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Nature-like Odorants by Stereoselective Ring Enlargement of Cyclohexanone and Cyclododecanone[1]

Birgit Bollbuck, Philip Kraft, and Werner Tochtermann*

Institut für Organische Chemie der Universität Kiel,
Olshausenstraße 40, D-24098 Kiel, Germany

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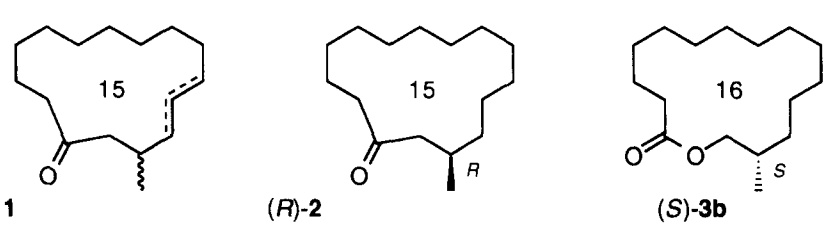
Abstract: Both enantiomers of muscolide (**3a/b**), (*R*)-(–)-phoracantholide I [(*R*)-**3c**] and the homologous (9*R*)-(–)-9-tetradecanolide [(*R*)-**3d**] were synthesized by ring enlargement of cyclohexanone (**6c**) and cyclododecanone (**6a**). The ring-enlargement sequence was improved by oxidation of **9/10** with ruthenium tetroxide and reduction of **8** using catecholborane.

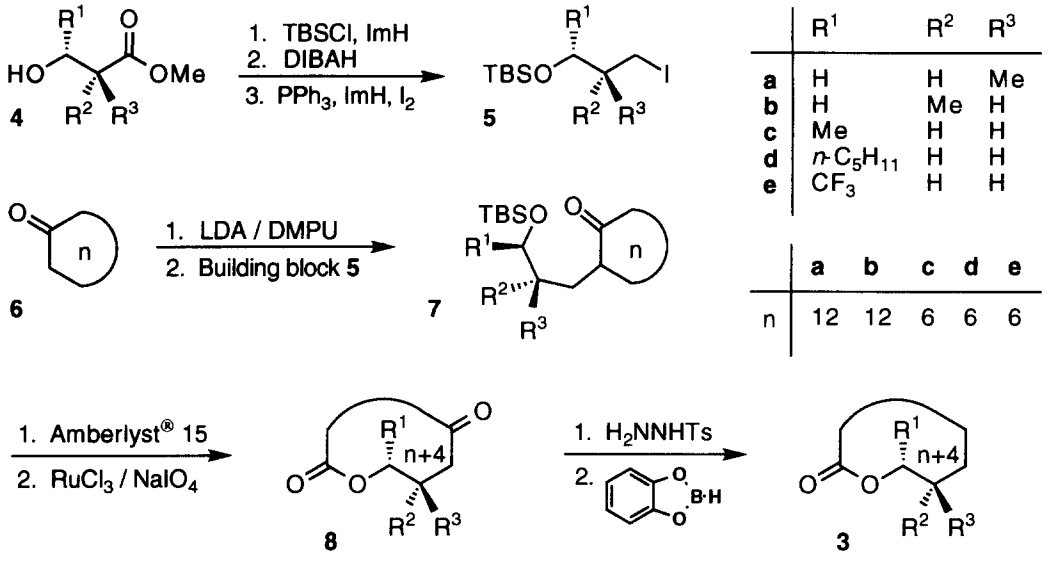
The essence and purpose of perfumes is to enchant and delight. Having served this purpose perfumes should discretely disappear; they should be biodegraded. In this respect, the nitromusks ambrette musk and partially musk xylol were withdrawn from the market and hard pressure was put on polycyclic musks.[2,3] Hence, there definitely is a need for new nature-like macrocyclic odorants to both substitute these compounds and stimulate new creations in perfumery. Muscenone (**1**) patented in 1990 for Firmenich SA was the first in this new musk generation, and inspired the oriental-ambery feminine fragrance »Jean-Paul Gaultier« launched in 1993.[3]



1 (*R*)-**2** (*S*)-**3b**

Scheme 1. Muscenone (**1**), (*R*)-muscone [(*R*)-**2**], and (*S*)-muscolide [(*S*)-**3b**]

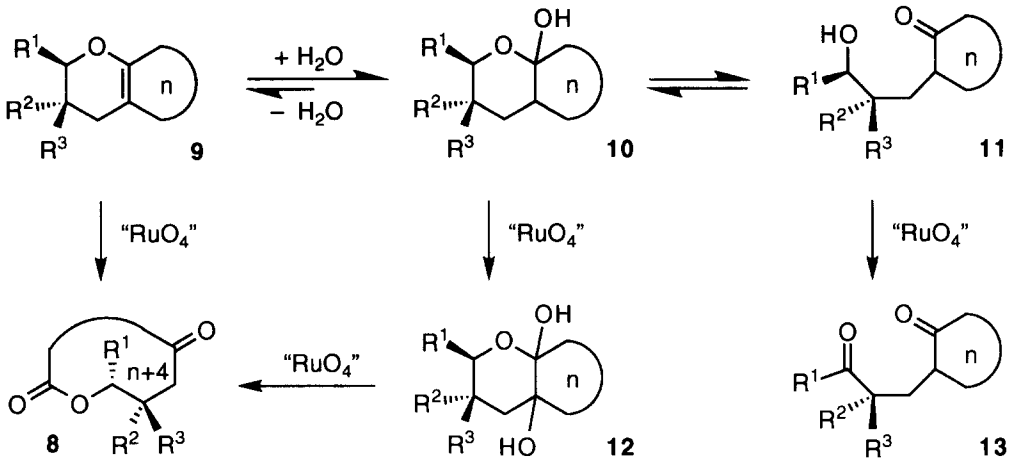
Modified Baeyer-Villiger oxidation of muscone (*rac*-**2**) with Caro's acid gives muscolide (*rac*-**3a/b**), which was prepared this way by Ruzicka in 1928.[4] Muscolide (*rac*-**3a/b**) was also prepared *via* ring enlargement by Becker and Ohloff in 1971,[5] and more recently by Zakharkin and Pryanishnikov;[6] however, no enantioselective approach has been reported so far. Since enantiomers of macrocyclic odorants may differ significantly in their olfactory properties,[7] we looked upon both enantiomers of the nature-like odorant **3a/b** as suitable synthetic targets for our stereoselective ring-enlargement sequence.[7,8]



Scheme 2. Synthesis of target compounds **3** by improved ring enlargement of cycloalkanones **6**

Employing chiral building blocks **5a/b**, readily available from enantiopure methyl 3-hydroxy-2-methyl-propanoates **4a/b**,[7] cyclododecanone (**6a**) was alkylated in 50% and 65% yield respectively, according to our general procedure.[7] The next step in the elaborated ring-enlargement sequence[7,8] was the cyclization of the alkylation products **7** to enol ethers **9** catalyzed by the Amberlyst® 15 ion exchange resin. Yet, due to hydration of **10a/b** upon chromatography purification of **9a/b** turned out to be tedious. In addition, it emerged that oxidative cleavage of the enol-ether double bond of **9a/b** was a serious problem. Pyridinium chlorochromate (PCC) on Celite® introduced by Chandrasekaran *et al.*[9] gave complex product mixtures as did ozonolysis.[7] Amazingly, the aqueous two-phase ruthenium-tetroxide oxidation established by Sharpless *et al.*[10] was the reagent of choice. Even the crude products **9a/b** were cleaved to oxo lactones **8a/b** in excellent yields, so that we were able to shorten the sequence. For instance, alkylation product **7b** was transformed in 68% yield to **8b** by treatment with Amberlyst® 15 followed by oxidation with *in situ* prepared ruthenium tetroxide. A further improvement to the sequence was made by reduction of the tosylhydrazones of **8a/b** to target compounds **3a/b** using catecholborane[11] instead of bis(triphenylphosphine)copper(I) tetrahydridoborate.[7,8] Significant advantages over the previously applied reagent are higher yields up to 83% and simplified work-up of the reaction.

