Reptilian Chemistry: Enantioselective Syntheses of Novel Components from a Crocodile Exocrine Secretion

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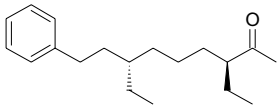
Received 4 August 2000

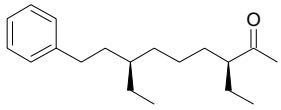
Abstract: Enantioselective syntheses of the two naturally-occurring diastereomers of dianeackerone (**1a** and **1b**) and of a closely related steroidal β-oxo ester (**2**), characterized from the paracloacal glandular secretion of the African dwarf crocodile, *Osteolaemus tetraspis*, are described.

Key words: enantioselective alkylation, crocodile, dianeackerone, natural products, steroids

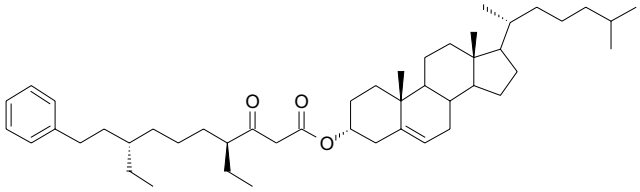
The "ruling reptiles" (Archosauria), which dominated terrestrial animal communities during the Mesozoic era (245−65 million years ago), are now represented on earth by only about two dozen species of crocodilians.[1] All of these surviving species possess a pair of skin glands, designated the paracloacal glands, secretions of which are thought to serve a pheromonal role.[2] We recently elucidated the structures of the major constituents of the paracloacal gland secretion of the African dwarf crocodile (*Osteolaemus tetraspis*), and we have established the absolute configuration of both naturally occurring diastereomers of dianeackerone (**1a** and **1b**), the secretion's chief volatile component, by synthesis.[3,4] In this paper, we report in detail the enantioselective syntheses of **1a** and **1b**, as well as the synthesis of a steroidal β-oxo ester **2**, which would appear to serve as the immediate biosynthetic precursor of the dianeackerones.



1a

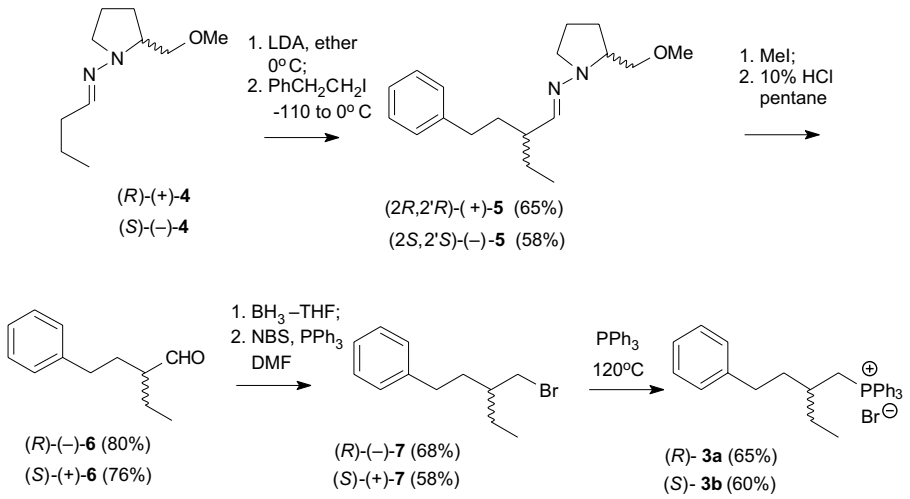


1b



2

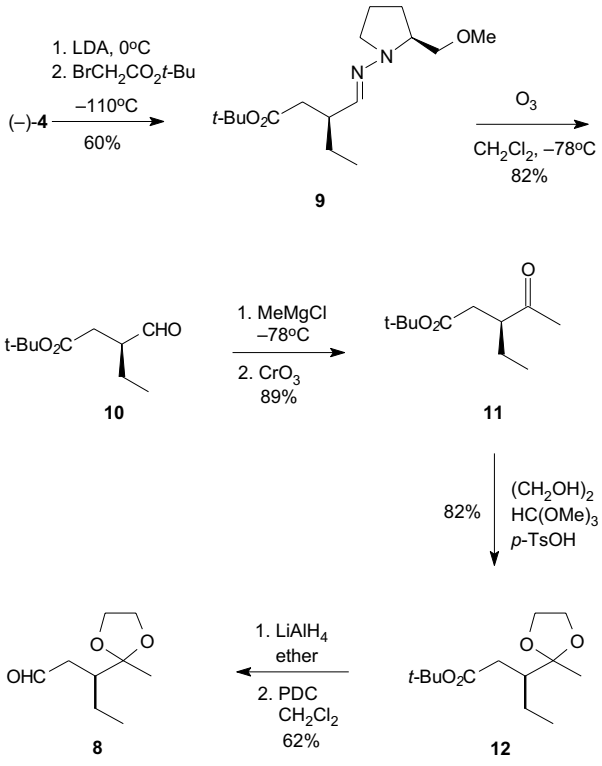
The methodology described by Enders and co-workers,[5,6] based on the alkylation of optically active hydrazones derived from (*S*)-(−)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) and its (*R*)-(+) enantiomer provided highly stereoselective syntheses of phosphonium salts **3a** and **3b** (Scheme 1). Asymmetric alkylation of the SAMP-hydrazone (+)-**4** or (−)-**4**[7] provided the products (+)-**5** or (−)-**5** in good yield and more than 95% de.[8] Treatment of hydra-



Scheme 1

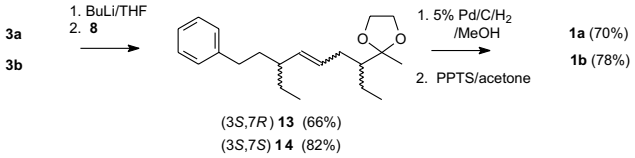
zones (+)-**5** or (−)-**5** with CH_3I, followed by acidic hydrolysis with HCl in a two phase system readily formed the aldehydes (+)-**6** or (−)-**6**. Reduction of (+)-**6** or (−)-**6** with borane-THF complex, followed by bromination with NBS in the presence of Ph_3P, yielded the bromides (+)-**7** or (−)-**7** in good yield. Reaction of these bromides with Ph_3P gave the desired chiral phosphonium salts, **3a** or **3b**.

Similarly, the chiral precursor **8** was prepared via the SAMP-hydrazone (−)-**4** (Scheme 2). Asymmetric alkylation of (−)-**4** with *t*-butyl bromoacetate produced the hydrazone **9** in 60% yield and better than 95% de.[8] Ozonolysis of **9** in CH_2Cl_2 at −78 °C gave the corresponding aldehyde **10**. Reaction of the aldehyde **10** with CH_3MgI at −78 °C yielded an unstable alcohol, which was immediately oxidized by Jones' reagent to afford the ketone **11**. Protection of the carbonyl group in **11** with ethylene glycol and trimethyl orthoformate in the presence of p-TsOH provided the ketal **12** in excellent yield. Reduction of the ester **12** with $LiAlH_4$, followed by oxidation with PDC, supplied the desired aldehyde **8**.



