116. An Unexpected Asymmetric Reduction of 4-(1-Nitro-2-oxocyclododecyl)butan-2-one. Determination of the Absolute Configuration of (−)-15-Hexadecanolide

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Reduction of the carbonyl group in the side chain of 4-(1-nitro-2-oxocyclododecyl)butan-2-one (**3**) with organoboron complexes are influenced by the chiral center, in 4-position with respect to the carbonyl C-atom, to which the NO_2 group is attached, a rare type for an asymmetric reduction. Independent of the (*R*)- or (*S*)-configuration of the *Alpine-Hydride*, (+)-**3** is reduced *only* to the (15*S*)-nitrolactone (+)-**5** and, after subsequent transformations, to (+)-(*S*)-15-hexadecanolide ((+)-**1**), enantiomer of the naturally occurring (−)-**1**.

Introduction. – Besides other macrocyclic compounds, (−)-15-hexadecanolide ((−)-**1**; $[\alpha]_D^{20} = -16.5$, $CHCl_3$) was isolated from *Galbanum* oleo-gum-resin, a commercial product which is obtained from *Ferula galbaniflua* BOISSIER *et* BUHSE and *F. rubicaulis* BOISSIER [1]. The 15-hexadecanolide was first isolated from galbanum gum-resins by *Naves* [2] who also described its first synthesis starting from (+)-15-hydroxypalmitic acid[2]). The absolute configuration of the natural (−)-**1** remained unknown. In this paper, we will establish it as (*R*).

Besides the synthesis mentioned above, several other syntheses of lactone **1** has been reported. The methods were based either on ring closure [2] [3] or on ring enlargement [1] [4] [5]. In all cases, the racemate was obtained. Our aim, however, was to synthesize the optically active 15-hexadecanolide. We tried two different routes: asymmetric methylation of 3-(1-nitro-2-oxocyclododecyl)propanal [5] ((±)-**2**; *Scheme 1*) and asymmetric reduction of 4-(1-nitro-2-oxocyclododecyl)butan-2-one ((±)-**3**; *Scheme 2*). In both cases, the resulting alcohol required rearrangement and removal of the NO_2 group.

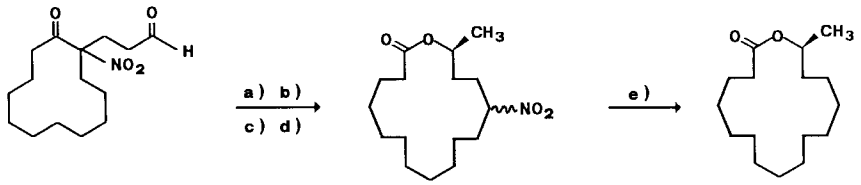
Results and Discussion. – In our first published synthesis of 15-hexadecanolide ((±)-**1**) the aldehyde (±)-**2** was used as starting material [5]. This compound was methylated with $(i\text{-}PrO)_3MeTi$ in order to obtain the secondary alcohol (±)-**4**. Under the influence of Bu_4NF in THF, (±)-**4** underwent a ring-enlargement reaction to give the nitrolactone (±)-**5** (*Scheme 1*) [5].

For the enantioselective Me addition to the aldehyde **2**, we tried to use an optically active Ti reagent. *Seebach et al.* [6] proposed, that the 'secondary alcohols without aromatic groups on the carbinol centre have so far been obtained in highest optical activities using the acetonide **6** for Me group transfer to aliphatic aldehydes'. For

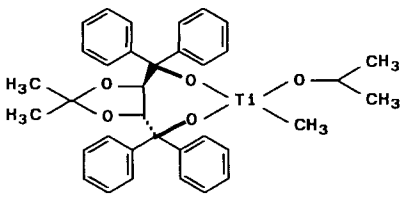
[1]) Part of the planned Ph. D. thesis of *St. St.*, guest from the Bulgarian Academy of Sciences, Sofia.

[2]) In [2], optical rotation of the natural product was not indicated. It is not clear, whether the author compared the synthetic and the natural product on the basis of spectroscopic, chromatographic, and chiroptical data.

Scheme 1



(±)-**2** (+)-**5** (63%) (+)-**1** (47%)



6

a) Isopropoxy(methyl)[(2*R*,3*R*)-1,1,4,4-tetraphenyl-2,3-(isopropylidenedioxy)butan-1,4-dioxy]titanium (**6**), Et_2O, 3 h, −30°.
b) 20% KF/H_2O.
c) Silica-gel chromatography.
d) Bu_4NF, THF, 1 h, 20°.
e) Bu_3SnH, AIBN, toluene, reflux.