As result, these modifications enabled us to carry out our ring-enlargement sequence on a much larger scale. The (*R*)-enantiomer of muscolide [(*R*)-**3a**], related to naturally occurring (*R*)-muscone [(*R*)-**2**] – the principal odorous constituent of the male musk deer (*Moschus moschiferus* L., Ungulata), was prepared in 23% overall yield from chiral building block **5a** and cyclododecanone (**6a**). The odor of (*R*)-**3a** is slightly erogenous, animalic and resembles that of natural musk tincture. But compared with 15-pentadecanolide the pleasant note of **3a** lacks intensity and freshness. Its enantiomer **3b** was analogously synthesized on a 2 g scale in 37% overall yield starting with chiral building block **5b**. (*S*)-Muscolide [(*S*)-**3b**] also is of weak intensity but possesses a very pleasant musk note with a more distinctive erogenous-animalic character. This parallels the 12-methyl-13-tridecanolides,[7] where the (*S*)-enantiomer has animalic facets while its optical antipode has not. Although Stoll[12] stated that an additional carbonyl group completely destroys the musk odor of macrocycles, we found oxo

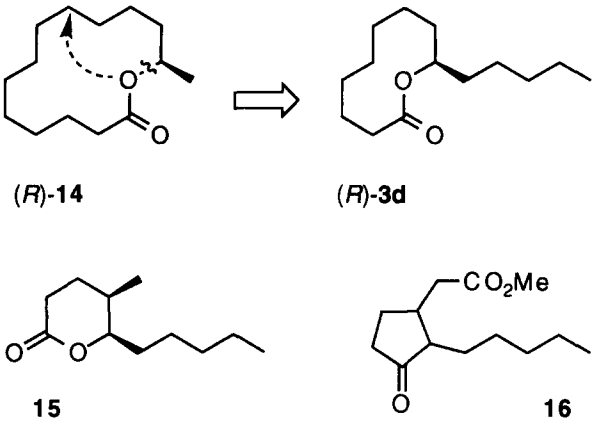


Scheme 3. Oxidation products caused by equilibrium between enol ethers **9**, hemiacetals **10** and carbonyl compounds **11**

lactones **8a/b** to be musk odorants too, though not as pleasant as the muscolides (**3a/b**). (*R*)-**8a** smells slightly musky and sweet but not erogenous-animalic, (*S*)-**8b** also possesses a weak yet recognizable musk note without animalic character that in contrast to (*R*)-**8a** is dominated by an odor reminiscent of ironed linen.

Exploring the versatility of our ring-enlargement sequence we were looking for a new naturally occurring target molecule, and that synthetic target we discovered in (*R*)-phoracantholide I (**3c**) – a constituent of the defensive secretion of the eucalypt longicorn (*Phoracantha synonyma* Newman, Cerambycidae), which possesses a pineapple-like odor.[13] Several enantioselective syntheses of **3c** have been reported,[14–21] but the odor of (*R*)-phoracantholide I (**3c**) has not been described in detail, and the question if it has any perfumistic value remained open. Starting from cyclohexanone (**6c**) and chiral building block **5c**[7] we prepared **7c** in 35% yield on a 7 g scale. Cyclization with Amberlyst® 15 provided enol ether **9c**, which was even more sensitive to hydration than was **9a/b**.[22] Even so, we isolated the desired oxo lactone **8c** in 47% yield using the Sharpless ruthenium-tetroxide oxidation[10] in a carbon tetrachloride/acetonitrile/water system. But in contrast to **9a/b** we isolated **13c** in 34% yield as by-product to **8c**. Therefore, we suppose that while **9a/b** were directly cleaved to the oxo lactones **8a/b** by "ruthenium tetroxide," **9c** was cleaved *via* its hemiacetal **10c** after oxidation to **12c**.[23] Glycol cleavage of **12c** also mediated by "ruthenium tetroxide"[24] then gives oxo lactone **8c**. By-product **13c** will be formed by opening of hemiacetal **10c** and subsequent oxidation with "ruthenium tetroxide." Reduction of oxo lactone **8c** with catecholborane *via* its tosylhydrazone afforded target compound **3c** in 31% yield. (*R*)-Phoracantholide I (**3c**) possesses a very strong camphoraceous, coniferous and somewhat woody note accompanied by a musty undertone. Neither does **3c** contribute to the pineapple-like odor of the gland secretion of eucalypt longicorn, nor can it be utilized in the creation of fragrances.

Methyl dihydrojasmonate (**16**), known as Hedione® (Firmenich SA), was first synthesized in the course of the structure elucidation of a natural product isolated from jasmine absolute (*Jasminum grandiflorum* L., Oleaceae)[25] and became one of the most important synthetics in perfumery. Hedione® (**16**) was the olfactory basis of »Eau Sauvage« by Dior (1966), and »First« by Van Cleef & Arpels (1976) contains 22% of it.[26] »Cristalle« by Chanel (1993) set up a record with 30% of **16**.[27] Aerangis lactone (**15**), the attractively scented Baeyer-Villiger oxidation product of *cis*-tetrahydrojasmone, may become the next trend-setter in perfumery. It was identified as the main odor component of the African "moth orchids" *Aerangis confusa* J. Stewart and *Aerangis*



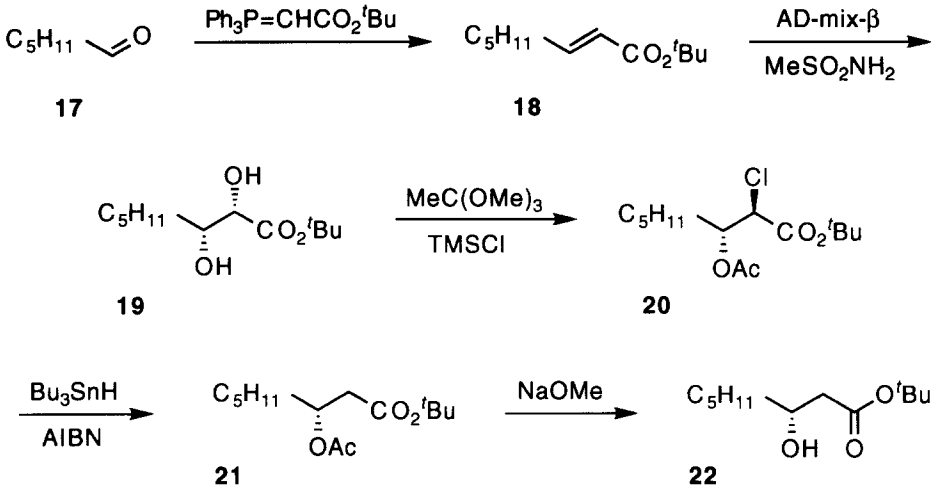
Scheme 4. (9*R*)-(–)-9-Tetradecanolide [(*R*)-**3d**] as constitutional isomer of the naturally occurring Galbanum methyl macrolide (*R*)-**14**, and related odorants **15** and **16**

kirkii (Rolfe) Schltr. by Kaiser[28] and is characterized by aspects reminiscent of tuberose and gardenia. As the "white-floral" aspects of **15** and **16** are supposed to originate from the pentyl side chain,[29] we were eager to substitute the methyl group of (*R*)-phoracantholide I (**3c**) by a pentyl group. The resulting target molecule (*R*)-**3d** has almost the same mass (226.36 amu, $C_{14}H_{26}O_2$) as **16** (226.32 amu, $C_{13}H_{22}O_3$) and is a constitutional isomer of methyl macrolide (*R*)-**14**, which was isolated from Galbanum gum resin – the dried latex of *Ferula galbaniflua* Boiss. et Buhse and *Ferula rubicaulis* Boiss., Umbelliferae – by Kaiser and Lamparsky.[30] We had found (*R*)-**14** to possess a dominant cedarwood odor with a relatively weak musk note and a bit of a musty-algoid tonality,[7] so we were curious for the olfactory properties of the nature-like odorant (*R*)-**3d**.

To introduce the pentyl side chain by means of our ring-enlargement sequence β-hydroxy ester **22** had to be synthesized stereoselectively. Following the sequence of Oikawa and Kusumoto[31] the α,β-unsaturated *tert*-butyl ester **18** was prepared by Wittig reaction of *n*-hexanal (**17**) with *tert*-butyl (triphenylphosphoranylidene)-acetate,[32] and then dihydroxylated with the Sharpless AD-mix-β[33] to provide **19** in 89% yield with 85% ee, determined by ^{1}H NMR of the corresponding (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) ester.[34] Diol **19** was subsequently treated with trimethyl orthoacetate and chlorotrimethylsilane (TMSCl)[35] to furnish **20** regioselectively in 55% yield with 45% recovery of **19**. Reductive removal of the chloro atom of **20** was achieved by tri-*n*-butyltin hydride in the presence of α,α'-azobisisobutyronitrile (AIBN) in 98% yield applying the improved work-up procedure of Roberts.[36] Next, the hydroxyl group of **21** was deprotected by sodium methoxide in methanol to give β-hydroxy ester **22** on a 9 g scale in 31% overall yield.

tert-Butyl β-hydroxy ester **22** was utilized for the synthesis of chiral building block **5d**, which was obtained in 60% yield over three steps by the published procedure.[7] Bringing **5d** into use in the optimized ring-enlargement sequence the nature-like odorant **3d** was then synthesized in 11% overall yield. Yet, the expectations placed in the odor of (9*R*)-(–)-9-tetradecanolide (**3d**) were not fulfilled. The relatively weak odor of **3d** was not floral, but strangely fruity, somewhat woody, and best described by the olfactory impression of an old wooden basket used for storage of fruits.