Scheme 2

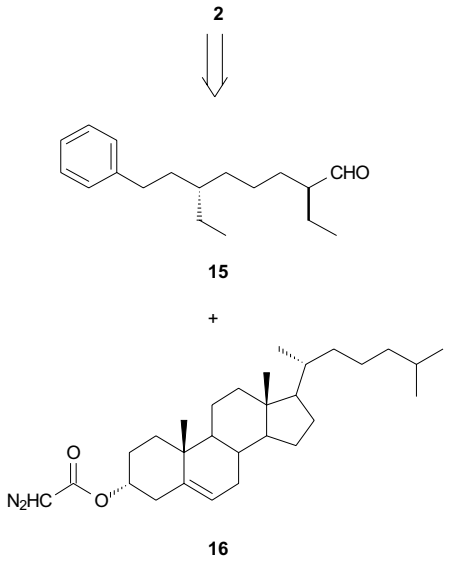
Coupling of aldehyde **8** with the Wittig reagent derived from phosphonium salt **3a** provided the alkene **13** as a mixture of *cis*- and *trans*-isomers (*cis*:*trans*, approx. 9:1) (Scheme 3). Hydrogenation of **13** with Pd/C in MeOH, followed by deprotection with PPTS provided **1a**, $[\alpha]_D$ −8.7 (*c* 0.2, $CHCl_3$) {Lit.[3] $[\alpha]_D$ −9 (*c* 0.1, $CHCl_3$)}. In a completely analogous fashion, coupling of aldehyde **8** with the Wittig reagent prepared from **3b** furnished the alkene **14** as a 9:1 mixture of *cis*- and *trans*-isomers. Subsequent hydrogenation and deprotection provided the desired **1b**, $[\alpha]_D$ +3.2 (*c* 0.2, $CHCl_3$) {Lit.[3] $[\alpha]_D$ +4 (*c* 0.8, $CHCl_3$)}.



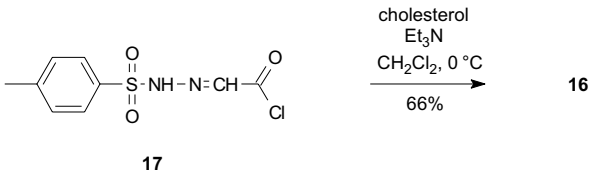
Scheme 3

While **1a** and **1b** are the major volatile constituents of the *O. tetraspis* paracloacal glandular fluid, the bulk of the secretion is made up of a series of steroidal esters of aromatic acids closely related to dianeackerone. Of these compounds, the β-oxo ester **2** is especially interesting, since it would appear to be the immediate precursor (upon hydrolysis and decarboxylation) of dianeackerone itself.

A retrosynthetic analysis of β-oxo ester **2** suggested that this target compound should be obtained by the reaction of aldehyde **15** with cholesteryl diazoacetate **16**[9](Scheme 4), which is readily prepared via by the treatment of cholesterol with the acid chloride **17**[10] (Scheme 5).



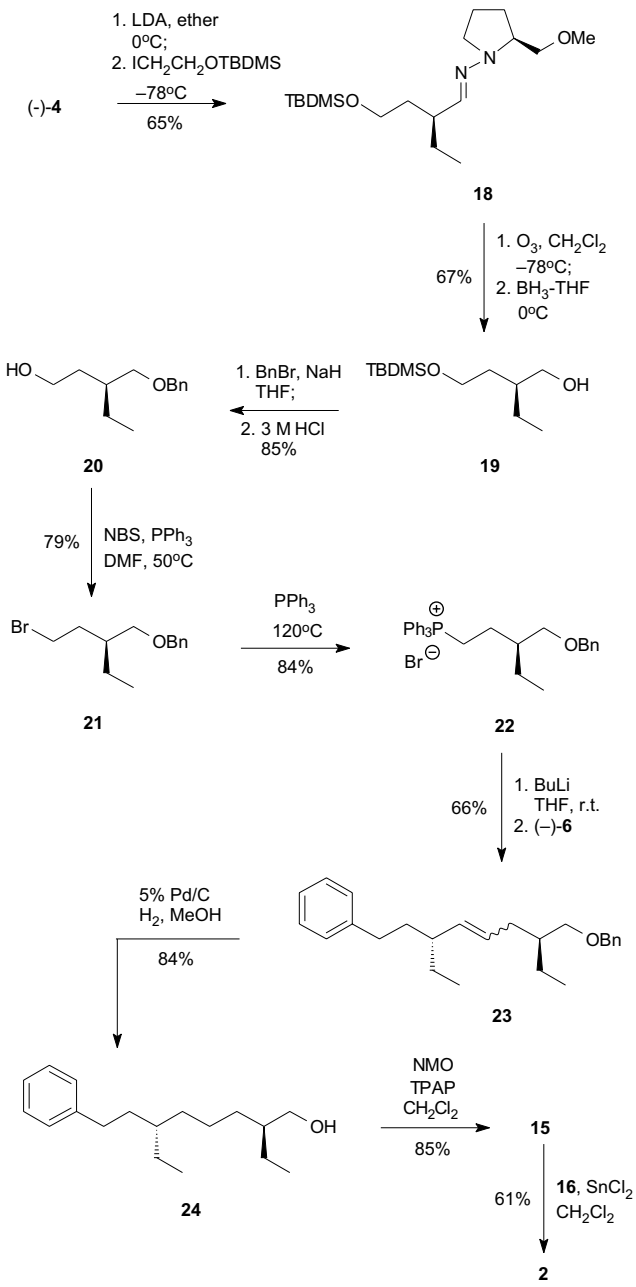
Scheme 4



Scheme 5

Using the methodology described earlier, aldehyde **15** was synthesized as outlined in Scheme 6. Alkylation of the SAMP-hydrazone (−)-**4** afforded hydrazone **18** in excess of 95% de.[8] Ozonolysis of the **18** yielded a crude aldehyde, which was immediately reduced with borane-THF complex to give alcohol **19**. Protection of **19** with benzyl bromide in the presence of NaH, followed by the removal of the silyl ether with HCl, provided alcohol **20** in good yield. Bromination of **20** with NBS in the presence of Ph_3P provided bromide **21**, which was converted into the chiral phosphonium salt **22**. Coupling of the Wittig, the reagent derived from **22,** with aldehyde (−)-**6** generated a mixture of *cis*- and *trans*-alkene **23** (*cis:trans*, approx. 9:1). Hydrogenation and hydrogenolysis of **23** with Pd/C in MeOH gave the alcohol **24** in good yield. Oxidation of **24** with *N*-morpholine *N*-oxide (NMO) mediated by tetrapropylammonium perruthenate (TPAP) afforded aldehyde **15**. Coupling of **15** with the diazoacetate **16** in the presence of a catalytic amount of $SnCl_2$ afforded the desired β-oxo ester **2**.