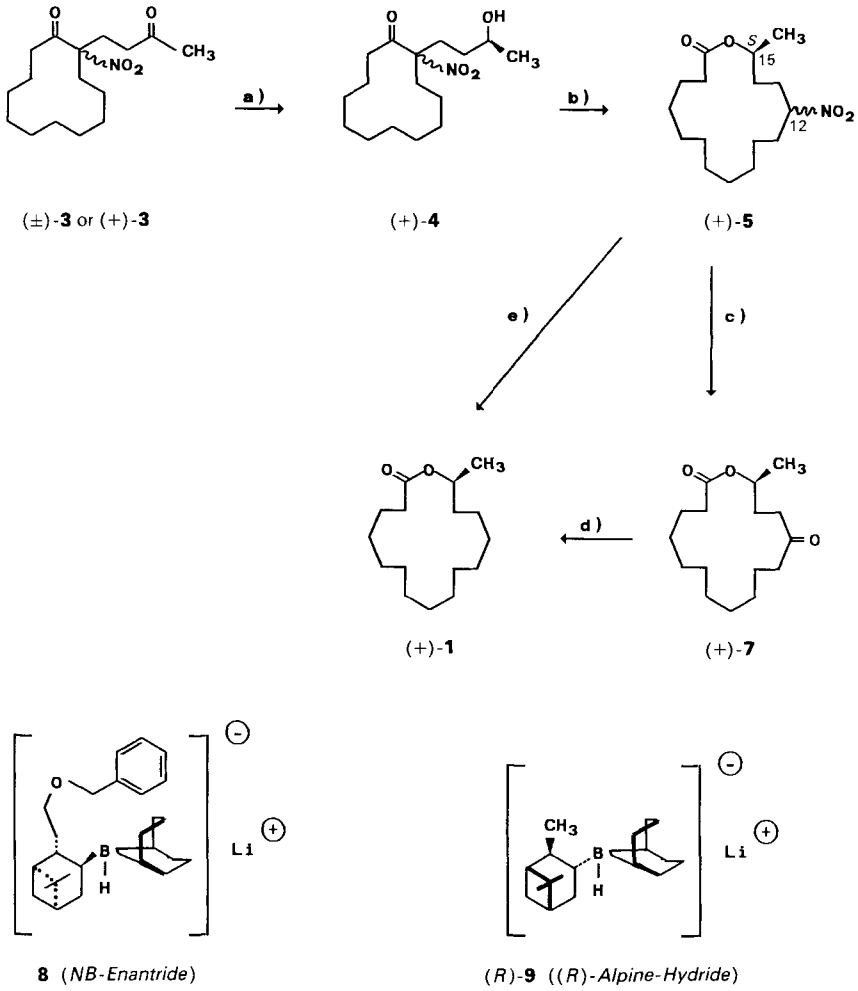
example, reaction of hexanal with **6** led to the corresponding (*S*)-alcohol in 67% yield and with 83% ee [6]. By treatment of our (±)-**2** with the optical active Ti reagent **6**, under several different reaction conditions (see *Exper. Part*), the highest yield of (+)-**5** achieved was 63%[3]) (8.5% ee[4]); *Scheme 1*). The absolute configuration of (+)-**5** is (*S*) (see below); the same absolute configuration was established for the methylated products obtained from a number of different aliphatic aldehydes when using the same chiral reagent **6** [6]. Due to the low ee values observed, we did not perform any further experiments with optically active Ti reagents.

In the second approach for the synthesis of the optically active 15-hexadecanolide ((+)-**1**), ketone (±)-**3**, prepared by *Michael* reaction of 2-nitrocyclododecanone with methyl vinyl ketone, was subjected to asymmetric reduction *(Scheme 2)*. The regiospecific reduction of the side-chain C=O group in (±)-**3** was expected when using $NaBH_4$ [7] or boranes. Indeed, treatment of (±)-**3** with $NaBH_4$/MeOH led to the secondary alcohol (±)-**4** and its ring-enlargement product (±)-**5**, the yield of (±)-**5** with respect to (±)-**4** being 88%[5]) (see the *Table, Entry A*).

Stimulated by these results, we attempted the reduction of (±)-**3** with chiral organoboron reagents. *Brown et al.* [9] have published a critical examination of various reducing agents for the asymmetric reductions of different classes of ketones. On the basis of these investigations and of the experiences of other authors [10], we decided to use *NB-Enan-*

[3]) For comparison, methylation of (±)-**2** with $(i\text{-PrO})_3MeTi$ gave (±)-**5** in 83.5% yield [5].
[4]) The enantiomeric excess (ee) was calculated after (+)-**5** was transformed to (+)-**1**. The $[\alpha]_D$ values of (+)-**1** were compared with those of the natural (−)-**1** [1].
[5]) By TLC, no (±)-**3** was detectable in the product mixture; some ketolactone **7** was found, *cf.* [5].

Scheme 2



a–d) See *Entries B* and *D–G* in the *Table*. e) Bu_3SnH, AIBN, toluene, reflux.

tride[6]) (**8**) [11] as well as (*S*)- and (*R*)-*Alpine-Hydride*[6]) ((*S*)- and (*R*)-**9**, resp.) [12] as reducing agents (*Scheme 2*). Treatment of (±)-**3** with (*S*)-**9** in THF at −78° gave, in 82% yield, the ring-enlargement product (+)-**5**[7]). The yield, but not the enantiomeric excess (*ca.* 15%), is temperature-dependent (78% at −55° and 65% at −30°). As shown later, the absolute configuration at the new chiral center C(15) of (+)-**5** is (*S*). From the reduction of (±)-**3** with (*R*)-**9**, (−)-**5** resulted in a somewhat lower chemical (72 *vs.* 82%) but higher optical yield (see the *Table*). These differences in yields can be explained in terms of

[6]) *NB-Enantride* and *S*- and *R-Alpine-Hydride* are trade names of *Aldrich Chemical Company*.