Future perfumery work will greatly depend on making available new nature-like, biodegradable odorants in optically active form.[37] We demonstrated the application of our stereoselective ring-enlargement sequence[7,8] to the synthesis of potential fragrance chemicals. Finally, we have to mention a restriction to our method: We were not able to synthesize 10,10,10-trifluorophoracantholide I (**3e**, *cf* ref[38]) from ethyl 4,4,4-trifluoro-3-hydroxybutanoate[39] because cyclization of **7e** failed due to the effect of the electron-withdrawing trifluoromethyl group. This is quite evident from the assumed mechanism of the reaction.[7]



Scheme 5. Stereoselective synthesis of the β-hydroxy ester **22** *via* asymmetric dihydroxylation[31]

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer Paragon 1000 FTIR-spectrometer. ^1H / ^{13}C NMR spectra (reference: TMS int) were taken in $CDCl_3$ on a Bruker AC 200 P and a Bruker AM 300, respectively. EI (70 eV) and CI (^{i}BuH) mass spectra were obtained on a Finnigan-MAT 8230 spectrometer. Column chromatography was performed on Baker Silicagel 30–60 μm and analytical TLC on Macherey-Nagel SIL G/UV_{254} plates. Melting points were determined on a Büchi 510 apparatus and are uncorrected. Elemental analyses were performed by the Mikroanalytisches Laboratorium Ilse Beetz, D-96301 Kronach. The synthesis of chiral building blocks **5a**–**5c** was described in ref.[7]

Stereoselective synthesis of β-Hydroxy Ester 22

Procedure: A soln of *tert*-butyl (triphenylphosphoranylidene)acetate (50.0 g, 133 mmol) and **17** (16.0 mL, 133 mmol) in CH_2Cl_2 (600 mL) was stirred at room temp for 45 h. The solvent was then removed under reduced pressure, and after addition of Et_2O/*n*-pentane (1:1, 120 mL) the resulting suspension was filtered. The filtrate was concentrated, the residue purified by silica-gel column chromatography to give **18** (22.8 g, 87%) as a colorless oil.

tert-Butyl (2E)-Oct-2-enoate (**18**). hR_f 79 (*n*-pentane:Et_2O, 10:1); IR (film, cm^{-1}) $\tilde{\nu}$ 1715 (s, ν C=O), 1156 / 1287 (s, ν C-O), 1654 (s, ν C=C), 983 (m, δ C=CH oop, *trans*); ^1H NMR ($CDCl_3$, ppm) δ 0.89 (ψ-t, J = 6.9 Hz, 3H, 8-H_3), 1.48 (s, 9H, CMe_3), 1.30 (m_c, 4H, 6-,7-H_2), 1.44 (m_c, 2H, 5-H_2), 2.16 (tdd, J = 7.0, 6.9 and 1.6 Hz, 2H, 4-H_2), 5.73 (dt, J = 15.6 and 1.6 Hz, 1H, 2-H), 6.86 (dt, J = 15.6 and 6.9 Hz, 1H, 3-H); ^{13}C NMR ($CDCl_3$, ppm) δ 13.91 (q, C-8), 22.44 (t, C-7), 27.81 (t, C-5), 28.20 (q, CMe_3), 31.36 (t, C-6), 32.01 (t, C-4), 79.88 (s, CMe_3), 122.98 (d, C-2), 148.00 (d, C-3), 166.09 (s, C-1); MS (CI, %) *m/z* 199 (6) [$M^{\oplus}$ + H], 143 (100) [$M^{\oplus}$ - C_4H_7], 125 (2) [$M^{\oplus}$ - C_4H_9O], 99 (3) [$C_7H_{15}^{\oplus}$].

Procedure: *tert*-Butanol (200 mL) and water (250 mL) were added to AD-mix-β (140 g), and the mixture was stirred at room temp until both phases were clear (15 min). Then methanesulfonamide (9.50 g, 99.9 mmol) was added followed at 0 °C by **18** (22.80 g,115 mmol) in *tert*-butanol (50 mL), and the heterogeneous slurry was

stirred at +10 °C for 24 h. The reaction was quenched at 0 °C by addn of Na_2SO_3 (150 g, 1.19 mol), and then warmed to room temp and stirred for 2 h. The reaction mixture was poured into EtOAc (750 mL), the organic layer was separated and the aqueous was extracted with EtOAc (3× 250 mL). The combined extracts were washed with 2N KOH aq (250 mL), dried with Na_2SO_4 and concentrated under reduced pressure. Purification by silica-gel column chromatography furnished **19** (23.7 g, 89%) as colorless oil.

tert-Butyl (2S,3R)-(+)-2,3-Dihydroxyoctanoate (**19**). hR_f 45 (*n*-pentane:Et_2O, 1:1); IR (film, cm^{-1}) $\tilde{\nu}$ 1732 (s, ν C=O), 1136 (s, ν_{as} C-CO-O), 1164 / 1369 / 1256 / 1282 (s, ν C-O),1093 (s, ν_{as} O-C-C), 3448 (s, ν O-H); ^{1}H NMR ($CDCl_3$, ppm) δ 0.90 (ψ-t, J = 6.6 Hz, 3H, 8-H_3), 1.27–1.49 (m, 6H, 7-H_2–5-H_2), 1.51 (s, 9H, C*Me*$_3$), 1.59 (dddd, J = 8.9, 6.7, 6.7 and 2.6 Hz, 2H, 4-H_2), 1.90 (br s, 1H, 3-O*H*), 3.14 (br s, 1H, 2-O*H*), 3.83 (td, J = 6.7 and 2.2 Hz, 1H, 3-H), 3.97 (d, J = 2.2 Hz, 1H, 2-H); ^{13}C NMR ($CDCl_3$, ppm) δ 14.03 (q, C-8), 22.63 (t,C-7), 25.51 (t, C-5), 28.06 (q, C*Me*$_3$), 31.83 (t, C-4), 33.89 (t, C-6), 72.83 / 73.41 (d, C-2,-3), 82.90 (s, *C*Me$_3$), 172.99 (s, C-1); MS (CI, %) *m/z* 233 (14) [$M^{\oplus}$ + H], 215 (2) [$M^{\oplus}$ + H - H_2O], 177 (100) [$M^{\oplus}$ - C_4H_7]; $[\alpha]_D^{26}$ +6.3, $[\alpha]_{546}^{26}$ +8.3 (*c* 1.6, $CHCl_3$).

(S)-α-Methoxy-α-(trifluoromethyl)phenylacetic Acid (MTPA) Ester of **19**.[34] ^{1}H NMR ($CDCl_3$, ppm) δ 5.62 (ddd, J = 8.0, 6.3 and 2.3 Hz, 1H, 3-H), 5.38 (3-H, 7.5% (2*R*,3*S*)-diastereomer), 85% ee.

Procedure: To a soln of **19** (23.2 g, 100 mmol) in CH_2Cl_2 (650 mL) were added in turn trimethyl orthoacetate (19.0 mL, 151 mmol) and chlorotrimethylsilane (19.0 mL, 150 mmol). The mixture was stirred at ambient temp for 20 h and then concentrated under reduced pressure. Purification by silica-gel column chromatography furnished **20** (16.0 g, 55%), whereupon the starting material **19** (10.6 g, 45%) was eluted with Et_2O.

tert-Butyl (2R,3R)-(+)-3-Acetoxy-2-chlorooctanoate (**20**). hR_f 36 (*n*-pentane:Et_2O, 20:1); IR (film, cm^{-1}) $\tilde{\nu}$ 1751 (s, ν OC=O), 1228 / 1151 / 1294 (s, ν C-O), 1026 (s, ν_{as} O-C-C); ^{1}H NMR ($CDCl_3$, ppm) δ 0.89 (ψ-t, J = 6.7 Hz, 3H, 8-H_3), 1.21–1.40 (m, 6H, 5-H_2–7-H_2), 1.48 (s, 9H, C*Me*$_3$), 1.60 (s, 3H, OCO*Me*), 1.73 (m_c, 2H, 4-H_2), 4.36 (d, J = 6.3 Hz, 1H, 2-H), 5.27 (ddd, J = 7.1, 6.3 and 4.9 Hz, 1H, 3-H);^{13}C NMR ($CDCl_3$, ppm) δ 13.94 (q, C-8), 20.85 (q, OCO*Me*), 22.45 (t, C-7), 24.43 (t, C-5), 27.78 (q, C*Me*$_3$), 30.10 / 31.50 (t, C-4,-6), 59.37 (d, C-2), 73.50 (d, C-3), 83.12 (s, *C*Me$_3$), 166.12 (s, C-1), 169.80 (s, O*C*OMe); MS (CI, %) *m/z* 295 (12) [$^{12}C_{14}{}^1H_{25}{}^{16}O_4{}^{37}Cl^{\oplus}$ + H], 293 (9) [$^{12}C_{14}{}^1H_{25}{}^{16}O_4{}^{35}Cl^{\oplus}$ + H], 239 (33) [$^{12}C_{14}{}^1H_{25}{}^{16}O_4{}^{37}Cl^{\oplus}$ - C_4H_8], 237 (100) [$^{12}C_{14}{}^1H_{25}{}^{16}O_4{}^{35}Cl^{\oplus}$ - C_4H_8]; $[\alpha]_D^{24}$ +2.9, $[\alpha]_{546}^{24}$ +3.1 (*c* 2.0, $CHCl_3$).

