Pergamon

Tetrahedron 55 (1999) 7191–7208

TETRAHEDRON

Novel Chiral Building Blocks Derived from Baker's Yeast Reduction Products: Synthesis and Odour of Mono- and Bicyclic Macrolides

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Received 18 March 1999; accepted 20 April 1999

Abstract

A number of bicyclic macrolides with two stereogenic centres formally derived from ω-cycloalkyl fatty acids were synthesised by ring enlargement of cycloalkanones with novel chiral building blocks, easily available from yeast reduction products of β-keto esters. A comparison with structurally related monocyclic macrolides revealed surprising effects of structural variations on the olfactory properties. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Hydroxy acids and derivatives; Macrolides; Enantiomeric purity; Flavours and fragrances.

Introduction

Chaulmoogra oil which is well known for its medicinal properties was used in India for centuries for the treatment of tuberculosis and leprosy. Its main constituents are some rather unusual fatty acids named chaulmoogric acid and hydnocarpic acid. Since new petrochemically derived raw materials and natural intermediates had always great impact on the synthesis of macrocyclic musks [1], Baba et al. converted these two ω-cyclopentenyl fatty acids to the macrocyclic bicyclic lactones **1a** and **1b** (Scheme 1) having musk-like odour [2]. The bicyclic lactones were obtained as a mixture of their *cis*- and *trans*-fused regioisomers and no attempt to separate this complex mixture was made. There is no natural source of these quite unusual type of bicyclic lactones known, yet.

Investigating the structure-odour relationships of polycyclic steroid derivatives, Ruzicka and Prelog prepared a series of bicyclic polymethylene cyclohexanones like *rac*-**2** and reported a slight but distinctive musk odour for the higher homologues with 16, 19 and 20 ring atoms [3].

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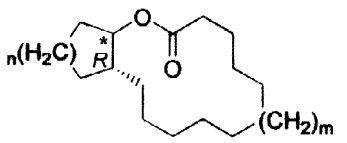
0040-4020/99/$ - see front matter
PII: S0040-4020(99)00362-2

With this knowledge in mind and looking at ω-cyclohexylundecanoic acid, which is a major constituent of the cellular fatty acids of certain thermo-acidophilic bacteria [4], we formulated the interesting lead structure **1c**.

1	n	m
a	1	1
b	1	3
c	2	1



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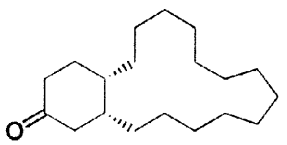


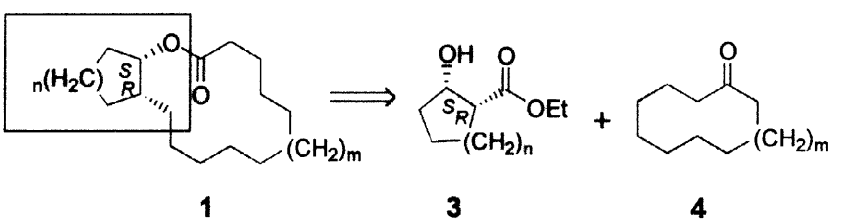
***rac*-2**

Scheme 1: Bicyclic macrolides **1** derived from ω-cycloalkyl fatty acids and structural related bicyclic ketones like *rac*-**2**.

In the course of our studies concerning the olfactory properties of several monocyclic macrolides [5,6] we have shown that the odour impression strongly depends on the number, the position and the absolute configuration of methyl substituents present in the macrocyclic ring. Recently, we presented our synthetic strategy [6c] for the introduction of two stereogenic centres into monocyclic macrolides by ring enlargement of cycloalkanones with chiral building blocks derived from acyclic β-hydroxy esters *via* diastereoselective Fráter alkylation [7].

In order to investigate the effect of different ring sizes on the olfactory properties of bicyclic macrolides, *cis*-fused optically active macrolides **1** attracted our attention as synthetic targets. The retrosynthetic analysis of *cis*-fused bicyclic macrolides **1**, based on our well-established ring-enlargement sequence, revealed optically active cyclic β-hydroxy esters **3** and commercially available cycloalkanones **4** as very attractive starting materials (Scheme 2). The required chiral β-hydroxy esters **3** can easily be prepared by yeast reduction of the corresponding β-keto esters on a preparative scale by well-known literature procedures [8].

1	n	m
a	1	1
b	1	3
c	2	1
d	1	2
e	2	2
f	2	3



1 **3** **4**

3	n
a	1
b	2

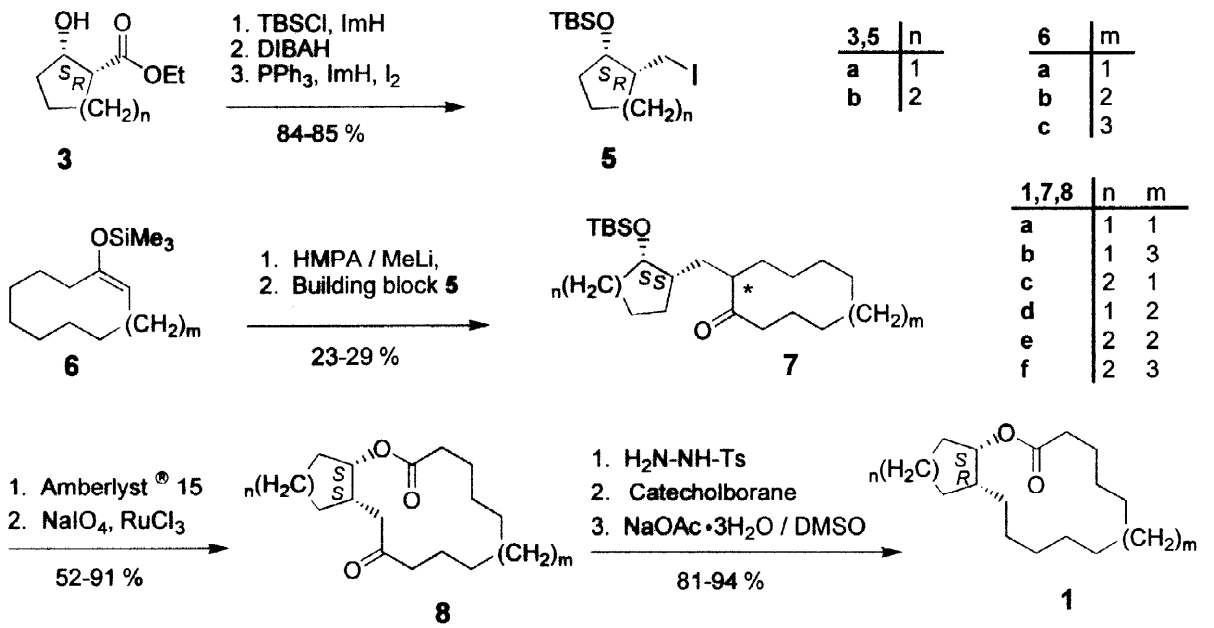
4	m
a	1
b	2
c	3

Scheme 2: Retrosynthetic analysis of *cis*-fused bicyclic macrolides **1** based on our ring-enlargement approach.

Results and Discussion

For the preparation of chiral hydroxy esters **3**, yeast reduction of ethyl 3-oxo-cyclopentanecarboxylate and -cyclohexanecarboxylate, respectively, under non-fermenting conditions according to the procedure of Seebach et al. [9] was chosen. Protection of hydroxy esters **3a,b** with the *tert*-butyldimethylsilyl group (TBS), reduction with DIBAH, and

iodination of the resulting hydroxy function with triphenylphosphine, imidazole (ImH) and iodine furnished chiral building blocks **5a,b** in 84-85% overall yield without purification of intermediates (Scheme 3). Unfortunately, iodides **5a,b** turned out to be very weak alkylating reagents in standard enolate alkylation reactions. Presumably this is due to steric congestion caused by *cis*-arrangement of the iodomethyl side-chain and the bulky *tert*-butyldimethylsiloxy group. Better yields in this reaction step were obtained by generating the ketone enolate under amine-free conditions. Treating silyl enol ethers **6** [10] with methyllithium [11] using HMPA as a cosolvent followed by addition of chiral iodides **5** furnished alkylation products 7 in moderate yields after all.



Scheme 3: Synthesis of enantiopure bicyclic lactones **1**.

Transformation of alkylation products **7** into bicyclic keto lactones **8** based upon our optimised ring-enlargement sequence proceeded in good to excellent yields [6d]. Ketones **7** were transformed into tricyclic enol ethers by treatment with Amberlyst® 15 in dichloromethane. The bridging double bonds of the crude cyclisation products were cleaved by oxidation with in situ generated ruthenium tetroxide and provided the corresponding keto lactones **8** in 52 to 91% yield over the two steps. The synthesis of bicyclic lactones **1** was completed by reduction of the tosylhydrazones of **8** by catecholborane [12], which proved to be a powerful method for the reduction of monocyclic keto lactones [6c] in the past. This reaction steps proceeded in excellent yields ranging from 81 to 94% without isolation of the tosylhydrazone intermediates. GC analyses on a chiral permethylated β-cyclodextrin column established enantiomeric excesses between 91 and 98 %. These results are in good agreement with the reported

selectivities (86-99 %ee) for the yeast reduction of the cyclic β-keto esters leading to hydroxy esters **3a,b** [9,13].

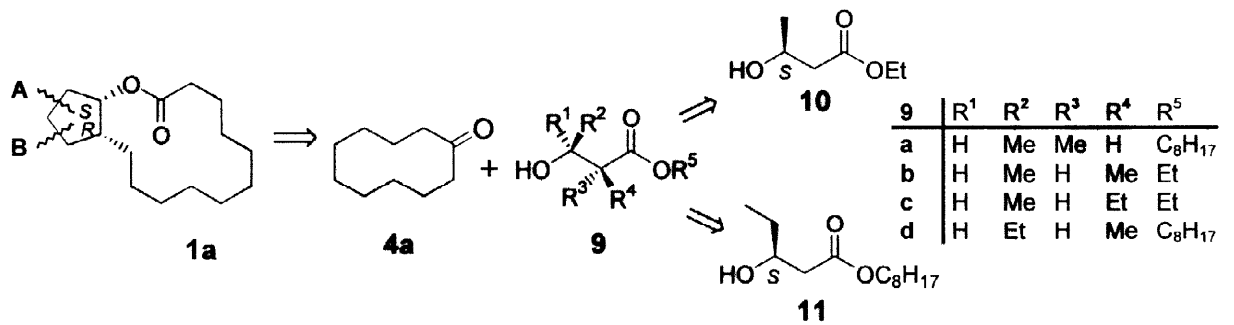
Table 1.
Olfactory properties and optical purity of bicyclic macrolides **1**.