[7]) The reduction product (±)-**4** was only isolated, when $NaBH_4$ was used. In all other cases, the ring-enlarged product **5** was formed directly.

Table. *Chemical Yields and Enantiomeric Excess of* **5** *Obtained by Asymmetric Reduction of* **3** *Followed by Ring Enlargement*

Ketone	*Entry*[a])	Reducing agent	Product	Yield [%][b])	ee from $[\alpha]_D$[c])	ee from ^{1}H-NMR[d])	Configuration at C(15)
(±)-**3**	*A*	$NaBH_4$	(±)-**5**	88	–	–	–
	B	(*S*)-**9**	(+)-**5**	82	15	15.5	(*S*)
	C	(*R*)-**9**	(−)-**5**	72	24	18.8	(*R*)
	D	**8**	(+)-**5**	85	10	10.3	(*S*)
(+)-**3**	*E*	$NaBH_4$	(+)-**5**	84	14	–	(*S*)
	F	(*S*)-**9**	(+)-**5**	76	74	74.3	(*S*)
	G	(*R*)-**9**	(+)-**5**	40	45	45.5	(*S*)

[a]) *A:* a) $NaBH_4$, MeOH, 4 h, 0°, 91%. b) Bu_4NF, THF, 15 min, 20°, 97%.
B: a) and b) (*S*)-**9**, THF, 2 h, −78°; $HOCH_2CH_2NH_2$, 1 h, 20°, 82%. c) NaOMe, MeOH, 15 min, 20°, NaOAc, $TiCl_3$, 1.5 h, 20°, 85%. d) NH_2NHTs, MeOH, 1 h, reflux, $(Ph_3P)_2CuBH_4$, $CHCl_3$, 4 h, reflux, 78%.
C: a) and b) (*R*)-**9**, THF, 2 h, −78°; $HOCH_2CH_2NH_2$, 1 h, 20°, 72%. e) Bu_3SnH, AIBN, toluene, 40 min, reflux, 47%.
D: a) and b) **8**, THF/Et_2O/pentane 4:1:1, 1 h, −100°; $HOCH_2CH_2NH_2$, 1 h, 20°, 85%. c) NaOMe, MeOH, 15 min, 20°; NaOAc, $TiCl_3$, 1.5 h, 20°, 85%. d) Zn, Et_2O, HCl, 2.5 h, 0°, 86%.
E: a) $NaBH_4$, MeOH, 4 h, 0°, 89%. b) Bu_4NF, THF, 15 min, 20°, 94%. c) NaOMe, MeOH, 15 min, 20°; NaOAc, $TiCl_3$, 1.5 h, 20°, 75%.
F: a) and b) (*S*)-**9**, THF, 2 h, −78°; $HOCH_2CH_2NH_2$, 1 h, 20°, 76%. e) Bu_3SnH, AIBN, toluene, 40 min, reflux, 49%.
G: a) and b) (*R*)-**9**, THF, 2 h, −78°; $HOCH_2CH_2NH_2$, 1 h, 20°, 39%. e) Bu_3SnH, AIBN, toluene, 40 min, reflux, 45%.

[b]) In some experiments, the reduction product **4** was accompanied by the rearrangement product **5**. To compare chemical yields, all products and product mixtures were rearranged to **5**.

[c]) Because of its diastereoisomeric nature, (+)-**5** was converted to (+)-**1**; thus, the ee values refer to (+)-**1**. Only in case of *Entry E*, the ee value refers to (+)-**7**. The %-ee values were determined by comparison of the $[\alpha]_D$ values of the product and those of (−)-**1**.

[d]) The enantiomeric purities of **1**[c]) were determined by ^{1}H-NMR measurements (400 MHz, $CDCl_3$) of the CH_3–C(15) signal, using [Eu(hfc)$_3$] as chiral shift reagent.

[e]) The optical purity of (+)-**3** was > 95% (^{1}H-NMR measurement [8]).

experimental fluctuations. Finally, reduction of (+)-**3** with **8** afforded (+)-**5** in 85% yield (10% ee).

In all cases discussed, the boron complex was destroyed by use of 2-aminoethanol before workup. Under these conditions, only **5** was formed. Usual oxidative workup ($NaOH/H_2O_2$) gave a mixture of **5**, the *Nef*-reaction product **7**, and ring-opened compounds of unknown structures.

Compound (+)-**5** contains two chiral centers, C(12) and C(15). On ring enlargement, the sense of chirality of the center bearing the NO_2 group (C(12) in (+)-**5**) has changed to an unknown extent. Thus, the stereoselectivity for the asymmetric reduction of the side-chain C=O group in (±)-**3** could not be determined from the diastereoisomeric mixture (+)-**5**. Accordingly, the mixture (+)-**5**[8]) had to be converted to the enantiomer (+)-**1**; *i.e.* all ee values given in the *Table* are calculated by comparison with the optically pure (−)-**1**. For the transformation of (+)-**5** to 15-hexadecanolide ((+)-**1**), Bu_3SnH reduction of the NO_2 group was used [13] *(Scheme 2)*. Applying modified *Nef*-reaction conditions, (+)-**5** afforded (+)-**7** which, by standard procedures was also converted to (+)-**1** (see *Exper. Part*).