Procedure: To a soln of **20** (16.0 g, 54.6 mmol) in toluene (300 mL) was added tri-*n*-butyltin hydride (19.1 mL, 71.0 mmol) followed by α,α'-azobisisobutyronitrile (450 mg, 2.74 mmol), and the mixture was heated to reflux for 6 h. The solvent was removed under reduced pressure to leave a residue, which was dissolved in *n*-hexane (300 mL) and extracted with MeCN (3× 300 mL). The extracts were concentrated, and the resulting residue was purified by silica-gel column chromatography to provide **21** (13.8 g, 98 %) as colorless oil.

tert-Butyl (3R)-(+)-3-Acetoxyoctanoate (**21**). hR_f 15 (*n*-pentane:Et_2O, 20:1); IR (film, cm^{-1}) $\tilde{\nu}$ 1742 (s, ν C=O), 1241 / 1158 (s, ν C-O), 1025 (m, ν_{as} O-C-C); ^{1}H NMR ($CDCl_3$, ppm) δ 0.88 (ψ-t, 3H, 8-H_3, J = 6.7 Hz), 1.12–1.36 (m, 6H, 5-H_2–7-H_2), 1.44 (s, 9H, C*Me*$_3$), 1.58 (m_c, 2H, 4-H_2), 2.03 (s, 3H, OCO*Me*), 2.43 (dd, J = 15.1 and 6.1 Hz, 1H, 2-H_b), 2.51 (dd, J = 15.1 and 7.0 Hz, 1H, 2-H_a), 5.20 (dtd, J = 7.0, 6.4 and 6.1 Hz, 1H, 3-H); ^{13}C NMR ($CDCl_3$, ppm) δ 13.95 (q, C-8), 21.06 (q, OCO*Me*), 22.51 (t, C-7), 24.82 (t, C-5), 28.03 (q, C*Me*$_3$), 31.61 (t, C-6), 34.07 (t, C-4), 40.66 (t, C-2), 70.84 (d, C-3), 80.70 (s, *C*Me$_3$), 169.65 (s, C-1), 170.20 (s, O*C*OMe); MS (EI, %) *m/z* 203 (19) [$M^{\oplus}$ - C_4H_7], 185 (21) [$M^{\oplus}$ - C_4H_9O], 159 (19) [$M^{\oplus}$ - C_4H_7 - C_3H_8], 143 (43) [$M^{\oplus}$ - $C_6H_{11}O_2$], 125 (100) [$M^{\oplus}$ - C_4H_9O - $C_2H_3O_2$]; $[\alpha]_D^{26}$ +4.7, $[\alpha]_{546}^{26}$ +5.6 (*c* 2.1, $CHCl_3$).

Procedure: To a soln of **21** (13.8 g, 53.4 mmol) in MeOH (150 mL) was added NaOMe (2.89 g, 53.5 mmol) in MeOH (150 mL) at 0 °C in one dash. The mixture was stirred at this temp for 5 h, and concentrated after addn of glacial acetic acid (4.56 ml, 80.1 mmol). Purification by silica-gel column chromatography gave **22** (8.65 g, 75%) as colorless oil.

tert-Butyl (3R)-(–)-3-Hydroxyoctanoate (**22**). hR_f 61 (*n*-pentane:Et_2O, 2:1); IR (film, cm^{-1}) $\tilde{\nu}$ 1155 / 1256 (s, ν C-O), 1730 (s, ν C=O), 3445 (br, ν O-H); ^{1}H NMR ($CDCl_3$, ppm) δ 0.89 (ψ-t, J = 6.8 Hz, 3H, 8-H_3), 1.25–1.47 (m, 8H, 4-H_2–7-H_2), 1.47 (s, 9H, C*Me*$_3$), 2.36 (dd, J = 16.4 and 8.6 Hz, 1H, 2-H_B, part of an AB-system), 2.39 (dd, J = 16.4 and 3.5 Hz, 1H, 2-H_A, part of an AB-system), 3.11 (br s, 1H, OH), 3.95 (dddd, J = 8.6, 5.3, 3.5 and 3.5 Hz, 1H, 3-H); ^{13}C NMR ($CDCl_3$, ppm) δ 14.02 (q, C-8), 22.63 (t, C-7), 25.20 (t, C-5), 28.14 (q, C*Me*$_3$),

31.82 (t, C-6), 36.57 (t, C-4), 42.50 (t, C-2), 68.18 (d, C-3), 81.05 (s, *C*Me$_3$), 172.53 (s, C-1); MS (EI, %) *m/z* 159 (15) [M$^{\oplus}$ - C_4H_9], 143 (45) [M$^{\oplus}$ - C_4H_9O], 127 (100) [M$^{\oplus}$ - $C_4H_9O_2$]; $[\alpha]_D^{24}$ -23.6, $[\alpha]_{546}^{24}$ -27.8 (*c* 2.1, $CHCl_3$); Anal calcd for $C_{12}H_{24}O_3$ (216.3), C 66.63, H 11.18; found C 66.39, H 11.17.

Preparation of Chiral Building Blocks 5d and 5e

General Procedure: See ref.[7]

(3R)-(−)-(tert-Butyldimethyl)-(1-iodooctyl-3-oxy)-silane (**5d**). Scale 40.0 mmol, yield 60% (8.82 g), hR_f 38 (*n*-pentane); IR (film, cm^{-1}) $\tilde{\nu}$ 836 (s, ν_s Si-O-C), 774 (s, ν O-Si-CH_3); ^{1}H NMR ($CDCl_3$, ppm) δ 0.07 / 0.09 (2s, 6H, $SiMe_2$), 0.89 (s, 9H, C*Me*$_3$), 0.89 (t, *J* = 6.9 Hz, 3H, 8-H_3), 1.24–1.34 (m, 6H, 5-H_2–7-H_2), 1.41–1.49 (m, 2H, 4-H_2), 1.93 (dddd, *J* = 14.0, 7.7, 7.0 and 5.7 Hz, 1H, 2-H_b), 1.96 (dddd, *J* = 14.0, 7.6, 7.3 and 4.9 Hz, 1H, 2-H_a), 3.19 (ddd, *J* = 9.4, 7.7 and 7.6 Hz, 1H, 1-H_b), 3.25 (ddd, *J* = 9.4, 7.3 and 5.7 Hz, 1H, 1-H_a), 3.71 (dtd, *J* = 7.0, 5.7 and 4.9 Hz, 1H, 3-H); ^{13}C NMR ($CDCl_3$, ppm) δ -4.38 / -4.28 (q, $SiMe_2$), 3.22 (t, C-1), 14.01 (q, C-8), 18.05 (s, *C*Me$_3$), 22.63 (t, C-7), 24.61 (t, C-5), 25.91 (q, C*Me*$_3$), 32.00 (t, C-6), 36.90 (t, C-4), 40.95 (t, C-2), 72.21 (d, C-3); MS (CI, %) *m/z* 371 (76) [M$^{\oplus}$ + H], 313 (81) [M$^{\oplus}$ - C_4H_9], 239 (32) [M$^{\oplus}$ - $C_6H_{15}OSi$], 215 (26) [$C_3H_8IOSi^{\oplus}$], 133 (100) [$C_6H_{17}OSi^{\oplus}$]; $[\alpha]_D^{20}$ -32.6, $[\alpha]_{546}^{20}$ -38.5 (*c* 2.0, $CHCl_3$).

(±)-(tert-Butyldimethylsilyl)-(1,1,1-trifluoro-4-iodobut-2-oxy)-silane (**5e**). Scale 26.4 mmol, yield 50% (4.83 g),hR_f 73 (*n*-pentane); IR (film, cm^{-1}) $\tilde{\nu}$ 1155 / 1192 (s, ν C-F), 1252 (s, ν C-OSi), 838 (s, ν Si-OC), 780 (s, ν O-Si-CH_3); ^{1}H NMR ($CDCl_3$, ppm) δ 0.16 (d, *J* = 0.7 Hz, 3H, $SiMe_b$), 0.18 (s, 3H, $SiMe_a$), 0.91 (s, 9H, C*Me*$_3$), 2.13 (ddd, *J* = 8.1, 5.9 and 5.8 Hz, 2H, 3-H_2), 3.21 (dt, *J* = 10.0 and 8.1 Hz, 1H, 4-H_B, part of an AB-system), 3.33 (dt, *J* = 10.0 and 5.8 Hz, 1H, 4-H_A, part of an AB-system), 4.07 (qt, *J* = 6.5, 5.9 Hz, 1H, 2-H); ^{13}C NMR ($CDCl_3$, ppm) δ -5.12 / -4.58 (2q, $SiMe_2$), 0.79 (t, C-4), 18.15 (s, *C*Me$_3$), 25.66 (q, C*Me*$_3$), 34.69 (tq, $^3J_{CF}$ = 1.5 Hz, C-3), 71.10 (dq, $^2J_{CF}$ = 31.2 Hz, C-2), 124.87 (q, $^1J_{CF}$ = 283.1 Hz, C-1); ^{19}F NMR ($CDCl_3$, ppm) δ - 78.39 (d, *J*= 6.5 Hz, CF_3); MS (CI, %) *m/z* 369 (100) [M$^{\oplus}$ + H], 311 (62) [M$^{\oplus}$ + H - C_4H_9], 241 (62) [M$^{\oplus}$ - I], 215 (38) [$C_3H_8OISi^{\oplus}$], 99 (24) [$C_2H_2OF_3^{\oplus}$], 69 (40) [$CF_3^{\oplus}$].