We would like to emphasize, in conclusion, is only by virtue of having synthesized the dianeackerone diastereomers by the Enders' technique of stereoselective alkylation was it possible to assign absolute configurations to the natural products. The same technique has also enabled us to confirm the structure of cholesteryl β-oxo ester **2** by synthesis.



Scheme 6

GC/MS analyses were performed using a Hewlett−Packard (HP) 5890 gas chromatograph installed with a 30 m × 0.25 mm fused silica column coated with DB-5 (J & W Scientific, Folsom, CA) coupled to an HP-5970 Mass Selective Detector. MS analyses were performed using a Micromass Autospec instrument operated in electron ionization (EI), chemical ionization (CI) (CH_4 as the reagent gas), or electrospray ionization modes. ^1H and ^{13}C NMR spectra were recorded on a Varian XL 400 instrument using $CDCl_3$ or C_6D_6 as solvent. Chemical shifts (δ) are given in ppm downfield from TMS.

Alkylation of Butyraldehyde (+)-(*R*)-1-Amino-2-(methoxymethyl)pyrrolidinehydrazone [(+)-4] with 2-Phenylethyl Iodide

To a solution of LDA (1.5 M, 5.8 mL, 8.7 mmol) in anhyd Et_2O (20 mL), hydrazone (+)-**4** (1.6 g, 8.7 mmol) in anhyd Et_2O (10 mL) was added dropwise at 0 °C over 10 min. The mixture was stirred at 0 °C under N_2 for 5 h and then cooled to −110 °C using a dry-ice/liquid N_2 bath. 2-Phenylethyl iodide (1.64 mL, 11.3 mmol) in Et_2O (20 mL) was added dropwise over 30 min. The mixture was slowly warmed up to 0 °C and quenched with sat. NH_4Cl (20 mL). The organic layer was separated, the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (EtOAc/hexanes, 1:9) to afford (*R*)-2-ethyl-4-phenylbutyraldehyde (2′*R*)-1′-amino-2′-(methoxymethyl)pyrrolidinehydrazone [(+)-**5**] as a colorless oil.

Yield: 1.63 g (65%); $[\alpha]_D$ +64 (*c* 1.4, $CHCl_3$).

^1H NMR (400 MHz,$CDCl_3$): δ = 0.92 (t, 3H, *J* = 7.2 Hz), 1.40−1.56 (m, 2H), 1.71−2.00 (m, 5H), 2.15−2.24 (m, 1H), 2.58−2.74 (m, 3H), 3.34−3.50 (m, 4H), 3.39 (s, 3H), 3.36 (m, 1H), 6.49 (d, 1H, *J* = 6.8 Hz), 7.16−7.30 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.0, 142.8, 128.4 (2C), 128.2 (2C), 125.5, 74.7, 63.5, 59.2, 50.5, 43.9, 35.1, 33.6, 26.7, 26.5, 22.0, 11.4.

GC/MS (EI): *m/z* = 288 (M^+), 243, 197, 184, 139, 123, 105, 91, 70.

HRMS (EI): *m/z* calcd for $C_{18}H_{28}N_2O$ (M^+): 288.2202. Found: 288.2202.

(−)-5

Prepared from (−)-**4** using above procedure, colorless oil, $[\alpha]_D$ = −64.9 (*c* 1.2, $CHCl_3$).

(−)-(*R*)-2-Ethyl-4-phenylbutyraldehyde [(−)-6]

A mixture of hydrazone (+)-**5** (900 mg, 3.12 mmol) and CH_3I (4 mL) was warmed to reflux under N_2 for 4 h. The surplus CH_3I was

removed in vacuo, and the residue was treated with 10% HCl (10 mL) in pentane (20 mL) with stirring at r.t. for 1 h. The organic layer was separated, the aqueous layer was extracted with pentane (2 × 40 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (EtOAc/hexanes, 1:9) to afford aldehyde (−)-**6** as a colorless oil.

Yield: 440 mg (80%); $[\alpha]_D$ −1.8 (*c* 4.0, $CHCl_3$).

^{1}H NMR (400 MHz,$CDCl_3$): δ = 0.94 (t, 3H, *J* = 7.2 Hz), 1.54−1.64 (m, 1H), 1.64−1.81 (m, 2H), 1.95−2.05 (m, 1H), 2.22−2.29 (m, 1H), 2.57−2.70 (m, 2H), 7.18−7.32 (m, 5H), 9.62 (d, 1H, *J* = 2.8 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.1, 141.5, 128.4 (2C), 128.3 (2C), 126, 52.6, 33.2, 30.1, 21.8, 11.3.

GC/MS (EI): *m/z* = 176 (M^+), 158, 115, 105, 104, 91, 77.

HRMS (EI): *m/z* calcd for $C_{12}H_{16}O$ (M^+): 176.1201. Found: 176.1201.

(+)-6

Prepared from (−)-**5** using above procedure, colorless oil, $[\alpha]_D$ = +1.5 (*c* 1.2, $CHCl_3$).

(−)-(*R*)-2-Ethyl-4-phenyl-1-butyl Bromide [(−)-7]

To a solution of aldehyde (−)-**6** (260 mg, 1.47 mmol) in THF (8 mL), borane-THF complex (1 M, 2.95 mL, 2.95 mmol) was added dropwise at 0 °C. The mixture was stirred at 0 °C under N_2 for 1 h and then quenched with 1 M HCl (5 mL) at 0 °C. The organic layer was separated, the aqueous layer was extracted with EtOAc (2 × 40 mL). The combined organic layers were washed with 3% $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo to provide the crude alcohol (260 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, 3H, *J* = 7.2 Hz), 1.61 (br s, 1H), 1.41−1.78 (m, 5H), 2.67 (t, 2H, *J* = 8.0 Hz), 3.62 (d, 2H, *J* = 5.6 Hz), 7.20−7.32 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.7, 128.3 (4C), 125.7, 65.0, 41.5, 33.2, 32.3, 23.2, 11.0.

GC/MS (EI): *m/z* = 178 (M^+).

The above crude alcohol (260 mg, 1.46 mmol) and Ph_3P (765 mg, 2.92 mmol) were dissolved in DMF (4 mL). NBS (520 mg, 2.92 mmol) was added to the solution in small portions at r.t over 20 min. The reaction mixture was warmed to 55 °C under N_2 overnight and then cooled to r.t. The mixture was diluted with Et_2O (100 mL), washed with 3% $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (EtOAc/hexanes, 1:9) to give bromide (−)-**7** as a colorless oil.

Yield: 240 mg (68%); $[\alpha]_D$ −10.5 (*c* 2.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (t, 3H, *J* = 7.2 Hz), 1.45−1.79 (m, 5H), 2.57−2.72 (m, 2H), 3.52 (d, 2H, *J* = 4.8 Hz), 7.20−7.32 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.1, 128.4 (2C), 128.3 (2C), 125.8, 40.4, 38.7, 34.1, 32.9, 25.1, 10.8.