[8]) The diastereoisomeric mixture (+)-**5** was separated into two compounds by HPLC (see *Exper. Part*).

In a second series of reactions, the pure enantiomer (+)-**3**[9]) (> 95% optical purity [8]) was reduced with different boron reagents (see the *Table*). Reduction of (+)-**3** with $NaBH_4$ gave a mixture of (+)-**4** (78% yield) and (−)-**5** (11%), which were separated by crystallization. Compound (+)-**4** was transformed to (+)-**5** (14% ee) under usual conditions. Due to the small amount obtained, (−)-**5** was not further investigated. The results of the two other reductions (*Entries F* and *G*) are remarkable. Reduction of (+)-**3** with (*S*)-**9** gave (+)-**5** in nearly the same yield as in *Entry B*, but the ee was much higher (74%). Reduction of (+)-**3** with (*R*)-**9** led also to (+)-**5** in lower yield (40%) and 45% ee, implying that the chiral center created on reduction (C(15) in (+)-**5**) has the same absolute configuration, independent of the chirality of the *Alpine-Hydride*. Thus, the chirality of this center is engraved only by the chirality of the quaternary chiral center in (+)-**3**!

The chemical yield of the reduction of (+)-**3** with (*R*)-**9** is characteristically lower than that observed with the corresponding (*S*)-**9**, implying that, in the formation of the diastereoisomeric complexes, (*R*)-*Alpine-Hydride*/(+)-**3** and (*S*)-*Alpine-Hydride*/(+)-**3**, the latter one is preferred. This observation is in agreement with results on a related reaction published by *Midland et al.* [14]. They observed, for example, that, after 3 days, the reduction of (+)-carvone with (*R*)-*Alpine-Borane* was more than 90% complete, whereas 'the reduction of (−)-carvone showed no significant progress after 5 days'. However, in contrast to our results, these authors have shown that, by reduction of chiral ketones, the influence of the remote chiral center on the optical purity is very strongly dependent on the distances between the two centers: already for 3-methylcyclohexanone with a 1,3-arrangement, they observed no enantiomeric excess anymore.

On reduction of (+)-**3** with (*S*)-**9**, we obtained the nitrolactone (+)-**5** with (15*S*)-configuration (see below). On reduction of aliphatic ketones with (*R*)-**9**, (*R*)-configurated alcohols were formed [12]. Thus, it was unexpected that, in our case, the reduction of (+)-**3** with (*R*)-**9** would also lead to the (+)-**5** with (15*S*)-configuration. This observation can be explained in terms of the strong polar nature of the NO_2 group. As mentioned above, the configuration of the new chiral center (C(15) in (+)-**5**) depends only on the chirality of the quaternary C-atom in **3**, bearing the NO_2 group (see the *Table*). The models indicate that the reduction of (+)-**3** with the selected borohydrides would yield, independently of their configuration, predominantly (+)-**5** with (15*S*)-configuration, implying that the complex between the NO_2 group and the B-atom is more important than that of the reagent with the C=O group in determining the sense of chirality of the new chiral center.

Determination of the Absolute Configuration of (−)-15-Hexadecanolide ((−)-1). – The following arguments support the (*R*)-configuration of the naturally occurring (−)-**1**: *i)* It was demonstrated that, by methylation of aliphatic aldehydes with the chiral Ti reagent **6**, the resulting alcohols possess (*S*)-configuration [6]. As illustrated in *Scheme 1*, methylation of the nitro-aldehyde (±)-**2** with the same reagent **6** afforded (+)-**5** which was converted to (+)-**1**. Hence, (+)-**1** should be (*S*)-configurated. *ii)* Reduction of aliphatic ketones such as butan-2-one with (*R*)-**9** gave alcohols with (*R*)-configuration ((−)-(*R*)-butan-2-ol; 29% ee) [12] and with **8** those with (*S*)-configuration ((+)-(*S*)-butan-2-ol; 76% ee) [11]. On reduction of the 4-substituted butan-2-one derivative (±)-**3** with (*S*)-**9** and **8**, we observed (*S*)-configuration at C(15) in (+)-**5**, and with (*R*)-**9** (*R*)-configuration. *iii)* Similar reductions were carried out with the 6- and 10-membered analogues of

[9]) So far, it was not possible to prepare (−)-**3**.