Compound	Olfactory properties*	Optical purity†
1a	sweet and fruity with an undertone of peach, musty, slight cedarwood-like musk note	95 %ee
1b	distinct odour: aldehydic, fatty, smells like skin, woody with a musky touch	98 %ee
1c	odourless	91 %ee
1d	neutral, low intensity	98 %ee
1e	a touch of moist wood	91 %ee
1f	musty, earthy, neutral, slightly musk and woody, with sweet aspects	91 %ee

The series of bicyclic macrolides with a cyclohexyl substructure showed weak olfactory properties and **1c** was even odourless. In contrast, the odour of the lower homologue **1a**, with a cyclopentyl-ring instead, was described as sweet and fruity with an undertone of peach accompanied by a slight cedarwood-like musk note. In general, the higher homologues of this series showed a more pronounced odour, but nevertheless none of these *cis*-fused bicyclic macrolides possessed a distinct musk odour. In general, macrolides with 14 to 17-membered rings have a distinct musk odour. Since macrolides **1** lack this expected odour impression, it seemed obvious that the interaction of the larger ring moiety of **1** with the musk receptor is hindered by the smaller ring. In addition, the rather rigid bicyclic structure offers little conformational flexibility for the adjustment to the receptor site.

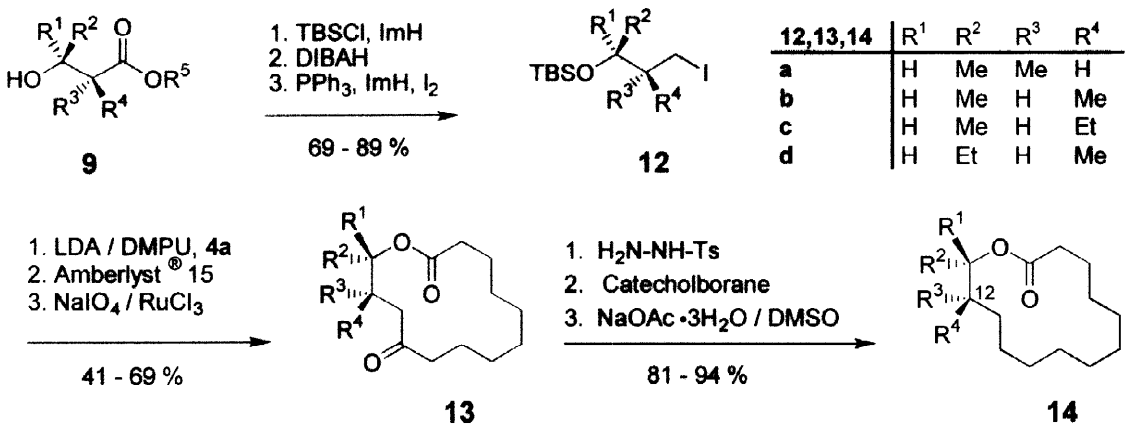
The indicated bond disconnections A and B (Scheme 4) transform the rather rigid bicyclic macrolide **1a** into more flexible monocyclic lactones. The retrosynthetic analysis of the resulting lead structures revealed chiral α-alkylated β-hydroxy esters **9** and cyclodecanone (**4a**). Amongst the variety of existing synthetic methods leading to chiral α-substituted hydroxy esters, we chose the yeast mediated reduction of octyl 2-methyl acetoacetate according to the protocol of Nakamura et al. [14]. Under the described fermenting conditions the building block **9a** with (2*R*,3*S*)-configuration was obtained and subsequently transformed into the desired chiral iodide **12a** on a multigram scale.

* Evaluated by the perfumers of Haarmann & Reimer GmbH, D-37601 Holzminden.
† Determined by chirospecific GC analyses.



Scheme 4: Retrosynthetic analyses of flexible monocyclic macrolides derived from **1a** by bond disconnections A and B.

The well established yeast reductions of ethyl acetoacetate [15] and octyl 3-oxo-pentanoate [16] gave appropriate chiral starting materials **10** and **11** for the diastereoselective synthesis of α-substituted β-hydroxy esters **9b-d** by Fráter alkylation [7]. In the usual manner **9b-d** were easily converted to chiral building blocks **12b-d** in 69 to 89 % yield (Scheme 5).



Scheme 5: Stereoselective syntheses of (ω,ω-1)-dialkylated macrolides **14**.

In contrast to the cyclic iodides **5**, which were applied for the synthesis of bicyclic macrolides **1**, optically active iodides **12a-d** showed better alkylation activities under standard reaction conditions. According to our optimised ring-enlargement sequence [6d] cyclodecanone (**4a**) yielded the corresponding crude alkylation products, direct acid catalysed cyclisation and subsequent oxidative cleavage led to keto lactones **13a-d** in excellent yields without purification of intermediates. Finally, the target compounds **14a-d** were obtained almost quantitatively by reduction of precursors **13a-d** in the usual manner with diastereomeric excesses in the range of 91 - 98%de (determined by 500 MHz ^{1}H NMR spectroscopy).

Table 2.
Olfactory properties and diastereomeric excesses of macrolides **14**.

Compound	Olfactory properties*	de†
14a	leather-like, naphthalene-like, cedarwood-like with a slight musk undertone	91 %de
14b	strong woody note with a relatively pronounced musk note	91 %de
14c	a slight touch of musk	98 %de
14d	distinct musk note, sweet and fruity-lactonic, flowery, jasmine-like	96 %de

The olfactory analyses of the flexible monocyclic (ω,ω−1)-dialkylated macrolides **14** revealed interesting results. The odour of **14a** is slightly musk, cedarwood-like and resembles that of bicyclic macrolide **1a**. This finding probably reflects the close structural relationship which is expressed by the *cis*-arrangement of methyl substituents in **14a**. Interestingly, inversion of the stereogenic centre at C-12 leads to the macrolide **14b** which possesses a very interesting overall odour impression with a relatively pronounced musk note accompanied by very strong woody aspects. These results emphasise the highly diastereoselective interaction of these macrocyclic lactones **14a,b** with the musk receptor. In addition the interaction shows also a very high degree of enantioselective discrimination, since the odour of the enantiomer *ent*-**14b** differs significantly and completely lacks any musk notes [6c]. Recently, Kraft and Cadalbert [17] reported such striking olfactory differences for 12-methyl-9-oxa-14-tetradecanolides, where the (*R*)-enantiomer was responsible for the powerful musk odour, while its enantiomer was odourless. These are, to the best of our knowledge, the most significant and distinctive examples for macrocyclic musks known so far. Without change of the absolute configuration of the stereogenic centres of **14b**, the ethyl substitution of the ω-1 methyl group (**14b**→**14c**) weakens the musk scent substantially. In contrast, the replacement of the ω-methyl group by an ethyl group (**14b**→**14d**) changes the odour quality dramatically. **14d** completely lacks the strong woody note of **14b**. Instead a distinct musk note and some sweet and fruity-lactonic, flowery, jasmine-like aspects are markedly present – odour qualities which are normally supposed to originate from a pentyl side chain [18]. Minor structural changes like altering the chain length of alkyl substituents or the absolute configuration of stereogenic centres caused unpredictable changes in the olfactory properties, which indicate a highly specific but not entirely understood structure-activity relationship in the binding to olfactory receptor sites.

* Evaluated by the perfumers of Haarmann & Reimer GmbH, D-37601 Holzminden.
† Determined by 500 MHz ^{1}H NMR.

Conclusion

In summary, we demonstrated the powerful potential of our ring-enlargement sequence [6] for the diastereoselective syntheses of mono- and bicyclic macrolides with two defined stereogenic centres in high optical purity. A broad spectrum of cyclic and acyclic chiral building blocks for this transformation, easily obtainable by yeast reductions and Fráter alkylations, gave rise to a plethora of macrocyclic lactones with attractive olfactory properties. These results will clearly stimulate further investigations, since the scope of this approach is by far not exhausted yet [19].

Experimental

IR spectra were recorded on a Perkin-Elmer Paragon 1600 FTIR spectrometer. ^{1}H and ^{13}C NMR spectra (reference: TMS int) were taken in $CDCl_3$ on Bruker AM 300 or Bruker DRX 500 spectrometers, respectively. EI (70 eV) and CI (*i*BuH) mass spectra were obtained on a Finnigan-MAT 8230 spectrometer. Gas chromatography (GC) was performed on a Satochrom gas chromatograph equipped with a 50 m PM β-cyclodextrin column (J&W), carrier gas H_2 (1.5 bar). 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 melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin Elmer 241 spectropolarimeter in $CHCl_3$ using 1 dm cells. Elemental analyses were performed by the Mikroanalytisches Laboratorium Ilse Beetz, D-96301 Kronach. Yeast reductions were carried out according to the cited literature procedures using normal laboratory equipment. Yeast purchased from Deutsches Hefewerk Hamburg performed very well in this transformations.

Yeast reductions

Preparation of chiral β-hydroxy esters

*Ethyl (1R,2S)-(+)-2-hydroxycyclopentanecarboxylate (**3a**)* [9]. Scale 460 mmol, yield 40% (29.1 g), hR_f 39, (*n*-pentane:Et_2O, 1:1); $[\alpha]_D^{25}$ +14.7, $[\alpha]_{546}^{25}$ +17.6 (c 4.0, $CHCl_3$) [ref. [9] $[\alpha]_D^{RT}$ +14.9 (c 1.7, $CHCl_3$)].

*Ethyl (1R,2S)-(+)-2-hydroxycyclohexanecarboxylate (**3b**)* [9]. Scale 424 mmol, yield 78% (56.9 g), hR_f 31, (*n*-pentane:Et_2O, 3:1); $[\alpha]_D^{21}$ +28.0, $[\alpha]_{546}^{21}$ +33.5 (c 4.0, $CHCl_3$) [ref. [9] $[\alpha]_D^{RT}$ +28.1 (c 3.5, $CHCl_3$)].