Alkylations of Cycloalkanones 6 by Chiral Building Blocks 5

General Procedure: See ref.[7]

(2RS,2'R)-2-[3'-(tert-Butyldimethylsiloxy)-2'-methylprop-1'-yl]cyclododecan-1-one (**7a**). Scale 40.1 mmol, yield 50% (7.33 g), hR_f 14 (*n*-pentane:Et_2O, 100:1); IR (film, cm^{-1}) $\tilde{\nu}$ 837 / 1093 (s, ν Si-OC), 1706 (s, ν C=O), 775 (s, ν O-Si-CH_3); ^{1}H NMR ($CDCl_3$, ppm) δ 0.03 (s, 6H, $SiMe_2$), 0.87 (d, *J* = 6.8 Hz, 3H, 2'-Me), 0.89 (s, 9H, C*Me*$_3$), 1.05 (ddd, *J* = 13.9, 8.5 and 5.5 Hz, 1H, 1'-H_b), 1.15–1.32 (m, 14H, 4-H_2–10-H_2), 1.36 (dddd, *J* = 14.8, 6.7, 6.6 and 6.6 Hz, 1H, 3-H_b), 1.47 (dqddd, *J* = 8.5, 6.8, 5.0, 2.0 and 1.5 Hz, 1H, 2'-H), 1.58 (m_c, 1H, 3-H_a), 1.70 (m_c, 2H, 11-H_2), 1.82 (ddd, *J* = 13.9, 9.3 and 5.0 Hz, 1H, 1'-H_a), 2.43 (ddd, *J* = 17.0, 7.4 and 3.7 Hz, 1H, 12-H_b), 2.56 (ddd, *J* = 17.0, 9.7 and 3.6 Hz, 1H, 12-H_a), 2.64 (dddd, *J* = 19.5, 9.3, 6.7 and 5.5 Hz, 1H, 2-H), 3.37 (dd, *J* = 5.9 and 1.5 Hz, 1H, 3'-H_b), 3.40 (dd, *J* = 5.9 and 2.0 Hz, 1H, 3'-H_a); ^{13}C NMR ($CDCl_3$, ppm) δ -5.41 (q, 2C, $SiMe_2$), 16.89 / 17.03 (q, 1C, 2'-Me), 18.32 (s, 1C, *C*Me$_3$), 21.81 / 21.99 / 22.29 / 22.33 / 22.33 / 22.59 / 23.07 / 23.32 / 23.52 / 23.63 / 23.83 / 24.10 / 25.81 / 25.94 / 26.19 / 26.34 (t, 8C, C-4–C-11), 25.94 (q, 3C, C*Me*$_3$), 29.43 / 30.67 (t, 1C, C-3), 33.70 / 33.90 (d, 1C, C-2'), 34.52 / 35.41 (t, 1C, C-1'), 36.09 / 36.89 (t, 1C, C-12), 49.62 / 50.47 (d, 1C, C-2), 68.10 (t, 1C, C-3'), 214.80 (s, 1C, C-1); MS (CI, %) *m/z* 369 (100) [M$^{\oplus}$ + H], 311 (27) [M$^{\oplus}$ - C_4H_9], 237 (38) [M$^{\oplus}$ + H - $C_6H_{16}OSi$], 75 (5) [$C_4H_{11}O^{\oplus}$], 69 (6) [$C_5H_9^{\oplus}$]; Anal calcd for $C_{22}H_{44}O_2Si$ (368.7), C 71.67, H 12.03; found C 71.75, H 11.98.

(2RS,2'S)-2-[3'-(tert-Butyldimethylsiloxy)-2'-methylprop-1'-yl]cyclododecan-1-one (**7b**). Scale 40.9 mmol, yield 65% (9.80 g), hR_f 14 (*n*-pentane:Et_2O, 100:1).

(2RS,3'R)-2-[3'-(tert-Butyldimethylsiloxy)but-1'-yl]cyclohexan-1-one (**7c**). Scale 69.4 mmol, yield 35% (6.99 g), hR_f 28 (*n*-pentane:Et_2O, 25:1); IR (film, cm^{-1}) $\tilde{\nu}$ 1713 (s, ν C=O), 835 / 1070 (s, ν Si-OC), 774 (s, ν O-Si-CH_3); ^{1}H NMR ($CDCl_3$, ppm) δ 0.04 / 0.05 (2s, 6H, $SiMe_2$), 0.88 (s, 9H, C*Me*$_3$), 1.12 (d, *J* = 6.1 Hz, 3H, 3'-Me), 1.27 (m_c, 2H, 4-H_2), 1.40 (m_c, 2H, 2'-H_2), 1.67 (m_c, 1H, 3-H_b), 1.72 (m_c, 2H, 5-H_2), 1.85 (m_c, 1H, 3-H_a), 2.10 (m_c, 2H, 1'-H_2), 2.26 (m_c, 1H, 2-H), 2.28 (ddddd, *J* = 19.1, 11.2, 6.0, 1.1 and 1.0 Hz, 1H, 6-H_b), 2.37 (ddddd, *J* = 19.1, 7.7, 4.4, 1.3 and 1.2 Hz, 1H, 6-H_a), 3.78 (dqd, *J* = 12.1, 6.1 and 2.8 Hz, 1H, 3'-H); ^{13}C NMR

($CDCl_3$, ppm) δ -4.77 / -4.49 / -4.45 (q, $SiMe_2$), 18.00 (s, CMe_3), 23.48 / 23.72 (q, C-4'), 24.72 / 24.81 (t, C-3), 25.41 (t, C-4), 25.82 (q, CMe_3), 27.89 / 27.96 (t, C-5), 33.80 / 34.00 (t, C-1'), 36.92 / 37.27 (t, C-2'), 41.76 / 41.86 (t, C-6), 50.58 / 50.80 (d, C-2), 68.51 / 68.70 (d, C-3'), 212.50 (s, C-1); MS (CI, %) *m/z* 285 (3) [$M^{\oplus}$ + H], 227 (28) [$M^{\oplus}$ - C_4H_9], 185 (9) [$M^{\oplus}$ - $C_6H_{11}O$], 153 (100) [$M^{\oplus}$ + H - $C_6H_{16}OSi$]; Anal calcd for $C_{16}H_{32}O_2Si$ (284.5), C 67.55, H 11.34; C 67.58, H 11.35.

(2RS,3'R)-2-[3'-(tert-Butyldimethylsiloxy)oct-1'-yl]cyclohexan-1-one (**7d**). Scale 11.9 mmol, yield 39% (1.57 g), hR_f 17 (*n*-pentane:Et_2O, 50:1); IR (film, cm^{-1}) $\tilde{\nu}$ 1713 (s, ν C=O), 836 (s, ν_s Si-O-C), 774 (s, ν O-Si-CH_3); ^1H NMR ($CDCl_3$, ppm) δ 0.04 (s, 6H, $SiMe_2$), 0.88 (s, 9H, CMe_3), 0.88 (t, J = 6.9 Hz, 3H, 8-H_3), 1.19–1.51 (m, 12H, 4-,2'-H_2 and 4'-H_2–7'-H_2), 1.61–1.89 (m, 4H, 3-,5-H_2), 2.00 / 2.08 (m_c, 2H, 1'-H_2), 2.25 (m_c, 1H, 2-H), 2.37 / 2.33 (m_c, 2H, 6-H_2), 3.63 (dddd, J = 11.6, 5.6, 5.5 and 2.2 Hz, 1H, 3'-H); ^{13}C NMR ($CDCl_3$, ppm) δ -4.38 / -4.32 (q, 2C, $SiMe_2$), 14.02 (q, 1C, C-8'), 18.21 (s, 1C, CMe_3), 22.70 (t, 1C, C-7'), 24.85 / 24.90 / 24.99 / 25.05 (t, 2C, C-3,-4), 25.18 / 25.61 (t, 1C, C-5'), 26.02 (q, 3C, CMe_3), 28.03 / 28.06 (t, 1C, C-5), 32.17 (t, 1C, C-6'), 33.98 / 34.05 (t, 1C, C-1'), 34.61 / 34.75 (t, 1C, C-4'), 36.93 / 37.25 (t, 1C, C-2'), 41.91 / 41.98 (t, 1C, C-6), 51.02 / 51.12 (d, 1C, C-2), 72.48 / 72.70 (d, 1C, C-3'), 212.88 (s, 1C, C-1); MS (CI, %) *m/z* 341 (20) [$M^{\oplus}$ + H], 283 (9) [$M^{\oplus}$ - C_4H_9], 209 (100) [$M^{\oplus}$ - $C_6H_{15}OSi$]; Anal calcd for $C_{20}H_{40}O_2Si$ (340.6), C 70.52, H 11.84; found C 70.57, H 11.86.