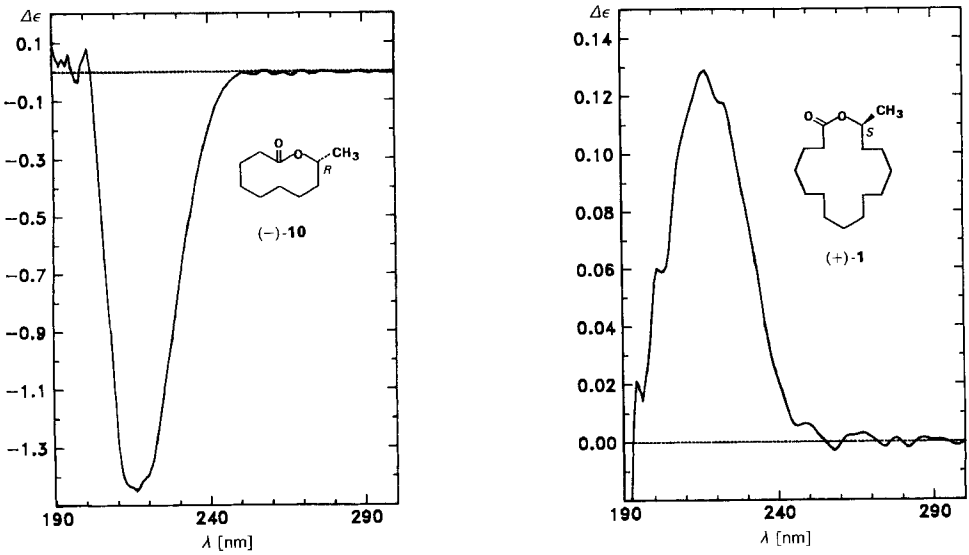


Fig. *CD Spectra* (MeCN) *of (−)-(R)-phoracantolide I* ((−)-**10**) *and (+)-(S)-15-hexadecanolide* ((+)-**1**)

(±)-**3**. The ring-enlargement products were homochiral to (+)-**1** and correlated with natural products of known absolute configuration [8]. *iv)* The CD spectra of (+)-15-hexadecanolide ((+)-**1**) and that of synthetic (−)-(*R*)-phoracantholide I ((−)-**10**) in MeCN solution show a good mirror relationship (see the *Fig.*), both having the *Cotton* effect at 216 nm. Therefore, the absolute configuration of (+)-**1** is established as (*S*). In addition to our observations, similar results from chiral 12-tridecanolides were published by *Meyers et al.* [15].

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Experimental Part

General. See [16]. All solvents and reagents are from *Fluka*, except (*S*)- and (*R*)-*Alpine-Hydride*®[6] (= (*R*)-lithium β-isopinocamphenyl-9-borabicyclo[3.3.1]nonyl hydride) as 0.5M soln. in THF, *NB-Enantride*[6] (= lithium 9-borabicyclo[3.3.1]nonyl hydride nopol benzyl ether adduct) as 0.5M soln. in THF, and tris[3-(heptafluoropropylhydroxymethylidene)-*d*-camphorato]europium(III) ([Eu(hfc)$_3$]), and were used without further purification, except THF which was distilled over $LiAlH_4$ before use. AIBN = 2,2′-azobis(isobutyronitrile) (= 2,2′-dimethyl-2,2′-azobis[propanenitrile]). All reactions involving air-sensitive reagents or organometallics were done under N_2. All glassware for reactions was dried in an oven overnight at 125° and cooled under a stream of dry N_2. Temp. of 0°: ice/water bath; of −78°: acetone/dry ice bath; of −100°: Et_2O/dry ice bath; of −20 to −60°: cryostat *Cryocool CC-100 II.* All isolated compds. were identified by GC and TLC comparison with authentic material. Chromatography: *Merck Lobar* pre-packed column, size *B* (310-25), *LiChroprep*® *Si 60* (40–63 μm); FC = flash chromatography. Optical rotations: *Perkin-Elmer-241* polarimeter; in $CHCl_3$. CD spectra: *JASCO J-500A.* Determination of ee by ^{1}H-NMR: observation of the lanthanide-shifted Me group of **1**; *Bruker AM 400* (400 MHz) spectrometer; in $CDCl_3$; molar ratio [Eu(hfc)$_3$]/**1**, from 1:1.25 to 1:1.40.

1. *Lactone* (+)-**1** *by Methylation of Aldehyde* (+)-**2**. 1.1. *(+)-12-Nitro-15-hexadecanolide* ((+)-**5**). To a stirred soln. of 2 mmol of isopropoxy(methyl)[(2*R*,3*R*)-1,1,4,4-tetraphenyl-2,3-(isopropylidenedioxy)butane-1,4-

dioxy]titanium (**6**) [17] in 30 ml of Et_2O at −30°, 283 mg (1 mmol) of (±)-**2** [5] [18] in 10 ml of Et_2O were added within 10 min and stirred at −30° for 3 h. Then, the mixture was hydrolyzed with 20% aq. KF soln. and extracted with CH_2Cl_2, the extract dried and evaporated, and the crude product purified by FC (hexane/Et_2O 3:1): 50 mg of (+)-**5** (16%) and 185 mg of (+)-**5**/*2-nitro-2-(3-hydroxybutyl)cyclododecanone* (**4**). The mixture was treated with 0.5 mol-equiv. of Bu_4NF in 5 ml of dry THF, for 1 h at 20° (rearrangement complete). Purification on a *Lobar* column gave 190 mg (63%) of (+)-**5**. $[\alpha]_D^{22} = +1.56$ ($c = 1.23$).

Results obtained using different ratios: (±)-**2**/**6** 1:1.5 (mol-equiv.), 20% (+)-**5** ($[\alpha]_D^{22} = +2.79$ ($c = 1.12$)); (±)-**2**/**6** 1:1, 9% (+)-**5** ($[\alpha]_D^{22} = +4.13$ ($c = 1.21$)).