Octyl (2R,3S)-(+)-2-methyl-3-hydroxybutanoate (9a) [14]. Scale 78.8 mmol, yield 56% (10.2 g), hR_f 11, (*n*-pentane:Et_2O, 5:1); $[\alpha]_D^{24}$ +3.3, $[\alpha]_{546}^{24}$ +3.9 (c 4.0, $CHCl_3$) [ref. [14] $[\alpha]_D^{24}$ +3.3 (c 3.0, $CHCl_3$)].

Ethyl (3S)-(+)-3-hydroxybutanoate (10) [15]. Scale 115 mmol, yield 80% (12.2 g), hR_f 16, (*n*-pentane:Et_2O, 5:1); $[\alpha]_D^{20}$ +40.8, $[\alpha]_{546}^{20}$ +48.3 (c 4.0, $CHCl_3$) [ref. [15] $[\alpha]_D^{RT}$ +40.9 (c 1.0, $CHCl_3$)].

Octyl (3S)-(+)-3-hydroxypentanoate (11) [16]. Scale 65.7 mmol, yield 65% (9.84 g), hR_f 23, (*n*-pentane:Et_2O, 5:1); $[\alpha]_D^{22}$ +22.5, $[\alpha]_{546}^{22}$ +26.6 (c 4.0, $CHCl_3$) [ref. [16] $[\alpha]_D^{RT}$ +21.7 (c 5.9, $CHCl_3$)].

Preparation of Chiral Building Blocks 5 and 12

General Procedure: See ref. [6a,b]

(1S,2R)-(+)-(tert-Butyldimethyl)-(2-iodomethylcyclopentyloxy)silane (5a). Scale 134 mmol of ethyl (1*R*,2*S*)-(+)-2-hydroxycyclopentanecarboxylate (**3a**) [9], yield 84% (38.5 g), hR_f 72 (*n*-pentane); IR (film, cm^{-1}) $\tilde{\nu}$ 834 (s, ν_s Si-O-C), 775 (s, ν O-Si-CH_3); ^1H NMR ($CDCl_3$, ppm) δ 0.11 / 0.07 (2s, 6H, Si*Me*$_2$), 0.89 (s, 9H, C*Me*$_3$), 1.44 (m_C, 1H, 3-H_b), 1.68 (m_C, 1H, 4-H_b), 1.72 (m_C, 2H, 5-H_2), 1.83 (m_C, 1H, 3-H_a), 1.87 (m_C, 1H, 4-H_a), 2.15 (m_C, 1H, 2-H), 3.16 (dd, J = 6.6 and 9.3 Hz, 1H, 1'-H_B, part of an AB-system), 3.29 (dd, J = 8.4 and 9.3 Hz, 1H, 1'-H_A, part of an AB-system), 4.19 (ddd, J = 2.0, 3.9 and 3.9 Hz, 1H, 1-H); ^{13}C NMR ($CDCl_3$, ppm) δ -4.33 /-4.61 (2q, Si*Me*$_2$), 7.36 (t, C-1'), 18.02 (s, *C*Me$_3$), 22.32 (t, C-4), 25.86 (q, C*Me*$_3$), 29.64 (t, C-3), 34.98 (t, C-5), 49.91 (d, C-2), 74.83 (d, C-1); MS (CI, %) m/z 341 (33) [$M^{\oplus}$ + H], 283 (59) [$M^{\oplus}$ - C_4H_9], 213 (45) [$M^{\oplus}$ - I], 209 (13) [$M^{\oplus}$ - $C_6H_{15}OSi$], 133 (61) [$C_6H_{17}OSi^{\oplus}$]; $[\alpha]_D^{21}$ +71.3, $[\alpha]_{546}^{21}$ +84.7 (c = 3.6, $CHCl_3$).

(1S,2R)-(+)-(tert-Butyldimethyl)-(2-iodomethyl-cyclohexyloxy)silane (5b). Scale 119 mmol, of ethyl (1*R*,2*S*)-2-hydroxycyclohexanecarboxylate (**3b**) [9], yield 85% (35.8 g), hR_f 64 (*n*-pentane); IR (film, cm^{-1}) $\tilde{\nu}$ 836 (s, ν_s Si-O-C), 776 (s, ν O-Si-CH_3); ^1H NMR ($CDCl_3$, ppm) δ 0.11 / 0.08 (2s, 6H, Si*Me*$_2$), 0.90 (s, 9H, C*Me*$_3$), 1.23 (ddddd, J = 12.4, 12.4, 12.3, 4.0 and 3.9 Hz, 1H, 4-H_b), 1.33 (m_C, 1H, 5-H_b), 1.35 (dddd, J = 13.4, 13.4, 2.2 and 4.0 Hz, 1H, 6-H_b), 1.44 (dddd, J = 12.0, 12.1, 12.3 and 3.6 Hz, 1H, 3-H_b), 1.54 (m_C, 1H, 3-H_a), 1.59 (m_C, 1H, 5-H_a), 1.63 (m_C, 1H, 4-H_a), 1.66 (m_C, 1H, 2-H), 1.74 (m_C, 1H, 6-H_a), 3.05 (dd, J = 5.9 and 9.5 Hz, 1H, 1'-H_B, part of an AB-system), 3.19 (dd, J = 8.6 and 9.5 Hz, 1H, 1'-H_A, part of an AB-system), 4.19 (ddd, J = 2.2, 2.2 and 4.4 Hz, 1H, 1-H);^{13}C NMR ($CDCl_3$, ppm) δ -4.27 / -4.60 (2q, Si*Me*$_2$), 12.01 (t, C-1'), 18.16 (s, *C*Me$_3$), 19.90 (t, C-5), 25.45 (t, C-4), 25.89 (q, C*Me*$_3$), 27.36 (t, C-3), 33.55 (t, C-6), 45.84 (d, C-2), 68.85 (d, C-1); MS (CI, %) m/z 355 (13)

$[M^{\oplus} + H]$, 297 (34) $[M^{\oplus} - C_4H_9]$, 282 (32) $[M^{\oplus} - C_4H_9 - CH_3]$, 227 (47) $[M^{\oplus} - I]$, 223 (10) $[M^{\oplus} - C_6H_{15}OSi]$; $[\alpha]_D^{22}$ +60.9, $[\alpha]_{546}^{22}$ +72.3 (c 4.0, $CHCl_3$).

(2S,3R)-(+)-(tert-Butyldimethyl)-(4-iodo-3-methylbut-2-oxy)silane (12a). Scale 39.1 mmol of octyl (2*R*,3*S*)-(+)-2-methyl-3-hydroxybutanoate (**9a**) [14], yield 89% (12.8 g), hR_f 47 (*n*-pentane); IR (film, cm^{-1}) $\tilde{\nu}$ 836 (s, ν_s Si-O-C), 775 (s, ν O-Si-CH_3); ^1H NMR ($CDCl_3$, ppm) δ 0.06 / 0.08 (2s, 6H, Si*Me*$_2$), 0.89 (s, 9H, C*Me*$_3$), 0.99 (d, J = 7.1 Hz, 3H, 3-Me), 1.09 (d, J = 6.3 Hz, 3H, 1-H_3), 1.68 m_c (1H, 3-H), 3.04 (dd, J = 6.9 and 9.5 Hz, 1H, 4-H_B, part of an AB-system), 3.30 (dd, J = 6.3 and 9.5 Hz, 1H, 4-H_A, part of an AB-system), 3.90 (qd, J = 12.5 and 3.6 Hz, 1H, 2-H); MS (CI, %) m/z 329 (100) $[M^{\oplus} + H]$, 271 (53) $[M^{\oplus} - C_4H_9]$, 201 (41) $[M^{\oplus} - I]$; $[\alpha]_D^{22}$ +21.5, $[\alpha]_{546}^{22}$ +25.5 (c 3.8, $CHCl_3$);

(2S,3S)-(+)-(tert-Butyldimethyl)-(4-iodo-3-methylbut-2-oxy)silane (12b). Scale 29.4 mmol of ethyl (2*S*,3*S*)-3-hydroxy-2-methyl-butyrate (**9b**) [6c,15], yield 89% (8.60 g), hR_f 35 (*n*-pentane); $[\alpha]_D^{22}$ +33.5, $[\alpha]_{546}^{22}$ +39.6 (c 3.5, $CHCl_3$); for spectroscopic data of the enantiomer, see ref. [6c].

(2S,3S)-(+)-(tert-Butyldimethyl)-(3-iodomethyl-pent-2-oxy)-silane (12c). Scale 44.7 mmol of ethyl (2*S*,3*S*)-3-hydroxy-2-ethyl-butyrate (**9c**) [6c,15], yield 69% (7.10 g), hR_f 48 (*n*-pentane); IR (film, cm^{-1}) $\tilde{\nu}$ 835 (s, ν_s Si-O-C), 775 (s, ν O-Si-CH_3); ^1H NMR ($CDCl_3$, ppm) δ 0.08 / 0.11 (2s, 6H, Si*Me*$_2$), 0.89 (s, 9H, C*Me*$_3$), 0.90 (t, J = 7.2 Hz, 3H, 5-H_3), 1.07 - 1.12 (m, 1H, 4-H_b), 1.14 (d, J = 6.2 Hz, 3H, 1-H_3), 1.17 - 1.27 (m, 1H, 4-H_a), 1.50 (ddtd, J = 5.0, 7.5, 7.5 and 13.8 Hz, 1H, 3-H), 3.28 (dd, J = 4.7 and 9.8 Hz, 1H, 1'-H_B, part of an AB-system), 3.45 (dd, J = 4.9 and 9.8 Hz, 1H, 1'-H_A, part of an AB-system), 3.72 (qd, J = 6.2 and 6.2 Hz, 1H, 2-H); ^{13}C NMR ($CDCl_3$, ppm) δ -4.00 /-4.55 (2q, Si*Me*$_2$), 11.54 (q, C-5), 12.07 (t, C-1'), 17.98 (s, *C*Me$_3$), 20.73 (q, C-1), 23.04 (t, C-4), 25.92 (q, C*Me*$_3$), 48.73 (d, C-3), 69.89 (d, C-2); MS (CI, %) m/z 343 (100) $[M^{\oplus} + H]$, 285 (73) $[M^{\oplus} - C_4H_9]$, 215 (59) $[M^{\oplus} - I]$, 133 (49) $[C_6H_{17}OSi^{\oplus}]$; $[\alpha]_D^{20}$ +24.9, $[\alpha]_{546}^{20}$ +29.5 (c 4.0, $CHCl_3$).