(±)-2-[3'(tert-Butyldimethylsiloxy)-4',4',4'-trifluorobut-1'-yl]cyclohexan-1-one (**7e**). Scale 12.1 mmol, yield 37% (1.53 g), hR_f 18 (*n*-pentane:Et_2O, 50:1); IR (film, cm^{-1}) $\tilde{\nu}$ 1141 / 1165 (s, ν C-F), 1712 (s, ν C=O), 839 (s, ν_s Si-O-C), 780 (s, ν O-Si-CH_3); ^1H NMR ($CDCl_3$, ppm) δ 0.10 / 0.11 (2s, 6H, $SiMe_2$), 0.90 (2s, 9H, CMe_3), 1.21–2.17 (m, 10H, 1'-, 2'-H_2 and 3-H_2–5-H_2), 2.20–2.43 (m, 3H, 2-H and 6-H_2), 3.90 (m_c, 1H, 3'-H); ^{13}C NMR ($CDCl_3$, ppm) δ -5.07 / -5.06 / -4.85 / -4.83 (4q, $SiMe_2$), 18.11 (s, CMe_3), 24.96 / 24.98 (t, C-4), 25.05 / 25.13 (t, C-5), 25.62 (q, CMe_3), 27.89 / 27.98 (t, C-3), 28.77 / 28.84 (t, C-1'), 33.86 / 34.17 (t, C-2'), 41.95 / 42.07 (t, C-6), 50.45 / 50.62 (d, C-2), 71.40 (dq, $^2J_{CF}$ = 30.7 Hz, C-3'), 125.11 / 125.15 (q, $^1J_{CF}$ = 283.0 Hz, C-4'), 211.90 / 212.03 (s, C-1); ^{19}F NMR ($CDCl_3$, ppm) δ -78.73 / -78.69 (2d, J= 35.6 Hz, CF_3); MS (CI, %) *m/z* 339 (100) [$M^{\oplus}$ + H], 281 (13) [$M^{\oplus}$ - C_4H_9]; Anal calcd for $C_{16}H_{29}O_2F_3Si$ (338.5), C 56.78, H 8.64; found C 56.68, H 8.62.

Cyclization of 7 and Subsequent Oxidative Cleavage to Oxo Lactones 8

General Procedure: Amberlyst® 15 (5.61 g) was added to a soln of **7b** (14.9 g, 40.4 mmol) in anhydrous CH_2Cl_2 (200 mL), and the mixture was stirred at room temp for 16 h. The resin was then filtered off, extracted with CH_2Cl_2 (3× 50 mL), and the combined organic solns were concentrated under reduced pressure. The resulting residue was dissolved in CCl_4 (80 mL), and MeCN (52 mL), water (80 mL), $RuCl_3 \cdot 3H_2O$ (442 mg, 1.69 mmol) and $NaIO_4$ (72.5 g, 339 mmol) were rapidly added in turn. After stirring for 18 h, in the course of which the black reaction mixture turned yellow, the organic layer was separated, and the colorless residue was dissolved in water (350 mL). The combined aqueous solns were extracted with CH_2Cl_2 (3× 200 mL), and the combined organic phases filtered through a pad of silica-gel and dried with Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by silica-gel column chromatography to provide **8b** as colorless crystals.

(14R)-(+)-14-Methyl-12-oxo-15-pentadecanolide (**8a**). Scale 3.19 mmol, yield 60% (513 mg), hR_f 32 (*n*-pentane:Et_2O, 5:1), mp 51.5–52.0 °C; IR (film, cm^{-1}) $\tilde{\nu}$ 1718 (s, ν C=O, lactone), 1703 (s, ν C=O, ketone), 1238 (s, ν_{as} C-CO-O, lactone); ^1H NMR ($CDCl_3$, ppm) δ 0.97 (d, J = 6.8 Hz, 3H, 14-Me), 1.27–1.37 (m, 12H, 4-H_2–9-H_2), 1.50–1.75 (m, 4H, 3-,10-H_2), 2.26 (dd, J = 16.5 and 6.9 Hz, 1H, 13-H_b), 2.27–2.50 (m, 5H, 2-,11-H_2 and 14-H), 2.70 (dd, J = 16.5 and 5.5 Hz, 1H, 13-H_a), 3.83 (dd, J = 10.9 and 7.4 Hz, 1H, 15-H_b), 4.13 (dd, J = 10.9 and 3.5 Hz, 1H, 15-H_a); ^{13}C NMR ($CDCl_3$, ppm) δ 23.45 / 24.24 (t, C-3,-10), 24.59 / 26.28 / 26.52 / 26.64 (t, C-5–C-8), 26.87 / 27.49 (t, C-4,-9), 28.58 (d, C-14), 34.13 (t, C-2), 42.22 (t, C-11), 46.24 (t, C-13), 67.98 (t, C-15), 173.62 (s, C-1), 210.46 (s, C-12); MS (EI, %) *m/z* 268 (12) [$M^{\oplus}$], 222 (4) [$M^{\oplus}$ - H_2O - CO], 211 (30) [$M^{\oplus}$ - C_4H_9], 167 (6) [$M^{\oplus}$ - $C_5H_9O_2$], 125 (20) [$C_9H_{17}^{\oplus}$], 111 (35) [$C_8H_{15}^{\oplus}$], 101 (11) [$C_5H_9O_2^{\oplus}$], 98 (100) [$C_6H_{10}O^{\oplus}$]; $[\alpha]_D^{19}$ +18.8, $[\alpha]_{546}^{19}$ +22.4 (*c* 2.0, $CHCl_3$); Anal calcd for $C_{16}H_{28}O_3$ (268.4), C 71.60, H 10.51; found C 71.64, H 10.46.

(14S)-(−)-14-Methyl-12-oxo-15-pentadecanolide (**8b**). Scale 40.4 mmol, yield 68% (7.38 g), hR_f 32 (*n*-pentane:Et_2O, 5:1), mp 51.5–52.0 °C; $[\alpha]_D^{19}$ -18.9, $[\alpha]_{546}^{19}$ -22.3 (*c* 2.0, $CHCl_3$); Anal calcd for $C_{16}H_{28}O_3$ (268.4), C 71.60, H 10.51; found C 71.69, H 10.49.

(9R)-(−)-6-Oxo-9-decanolide (**8c**). Scale 12.4 mmol, yield 47% (1.07 g), hR_f 24 (*n*-pentane:Et_2O, 2:1), mp 49–50 °C; IR (film, cm^{-1}) $\tilde{\nu}$ 1726 (s, ν C=O, lactone), 1701 (s, ν C=O, ketone), 1253 (s, ν_{as} C-CO-O); ^1H NMR ($CDCl_3$, ppm) δ 1.24 (d, *J* = 6.3 Hz, 3H, 10-H_3), 1.38 (ddddd, *J* = 14.3, 11.5, 5.3, 3.9 and 3.1 Hz, 1H, 4-H_b), 1.55 (ddddd, *J* = 14.5, 6.5, 4.9, 3.9 and 2.4 Hz, 1H, 3-H_b), 1.95 (ddddd, *J* = 14.9, 12.6, 11.6, 3.3 and 2.5 Hz, 1H, 3-H_a), 1.98 (dddd, *J* = 14.4, 7.1, 3.0 and 3.0 Hz, 1H, 8H_b), 2.13 (dddd, *J* = 14.3, 10.8, 9.6 and 3.1 Hz, 1H, 8-H_a), 2.15 (ddddd, *J* = 14.1, 12.3, 4.9, 3.9 and 3.3 Hz, 1H, 4-H_a), 2.18 (ddd, *J* = 16.7, 12.6 and 2.2 Hz, 1H, 2-H_b), 2.29 (ddd, *J* = 17.9, 5.4 and 3.9 Hz, 1H, 5-H_b), 2.30 (ddd, *J* = 12.9, 7.1 and 3.1 Hz, 1H, 7-H_b), 2.41 (ddd, *J* = 12.9, 10.7 and 3.2 Hz, 1H, 7-H_a), 2.51 (dddd, *J* = 16.8, 6.4, 2.4 and 0.5 Hz, 1H, 2-H_a), 2.59 (dddd, *J* = 17.8, 12.3, 3.2 and 0.9 Hz, 1H, 5-H_a), 5.04 (dqd, *J* = 9.5, 6.3 and 3.0 Hz, 1H, 9-H); ^{13}C NMR ($CDCl_3$, ppm) δ 19.71 (q, C-10), 20.58 (t, C-3), 22.79 (t, C-4), 33.82 (t, C-8), 34.62 (t, C-2), 40.30 / 40.54 (2t, C-5,-7), 71.63 (d, C-9), 172.84 (s, C-1), 210.56 (s, C-6); MS (EI, %) *m/z* 184 (22) [$M^{\oplus}$], 166 (5) [$M^{\oplus}$ - H_2O], 156 (8) [$M^{\oplus}$ - CO], 151 (4) [$M^{\oplus}$ - H_2O - CH_3], 129 (28) [$C_6H_9O_3^{\oplus}$], 111 (75) [$C_8H_{15}^{\oplus}$], 101 (99) [$C_5H_9O_2^{\oplus}$], 98 (100) [$C_6H_{10}O^{\oplus}$]; $[\alpha]_D^{19}$ -25.7, $[\alpha]_{546}^{19}$ -29.3 (*c* 1.2, $CHCl_3$); Anal calcd for $C_{10}H_{16}O_3$ (184.2),C 65.19, H 8.75; found C 65.23, H 8.67.