1.2. *(+)-(S)-15-Hexadecanolide* ((+)-**1**). To a soln. of 1.33 ml (5 mmol) of Bu_3SnH in 2 ml of toluene under reflux, 135 mg (0.8 mmol) of AIBN and 270 mg (0.9 mmol) of (+)-**5** ($[\alpha]_D^{22} = +1.56$) in 5 ml toluene were added within 30 min. Then, the mixture was refluxed for additional 10 min and passed through a short silica-gel column and evaporated. The crude product was purified on a *Lobar* column (hexane/Et_2O 99:1): 110 mg (47%) of (+)-**1** as colourless oil. $[\alpha]_D^{22} = +1.41$ ($c = 2.02$); 8.5% ee.

2. *Lactone* (+)-**1** *by Reduction with Borohydrides.* 2.1. *(±)-4-(1-Nitro-2-oxocyclododecyl)butan-2-one* ((±)-**3**). According to [19], (±)-**3** was synthesized from 2-nitrocyclododecanone [18]. Colourless crystals (93%). M.p. 149.5–150° (EtOH). IR: 2935, 2870, 1723, 1540, 1470, 1445, 1410, 1350, 1165. IR (KBr): 2940, 2910, 2860, 2850, 1728, 1718, 1538, 1470, 1435, 1410, 1165. ^{1}H-NMR: 2.89–2.73 (*m*, 2 H); 2.55–2.01 (*m*, 11 H); therein at 2.14 (*s*, CH_3); 1.48–0.94 (*m*, 14 H). ^{13}C-NMR: 205.8 (*s*, C(2′)); 200.9 (*s*, C(2)); 100.1 (*s*, C(1′)); 37.3, 32.6, 30.4, (3 *t*); 29.9 (*q*, CH_3); 26.9, 26.3, 26.2, 23.2, 22.5, 21.9, 21.8, 21.3, 19.1 (9 *t*). CI-MS: 298 ($[M + 1]^+$). Anal. calc. for $C_{16}H_{27}NO_4$ (297.400): C 64.62, H 9.15, N 4.71; found: C 64.44, H 9.17, N 4.55.

2.2. *Reductions with $NaBH_4$.* 2.2.1. *Reduction of (±)-3.* To a stirred soln. of 297 mg (1 mmol) of (±)-**3** in 80 ml of MeOH at 0°, 23 mg (0.6 mmol) of $NaBH_4$ were added in small portions within 2 h. After additional 2 h stirring at 0° (reaction complete), the mixture was acidified (pH *ca.* 1) with 0.5% HCl soln. and extracted with Et_2O. The org. extracts were washed with brine, dried, and evaporated. The crude product was crystallized from Et_2O/hexane 7:1: 239 mg (80%) of (±)-**4** as colourless crystals. M.p. 73.5–75.5°. IR: 3618, 2935, 2870, 1728, 1542, 1470, 1445. IR (KBr): 3560, 2930, 2870, 1725, 1538, 1740, 1450, 1350, 1130. ^{1}H-NMR (diastereoisomeric mixture): 3.88–3.72 (*m*, H–C(3′)); 2.96–2.74 (*m*, H–C(2′)); 2.45–2.00 (*m*, 7 H); 1.60–0.82 (*m*, 20 H, therein at 1.38 (*s*, OH, exchangeable with D_2O) and at 1.21, 1.20 (2*d*, $J_1 = J_2 = 6.2$, CH_3)). ^{13}C-NMR (diastereoisomeric mixture): 201.5 (*s*, C(1)); 101.1, 100.9 (2 *s*, C(2)); 67.4, 67.3 (2 *d*, C(3′)); 32.3, 32.27, 32.2, 32.1, 29.4, 29.2, 29.1, 28.6, 26.3 (2 C), 26.2 (2 C) (10 *t*); 23.7, 23.3 (2 *q*, CH_3); 23.2 (2 C), 22.5 (2 C), 21.9 (2 C), 21.3 (2 C), 19.0, 18.9 (6 *t*). CI-MS: 300 ($[M + 1]^+$). Anal. calc. for $C_{16}H_{29}NO_4$ (299.409): C 64.18, H 9.76, N 4.67; found: C 64.33, H 9.47, N 4.87.

FC (hexane/Et_2O 12:1) of the mother liquor gave 30.6 mg (10.2%) of (±)-**5** and 11.5 mg (4.2%) of *12-oxo-15-hexadecanolide* ((±)-**7**).

2.2.2. *Reduction of (+)-3.* The reduction of 297 mg (1 mmol) of (+)-**3** [8] ($[\alpha]_D^{22} = +84.5$ ($c = 1.48$); 95% ee) with 23 mg of $NaBH_4$ following *2.2.1* gave, after crystallization (hexane/Et_2O 7:1), 228 mg (76%) of (+)-**4**. M.p. 88.5–90.5° $[\alpha]_D^{22} = +97.0$ ($c = 1.92$).

The mother-liquor was purified on a *Lobar* column (hexane/Et_2O 18:1): 33 mg of (−)-**5** (fast running; $[\alpha]_D^{22} = -6.87$ ($c = 1.08$)) and 6.8 mg of **7**.

2.3. *Reduction with Optically Active Borohydrides.* 2.3.1. *General Procedure.* To a stirred soln. of 1 mmol of **3** in 10 ml of dry THF at −78°, 2.2 ml (1.1 mmol) of the corresponding reducing agent (0.5M soln. in THF, cooled to −78° for 10 min) were added. The mixture was stirred at −78° for 2 h, then the excess hydride destroyed by addition of 0.1 ml of EtOH and, at 0°, 1.5 mmol of 2-aminoethanol. The resulting mixture was stirred for 1 h at 20°, the solvent evaporated, and the residue purified by FC (hexane/Et_2O 12:1), followed by *Lobar* column chromatography (hexane/Et_2O 20:1).