(2S,3S)-(+)-(tert-Butyldimethyl)-(1-iodo-2-methylpent-3-oxy)silane (12d). Scale 34.4 mmol of octyl (2*S*,3*S*)-3-hydroxy-2-methyl-pentanoate (**9d**) [6c,16], yield 82% (9.66 g), hR_f 54 (*n*-pentane); IR (film, cm^{-1}) $\tilde{\nu}$ 835 (s, ν_s Si-O-C), 774 (s, ν O-Si-CH_3); ^1H NMR ($CDCl_3$, ppm) 0.09 / 0.07 (2s, 6H, Si*Me*$_2$), 0.89 (s, 9H, C*Me*$_3$), 0.88 (t, J = 7.4 Hz, 3H, 5-H_3), 0.86 (d, J = 6.7 Hz, 3H, 2-Me), 1.43 - 1.52 (m, 2H, 4-H_2), 1.67 (ddqd, J = 6.6, 6.7, 6.8 and 4.5 Hz, 1H, 2-H), 3.20 (dd, J = 9.6 and 6.9 Hz, 1H, 1-H_B, part of an AB-system), 3.31 (dd, J = 9.6 and 4.5 Hz, 1H, 1-H_A, part of an AB-system), 3.54 (ddd, J = 6.1, 5.0 and 5.0 Hz, 1H, 3-H); ^{13}C NMR ($CDCl_3$, ppm) δ -4.26 /-4.46 (2q, Si*Me*$_2$), 8.62 (q, C-5), 14.52 (t, C-1), 16.96 (q, 2-Me), 18.11 (s, *C*Me$_3$), 25.62 (t, C-4), 25.91 (q, C*Me*$_3$), 39.22 (d, C-2), 75.70 (d, C-3); MS (CI, %)

m/z 343 (100) [$M^{\oplus}$ + H], 285 (21) [$M^{\oplus}$ - C_4H_9], 215 (12) [$M^{\oplus}$ - I], 211 (5) [$M^{\oplus}$ - $C_6H_{15}OSi$]; $[\alpha]_D^{21}$ +23.5, $[\alpha]_{546}^{21}$ +27.8 (c 3.7, $CHCl_3$).

Synthesis of Bicyclic Lactones 1

*Alkylations of Trimethylsiloxy-cycloalkenes **6** with Chiral Building Blocks **5***

General procedure: To a soln of silyl enol ether **6c** [10] (4.05 g, 15.9 mmol) in anhydrous glyme (30 mL) at room temp was slowly added under argon methyllithium (9.94 mL of a 1.6 M solution in ether, 15.9 mmol). After stirring for 30 min, the reaction mixture was cooled to 0°C. Subsequently, the halide **5b** (5.64 g, 15.9 mmol) and dry HMPA (15 mL) were introduced. The alkylation was allowed to proceed for 16 h, while warming to room temp. At the end of this time, the reaction mixture was poured into Et_2O/H_2O (1:1, 250 mL), the organic layer was separated and the aqueous was extracted with Et_2O (3x 100 mL). The combined extracts were washed with H_2O (200 mL), dried with Na_2SO_4 and concentrated under reduced pressure. Purification by silica-gel column chromatography, hR_f 44 (*n*-pentane:Et_2O, 40:1), furnished **7f** (1.88 g, 29%) as colourless oil.

(2RS,1'S,2'S)-2-[(2'-tert-Butyldimethylsiloxy)cyclopentylmethyl]cyclodecan-1-one (7a). Scale 19.1 mmol of **5a** and 15.9 mmol of **6a**, yield 23% (1.33g), hR_f 47 (*n*-pentane:Et_2O, 40:1).

(2RS,1'S,2'S)-2-[(2'-tert-Butyldimethylsiloxy)cyclopentylmethyl]cyclododecan-1-one (7b). Scale 29.7 mmol, yield 25% (2.93g), hR_f 42 (*n*-pentane:Et_2O, 40:1).

(2RS,1'S,2'S)-2-[(2'-tert-Butyldimethylsiloxy)cyclohexylmethyl]cyclodecan-1-one (7c). Scale 19.2 mmol of **5b** and 15.9 mmol of **6a**, yield 26% (1.54g), hR_f 50 (*n*-pentane:Et_2O, 40:1).

(2RS,1'S,2'S)-2-[(2'-tert-Butyldimethylsiloxy)cyclopentylmethyl]cycloundecan-1-one (7d). Scale 29.7 mmol, yield 25% (2.82g), hR_f 48 (*n*-pentane:Et_2O, 40:1).

(2RS,1'S,2'S)-2-[(2'-tert-Butyldimethylsiloxy)cyclohexylmethyl]cycloundecan-1-one (7e). Scale 29.7 mmol, yield 26% (3.05g), hR_f 44 (*n*-pentane:Et_2O, 40:1).

(2RS,1'S,2'S)-2-[(2'-tert-Butyldimethylsiloxy)cyclohexylmethyl]cyclododecan-1-one (7f). IR (film, cm^{-1}) $\tilde{\nu}$ 1705 (s, ν C=O), 836 / 1022 (s, ν Si-O-C), 774 (s, ν O-Si-CH_3); ^1H NMR ($CDCl_3$, ppm) δ 0.03 / 0.04 (2s, 6H, Si*Me*$_2$), 0.89 (s, 9H, C*Me*$_3$), 1.08 - 1.88 (m, 29H, 3'-H_2-6'-H_2, 3-H_2-11-H_2, 1'-H and -CH_2), 2.36 - 2.63 (m, 3H, 2-H and 12-H_2), 3.75 - 3.83 (m, 1H, 2'-H); ^{13}C NMR ($CDCl_3$, ppm) δ -4.94 / -4.82 / -4.23 / -4.19 (q, 2C, Si*Me*$_2$), 18.18 / 18.19 (s, 1C, *C*Me$_3$), 25.89 / 25.92 (q, 3C, C*Me*$_3$), 20.37 / 20.58 / 21.81 / 21.94 / 22.23 / 22.27 / 22.86 / 22.99 / 23.25 / 23.37 / 23.57 / 23.71 / 24.06 / 24.08 / 25.23 / 25.51 / 25.93 / 25.98 / 26.33 / 26.37 / 26.51 / 27.12 / 30.13 / 30.42 / 33.63 / 33.68 (t, 13C, C-3 - C-11, -CH_2, C-3' - C-6'), 36.68 / 36.23 (t, 1C, C-12), 39.92 / 40.04 (d, 1C, C-1'), 49.84 / 49.73 (d, 1C, C-2), 70.62 / 69.31 (d,

1C, C-2'), 216.26 / 215.06 (s, 1C, C-1); MS (EI, %) m/z 409 (89) [$M^{\oplus}$ + H], 393 (4) [$M^{\oplus}$ - CH_3], 351 (26) [$M^{\oplus}$ - C_4H_9], 277 (100) [$M^{\oplus}$ - $C_6H_{15}SiO$].

Cyclization of 7 and Subsequent Oxidative Cleavage to Bicyclic Oxo Lactones 8

General procedure: See ref. [6d]

(1S,14S)-(+)-2-Oxabicyclo[12.3.0]heptadecan-3,12-dione (8a). Scale 3.66 mmol of **7a**, yield 86% (836 mg), hR_f 31 (*n*-pentane:Et_2O, 5:1), mp 145-146 °C; IR (film, cm^{-1}) $\tilde{\nu}$ 1716 (s, ν C=O, lactone), 1698 (s, ν C=O, ketone), 1264 (s, ν C-CO-O, lactone); ^1H NMR ($CDCl_3$, ppm) δ 1.17 - 1.81 (m, 10H, 6-H_2-9-H_2 and 16-H_2), 1.45 (m_C, 1H, 15-H_b), 1.50 (m_C, 1H, 10-H_b), 1.60 (m_C, 2H, 5-H_2), 1.75 (m_C, 1H, 15-H_a), 1.75 (m_C, 1H, 17-H_b), 1.78 (m_C, 1H, 10-H_a), 2.03 (m_C, 1H, 17-H_a), 2.19 (ddd, J = 15.0, 8.5 and 3.9 Hz, 1H, 11-H_b), 2.20 (ddd, J = 14.1, 9.0 and 3.8 Hz, 1H, 4-H_b), 2.35 (m_C, 1H, 14-H), 2.41 (ddd, J = 14.1, 8.5 and 3.6 Hz, 1H, 4-H_a), 2.50 (dd, J = 19.0 and 3.7 Hz, 1H, 13-H_b), 2.58 (ddd, J = 15.0, 9.3 and 3.7 Hz, 1H, 11-H_a), 2.83 (dd, J = 19.0 and 10.3 Hz, 1H, 13-H_a), 5.19 (ddd, J = 5.0, 5.0 and 1.9 Hz, 1H, 1-H); ^{13}C NMR ($CDCl_3$, ppm) δ 21.53 / 23.82 / 24.28 / 25.32 / 25.69 / 25.97 / 26.30 / 29.77 (t, C-5 - C-10, C-15, C-16), 32.87 (t, C-4), 34.88 (t, C-17), 38.28 (d, C-14), 41.41 / 41.50 (t, C-11 und C-13), 77.06 (d, C-1), 173.14 (s, C-3), 210.47 (s, C-12); MS (EI, %) m/z 266 (26) [$M^{\oplus}$], 248 (13) [$M^{\oplus}$ - H_2O], 238 (7) [$M^{\oplus}$ - CO], 223 (5) [$M^{\oplus}$ - C_3H_7], 220 (4) [$M^{\oplus}$ - H_2O - CO_2], 185 (66) [$C_{10}H_{17}O_3^{\oplus}$], 167 (32) [$C_{10}H_{15}O_2^{\oplus}$], 98 (100) [$C_6H_{10}O^{\oplus}$]; $[\alpha]_D^{21}$ +51.0, $[\alpha]_{546}^{21}$ +59.5 (c 1.2, $CHCl_3$); Anal calcd for $C_{16}H_{26}O_3$ (266.4), C 72.14, H 9.84; found C 72.18, H 9.72.