(9R)-(−)-6-Oxo-9-tetradecanolide(**8d**). Scale 4.62 mmol, yield 46% (506 mg), hR_f 21 (*n*-pentane:Et_2O, 4:1), liquid; IR (film, cm^{-1}) $\tilde{\nu}$ 1728 (s, ν C=O, lactone), 1712 (s, ν C=O, ketone),1251 (s, ν_{as} C-CO-O, lactone); ^1H NMR ($CDCl_3$, ppm) δ 0.87 (t, *J* = 6.9 Hz, 3H, 14-H_3), 1.22–1.32 (m, 6H, 11-H_2–13-H_2), 1.40 (m_c, 1H, 4-H_b), 1.50 (m_c, 1H, 10-H_b), 1.56 (m_c, 1H, 3-H_b), 1.59 (m_c, 1H, 10-H_a), 1.95 (ddddd, *J* = 14.5, 12.4, 11.4, 3.2 and 2.2 Hz, 1H, 3-H_a), 2.04 (dddd, *J* = 10.5, 7.4, 5.9 and 5.1 Hz, 1H, 8-H_b), 2.11 (dddd, *J* = 10.5, 10.0, 9.4 and 3.8 Hz, 1H, 8-H_a), 2.15 (m_c, 1H, 4-H_a), 2.18 (ddd, *J* = 16.3, 12.4 and 2.3 Hz, 1H, 2-H_b), 2.28 (ddd, *J* = 17.8, 5.3 and 3.8 Hz, 1H, 5-H_b), 2.29 (dddd, *J* = 13.4, 6.9, 5.1 and 3.8 Hz, 1H, 7-H_b), 2.41 (ddd, *J* = 13.4, 9.4 and 5.9 Hz, 1H, 7-H_a), 2.50 (ddd, *J* = 16.3, 6.4 and 2.2 Hz, 1H, 2-H_a), 2.62 (dddd, *J* = 17.8, 12.4, 3.1 and 0.7 Hz, 1H, 5-H_a), 4.99 (dddd, *J* = 10.0, 7.4, 5.9 and 3.3 Hz, 1H, 9-H); ^{13}C NMR ($CDCl_3$, ppm) δ 13.93 (q, C-14), 20.85 (t, C-3), 22.47 (t, C-4), 22.78 (t, C-13), 25.04 (t, C-11), 31.63 / 31.77 (t, C-10,-12), 33.84 (t, C-8), 34.66 (t, C-2), 39.86 (t, C-7), 40.11 (t, C-5), 74.95 (d, C-9), 173.20 (s, C-1), 210.70 (s, C-6); MS (EI, %) *m/z* 240 (23) [$M^{\oplus}$], 222 (5) [$M^{\oplus}$ - H_2O], 212 (8) [$M^{\oplus}$ - CO], 183 (5) [$M^{\oplus}$ - C_4H_9], 170 (5) [$M^{\oplus}$ - C_5H_{10}], 154 (47) [$C_9H_{14}O_2^{\oplus}$], 139 (59) [$C_9H_{15}O^{\oplus}$], 129 (80) [$C_6H_9O_3^{\oplus}$], 111 (100) [$C_8H_{15}^{\oplus}$]; $[\alpha]_D^{18}$ -15.7, $[\alpha]_{546}^{18}$ -18.0 (*c* 2.0, $CHCl_3$); Anal calcd for $C_{14}H_{24}O_3$ (240.3), C 69.96, H 10.07; found C 69.99, H 10.03.

3'-Oxy-2-butylcyclohexanone (**13c**). By-product to **8c**, yield 34% (715 mg), hR_f 23 (*n*-pentane:Et_2O, 2:1); IR (film, cm^{-1}) $\tilde{\nu}$ 1711 (s, ν C=O); ^1H NMR ($CDCl_3$, ppm) δ 1.40 (dddd, *J* = 13.4, 11.9, 11.8 and 3.7 Hz, 1H, 3-H_b), 1.52 (dddd, *J* = 13.4, 8.0, 6.6 and 4.9 Hz, 1H, 3-H_a), 1.62–1.75 (m, 2H, 5-H_2), 1.85 (m_c, 1H, 4-H_b), 1.95 (dddd, *J* = 14.1, 8.4, 8.2 and 6.0 Hz, 2H, 1'-H_2),2.06 (m_c, 1H, 4-H_a), 2.13 (s, 3H, 4'-H_3), 2.23–2.40 (m, 3H, 6-H_2, 2-H), 2.44 (dddd,*J* = 17.5, 8.4, 6.6 and 0.4 Hz, 1H, 2'-H_b), 2.57 (dddd, *J* = 17.5, 8.5, 6.0 and 0.4 Hz, 1H, 2'-H_a); ^{13}C NMR ($CDCl_3$, ppm) δ 23.86 / 25.00 (t, C-1',-5), 28.03 (t, C-4), 29.78 (q, C-4'), 34.33 (t, C-3), 41.29 / 42.10 (t, C-6,-2'), 49.81 (d, C-2), 208.43 (s, C-3'), 212.56 (s, C-1); MS (EI, %) *m/z* 168 (39) [$M^{\oplus}$], 150 (30) [$M^{\oplus}$ - H_2O], 135 (13) [$M^{\oplus}$ - H_2O - CH_3], 125 (14) [$M^{\oplus}$ - C_2H_3O], 111 (100) [$C_7H_{11}O^{\oplus}$].

3'-Oxy-2-octylcyclohexanone (**13d**). By-product to **8d**, yield 25% (256 mg), hR_f 29 (*n*-pentane:Et_2O, 4:1); IR (film, cm^{-1}) $\tilde{\nu}$ 1710 (s, ν C=O); ^1H NMR ($CDCl_3$, ppm) δ 0.88 (t, *J* = 7.0 Hz, 3H, 8'-H_3), 1.21–1.30 (m, 4H, 6'-, 7'-H_2), 1.31–1.74 (m, 6H, 3-H_2–5-H_2), 1.92 (m_c, 2H, 5'-H_2), 2.08 (m_c, 2H, 1'-H_2), 1.83–2.40 (m, 5H, 2-H_b and 6-,4'-H_2), 2.41 (ddd, *J* = 17.3, 8,2 and 6.7 Hz, 1H, 2'-H_b), 2.52 (ddd, *J* = 17.3, 8.5 and 6.2 Hz, 1H, 2'-H_a); ^{13}C NMR ($CDCl_3$, ppm) δ 13.89 (q, C-8'), 22.46 (t, C-7'), 23.61 / 23.92 (t, C-5,-5'), 25.00 (t , C-4), 28.06 (t, C-6'), 31.48 (t , C -1'), 34.37 (t, C-3), 40.29 (t, C-6), 42.10 / 42.75 (t, C-2',-4'), 49.93 (d, C-2), 210.88 (s, C-1), 212.57 (s, C-3'); MS (EI, %) *m/z* 224 (32) [$M^{\oplus}$], 181 (7) [$M^{\oplus}$ - C_3H_7], 168 (32) [$M^{\oplus}$ - C_4H_8], 153 (23) [$M^{\oplus}$ - C_5H_{11}], 135 (14) [$M^{\oplus}$ - H_2O - C_5H_{11}], 125 (53) [$M^{\oplus}$ - C_7H_{15}], 111 (100) [$C_7H_{11}O^{\oplus}$].