GC/MS (EI): *m/z* = 240 (M^+), 160, 145, 131, 105, 91, 77.

HRMS (EI): *m/z* calcd for $C_{12}H_{17}{}^{79}Br$ (M^+): 240.0513. Found: 240.0511.

(+)-7

Prepared from (+)-**6** using above procedure, colorless oil, $[\alpha]_D$ = +10.8 (*c* 1.5, $CHCl_3$).

(*R*)-2-Ethyl-4-phenylbutyltriphenylphosphonium Bromide (3a)

The mixture of bromide (−)-**7** (152 mg, 0.63 mmol) and Ph_3P (165 mg, 0.63 mmol) was heated at 120 °C under Ar for 18 h, and then cooled to r.t. The resulting solid was washed twice with H_2O and dried in vacuum overnight to give phosphonium salt **3a** (207 mg, 65%) as a white solid.

3b

Prepared from (+)-**7** using above procedure, white solid.

Alkylation of Hydrazone (−)-4 with *tert*-Butyl Bromoacetate

To a solution of hydrazone (−)-**4** (1.23 g, 6.68 mmol) in anhyd Et_2O (20 mL), LDA (1.5 M, 4.5 mL, 6.75 mmol) was added dropwise at 0 °C over 10 min. The mixture was stirred at 0 °C under Ar for 5 h and then cooled to −110 °C using a liquid N_2/95% EtOH bath. *t*-Bu bromoacetate (1.5 mL, 10 mmol) in Et_2O (20 mL) was added dropwise over 30 min. The mixture was slowly warmed up to 0 °C and quenched with sat. NH_4Cl (20 mL). The organic layer was separated, the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (EtOAc/hexanes, 1:9) to afford hydrazone **9** as a colorless oil.

Yield: 1.2 g (60%); $[\alpha]_D$ −74.3 (*c* 0.7, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, 3H, *J* = 7.2 Hz), 1.42 (s, 9H), 1.48 (m, 2H), 1.72−1.97 (m, 5H), 2.29 (dd, 1H, *J* = 14.8, 6.4 Hz), 2.39 (dd, 1H, *J* = 14.8, 8.0 Hz), 2.60 (m, 1H), 2.69 (dd, 1H, *J* = 16.8, 8.0 Hz), 3.35 (s, 3H), 3.38 (m, 2H), 3.56 (m, 1H), 6.51 (d, 1H, *J* = 6.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 140.1, 80.0, 74.7, 63.4, 59.1, 50.2, 40.6, 39.1, 28.1 (3C), 26.5, 26.2, 22.0, 11.3.

GC/MS (EI): *m/z* = 298 (M^+), 253, 242, 225, 197, 183, 128, 110, 82, 70, 57.

HRMS (EI): *m/z* calcd for $C_{16}H_{30}N_2O_3$ (M^+): 298.2256. Found: 298.2258.

(−)-*tert*-Butyl (3*S*)-3-Ethyl-4-oxobutyrate (10)

Ozone was bubbled into a solution of hydrazone **9** (2.6 g, 8.7 mmol) in CH_2Cl_2 (20 mL) at −78 °C until no starting material was detected by TLC. The reaction mixture was bubbled with N_2 while warming up to r.t. The mixture was concentrated in vacuo, and the residue was purified by chromatography on silica gel (EtOAc/hexanes, 1:9) to afford aldehyde **10** as a colorless oil.

Yield: 1.33 g (82%); $[\alpha]_D$ −39.4 (*c* 1.5, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (t, 3H, *J* = 7.2 Hz), 1.44 (s, 9H), 1.55 (m, 1H), 1.77 (m, 1H), 2.35 (dd, 1H, *J* = 16.0, 6.0 Hz), 2.62 (dd, 1H, *J* = 16.0, 8.0 Hz), 2.70 (m, 1H), 9.71 (d, 1H, *J* = 1.2 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.2, 171.2, 80.9, 49.3, 34.1, 28.0 (3C), 21.6, 11.2.

GC/MS (EI): *m/z* 171 (M^+−Me), 158, 129, 113, 101,85, 73, 57.

(−)-*tert*-Butyl (3*S*)-3-Ethyl-4-oxopentanoate (11)

To a solution of aldehyde **10** (633 mg, 3.4 mmol) in Et_2O (10 mL), CH_3MgCl (3.0 M, 1.24 mL, 3.7 mmol) was added dropwise at −78 °C. The mixture was stirred at −78 °C for 30 min and then quenched with sat. NH_4Cl at −78 °C. The organic layer was separated, the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) for 5 min, filtered, and concentrated in vacuo. The residue was dissolved in acetone (10 mL), and Jones' reagent was added dropwise at 0 °C within 2 min (a red color was retained). The reaction was quenched at 0 °C with H_2O (20 mL), and extracted with pentane (3 × 40 mL). The

combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (EtOAc/hexanes, 1:9) to afford ketone **11** as colorless oil.

Yield: 611 mg (89%); $[\alpha]_D$ −45.7 (*c* 0.9, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, 3H, *J* = 7.2 Hz), 1.43 (s, 9H), 1.42−1.53 (m, 1H), 1.58−1.69 (m, 1H), 2.22 (s, 3H), 2.28 (dd, 1H, *J* = 16.8, 4.8 Hz), 2.65 (dd, 1H, *J* = 16.8, 9.6 Hz), 2.85−2.92 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.9, 171.7, 80.6, 49.4, 36.1, 29.4, 28.0 (3C), 24.3, 11.3.

GC/MS (EI): *m/z* = 200 (M^+), 185, 172, 144, 127, 116, 109, 98, 85, 73, 71, 57.

HRMS (EI): *m/z* calcd for $C_{11}H_{20}O_3$ (M^+): 200.1412. Found: 200.1411.

(+)-*tert*-Butyl (3*S*)-3-Ethyl-4,4′-dioxoethylenepentanoate (12)

A mixture of ketone **11** (610 mg, 3.05 mmol), trimethyl orthoformate (1.62 mL, 12.2 mmol), *p*-TsOH (6 mg, 0.03 mmol) in ethylene glycol (4 mL) was stirred at r.t. under Ar overnight. The mixture was diluted with sat. $NaHCO_3$, extracted with pentane (3 × 40 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (EtOAc/hexanes, 1:9) to afford ketal **12** as a colorless oil.

Yield: 616 mg (82%); $[\alpha]_D$ +11.4 (*c* 2.2, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (t, 3H, *J* = 7.2 Hz), 1.21 (m, 1H), 1.25 (s, 3H), 1.44 (s, 9H), 1.65 (m, 1H), 2.09 (m, 1H), 2.10 (dd, 1H, *J* = 16.8, 6.4 Hz), 2.31 (dd, 1H, 16.8, 8.4 Hz), 3.91 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0, 111.8, 79.8, 64.5, 64.4, 44.9, 36.1, 28.0 (3C), 23.5, 20.8, 12.3.