(1S,16S)-(+)-2-Oxabicyclo[14.3.0]nonadecan-3,14-dione (8b). Scale 4.50 mmol of **7b**, yield 52% (690 mg), hR_f 31 (*n*-pentane:Et_2O, 5:1), mp 63-65 °C; IR (film, cm^{-1}) $\tilde{\nu}$ 1719 (s, ν C=O, lactone), 1704 (s, ν C=O, ketone), 1268 (s, ν C-CO-O, lactone); ^1H NMR ($CDCl_3$, ppm) δ 1.25 - 1.90 (m, 20H, 5-H_2-12-H_2 and 17-H_2-18-H_2), 1.70 (m_C, 1H, 19-H_b), 1.90 (m_C, 1H, 19-H_a), 2.30 (m_C, 2H, 4-H_2), 2.30 (m_C, 1H, 13-H_b), 2.35 (m_C, 1H, 16-H), 2.40 (m_C, 1H, 13-H_a), 2.48 (dd, J = 18.0 and 6.4 Hz, 1H, 15-H_B, part of an AB-system), 2.70 (dd, J = 18.0 and 7.5 Hz, 1H, 15-H_A, part of an AB-system), 5.21 (ddd, J = 5.1, 5.2 and 1.8 Hz, 1H, 1-H); ^{13}C NMR ($CDCl_3$, ppm) δ 21.88 / 23.05 / 24.49 / 25.54 / 25.72 / 26.49 / 26.69 / 26.69 / 27.50 / 29.71 (t, C-5 - C-12, C-17, C-18), 32.43 (t, C-19), 34.13 (t, C-4), 38.72 (d, C-16), 41.95 (t, C-15), 42.08 (t, C-13), 77.51 (d, C-1), 173.28 (s, C-3), 210.55 (s, C-14); MS (EI, %) m/z 294 (48) [$M^{\oplus}$], 276 (30) [$M^{\oplus}$ - H_2O], 248 (21) [$M^{\oplus}$ - H_2O - CO], 213 (100) [$C_{12}H_{21}O_3^{\oplus}$]; $[\alpha]_D^{23}$ +22.1, $[\alpha]_{546}^{23}$ +25.9 (c 2.8, $CHCl_3$); Anal calcd for $C_{18}H_{30}O_3$ (294.4), C 73.43, H 10.27; found C 73.49, H 10.25.

(1S,14S)-(+)-2-Oxabicyclo[12.4.0]octadecan-3,12-dione (8c). Scale 4.03 mmol of **7c**, yield 91% (1.03 g), hR_f 41 (*n*-pentane:Et_2O, 5:1), mp 106 °C; IR (film, cm^{-1}) $\tilde{\nu}$ 1718 (s, ν C=O, lactone), 1701 (s, ν C=O, ketone), 1257 (s, ν C-CO-O, lactone); ^1H NMR ($CDCl_3$, ppm)

δ 1.14 - 1.75 (m, 16H, 5-H_2-10-H_2 and 15-H_2 - 16-H_2), 1.40 (m_C, 1H, 17-H_b), 1.46 (m_C, 1H, 18-H_a), 1.47 (m_C, 1H, 17-H_a), 1.91 (m_C, 1H, 18-H_a), 2.15 (m_C, 1H, 11-H_b), 2.20 (m_C, 1H, 14-H), 2.20 (m_C, 1H, 4-H_b), 2.21 (m_C, 1H, 13-H_b), 2.45 (ddd, J = 14.1, 8.5 and 3.6 Hz, 1H, 4-H_a), 2.49 (ddd, J = 14.8, 8.3 and 4.7 Hz, 1H, 11-H_a), 2.74 (dd, J = 19.6 and 9.3 Hz, 1H, 13-H_a), 4.97 (ddd, J = 5.6, 2.8 and 2.8 Hz, 1H, 1-H); ^{13}C NMR ($CDCl_3$, ppm) δ 21.10 / 23.93 / 24.19 / 24.26 / 25.57 / 25.86 / 25.91 / 25.91 / 27.82 / (t, C-5 - C-10, C-15 - C-17), 28.96 (t, C-18), 34.42 (d, C-14), 34.68 (t, C-4), 42.25 (t, C-11), 42.79 (t, C-13), 72.32 (d, C-1), 173.13 (s, C-3), 210.80 (s, C-12); MS (EI, %) m/z 280 (29) [$M^{\oplus}$], 262 (9) [$M^{\oplus}$ - H_2O], 252 (29) [$M^{\oplus}$ - CO], 185 (45) [$C_{10}H_{17}O_3^{\oplus}$], 98 (100) [$C_6H_{10}O^{\oplus}$]; $[\alpha]_D^{22}$ +23.2, $[\alpha]_{546}^{22}$ +26.6 (c 1.7, $CHCl_3$); Anal calcd for $C_{17}H_{28}O_3$ (280.4), C 72.82, H 10.06; found C 72.75, H 10.01.

(1S,15S)-(+)-2-Oxabicyclo[13.3.0]octadecan-3,13-dione (8d). Scale 7.41 mmol of **7d**, yield 88% (1.83 g), hR_f 28 (*n*-pentane:Et_2O, 5:1), mp 70-72 °C; IR (film, cm^{-1}) $\tilde{\nu}$ 1719 (s, ν C=O, lactone), 1703 (s, ν C=O, ketone), 1256 (s, ν C-CO-O, lactone); ^{1}H NMR ($CDCl_3$, ppm) δ 1.20 - 1.44 (m, 10H, 6-H_2-10-H_2), 1.40 (m_C, 1H, 16-H_b), 1.49 - 1.79 (m, 6H, 5-H_2 and 11-H_2 and 17-H_2), 1.68 (m_C, 1H, 18-H_b), 1.81 (m_C, 1H, 16-H_a), 1.97 (m_C, 1H, 18-H_a), 2.27 (m_C, 2H, 4-H_2), 2.28 (m_C, 1H, 12-H_b), 2.31 (m_C, 1H, 15-H), 2.42 (ddd, J = 14.7, 8.6 and 4.6 Hz, 1H, 12-H_a), 2.51 (dd, J = 18.6 and 5.2 Hz, 1H, 14-H_b), 2.74 (dd, J = 18.6 and 8.7 Hz, 1H, 14-H_a), 5.30 (ddd, J = 4.9, 4.8 and 1.7 Hz, 1H, 1-H); ^{13}C NMR ($CDCl_3$, ppm) δ 21.52 / 23.94 / 24.35 / 25.64 / 25.99 / 26.54 / 26.61 / 26.95 (t, C-5 - C-11, C-17), 29.62 (t, C-16), 32.56 (t, C-18), 34.00 (t, C-4), 38.68 (d, C-15), 41.63 (t, C-12), 42.83 (t, C-14), 77.30 (d, C-1), 173.42 (s, C-3), 210.94 (s, C-13); MS (EI, %) m/z 280 (36) [$M^{\oplus}$], 262 (29) [$M^{\oplus}$ - H_2O], 252 (9) [$M^{\oplus}$ - CO], 199 (75) [$C_{11}H_{19}O_3^{\oplus}$], 98 (100) [$C_6H_{10}O^{\oplus}$]; $[\alpha]_D^{22}$ +42.8, $[\alpha]_{546}^{22}$ +49.8 (c 2.1, $CHCl_3$); Anal calcd for $C_{17}H_{28}O_3$ (280.4), C 72.82, H 10.06; found C 72.80, H 10.01.

(1S,15S)-(+)-2-Oxabicyclo[13.4.0]nonadecan-3,13-dione (8e). Scale 7.72 mmol of **7e**, yield 91% (2.07 g), hR_f 41 (*n*-pentane:Et_2O, 5:1), mp 48-49 °C; IR (film, cm^{-1}) $\tilde{\nu}$ 1725 (s, ν C=O, lactone), 1698 (s, ν C=O, ketone), 1221 (s, ν C-CO-O, lactone); ^{1}H NMR ($CDCl_3$, ppm) δ 1.24 - 1.54 (m, 16H, 6-H_2-10-H_2 and 16-H_2 - 18-H_2), 1.50 (m_C, 1H, 19-H_b), 1.58 - 1.79 (m, 4H, 5-H_2 and 11-H_2), 1.85 (m_C, 1H, 19-H_a), 2.24 (m_C, 1H, 15-H), 2.32 (m_C, 1H, 14-H_b), 2.32 (m_C, 1H, 4-H_b), 2.33 (m_C, 2H, 12-H_2), 2.39 (ddd, J = 15.3, 9.4 and 3.6 Hz, 1H, 4-H_a), 2.63 (dd, J = 18.4 and 6.8 Hz, 1H, 14-H_a), 5.03 (ddd, J = 5.3, 2.5 and 2.8 Hz, 1H, 1-H); ^{13}C NMR ($CDCl_3$, ppm) δ 20.99 / 24.37 / 24.37 / 24.61 / 25.77 / 26.27 / 26.54 / 26.85 / 27.30 / 27.45 / (t, C-5 - C-11, C-16 - C-18), 29.37 (t, C-19), 34.18 (t, C-4), 34.66 (d, C-15), 41.92 (t, C-12), 44.95 (t, C-14), 72.24 (d, C-1), 173.18 (s, C-3), 211.02 (s, C-13); MS (EI, %) m/z 294 (34) [$M^{\oplus}$], 276 (12) [$M^{\oplus}$ - H_2O], 266 (36) [$M^{\oplus}$ - CO], 248 (6) [$M^{\oplus}$ - H_2O - CO], 197 (75) [$C_{11}H_{17}O_3^{\oplus}$]; $[\alpha]_D^{22}$

+21.0, $[\alpha]_{546}^{22}$ +24.5 (c 2.4, $CHCl_3$); Anal calcd for $C_{18}H_{30}O_3$ (294.4), C 73.43, H 10.27; found C 73.38, H 10.33.