Chemoselective Carbonyl Reductions using Catecholborane

General Procedure: A soln of **8d** (427 mg, 1.78 mmol) and 4-toluenesulfonohydrazide (365 mg, 1.96 mmol) in MeOH (10 mL) was heated to reflux for 40 min. The solvent was evaporated on a rotary evaporator, and final traces were removed at a high-vacuum line during 3h. The reaction flask was purged with argon, and dry $CHCl_3$ (8 mL) followed by 1M catecholborane soln in toluene (3.9 mL, 3.9 mmol) were added *via* syringe at 0°C. The reaction mixture was stirred for 2 h at this temp and then quenched by dry MeOH (0.5 mL). After 10 min, $NaOAc{\cdot}3H_2O$ (267 mg, 1.96 mmol) and DMSO (0.8 mL) were added, and the mixture was heated to reflux forl h. The reaction mixture was allowed to cool and then poured into Et_2O/water (1:1, 80 mL). The organic layer was separated, washed with water (2× 40 mL), dried with Na_2SO_4,and concentrated under reduced pressure. Column chromatography on silica gel gave **3d** as odoriferous liquid.

(14R)-(+)-14-Methyl-15-pentadecanolide (**3a**). Scale 0.93 mmol, yield 75% (178 mg), hR_f 21 (*n*-pentane:Et_2O, 50:1); IR (film, cm^{-1}) $\tilde{\nu}$ 1736 (s, ν C=O), 1235 (s, ν_{as} C-CO-O), 1170 / 1112 (s, ν C-O); ^1H NMR ($CDCl_3$, ppm) δ 0.92 (d, J = 6.9 Hz, 3H, 14-Me), 1.08–1.18 (m, 1H, 13-H_b), 1.25–1.36 (m, 18H, 4-H_2–12-H_2), 1.49–1.56 (m, 1H, 13-H_a), 1.67 (m_c, 2H, 3-H_2), 1.80 (ddqdd, J = 15.4, 8.2, 6.9, 6.2 and 3.8 Hz, 1H, 14-H), 2.33 (ddd, J = 7.4, 6.7 and 0.4 Hz, 2H, 2-H_2), 3.28 (dd, J = 10.8 and 8.2 Hz, 1H, 15-H_b), 4.08 (dd, J = 10.8 and 3.8 Hz, 1H, 15-H_a); ^{13}C NMR ($CDCl_3$, ppm) δ 16.75 (q, 14-Me), 24.72 / 24.88 / 26.13 / 26.24 / 26.37 / 26.45 / 26.67 / 26.99 / 27.55 / 27.74 (t, C-3–C-12), 32.39 (d, C-14), 32.51 (t, C-13), 34.37 (t, C-2), 68.77 (t, C-15), 173.76 (s, C-1); MS (EI, %) *m/z* 254 (22) [$M^{\oplus}$], 236 (39) [$M^{\oplus}$ - H_2O], 199 (8) [$C_{12}H_{23}O_2^{\oplus}$, 14-H McLafferty rearrangement], 181 (11) [$C_{12}H_{23}O_2^{\oplus}$ - H_2O], 125 (14) [$C_9H_{17}^{\oplus}$], 111 (30) [$C_8H_{15}^{\oplus}$], 97 (52) [$C_7H_{13}^{\oplus}$], 83 (64) [$C_6H_{11}^{\oplus}$], 69 (100) [$C_5H_9^{\oplus}$]; $[\alpha]_D^{21}$ +18.1, $[\alpha]_{546}^{21}$ +21.5 (*c* 2.0, $CHCl_3$); Anal calcd for $C_{16}H_{30}O_2$ (254.4), C 75.54, H 11.89; found C 75.57, H 11.95.

(14S)-(−)-14-Methyl-15-pentadecanolide (**3b**). Scale 9.80 mmol, yield 83% (2.07 g), hR_f 21 (*n*-pentane:Et_2O, 50:1); $[\alpha]_D^{19}$ -18.6, $[\alpha]_{546}^{19}$ -22.0 (*c* 2.0, $CHCl_3$); Anal calcd for $C_{16}H_{30}O_2$ (254.4), C 75.54, H 11.89; found C 75.49, H 11.82.

(R)-(−)-Phoracantholide I (**3c**). Scale 5.75 mmol, yield 31% (305 mg), hR_f 25 (*n*-pentane:Et_2O, 25:1), IR (film, cm^{-1}) $\tilde{\nu}$ 1726 (s, ν C=O), 1256 / 1240 (s, ν_{as} C-CO-O);^1H NMR ($CDCl_3$, ppm) δ 1.02 (m_c, 1H, 5-H_b), 1.22 (m_c, 1H, 7-H_b), 1.27 (d, J = 6.6 Hz, 3H, 10-H_3), 1.33–1.58 (m, 6H, 4-,6-H_2, 5-H_a and 8-H_b), 1.52 (m_c, 1H, 3-H_b), 1.75 (ddddd, J = 14.0, 6.4, 6.3, 6.3 and 3.2 Hz, 1H, 7-H_a), 1.95 (dddd, J = 12.4, 6.4, 6.0 and 2.9 Hz, 1H, 8-H_a), 2.01 (ddddd, J = 19.7, 6.3, 6.0, 3.0 and 2.9 Hz, 1H, 3-H_a), 2.17 (ddd, J = 15.1, 11.9 and 2.9 Hz, 1H, 2-H_b), 2.49 (ddd, J = 15.1, 6.3 and 3.0 Hz, 1H, 2-H_a), 5.00 (qdd, J = 6.6, 6.6 and 2.9 Hz, 1H, 9-H); ^{13}C NMR ($CDCl_3$, ppm) δ 19.58 (q, C-10), 20.85 (t, C-7), 23.52 (t, C-3), 24.19 / 24.45 / 27.13 (t, C-4–C-6), 31.69 (t, C-8), 35.25 (t, C-2), 72.59 (d, C-9), 173.81 (s, C-1); MS (EI, %) *m/z* 171 (100) [$M^{\oplus}$ + H], 153 (12) [$M^{\oplus}$ + H - H_2O], 85 (11) [$C_4H_5O_2^{\oplus}$], 71 (13) [$C_4H_7O^{\oplus}$], 69 (21) [$C_5H_9O^{\oplus}$]; $[\alpha]_D^{22}$ -41.3, $[\alpha]_{546}^{22}$ -49.3 (*c* 1.6, $CHCl_3$) [ref[14] $[\alpha]_D^{22}$ -35.1 (88% ee, *c* 1.15, $CHCl_3$), *ent*-**3c**[16] $[\alpha]_D^{20}$ +40.3 (99% ee, *c* 0.67, $CHCl_3$)]; Anal calcd for $C_{10}H_{18}O_2$ (170.3), C 70.55, H 10.66; found C 70.60, H 10.66.

(9R)-(−)-9-Tetradecanolide (**3d**). Scale 1.78 mmol, yield 62% (250 mg), hR_f 46 (*n*-pentane:Et_2O, 20:1); IR (film, cm^{-1}) $\tilde{\nu}$ 1727 (s, ν C=O), 1239 / 1256 (s, ν_{as} C-CO-O);^1H NMR ($CDCl_3$, ppm) δ 0.89 (t, J = 6.8 Hz, 3H, 14-H_3), 1.03–1.59 (m, 16H, 3-,4-,7-,8-H_b and 5-,6-,10-,11-,12-,13-H_2), 1.62–1.77 (m, 2H, 4-,7-H_a), 1.96–1.99 (m, 1H, 3-H_a), 2.00 (dddd, J = 13.3, 9.8, 3.4 and 3.4 Hz, 1H, 8-H_a), 2.17 (ddd, J = 15.2, 11.7 and 2.4 Hz, 1H, 2-H_b), 2.49 (ddd, J = 15.2, 6.3 and 3.1 Hz, 1H, 2-H_a), 4.88 (dddd, J = 7.8, 5.9, 5.8 and 3.4 Hz, 1H, 9-H); ^{13}C NMR ($CDCl_3$, ppm) δ 14.00 (q, C-14), 21.00 (t, C-7), 22.59 (t, C-3), 23.08 (t, C-5), 23.57 / 24.39 / 25.39 / 27.10 (t, C-4,-6,-11,-13), 28.80 (t, C-12), 31.77 / 33.26 / 35.25 (t, C-2,-8,-10), 76.12 (d, C-9), 173.94 (s, C-1); MS (CI, %) *m/z* 227 (100) [$M^{\oplus}$ + H], 209 (8) [$M^{\oplus}$ + H - H_2O], 127 (3) [$M^{\oplus}$ - C_7H_{15}], 98 (6) [$M^{\oplus}$ - C_7H_{14}]; $[\alpha]_D^{20}$ -27.6, $[\alpha]_{546}^{20}$ -32.9 (*c* 0.5, $CHCl_3$); Anal calcd for $C_{14}H_{26}O_2$ (226.4), C 74.29, H 11.58; found C 74.36, H 11.51.

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