MS (CI): *m/z* = 245 (MH^+).

HRMS (CI): *m/z* calcd for $C_{13}H_{25}O_4$ (MH^+): 245.1753. Found: 245.1754.

(−)-(*S*)-3-Ethyl-4,4′-dioxoethylenepentanal (8)

To a solution of ester **12** (616 mg, 2.52 mmol) in H_2O (20 mL), $LiAlH_4$ (190 mg, 5.0 mmol) was added in portions at r.t. The mixture was stirred at r.t. for 2 h and then treated with H_2O (0.2 mL), 15% NaOH (0.2 mL) and H_2O (0.6 mL). The mixture was filtered and concentrated in vacuo to provide the crude alcohol (341 mg).

GC/MS (EI): *m/z* = 174 (M^+).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (t, 3H, *J* = 7.6 Hz), 1.12−1.22 (m, 1H), 1.28 (s, 3H), 1.53−1.58 (m, 1H), 1.63−1.72 (m, 4H), 3.58−3.76 (m, 2H), 3.92−3.99 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 112.5, 64.4, 64.2, 62.2, 46.6, 32.6, 23.8, 20.2, 12.5.

The crude alcohol (341 mg, 1.96 mmol) was dissolved in CH_2Cl_2 (10 mL), and PDC (1.47 g, 3.92 mmol) was added. The mixture was stirred at r.t. under Ar for 24 h and then filtered through a pad of silica gel. The filtrate was concentrated in vacuo, and the residue was purified by chromatography on silica gel (EtOAc/hexanes, 1:9) to afford aldehyde **8** as a colorless oil.

Yield: 275 mg (62%); $[\alpha]_D$ −8.4 (*c* 1.5, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (t, 3H, *J* = 7.6 Hz), 1.25 (m, 1H), 1.26 (s, 3H), 1.69 (m, 1H), 2.20 (m, 1H), 2.25 (ddd, 1H, *J* = 16.0, 4.0, 1.2 Hz), 2.37 (ddd, 1H, 16.0, 8.4, 4.0 Hz), 3.88 (m, 4H), 9.63 (dd, 1H, *J* = 4.0, 1.2 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.9, 111.4, 64.0, 44.4, 43.5, 23.2, 21.1, 12.3.

GC/MS (EI): *m/z* = 172 (M^+), 157, 144, 130, 113, 99, 87, 71, 55.

HRMS (CI): *m/z* calcd for $C_9H_{17}O_3$ (MH^+): 173.1178. Found: 173.1177.

(3*S*,7*R*)-3,7-Diethyl-9-phenylnon-5-en-2-one Ethylene Ketal (13)

To a suspension of phosphonium salt **3a** (50 mg, 0.1 mmol) in THF (2 mL), *n*-BuLi (1.5 M, 0.073 mL, 0.11 mmol) was added dropwise at r.t. The mixture was stirred at r.t. under Ar until the solid dissolved and a red solution appeared. Aldehyde **8** (19 mg, 0.11 mmol) in THF (1 mL) was added at r.t., and the mixture was stirred overnight at r.t. under Ar. The mixture was filtered through a pad of silica gel and the white precipitate was washed with Et_2O (20 mL). The filtrate was concentrated in vacuo, and the residue was purified by chromatography on silica gel (EtOAc/hexanes, 1:9) to give alkene **13** as a colorless oil.

Yield: 21 mg (66%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, 3H, *J* = 7.2 Hz), 0.96 (t, 3H, *J* = 7.2 Hz), 1.25 (m, 1H), 1.27 (s, 3H), 1.33 (m, 1H), 1.46 (m, 1H), 1.56 (m, 2H), 1.65 (m, 1H), 1.73 (m, 1H), 2.05 (m, 1H), 2.27 (m, 1H), 2.33 (m, 1H), 2.51 (ddd, 1H, *J* = 13.6, 11.2, 5.2 Hz), 2.64 (ddd, 1H, *J* = 13.6, 11.2, 5.2 Hz), 3.93 (m, 4H), 5.15 (m, 1H, *J* = 10.8, 1.0 Hz), 5.55 (m, 1H, *J* = 10.8, 7.2 Hz), 7.14−7.29 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.1, 134.6, 129.7, 128.3 (2C), 128.2 (2C), 125.5, 112.6, 64.4 (2C), 48.4, 38.8, 37.5, 33.8, 28.6, 28.2, 22.9, 20.9, 13.0, 11.8.

MS (CI): *m/z* = 317 (MH^+).

HRMS (CI): *m/z* calcd for $C_{21}H_{33}O_2$ (MH^+): 317.2483. Found: 317.2481.

Dianeackerone (1a)

The *cis*/*trans* mixture of alkene **13** (10 mg, 0.031 mmol) and 5% Pd/C (5 mg) in MeOH (1 mL) were stirred overnight at r.t. under H_2 (1 atm). The mixture was filtered through a pad of silica gel and the solid was washed with MeOH (20 mL). The filtrate was concentrated in vacuo to afford a crude product as a light yellow oil (8 mg).

$[\alpha]_D$ −10 (*c* 0.5, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, 3H, *J* = 7.2 Hz), 0.96 (t, 3H, *J* = 7.2 Hz), 1.26 (s, 3H), 1.20−1.42 (m, 10H), 1.52−1.62 (m, 4H), 2.59 (t, 2H, *J* = 8.8, 7.6 Hz), 3.90−3.95 (m, 4H), 7.17−7.30 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.3, 128.3 (2C), 128.2 (2C), 125.5, 112.9, 64.4, 64.3, 47.9, 38.5, 35.3, 33.5, 33.1, 30.5, 25.7, 25.6, 23.3, 20.7, 13.0, 10.7.

MS (CI): *m/z* = 319 (MH^+).

HRMS (CI): *m/z* calcd for $C_{21}H_{35}O_2$ (MH^+): 319.2637. Found: 319.2633.

The above crude product was dissolved in acetone and H_2O (9:1, 4 mL), and PPTS (6 mg, 0.025 mmol) was added. The mixture was refluxed for 1 h under N_2 and then cooled to r.t., diluted with Et_2O (20 mL), washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (EtOAc/hexanes, 1:9) to afford dianeackerone **1a** as a colorless oil.

Yield: 6 mg (70%); $[\alpha]_D$ +3.2 (*c* 0.2, $CHCl_3$).

^{1}H NMR (400 MHz, C_6D_6): δ = 0.75 (t, 3H, *J* = 7.2 Hz), 0.83 (t, 3H, *J* = 7.2 Hz), 1.16−1.52 (m, 13H), 1.76 (s, 3H), 2.14 (m, 1H), 2.55 (m, 2H), 7.15−7.25 (m, 5H).

^{13}C NMR (100 MHz, C_6D_6): δ = 210.34, 143.62, 129.06 (2C), 129.04 (2C), 126.36, 54.94, 38.90, 35.81, 33.84, 33.83, 32.15, 28.85, 26.36, 25.16, 25.12, 12.23, 11.27.