(1S,16S)-(+)-2-Oxabicyclo[14.4.0]eicosadecan-3,14-dione (8f). Scale 4.61 mmol of **7f**, yield 95% (1.35 g), hR_f 39 (*n*-pentane:Et_2O, 5:1); IR (film, cm^{-1}) $\tilde{\nu}$ 1729 (s, ν C=O, lactone), 1713 (s, ν C=O, ketone), 1250 (s, ν C-CO-O, lactone); ^1H NMR ($CDCl_3$, ppm) δ 1.25 - 1.85 (m, 22H, 5-H_2-12-H_2 and 17-H_2 - 19-H_2), 1.51 (m_C, 1H, 20-H_b), 1.82 (m_C, 1H, 20-H_a), 2.19 - 2.39 (m, 4H, 4-H_2 and 13-H_2), 2.25 (m_C, 1H, 16-H), 2.32 (dd, J = 17.6 and 7.3 Hz, 1H, 15-H_b), 2.50 (dd, J = 17.6 and 6.4 Hz, 1H, 15-H_a), 4.99 (ddd, J = 5.0, 2.5 and 2.6 Hz, 1H, 1-H); ^{13}C NMR ($CDCl_3$, ppm) δ 20.98 / 23.09 / 23.08 / 24.41 / 24.71 / 25.42 / 25.48 / 26.67 / 26.67 / 27.51 / 27.60 (t, C-5 - C-12, C-17 - C-19), 29.65 (t, C-20), 34.45 (t, C-4), 34.89 (d, C-16), 44.16 / 42.63 (t, C-13 and C-15), 72.25 (d, C-1), 173.34 (s, C-3), 210.73 (s, C-14); MS (EI, %) m/z 308 (19) [$M^{\oplus}$], 290 (6) [$M^{\oplus}$ - H_2O], 280 (23) [$M^{\oplus}$ - CO], 213 (34) [$C_{12}H_{21}O_3^{\oplus}$]; $[\alpha]_D^{22}$ +6.7, $[\alpha]_{546}^{22}$ +7.8 (c 1.7, $CHCl_3$); Anal calcd for $C_{19}H_{32}O_3$ (308.4), C 73.98, H 10.46; found C 73.94, H 10.42.

Chemoselective Reductions of Oxo Lactones 8 to Bicyclic Lactones 1

General procedure: See ref. [6d]

(1S,14R)-(+)-2-Oxabicyclo[12.3.0]heptadecan-3-one (1a). Scale 2.06 mmol of **8a**, yield 81% (421 mg), hR_f 31 (*n*-pentane:Et_2O, 40:1), mp 38 °C; IR (film, cm^{-1}) $\tilde{\nu}$ 1731 (s, ν C=O, lactone), 1250 (m, ν C-CO-O, lactone), 1148 (m, ν C-O) ; ^1H NMR ($CDCl_3$, ppm) δ 1.13 - 1.80 (m, 16H, 6-H_2-13-H_2), 1.24 (m_C, 1H, 15-H_b), 1.45 (m_C, 1H, 16-H_b), 1.53 (m_C, 1H, 15-H_a), 1.60 (m_C, 1H, 5-H_b), 1.67 (m_C, 1H, 5-H_a), 1.74 (m_C, 1H, 17-H_b), 1.77 (m_C, 1H, 16-H_a),1.79 (m_C, 1H, 14-H), 1.91 (m_C, 1H, 17-H_a), 2.23 (ddd, J = 14.2, 9.1 and 3.6 Hz, 1H, 4-H_b), 2.45 (ddd, J = 14.2, 8.7 and 3.4 Hz, 1H, 4-H_a), 5. 12 (ddd, J = 5.1, 4.7 and 1.2 Hz, 1H, 1-H); ^{13}C NMR ($CDCl_3$, ppm) δ 21.66 / 23.52 / 24.86 / 25.51 / 25.66 / 25.81 / 25.84 / 27.54 (t, C-6 - C-13), 24.48 (t, C-15), 28.18 (t, C-5), 30.47 (t, C-16), 32.83 (t, C-17), 34.83 (t, C-4), 45.02 (d, C-14), 76.68 (d, C-1), 173.69 (s, C-3); MS (EI, %) m/z 252 (17) [$M^{\oplus}$], 234 (7) [$M^{\oplus}$ - H_2O], 224 (3) [$M^{\oplus}$ - CO], 96 (44) [$C_7H_{12}^{\oplus}$], 82 (100) [$C_6H_{10}^{\oplus}$]; $[\alpha]_D^{24}$ +84.9, $[\alpha]_{546}^{24}$ +100.6 (c 3.8, $CHCl_3$); GC (100°C, 2°C/min to 180°C: 36.9 min (>97.5), >95.0%ee; Anal calcd for $C_{16}H_{28}O_2$ (252.4), C 76.14, H 11.18; found C 76.27, H 11.20.

(1S,16R)-(+)-2-Oxabicyclo[14.3.0]nonadecan-3-one (1b). Scale 1.70 mmol of **8b**, yield 81% (388 mg), hR_f 28 (*n*-pentane:Et_2O, 40:1); IR (film, cm^{-1}) $\tilde{\nu}$ 1732 (s, ν C=O, lactone), 1203 (m, ν C-CO-O, lactone), 1172 (m, ν C-O) ; ^1H NMR ($CDCl_3$, ppm) δ 1.15 - 1.95 (m, 29H, 5-H_2-15-H_2, 17-H_2-19-H_2 and 16-H), 2.27 (ddd, J = 15.1, 6.7 and 5.8 Hz, 1H, 4-H_B, part of an AB-system), 2.34 (ddd, J = 15.1, 8.6 and 5.6 Hz, 1H, 4-H_A, part of an AB-system), 5.19

(ddd, J = 5.1, 5.2 and 1.3 Hz, 1H, 1-H); ^{13}C NMR ($CDCl_3$, ppm) δ 22.15 / 24.68 / 25.48 / 25.62 / 26.06 / 26.31 / 26.59 / 26.64 / 27.34 / 27.60 / 28.08 / 29.39 / 30.07 (t, C-5 - C-15, C-17, C-18), 32.69 (t, C-19), 34.31 (t, C-4), 45.03 (d, C-16), 77.35 (d, C-1), 173.68 (s, C-3); MS (EI, %) m/z 280 (43) [$M^{\oplus}$], 262 (17) [$M^{\oplus}$ - H_2O], 252 (4) [$M^{\oplus}$ - CO]; $[\alpha]_D^{23}$ +29.5, $[\alpha]_{546}^{23}$ +34.9 (c 4.0, $CHCl_3$); GC (100°C, 2°C/min to 180°C: 47.6 min (>99.1), >98.0 %ee; Anal calcd for $C_{18}H_{32}O_2$ (280.4), C 77.09, H 11.50; found C 77.15, H 11.46.

(1S,14R)-(+)-2-Oxabicyclo[12.4.0]octadecan-3-one (1c). Scale 2.04 mmol of **8c**, yield 87% (473 mg), hR_f 28 (*n*-pentane:Et_2O, 40:1); IR (film, cm^{-1}) $\tilde{\nu}$ 1730 (s, ν C=O, lactone), 1215 (m, ν C-CO-O, lactone), 1176 (m, ν C-O) ; ^{1}H NMR ($CDCl_3$, ppm) δ 0.98 - 1.74 (m, 22H, 6-H_2-13-H_2, 15-H_2 - 17-H_2), 1.40 (m_C, 1H, 18-H_b), 1.53 (m_C, 1H, 14-H), 1.58 (m_C, 1H, 5-H_b), 1.67 (m_C, 1H, 5-H_a), 1.97 (m_C, 1H, 18-H_a), 2.24 (ddd, J = 14.1, 9.2 and 3.5 Hz, 1H, 4-H_b), 2.48 (ddd, J = 14.1, 8.7 and 3.4 Hz, 1H, 4-H_a), 4. 98 (ddd, J = 5.2, 2.6 and 2.6 Hz, 1H, 1-H); ^{13}C NMR ($CDCl_3$, ppm) δ 21.36 / 23.39 / 23.45 / 24.15 / 24.63 / 25.51 / 25.59 / 26.08 / 27.28 / 28.47 / 29.45 (t, C-6 - C-13, C-15 - C-17), 24.56 (t, C-5), 29.44 (t, C-18), 34.70 (t, C-4), 40.04 (d, C-14), 71.50 (d, C-1), 173.52 (s, C-3); MS (EI, %) m/z 266 (25) [$M^{\oplus}$], 248 (4) [$M^{\oplus}$ - H_2O], 223 (3) [$M^{\oplus}$ - C_3H_7], 96 (100) [$C_7H_{12}^{\oplus}$]; $[\alpha]_D^{23}$ +62.7, $[\alpha]_{546}^{23}$ +74.1 (c 3.9, $CHCl_3$); GC (100°C, 2°C/min to 180°C: 41.4 min (>95.4), >91.0%ee; Anal calcd for $C_{17}H_{30}O_2$ (266.4), C 76.64, H 11.35; found C 76.69, H 11.42.

(1S,15R)-(+)-2-Oxabicyclo[13.3.0]octadecan-3-one (1d). Scale 2.14 mmol of **8d**, yield 90% (512 mg), hR_f 22 (*n*-pentane:Et_2O, 50:1); IR (film, cm^{-1}) $\tilde{\nu}$ 1732 (s, ν C=O, lactone), 1212 (m, ν C-CO-O, lactone), 1170 (m, ν C-O) ; ^{1}H NMR ($CDCl_3$, ppm) δ 1.20 - 1.82 (m, 18H, 6-H_2-14-H_2), 1.30 (m_C, 1H, 16-H_b), 1.42 (m_C, 1H, 17-H_b), 1.48 (m_C, 1H, 16-H_a), 1.54 (m_C, 1H, 5-H_b), 1.69 (m_C, 1H, 18-H_b), 1.78 (m_C, 1H, 15-H), 1.79 (m_C, 1H, 17-H_a), 1.80 (m_C, 1H, 5-H_a), 1.90 (m_C, 1H, 18-H_a), 2.27 - 2.36 (m, 2H, 4-H_2), 5. 23 (ddd, J = 5.1, 5.1 and 1.7 Hz, 1H, 1-H); ^{13}C NMR ($CDCl_3$, ppm) δ 21.91 / 25.34 / 25.94 / 26.40 / 26.51 / 26.63 / 26.76 / 27.40 / 27.45 (t, C-6 - C-14), 24.56 (t, C-5), 29.97 (t, C-16), 30.13 (t, C-17), 32.75 (t, C-18), 34.09 (t, C-4), 45.16 (d, C-15), 77.05 (d, C-1), 173.91 (s, C-3); MS (EI, %) m/z 266 (20) [$M^{\oplus}$], 248 (8) [$M^{\oplus}$ - H_2O], 238 (3) [$M^{\oplus}$ - CO]; $[\alpha]_D^{22}$ +50.4, $[\alpha]_{546}^{22}$ +59.5 (c 4.1, $CHCl_3$); GC (100°C, 2°C/min to 180°C: 41.7 min (>98.8), >98.0%ee; Anal calcd for $C_{17}H_{30}O_2$ (266.4), C 76.64, H 11.35; found C 76.59, H 11.39.