2.3.2. *Reduction of (±)-3 with (S)-9.* Following *2.3.1*, 2.079 g (7 mmol) of (±)-**3** gave 1.723 g (82%) of (+)-**5**, colourless oil. B.p. 160°/0.02 Torr. $[\alpha]_D^{22} = +2.22$ ($c = 1.25$). IR: 2940, 2870, 1728, 1545. IR (film): 2930, 2860, 1730, 1550. ^{1}H-NMR (diastereoisomeric mixture): 5.11–4.88 (*m*, H–C(15)); 4.60–4.39 (*m*, H–C(12)); 2.35, 2.31 (2 *t*, $J_1 = 6.2$, $J_2 = 8.2$, 2 H–C(2)); 2.07–1.18 (*m*, 25 H), therein at 1.23 (*d*, $J = 6.4$, CH_3). ^{13}C-NMR (diastereoisomeric mixture): 173.4, 173.3 (2 *s*, C(1)); 87.7, 86.4 (2 *d*, C(12)); 70.4, 68.6 (2 *d*, C(15)); 34.8, 34.3, 33.0, 32.6, 32.1, 31.2, 28.8, 27.8, 27.6, 27.5, 27.2, 26.7, 26.5, 26.1, 25.8, 25.6 (2 C), 25.4, 25.2, 24.9, 24.6, 23.1, 23.0 (22 *t*); 20.6, 19.8 (2 *q*, CH_3). CI-MS: 300 ($[M + 1]^+$). Anal. calc. for $C_{16}H_{29}NO_4$ (299.420): C 64.18, H 9.76, N 4.68; found: C 64.27, H 9.91, N 4.60.

This reduction, carried out at −55 and −30°, gave (+)-**5** in 78 ($[\alpha]_D^{22} = +2.36$ ($c = 1.27$)) and 65% yield ($[\alpha]_D^{22} = +1.32$ ($c = 1.59$)), resp.

2.3.3. *Reduction of (±)-3 with (R)-9.* Following *2.3.1*, 891 mg (3 mmol) of (±)-**3** were converted to 646 mg (72%) of (−)-**5**. $[\alpha]_D^{22} = -3.62$ ($c = 1.33$).

2.3.4. *Reduction of (±)-***3** *with* **8**. To a stirred soln. of 743 mg (2.5 mmol) of (±)-**3** in 24 ml of THF/Et_2O/pentane 4:1:1 at −100°, 5.5 ml (2.75 mmol) of **8** (0.5M in THF) were added at −80° within 10 min. The mixture was stirred at −100° for 1 h, and at 0°, 0.1 ml of EtOH were added, followed by 0.22 ml (3.75 mmol) of 2-aminoethanol. Stirring was continued at 20° for 1 h. After evaporation, the crude product was chromatographed (FC, hexane/Et_2O 10:1, followed by a *Lobar* column (hexane/Et_2O 20:1)): 634 mg (85%) of (+)-**5** as colourless oil. $[\alpha]_D^{22} = +1.36$ ($c = 1.48$). Anal. calc. for $C_{16}H_{29}NO_4$ (299.420): C 64.18, H 9.76, N 4.68; found: C 64.36, H 10.07, N 4.32.

2.3.5. *Reduction of (+)-***3** *with (S)-***9**. Following *2.3.1*, 299 mg (1 mmol) of (+)-**3** (95% ee) were reduced to 228 mg (76%) of (+)-**5**. $[\alpha]_D^{22} = +8.86$ ($c = 1.40$).

2.3.6. *Reduction of (+)-***3** *with (R)-***9**. Following *2.3.1*, 386 mg (1.3 mmol) of (+)-**3** were converted to 155 mg (40%) of (+)-**5**. $[\alpha]_D^{22} = +5.34$ ($c = 0.58$).

2.4. *Rearrangement of (+)-***4** *to (+)-***5**. To a stirred soln. of 110 mg (0.36 mmol) of (+)-**4** ($[\alpha]_D^{22} = +97.00$) in 10 ml of dry THF, 50 mg (0.18 mmol) of Bu_4NF in 0.7 ml of THF were added at 20°. After 15 min (reaction complete), the mixture was passed through a short silica-gel column. The crude product was purified on a *Lobar* column (hexane/Et_2O 18:1): 104 mg (94%) of (+)-**5**. Colourless oil. $[\alpha]_D^{22} = +2.31$ ($c = 5.14$).

2.5. *Resolution of a Diastereoisomeric Mixture of (+)-***5**. The separation was performed at r.t. using a *Macherey-Nagel* HPLC column (250 mm × 10 mm i.d.) packed with *Nucleosil 50-7* normal-phase material (7 μm particles), protected by a normal-phase guard column (*MN*). Volumes of 50–100 μl of the soln. of (+)-**5** in the mobile phase (hexane/THF 100:0.5) were injected into the column (flow rate 8 ml/min, pressure *ca.* 70 bar, UV detection at 238 nm). From *ca.* 110 mg diastereoisomeric mixture (+)-**5** ($[\alpha]_D^{22} = +2.36$), two pure diastereoisomers (GC-controlled) were obtained. The first eluted diastereoisomer: 65 mg, $[\alpha]_D^{22} = +4.96$ ($c = 3.23$). Second diastereoisomer: 32 mg, $[\alpha]_D^{22} = -0.33$ ($c = 1.51$), m.p. 28–30°.