GC/MS (EI): *m/z* = 274 (M^+), 227, 186, 172, 157, 145, 123, 105, 99, 91, 86, 71, 55.

HRMS (EI): *m/z* calcd for $C_{19}H_{30}O$ (M^+): 274.2297. Found: 274.2298.

(3*S*,7*S*)-3,7-Diethyl-9-phenylnon-5-en-2-one Ethylene Ketal (14)

The phosphonium salt **3b** (62 mg, 0.12 mmol) in THF (2 mL) was converted to the ylide with *n*-BuLi (1.5 M, 0.088 mL, 0.13 mmol) by a procedure similar to that described for the ketal **13**. The ylide was coupled to aldehyde **8** (23 mg, 0.13 mmol) in THF (1 mL), and the product was purified to give alkene **14** as a colorless oil.

Yield: 34 mg (82%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, 3H, *J* = 7.2 Hz), 0.97 (t, 3H, *J* = 7.2 Hz), 1.24 (m, 1H), 1.27 (s, 3H), 1.35 (m, 1H), 1.42−1.60 (m, 4H), 1.73 (m, 1H), 2.05 (m, 1H), 2.26 (m, 1H), 2.32 (m, 1H), 2.52 (ddd, 1H, *J* = 13.6, 11.2, 5.6 Hz), 2.64 (ddd, 1H, *J* = 13.6, 11.2, 5.6 Hz), 3.94 (m, 4H), 5.15 (m, 1H), 5.55 (ddd, 1H, *J* = 10.8, 7.2, 4.0 Hz), 7.14−7.29 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.1, 134.7, 129.7, 128.3 (2C), 128.2 (2C), 125.5, 112.6, 64.4 (2C), 48.5, 38.8, 37.7, 33.9, 28.6, 28.2, 22.9, 20.9, 13.1, 11.8.

MS (CI): *m/z* = 317 (MH^+).

HRMS (CI): *m/z* calcd for $C_{21}H_{33}O_2$ (MH^+): 317.2483. Found: 317.2482.

Dianeackerone (1b)

The *cis*/*trans* mixture of alkene **14** (12 mg, 0.038 mmol) was hydrogenated by a procedure similar to that described for dianeackerone **1a** to afford a light yellow oil (11 mg).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, 3H, *J* = 7.2 Hz), 0.96 (t, 3H, *J* = 7.2 Hz), 1.26 (s, 3H), 1.20−1.42 (m, 10H), 1.52−1.62 (m, 4H), 2.59 (t, 2H, *J* = 8.4, 7.6 Hz), 3.90−3.95 (m, 4H), 7.17−7.30 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.3, 128.3 (2C), 128.2 (2C), 125.5, 112.9, 64.4, 64.3, 47.9, 38.5, 35.2, 33.5, 33.2, 30.5, 25.8, 25.6, 23.3, 20.7, 13.0, 10.8.

MS (CI): *m/z* = 319 (MH^+).

The above crude product was deprotected with PPTS (4 mg, 0.016 mmol) and purified by procedures similar to those described for dianeackerone **1a** to afford dianeackerone, **1b** as a colorless oil.

Yield: 8 mg (78%); $[\alpha]_D$ −8.7 (*c* 0.2, $CHCl_3$).

^{1}H NMR (400 MHz, C_6D_6): δ = 0.75 (t, 3H, *J* = 7.2 Hz), 0.83 (t, 3H, *J* = 7.2 Hz), 1.16−1.52 (m, 13H), 1.76 (s, 3H), 2.14 (m, 1H), 2.55 (m, 2H), 7.15−7.25 (m, 5H).

^{13}C NMR (100 MHz, C_6D_6): δ = 210.34, 143.62, 129.06 (2C), 129.04 (2C), 126.36, 54.94, 38.89, 35.89, 33.88, 33.83, 32.16, 28.84, 26.27, 25.16, 25.10, 12.23, 11.22.

GC/MS (EI): *m/z* = 274 (M^+), 227, 186, 172, 157, 145, 123, 105, 99, 91, 86, 71, 55.

HRMS (EI): *m/z* calcd for $C_{19}H_{30}O$ (M^+): 274.2297. Found: 274.2297.

Cholesterol Diazoacetate (16)

To a solution of acid chloride **17** (1.39 g, 5.0 mmol) and cholesterol (1.93 g, 5.0 mmol) in CH_2Cl_2 (25 mL), Et_3N (1.4 mL, 10 mmol) was added dropwise at 0 °C over 20 min. The mixture was stirred at 0 °C under Ar for 3 h and the solvent was removed in vacuo. The residue was dissolved in benzene (30 mL) and mixed with Florisil (15 g). The mixture was filtered and washed with benzene (30 mL). The filtrate was concentrated in vacuo at 30 °C and the residue was purified by chromatography on Florisil (Et_2O/pentane, 1:4) to give the diazoacetate **16** as a yellow solid.

Yield: 1.5 g (66%); $[\alpha]_D$ −23.6 (*c* 1.8, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.68 (s, 3H), 0.86 (d, 3H, *J* = 6.4 Hz), 0.87 (d, 3H, *J* = 6.4 Hz), 0.92 (d, 3H, *J* = 6.4 Hz), 1.02 (s, 3H), 1.11−1.65 (m, 20H), 1.79−2.03 (m, 6H), 2.29−2.39 (m, 2H), 4.69 (m, 1H), 4.71 (s, 1H), 5.39 (d, 1H, *J* = 5.2 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.4, 139.6, 122.8, 74.6, 56.7, 56.2, 50.0, 42.3, 39.7, 39.5, 38.3, 36.9, 36.6, 36.2, 35.8, 31.9, 31.8, 28.2, 28.0 (2C), 24.3, 23.8, 22.8, 22.5, 21.0, 19.3, 18.7, 11.8.

Alkylation of Hydrazone (−)-4 with 2-Iodoethanol *tert*-Butyldimethylsilyl Ether

To a solution of hydrazone (−)-**4** (3.0 g, 15.3 mmol) in anhyd Et_2O (40 mL), LDA (1.5 M, 11 mL, 16.5 mmol) was added dropwise at 0 °C over 10 min. The mixture was stirred at 0 °C under Ar for 5 h and cooled to −78 °C. 2-Iodoethanol *tert*-butyldimethylsilyl ether (5.5 g, 19.2 mmol) in Et_2O (20 mL) was added dropwise at −78 °C over 30 min. The reaction mixture was slowly warmed up to 0 °C and quenched with sat. NH_4Cl (30 mL). The organic layer was separated, the aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexanes/EtOAc/Et_3N, 95:5:2) to afford hydrazone **18** as a colorless oil

Yield: 3.65 g (65%) $[\alpha]_D$ −47.9 (*c* 1.9, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03 (s, 6H), 0.88 (s, 9H), 0.89 (t, 3H, *J* = 7.2 Hz), 1.44 (m, 2H), 1.65 (m, 2H), 1.76−1.95 (m, 4H), 2.20 (m, 1H), 2.69 (dd, 1H, *J* = 16.4, 8.0 Hz), 3.36 (s, 3H), 3.31−3.43 (m, 3H), 3.54−3.67 (m, 3H), 6.46 (d, 1H, *J* = 6.8 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.7, 74.7, 63.5, 61.5, 59.1, 50.4, 40.7, 36.1, 26.8, 26.5, 25.9 (3C), 22.0, 18.3, 11.4, −5.2 (2C).