(1S,15R)-(+)-2-Oxabicyclo[13.4.0]nonadecan-3-one (1e). Scale 2.04 mmol of **8e**, yield 94% (540 mg), hR_f 36 (*n*-pentane:Et_2O, 40:1); IR (film, cm^{-1}) $\tilde{\nu}$ 1731 (s, ν C=O, lactone), 1208 (m, ν C-CO-O, lactone), 1169 (m, ν C-O); ^{1}H NMR ($CDCl_3$, ppm) δ 1.06 - 1.50 (m, 22H, 6-H_2-14-H_2, 16-H_2 and 17-H_2), 1.27 (m_C, 1H, 18-H_b), 1.40 (m_C, 1H, 19-H_b), 1.45 (m_C, 1H, 15-H), 1.56 (m_C, 1H, 5-H_b), 1.66 (m_C, 1H, 18-H_a), 1.78 (m_C, 1H, 5-H_a), 1.89 (m_C, 1H, 19-H_a), 2.33

(ddd, J = 15.5, 7.1 and 4.0 Hz, 1H, 4-H_b), 2.38 (ddd, J = 15.5, 9.9 and 3.7 Hz, 1H, 4-H_a), 5.05 (ddd, J = 4.3, 2.2 and 2.0 Hz, 1H, 1-H); ^{13}C NMR ($CDCl_3$, ppm) δ 21.01 / 24.58 / 24.99 / 26.32 / 26.35 / 26.37 / 26.66 / 27.41 / 27.64 / 28.10 / 31.52 (t, C-6 - C-14, C-16, C-17), 24.44 (t, C-5), 25.19 (t, C-18), 29.97 (t, C-19), 34.01 (t, C-4), 40.67 (d, C-15), 71.48 (d, C-1), 173.65 (s, C-3); MS (EI, %) m/z 280 (25) [$M^{\oplus}$], 262 (5) [$M^{\oplus}$ - H_2O], 252 (3) [$M^{\oplus}$ - CO]; $[\alpha]_D^{22}$ +44.6, $[\alpha]_{546}^{22}$ +52.6 (c 3.9, $CHCl_3$); GC (100°C, 2°C/min to 180°C: 47.2 min (>95.4), >91.0%ee; Anal calcd for $C_{18}H_{32}O_2$ (280.4), C 77.09, H 11.50; found C 77.05, H 11.42.

(1S,16R)-(+)-2-Oxabicyclo[14.4.0]eicosadecan-3-one (1f). Scale 2.59 mmol of **8f**, yield 96% (730 mg), hR_f 39 (*n*-pentane:Et_2O, 40:1); IR (film, cm^{-1}) $\tilde{\nu}$ 1731 (s, ν C=O, lactone), 1168 (m, ν C-O); ^{1}H NMR ($CDCl_3$, ppm) δ 1.14 - 1.61 (m, 25H, 6-H_2-15-H_2, 18-H_2, 19-H_2 and 17-H_b), 1.45 (m_C, 1H, 20-H_b), 1.50 (m_C, 1H, 20-H_a), 1.56 (m_C, 1H, 5-H_b), 1.68 (m_C, 1H, 17-H_a), 1.75 (m_C, 1H, 5-H_a), 1.90 (m_C, 1H, 16-H), 2.30 (ddd, J = 14.7, 7.1 and 5.4 Hz, 1H, 4-H_B, part of an AB-system), 2.37 (ddd, J = 14.7, 8.8 and 5.3 Hz, 1H, 4-H_A, part of an AB-system), 5.00 (ddd, J = 7.4, 2.4 and 2.5 Hz, 1H, 1-H); ^{13}C NMR ($CDCl_3$, ppm) δ 21.25 / 24.80 / 24.89 / 25.51 / 25.51 / 25.71 / 26.05 / 26.11 / 26.67 / 26.83 / 27.67 / 27.71 / 28.01 / 29.86 (t, C-5 - C-15, C-17 -C-19), 31.67 (t, C-20), 34.42 (t, C-4), 40.19 (d, C-16), 72.35 (d, C-1), 173.58 (s, C-3) ; MS (EI, %) m/z 294 (32) [$M^{\oplus}$], 276 (7) [$M^{\oplus}$ - H_2O], 248 (3) [$M^{\oplus}$ - CO - H_2O]; $[\alpha]_D^{22}$ +18.8, $[\alpha]_{546}^{22}$ +22.3 (c 1.6, $CHCl_3$); GC (100°C, 2°C/min to 180°C: 55.3 min (>95.7), >91.0%ee; Anal calcd for $C_{19}H_{34}O_2$ (294.5), C 77.50, H 11.64; found C 77.45, H 11.62.

Synthesis of Substituted Monocyclic Lactones 14

*Alkylations of Cyclodecanone **4a** by Chiral Building Blocks **12**, Subsequent Cyclisation and Oxidative Cleavage to Oxo Lactones **13***

General procedure: See ref. [6b,d]

(12S,13S)-(+)-12-Methyl-10-oxo-13-tetradecanolide (13a). Scale 12.1 mmol of **12a**, yield 56% (1.72 g), hR_f 36 (*n*-pentane:Et_2O, 5:1), mp 58-59 °C; IR (film, cm^{-1}) $\tilde{\nu}$ 1728 (s, ν C=O, lactone), 1710 (s, ν C=O, ketone), 1148 (m, ν C-O) ; ^{1}H NMR ($CDCl_3$, ppm) δ 0.98 (d, J = 7.0 Hz, 3H, 12-Me), 1.16 (d, J = 6.5 Hz, 3H, 14-H_3), 1.25-1.40 (m, 8H, 4-H_2-7-H_2), 1.55-1.75 (m, 4H, 3-H_2 and 8- H_2), 2.09 (dd, J = 17.3 and 8.2 Hz, 1H, 11-H_b), 2.20-2.50 (m, 5H, 9-H_2, 2-H_2 and 12-H), 2.87 (dd, J = 17.3 and 5.0 Hz, 1H, 11-H_a), 4.96 (dq, J = 13.1 and 3.2 Hz, 1H, 13-H); MS (EI, %) m/z 254 (15) [$M^{\oplus}$], 239 (7) [$M^{\oplus}$ - CH_3], 226 (12) [$M^{\oplus}$ - CO]; Anal calcd for $C_{15}H_{26}O_3$ (254.4), C 70.83, H 10.30; found C 70.96, H 10.29.

(12R,13S)-(+)-12-Methyl-10-oxo-13-tetradecanolide (13b). Scale 12.1 mmol of **12b**, yield 59% (1.83 g), hR_f 36 (*n*-pentane:Et_2O, 5:1), mp 44-45 °C; for spectroscopic data of the corresponding enantiomer, see ref. [6c].

(12R,13S)-(+)-12-Ethyl-10-oxo-13-tetradecanolide (13c). Scale 21.4 mmol of **12c**, yield 69% (3.93 g), hR_f 36 (*n*-pentane:Et_2O, 5:1), mp 29-30 °C; IR (film, cm^{-1}) $\tilde{\nu}$ 1713 (s, ν C=O, lactone), 1698 (s, ν C=O, ketone), 1220 (s, ν C-CO-O, lactone); ^1H NMR ($CDCl_3$, ppm) δ 0.87 (t, J = 7.5 Hz, 3H, 2'-H_3), 1.24 (d, J = 6.2 Hz, 3H, 14-H_3), 1.28 - 1.41 (m, 8H, 4-H_2-7-H_2), 1.37 (m_C, 1H, 1'-H_b), 1.46 (dqd, J = 4.8, 7.6 and 14.6 Hz, 1H, 1'-H_a), 1.61 - 1.73 (m, 4H, 3-H_2 and 8-H_2), 2.13 (tddd, J = 6.7, 1.9, 4.9 and 13.4 Hz, 1H, 12-H), 2.29 - 2.41 (m, 4H, 2-H_2 and 9-H_2), 2.38 (m_C, 1H, 11-H_b), 2.64 (dd, J = 4.9 and 17.9 Hz, 1H, 11-H_a) 4.84 (qd, J = 6.2 and 8.5 Hz, 1H, 13-H); ^{13}C NMR ($CDCl_3$, ppm) δ 10.31 (q, C-2'), 18.93 (q, C-14), 23.20/23.56 (t, C-1', C-8), 24.17 (t, C-3), 26.14 / 25.57 / 25.57 / 25.38 (t, C-4 - C-7), 34.32 (t, C-2), 39.43 (d, C-12), 41.93 (t, C-11), 42.38 (t, C-9), 73.06 (d, C-13), 173.45 (s, C-1), 211.05 (s, C-10); MS (EI, %) m/z 268 (30) [$M^{\oplus}$], 253 (7) [$M^{\oplus}$ - CH_3], 239 (10) [$M^{\oplus}$ - C_2H_5], 126 (56) [$C_8H_{14}O^{\oplus}$], 98 (65) [$C_6H_{10}O^{\oplus}$]; $[\alpha]_D^{21}$ +12.8, $[\alpha]_{546}^{21}$ +14.7 (c 1.8, $CHCl_3$); Anal calcd for $C_{16}H_{28}O_3$ (268.4), C 71.60, H 10.51; found C 71.61, H 10.54.

