under Swern conditions. Stegobiol (0.06 g, 0.25 mmol), oxalyl chloride (0.1 mL, 1 mmol), DMSO (0.14 mL, 2 mmol), and *i*-Pr_2EtN (0.4 mL, 2.2 mmol) gave after purification 45 mg (81%) of stegobinone; oil. GC: TRB-1, temp. 180°C, Rt 4.73 min (single peak). $[\alpha]_D^{23}$ –286±3 (*c* = 0.53, $CHCl_3$) {Lit[7b] $[\alpha]_D^{23}$ –282±10 (*c* = 0.11, $CHCl_3$)}.
IR (Neat): ν = 1720 (C=O), 1665 (C=O, α,β-unsaturated), 1663 cm^{-1} (C=C).

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^{1}H NMR: δ = 0.97–l.05 (d, J = 7.3 Hz, 3 H, t, J = 7.6 Hz, 3 H), 1.25 (d, J = 6.6 Hz, 3 H), 1.26 (d, J = 7.0 Hz, 3 H), 1.75 (s, 3 H), 2.24–2.50 (m, 3 H), 3.59 (q, J = 7.0 Hz, 1 H), 4.41 (dq, J = 6.6 and 3.6 Hz, 1 H).
^{13}C NMR: δ = 7.91, 9.46, 12.83, 15.73, 33.88, 43.67, 49.15, 77.12, 109.31, 168.77, 196.84, 207.31.

(1′*S*,2′*R*)-1′-Ethyl-2′-methyl-3′-oxopentyl (2*S*,3*S*)-3-*tert*-Butyldimethylsilyloxy-2-methylpentanoate (18):
Following the same procedure as for **17**, acid **3** (0.66 g, 2.7 mmol), 2,6-dichlorobenzoyl chloride (0.4 mL, 2.8 mmol), Et_3N (0.42 mL, 3 mmol), **9** (0.3 g, 2.1 mmol), and DMAP (0.28 g, 2.3 mmol) gave, after purification by column chromatography on silica gel (hexane/EtOAc, 50:1), 0.66 g (86%) of **18**; oil.
IR (Neat): ν = 1738 (C =O, ester), 1720 cm^{-1} (C=O, ketone).
^{1}H NMR: δ = –0.02 (s, 3 H), –0.01 (s, 3 H), 0.65–0.85 (s, 9H, m, 6 H), 0.94 (t, J = 7.2 Hz, 3 H), 1.00 (d, J = 7.0 Hz, 3 H), 1.01 (d, J = 7.2 Hz, 3 H), 1.22–l.63 (m, 4 H), 2.25–2.60 (m, 3 H), 2.69 (dq, J = 7.0 and 5.2 Hz, 1 H), 3.70–3.90 (m, 1 H), 5.04 (q, J = 6.1 Hz, 1 H).
^{13}C NMR: δ = –4.66*, –4.56*, 7.69, 9.81, 10.04, 11.07, 11.39, 18.06*, 25.10, 25.62, 25.82*, 35.06, 45.47, 48.82, 74.21, 74.94, 173.56, 211.40 (* TBDMS).

(2*S*,3*R*)-2-Ethyl-2,3-dihydro-6-[(1′*S*,2′*S*)-2′-hydroxy-1′-methylbutyl]-3,5-dimethyl-4*H*-pyran-4-one (Serricorole):
As described for stegobiol, **18** (0.55 g, 1.5 mmol) was treated with *i*-Pr_2EtN (2.1 mL, 11.8 mmol) and $TiCl_4$ (0.82 mL, 7.4 mmol), and then deprotected with HF. Purification gave 0.22 g (64%) of serricorole; oil. GC: TRB-1, temp. 180 °C, R_t 5.25 min (single peak). $[\alpha]_D^{22}$ –124±2 (c = 2.18, $CHCl_3$) {Lit[10a] $[\alpha]_D^{24}$–124 (c = 2.34, $CHCl_3$)}.
IR (Neat): ν = 3435 (OH), 1654 (C =O), 1598 cm^{-1} (C=C).
^{1}H NMR: δ = 0.85–1.00 (t, J = 7.1 Hz, 6 H, d, J = 7.1 Hz, 3 H), 1.14 (d, J = 7.0 Hz, 3 H), 1.27–1.64 (m, 3 H), 1.64–l.89 (s, 3 H, m, 1 H), 1.89–2.07 (m, 1 H), 2.32 (dq, J = 7.4 and 3.3 Hz, 1 H), 2.83 (qnt, J = 7.0 Hz, 1 H), 3.54 (br s, 1 H), 4.05–4.21 (m, 1 H).
^{13}C NMR: δ = 9.37, 9.63, 9.98, 10.15, 14.82, 23.45, 28.21, 41.05, 42.54, 75.29, 81.92, 109.29, 173.06, 197.31.

(2*S*,3*R*)-2-Ethy1-2,3-dihydro-3,5-dimethyl-6-[(*R*)-1′-methyl-2′-oxobutyl]-4*H*-pyran-4-one (Serricorone):
Oxidation of serricorole (0.22 g, 0.91 mmol) with oxalyl chloride (0.17 mL, 2 mmol) and DMSO (0.18 mL, 2.5 mmol) in the presence of *i*-Pr_2EtN (0.8 mL, 4.5 mmol) yielded after purification 180 mg (83%) of serricorone; oil. GC: TRB-1, temp. 180 °C, R_t 5.79 min (single peak); $[\alpha]_D^{24}$ –272±3 (c = 0.47, $CHCl_3$) {Lit[9] $[\alpha]_D^{24}$ –269±4 (c = 0.11, $CHCl_3$)}.
IR (Neat): ν = 1725 (C=O), 1669 (C=O, α,β-unsaturated), 1611 cm^{-1} (C=C).
^{1}H NMR: δ = 0.80–1.05 (t, J = 7.8 Hz, 3 H, d, J = 7.4 Hz, 3 H, t, J = 7.2 Hz, 3 H), 1.23 (d, J = 7.0 Hz, 3 H), 1.31–l.54 (m, 1 H), 1.60–1.85 (s, 3 H, m, 1 H), 2.19–2.45 (m, 3 H), 3.58 (q, J = 7.0 Hz, 1 H), 3.96–4.11 (m, 1 H).
^{13}C NMR: δ = 7.81, 9.41, 9.57, 9.78, 12.97, 23.34, 33.84, 42.63, 49.02, 82.47, 109.36, 169.12, 197.16, 207.15.

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