GC/MS (EI): *m/z* = 342 (M^+), 327, 297, 285, 253, 228, 184, 170, 139, 120, 96, 89, 73, 70.

HRMS (ESI): *m/z* calcd for $C_{18}H_{39}N_2O_2Si$ (MH^+): 343.2780. Found: 343.2764.

(−)-(*S*)-2-Ethyl-4-*tert*-butyldimethylsiloxybutan-1-ol (19)

Ozone was bubbled into a solution of hydrazone **18** (910 mg, 2.66 mmol) in CH_2Cl_2(10 mL) at −78 °C until no starting material was detected by TLC. The reaction mixture was purged with N_2 while warming up to r.t. and then concentrated in vacuo. The residue was dissolved in Et_2O (10 mL), and borane-THF complex (1.0 M, 6 mL, 6 mmol) was added dropwise at 0 °C over 10 min. The mixture was stirred at 0 °C under Ar for 1 h and quenched with H_2O at 0 °C. The organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 5:1) to afford the alcohol **19** as a colorless oil.

Yield: 420 mg, (67%); $[\alpha]_D$ −6.8 (*c* 2.6, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.08 (s, 3H), 0.09 (s, 3H), 0.91 (s, 9H), 0.91 (t, 3H, *J* = 7.2 Hz), 1.28 (m, 1H, *J* = 7.2 Hz), 1.37 (m, 1H, *J* = 7.2 Hz), 1.53 (m, 2H), 1.68 (m, 1H), 3.24 (br s, 1H), 3.46 (dd, 1H, *J* = 10.8, 6.4 Hz), 3.60 (dd, 1H, *J* = 10.8, 3.6 Hz), 3.65 (m, 1H), 3.77 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 65.8, 61.9, 41.3, 35.2, 25.8 (3C), 24.4, 18.2, 11.5, -5.5, -5.5.

GC/MS (EI): *m/z* = 232 (M^+), 202, 191, 175, 157, 132, 105, 101, 83, 75.

(−)-(*S*)-4-Benzyloxy-3-ethylbutan-1-ol (20)

To a solution of alcohol **19** (380 mg, 1.63 mmol) in THF (10 mL), NaH (98 mg, 60% in oil, 2.45 mmol) was added at r.t. The mixture was stirred at r.t. under Ar for 30 min, and benzyl bromide (0.29 mL, 2.45 mmol) was added dropwise. The mixture was stirred at r.t. under Ar overnight and then cooled to 0 °C. H_2O (2 mL) was added dropwise at 0 °C, followed by the addition of 3 M HCl (5 mL, 15 mmol). The mixture was stirred at r.t. for 1 h. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with 5% $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 4:1) to afford alcohol **20** as a colorless oil.

Yield: 290 mg (85%); $[\alpha]_D$ −9.0 (*c* 2.3, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, 3H, *J* = 7.2 Hz),1.36 (m, 2H, *J* = 7.2 Hz), 1.58 (m, 1H), 1.70 (m, 2H), 2.72 (br s, 1H), 3.36 (dd, 1H, *J* = 9.2, 7.2 Hz), 3.48 (dd, 1H, *J* = 9.2, 4.0 Hz), 3.63 (m, 1H), 3.70 (m, 1H), 4.53 (t, 2H, *J* = 13.2 Hz), 7.27−7.38 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.9, 128.4 (2C), 127.7 (2C), 127.6, 73.9, 73.3, 61.2, 38.1, 35.8, 24.8, 11.4.

GC/MS (EI): *m/z* = 208 (M^+), 190, 178, 161, 137, 117, 107, 99, 91, 79, 69.

HRMS (ESI): *m/z* calcd for $C_{13}H_{21}O_2$ (MH^+): 209.1541. Found: 209.1521.

(+)-(*S*)-1-Benzyloxy-4-bromo-2-ethylbutane (21)

To a solution of alcohol **20** (230 mg, 1.1 mmol), Ph_3P (576 mg, 2.2 mmol) in DMF (4 mL), NBS (390 mg, 2.2 mmol) was added in portions at r.t. The reaction mixture was stirred at 50 °C under Ar for 2 h and cooled to r.t. The mixture was diluted with Et_2O (40 mL), washed with 5% $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 9:1) to afford bromide **21** as a colorless oil.

Yield: 238 mg (79%); $[\alpha]_D$ +8.4 (*c* 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, 3H, *J* = 7.2 Hz), 1.32−1.49 (m, 2H), 1.76 (m, 1H), 1.91 (m, 1H), 1.98 (m, 1H), 3.37 (dd, 1H, *J* = 9.2, 5.6 Hz), 3.43 (dd, 1H, *J* = 9.2, 4.8 Hz), 3.47 (m, 2H), 4.50 (s, 2H), 7.29−7.38 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.5, 128.3 (2C), 127.5 (2C), 127.4, 73.1, 72.1, 38.8, 35.1, 32.2, 23.8, 11.2.

GC/MS (EI): *m/z* = 270 (M^+), 242, 223, 311, 190, 172, 163, 149, 121, 107, 92, 91, 69, 65.

HRMS (EI): *m/z* calcd for $C_{13}H_{19}{}^{79}BrO$ (M^+): 270.0619. Found: 270.0619.

(*S*)-3-Ethyl-4-benzyloxybutyltriphenylphosphonium Bromide (22)

The mixture of bromide **21** (215 mg, 0.793 mmol) and Ph_3P (208 mg, 0.793 mmol) was heated at 120 °C under Ar for 2 h and then cooled to r.t. The resulting solid was washed with Et_2O, and dried in vacuum at 60 °C for 8 h to provide the phosphonium salt **22** (355 mg, 84%) as a white solid.

(2*S*,6*R*)-1-Benzyloxy-2,6-diethyl-8-phenyloct-4-ene (23)

The phosphonium salt **22** (266 mg, 0.5 mmol) in THF (5 mL) was converted to the ylide with BuLi (1.5 M, 0.37 mL, 0.55 mmol) by a procedure similar to that described for the ketal **13**. Aldehyde (−)-**6** (105 mg, 0.6 mmol) in THF (2 mL) was coupled to the ylide and the product was purified by chromatography on silica gel (EtOAc/hexanes, 1:14) to give alkene **23** as a colorless oil.