(12R,13S)-(+)-12-Methyl-10-oxo-13-pentadecanolide (13d). Scale 13.0 mmol of **12d**, yield 41% (1.44 g), hR_f 36 (*n*-pentane:Et_2O, 5:1); IR (film, cm^{-1}) $\tilde{\nu}$ 1729 (s, ν C=O, lactone), 1711 (s, ν C=O, ketone), 1251 (s, ν C-CO-O, lactone); ^1H NMR ($CDCl_3$, ppm) δ 0.88 (t, J = 7.4 Hz, 3H, 15-H_3), 0.93 (d, J = 6.7 Hz, 3H, 12-Me), 1.22 - 1.44 (m, 8H, 4-H_2-7-H_2), 1.53 (dqd, J = 14.7, 7.4 and 7.5 Hz, 1H, 14-H_b), 1.73 (dqd, J = 14.7, 7.4 and 3.7 Hz, 1H, 14-H_a), 1.59 - 1.74 (m, 4H, 3-H_2 and 8-H_2), 2.18 (dd, J = 9.4 and 16.8 Hz, 1H, 11-H_b), 2.25 (m_C, 1H, 12-H), 2.29 - 2.46 (m, 4H, 2-H_2 and 9-H_2), 2.68 (m_C, 1H, 11-H_a), 4.71 (ddd, J = 8.8, 7.5 and 3.7 Hz, 1H, 13-H); ^{13}C NMR ($CDCl_3$, ppm) δ 8.92 (q, C-15), 16.98 (q, 12-Me), 23.41 / 24.64 / 24.95 (t, C-14, C-3 and C-8), 26.37 / 25.50 / 25.54 / 25.89 (t, C-4 - C-7), 31.89 (d, C-12), 34.09 (t, C-2), 42.48 (t, C-11), 45.15 (t, C-9), 78.38 (d, C-13), 173.89 (s, C-1), 211.41 (s, C-10); MS (EI, %) m/z 268 (33) [$M^{\oplus}$], 250 (7) [$M^{\oplus}$ - H_2O], 239 (30) [$M^{\oplus}$ - C_2H_5], 183 (62) [$M^{\oplus}$ - C_6H_{13}], 139 (40) [$M^{\oplus}$ - $C_8H_{17}O$]; $[\alpha]_D^{21}$ +6.7, $[\alpha]_{546}^{21}$ +7.3 (c 4.0, $CHCl_3$); Anal calcd for $C_{16}H_{28}O_3$ (268.4), C 71.60, H 10.51; found C 71.69, H 10.59.

Chemoselective Reductions of Oxo Lactones 13 to Monocyclic Lactones 14

General procedure: See ref. [6d]

(12S,13S)-(+)-12-Methyl-13-tetradecanolide (14a). Scale 2.75 mmol of **13a**, yield 94% (620 mg), hR_f 28 (*n*-pentane:Et_2O, 50:1); IR (film, cm^{-1}) $\tilde{\nu}$ 1733 (s, ν C=O), 1220 (m, ν C-CO-O) ; ^1H NMR ($CDCl_3$, ppm) δ 0.96 (d, J = 6.9 Hz, 3H, 12-Me), 1.14 (d, J = 6.6 Hz, 3H, 14-H_3), 0.95-1.80 (m, 19H, 3-H_2-11-H_2, 12-H), 2.22-2.45 (m, 2H, 2-H_2), 4. 95 (dq, J = 6.5 and 3.1 Hz, 1H, 13-H); minor diastereomer δ 4.64 (dq, J = 9.9 and 6.2 Hz, 1H, 13-H, 4.5%, 91%de);

MS (EI, %) m/z 240 (11) [$M^{\oplus}$], 222 (7) [$M^{\oplus}$ - H_2O], 296 (74) [$M^{\oplus}$ - CO_2]; $^{\oplus}$];$[\alpha]_D^{22}$ +7.1, $[\alpha]_{546}^{22}$ +8.4 (c 4.0, $CHCl_3$); Anal calcd for $C_{15}H_{28}O_2$ (240.4), C 74.95, H 11.74; found C 75.07, H 11.85.

(12R,13S)-(+)-12-Methyl-13-tetradecanolide (14b). Scale 2.75 mmol of **13b**, yield 84% (553 mg), hR_f 22 (*n*-pentane:Et_2O, 50:1); ^{1}H NMR ($CDCl_3$, ppm) minor diastereomer δ 4.95 (dq, J = 3.1 and 6.5 Hz, 1H, 13-H, 4.5%, 91%de); spectroscopic data are identical with the enantiomer, see ref. [6c]; $[\alpha]_D^{21}$ +47.0, $[\alpha]_{546}^{21}$ +55.3 (c 3.8, $CHCl_3$); Anal calcd for $C_{15}H_{28}O_2$ (240.4), C 74.95, H 11.74; found C 75.09, H 11.72.

(12R,13S)-(+)-12-Ethyl-13-tetradecanolide (14c). Scale 1.86 mmol of **13c**, yield 91% (431 mg), hR_f 47 (*n*-pentane:Et_2O, 20:1); IR (film, cm^{-1}) $\tilde{\nu}$ 1730 (s, ν C=O, lactone), 1248 (s, ν C CO-O, lactone); ^{1}H NMR ($CDCl_3$, ppm) δ 0.87 (t, J = 7.5 Hz, 3H, 2'-H_3), 1.22 (d, J = 6.2 Hz, 3H, 14-H_3), 1.23 - 1.53 (m, 16H, 4-H_2-11-H_2), 1.31 (m_C, 1H, 1'-H_b), 1.42 (m_C, 1H, 1'-H_a), 1.49 (ddddd, J = 4.0, 4.0, 3.7, 6.2 and 13.9 Hz, 1H, 12-H), 1.57 (m_C, 1H, 3-H_b), 1.72 (ddddd, J = 3.6, 5.2, 7.9, 9.5 and 14.4 Hz, 1H, 3-H_a), 2.29 (ddd, J = 3.7, 8.1 and 14.4 Hz, 1H, 2-H_b), 2.40 (ddd, J = 3.5, 9.6 and 14.4 Hz, 1H, 2-H_a), 4.75 (qd, J = 6.2 and 9.6 Hz, 1H, 13-H); minor diastereomer δ 5.12 (dq, J = 3.1 and 6.6 Hz, 1H, 13-H, 1.0%, 98%de); ^{13}C NMR ($CDCl_3$, ppm) δ 10.29 (q, C-2'), 18.98 (q, C-14), 21.28 / 21.45 (t, C-1', C-10), 23.79 (t, C-3), 26.67 / 26.04 / 25.77 / 25.53 (2C) / 24.50 / 24.45 (t, C-4 - C-9, C-11), 34.46 (t, C-2), 43.31 (d, C-12), 73.17 (d, C-13), 173.68 (s, C-1); MS (EI, %) m/z 254 (11) [$M^{\oplus}$], 225 (7) [$M^{\oplus}$ - C_2H_5], 210 (100) [$M^{\oplus}$ - CO_2], 167 (17) [$M^{\oplus}$ - $C_5H_{11}O$]; $[\alpha]_D^{20}$ +36.0, $[\alpha]_{546}^{20}$ +42.5 (c 2.2, $CHCl_3$); Anal calcd for $C_{16}H_{30}O_2$ (254.4), C 75.54, H 11.88; found C 75.50, H 11.80.

(12R,13S)-(+)-12-Methyl-13-pentadecanolide (14d). Scale 1.49 mmol of **13d**, yield 81% (308 mg), hR_f 44 (*n*-pentane:Et_2O, 20:1); IR (film, cm^{-1}) $\tilde{\nu}$ 1731 (s, ν C=O, lactone), 1246 (s, ν C-CO-O, lactone); ^{1}H NMR ($CDCl_3$, ppm) δ 0.87 (d, J = 6.8 Hz, 3H, 12-Me), 0.87 (t, J = 7.4 Hz, 3H, 15-H_3), 1.20 - 1.53 (m, 17H, 4-H_2-11-H_2 and 3-H_b), 1.49 (m_C, 1H, 14-H_b), 1.63 (m_C, 1H, 12-H), 1.73 (m_C, 1H, 3-H_a), 1.75 (m_C, 1H, 14-H_a), 2.34 (ddd, J = 3.5, 7.8 and 14.6 Hz, 1H, 2-H_b), 2.43 (ddd, J = 3.3, 10.1 and 14.6 Hz, 1H, 2-H_a), 4.66 (ddd, J = 3.5, 7.4 and 9.8 Hz, 1H, 13-H); minor diastereomer δ 4.74 (ddd, J = 3.1, 4.4 and 9.4 Hz, 1H, 13-H, 2.0%, 96%de); ^{13}C NMR ($CDCl_3$, ppm) δ 8.78 (q, C-15), 15.54 (q, 12-Me), 22.47 (t, C-14), 23.74 / 23.81 (t, C-3 and C-11), 24.76 / 25.07 / 25.28 / 25.80 / 25.93 / 26.36 / 30.25 (t, C-4 - C-10), 33.94 (t, C-2), 35.10 (d, C-12), 78.83 (d, C-13), 173.98 (s, C-1); MS (EI, %) m/z 254 (23) [$M^{\oplus}$], 225 (17) [$M^{\oplus}$ - C_2H_5], 196 (100) [$M^{\oplus}$ - C_4H_{10}], 167 (13) [$M^{\oplus}$ - $C_5H_{11}O$]; $[\alpha]_D^{21}$ +25.9, $[\alpha]_{546}^{21}$ +30.7 (c 1.9, $CHCl_3$); Anal calcd for $C_{16}H_{30}O_2$ (254.4), C 75.54, H 11.88; found C 75.59, H 11.84.

Acknowledgement

We wish to thank Dr. H. Surburg and the perfumers of Haarmann & Reimer GmbH, D-37601 Holzminden, for olfactory evaluation. We are also very grateful to Dr. P. Werkhoff for chirospecific GC analyses. We are indebted to Dr. C. Wolff, Universität Kiel, for his kind assistance in NMR assignment problems. B.B. is most grateful to the *Deutsche Forschungsgemeinschaft* (Grant To 28/16-1) for financial support. Additional financial support by the *Fonds der Chemischen Industrie* is also acknowledged with gratitude.

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