Yield: 115 mg (66%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, 3H, *J* = 7.2 Hz), 0.89 (t, 3H, *J* = 7.2 Hz), 1.23 (m, 1H), 1.34−1.52 (m, 4H), 1.61−1.76 (m, 2H), 2.09 (m, 2H), 2.30 (m, 1H), 2.49 (ddd, 1H, *J* = 13.6, 10.4, 5.6 Hz), 2.63 (ddd, 1H, *J* = 13.6, 10.4, 5.6 Hz), 3.38 (m, 2H), 4.50 (s, 2H), 5.18 (tt, 1H, *J* = 10.8, 1.6 Hz), 5.48 (dt, 1H, *J* = 10.8, 7.6 Hz), 7.15−7.34 (m, 10H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.1, 138.8, 135.5, 128.5, 128.3 (2C), 128.3 (2C), 128.2 (2C), 127.5 (2C), 127.4, 125.5, 73.0, 72.9, 40.6, 38.8, 37.6, 33.9, 29.2, 28.6, 23.8, 11.8, 11.3.

GC/MS (EI): *m/z* = 350 (M^+), 332, 304, 282, 259, 242, 213, 199, 171, 145, 117, 104, 91, 67.

HRMS (EI): *m/z* calcd for $C_{25}H_{34}O$ (M^+): 350.2610. Found: 350.2609.

(+)-(2*S*,6*S*)-2,6-Diethyl-8-phenyloctan-1-ol (24)

The *cis*/*trans* mixture of alkene **23** (92 mg, 0.26 mmol) was hydrogenated by a procedure similar to that described for dianeackerone **1a** and the product was purified by chromatography on silica gel (EtOAc/hexanes, 1:9) to give the alcohol **24** as a colorless oil.

Yield: 58 mg (84%); $[\alpha]_D$ +2.7 (*c* 1.6, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, 3H, *J* = 7.2 Hz), 0.91 (t, 3H, *J* = 7.2 Hz), 1.22−1.43 (m, 12H), 1.54−1.59 (m, 2H), 1.61 (br s, 1H), 2.58 (dd, 2H, *J* = 10.4, 7.6 Hz), 3.55 (d, 2H, *J* = 5.2 Hz), 7.15−7.30 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.2, 128.3 (2C), 128.2 (2C), 125.5, 65.3, 41.9, 38.5, 35.2, 33.4, 33.2, 30.8, 25.7, 23.9, 23.3, 11.1, 10.7.

GC/MS (EI): *m/z* = 262 (M^+), 244, 225, 215, 180, 174, 160, 145, 131, 117, 105, 104, 92, 91, 83, 69, 55.

HRMS (EI): *m/z* calcd for $C_{18}H_{30}O$ (M^+): 262.2297. Found: 262.2296.

(+)-(2*S*,6*S*)-2,6-Diethyl-8-phenyloctanal (15)

To a mixture of alcohol **24** (20 mg, 0.076 mmol), NMO (13 mg, 0.11 mmol), 4 Å molecular sieves (30 mg) in CH_2Cl_2 (1 mL), TPAP (2 mg, 0.005 mmol) was added at r.t. The mixture was stirred at r.t. under Ar for 30 min, then filtered through a pad of silica gel, and washed with CH_2Cl_2. The filtrate was concentrated in vacuo, and the residue was purified by chromatography on silica gel (EtOAc/hexanes, 1:9) to give the aldehyde **15** as a colorless oil.

Yield: 17 mg (85%); $[\alpha]_D$ +5.9 (*c* 0.9, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, 3H, *J* = 7.2 Hz), 0.92 (t, 3H, *J* = 7.2 Hz), 1.27−1.72 (m, 13H), 2.18 (m, 1H), 2.58 (dd, 2H, *J* = 9.6, 5.6 Hz), 7.18−7.30 (m, 5H), 9.58 (d, 1H, *J* = 3.2 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.6, 143.1, 128.3 (2C), 128.2 (2C), 125.5, 53.4, 38.4, 35.1, 33.1, 28.9, 25.5, 24.1, 21.9, 11.5, 10.7.

GC/MS (EI): *m/z* = 260 (M^+), 242, 231, 213, 185, 171, 145, 138, 117, 105, 104, 92, 91, 65, 55.

HRMS (EI): *m/z* calcd for $C_{18}H_{28}O$ (M^+): 260.2140. Found: 260.2140.

(−)-Cholesteryl (4*S*,8*S*)-4,8-diethyl-3-oxo-10-phenyldecanoate (2)

To a solution of aldehyde **15** (5 mg, 0.019 mmol) and diazoacetate **16** (10 mg, 0.022 mmol) in CH_2Cl_2(1 mL), $SnCl_2$ (5 mg, 0.026 mmol) was added in portions at r.t. The mixture was stirred overnight at r.t. under Ar, then diluted with CH_2Cl_2 (10 mL), washed with 0.1 M HCl and brine, dried (Na_2SO_4), filtered and concentrated

in vacuo. The residue was purified by chromatography on silica gel (hexanes/EtOAc, 9:1) to afford β-oxo ester **2** as a colorless oil.

Yield: 8 mg (61%); $[\alpha]_D$ −11.0 (*c* 0.2, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.68 (s, 3H), 0.86 (t, 3H, *J* = 8.0 Hz), 0.87 (d, 3H, *J* = 6.4 Hz), 0.88 (d, 3H, *J* = 6.4 Hz), 0.88 (t, 3H, *J* = 8.0 Hz), 0.92 (d, 3H, *J* = 6.4 Hz), 1.00 (s, 3H), 1.06−1.68 (m, 35H), 1.81−1.91 (m, 2H), 1.94−2.03 (m, 2H), 2.35 (m, 2H), 2.52 (m, 1H), 2.57 (dd, 2H, *J* = 9.2, 6.8 Hz), 3.42 (s, 2H), 4.68 (m, 1H), 5.38 (d, 1H, *J* = 4.8 Hz), 7.17−7.30 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.4, 166.6, 143.1, 139.4, 128.3 (2C), 128.2 (2C), 125.5, 122.8, 75.0, 56.7, 56.1, 54.0, 50.0, 48.7, 42.3, 39.7, 39.5, 38.4, 38.0, 36.9, 36.6, 36.2, 35.8, 35.1, 33.2, 33.1, 33.1, 31.9, 31.8, 31.1, 28.0, 27.7, 25.6, 24.4, 24.3, 24.1, 23.8, 22.8, 22.6, 21.0, 19.3, 18.7, 11.9, 11.6, 10.7.

MS (ESI): *m/z* = 687 (MH^+).

HRMS (CI): *m/z* calcd for $C_{47}H_{75}O_3$ (MH^+): 687.5716. Found: 687.5718.

Acknowledgement

This research was supported in part by grant no. GM53830 from the National Institutes of Health. We thank Dr. Authrine Whyte and Mr. Kittichoat Tiyanont for their enthusiastic participation in this project.

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Article Identifier:
1437-210X,E;2000,0,13,1936,1943,ftx,en;E11100SS.pdf