2.6. *(+)-(S)-12-Oxo-15-hexadecanolide* ((+)-**7**). To a stirred soln. of 563 mg (1.88 mmol) of (+)-**5** ($[\alpha]_D^{22} = +2.22$) in 5 ml of MeOH were added 4 ml of 0.5M MeONa in MeOH. After 15 min stirring at 20°, 12 ml of an aq. NaOAc/$TiCl_3$ soln. (6 ml of aq. NaOAc·3 H_2O (6.90 g, 50 mmol) soln. and 6 ml of aq. $TiCl_3$ (1.74 g, 11.8 mmol) soln.) were added, and the mixture was stirred for 1.5 h at 20°. The mixture was acidified (pH *ca.* 1) with conc. HCl soln., extracted several times with CH_2Cl_2, the combined org. layer washed with 5% $NaHCO_3$ soln. and brine, dried, and evaporated. The crude product was chromatographed (hexane/Et_2O 7:1): 430 mg (85%) of (+)-**7** (*S*) as colourless crystals. M.p. 28.5–29°. $[\alpha]_D^{22} = +2.62$ ($c = 1.67$); 15% ee. IR: 2930, 2860, 1715, 1460. IR (KBr): 2930, 2860, 1730, 1715, 1460. ^{1}H-NMR: 5.08–4.92 (*m*, H–C(15)); 2.52 (*t*, $J = 7.4$, 2 H); 2.42–2.26 (*m*, 4 H); 2.00–1.20 (*m*, 21 H), therein at 1.24 (*d*, $J = 6.2$, CH_3). ^{13}C-NMR: 211.1 (*s*, C(12)); 173.4 (*s*, C(1)); 69.7 (*d*, C(15)); 42.1, 38.0, 34.5, 29.5, 27.6, 26.8, 26.7, 26.6, 26.0 (2 C), 24.7, 23.5 (11 *t*); 20.2 (*q*, CH_3). CI-MS: 269 ($[M + 1]^+$). Anal. calc. for $C_{16}H_{28}O_3$ (268.395): C 71.60, H 10.51; found: C 71.31, H 10.32.

Under the same conditions, 670 mg (2.24 mmol) of (+)-**5** from *2.3.4* with $[\alpha]_D^{22} = +1.36$ ($c = 1.48$) was transformed to 512 mg (85%) of (+)-**7**. Colourless crystals. M.p. 28.5–30°. $[\alpha]_D^{22} = +1.60°$ ($c = 2.00$); 10% ee.

Under the same conditions, 75 mg (0.25 mmol) of (+)-**5** from *2.4* ($[\alpha]_D^{22} = +2.31$) gave 50 mg (75%) of (+)-**7** as colourless crystals. M.p. 28.5–29.5°. $[\alpha]_D^{22} = +2.45$ ($c = 1.26$); 14% ee.

2.7. *(+)-(S)-15-Hexadecanolide* ((+)-**1**). 2.7.1. To a stirred soln. of 268 mg (1 mmol) of (+)-**7** ($[\alpha]_D^{22} = +2.61$) in 2 ml of MeOH, 205 mg (1.1 mmol) of $TsNHNH_2$ were added and refluxed for 1 h. The solvent was removed and the resulting oil crystallized (hexane/Et_2O): 430 mg (100%), m.p. 99.5–100°. These crystals were dissolved in 11 ml of $CHCl_3$, 724 mg (1.2 mmol) of $(Ph_3P)_2CuBH_4$ were added, and the mixture was refluxed for 4 h. The solvent was removed, the residue extracted 6 times with hot hexane, the extract evaporated, and the crude product purified by FC (hexane/Et_2O 98:2) and distilled: 198 mg (78%) of (+)-**1** as colourless oil. B.p. 110–115°/0.05 Torr ([5]: 130°/0.06 Torr; [1]: 110–117°/0.05 Torr). $[\alpha]_D^{22} = +2.41$ ($c = 1.66$); 14.6% ee ([1]: $[\alpha]_D^{20} = -16.5$ ($c = 1.03$) for the natural (−)-**1**). IR: 2930, 2860, 1720, 1460. IR (film): 2930, 2860, 1730, 1460. ^{1}H-NMR: 5.06–4.90 (*m*, H–C(15)); 2.36–2.24 (*m*, 2 H–C(2)); 1.78–1.07 (*m*, 27 H), therein at 1.21 (*d*, $J = 6.2$, CH_3). ^{13}C-NMR: 173.7 (*s*, C(1)); 70.6 (*d*, C(15)); 35.9, 34.8, 27.8, 27.5, 27.2 (2 C), 26.7, 26.3, 26.1, 25.7, 25.0, 24.3 (11 *t*); 20.4 (*q*, CH_3). CI-MS: 255 ($[M + 1]^+$). Anal. calc. for $C_{16}H_{30}O_2$ (254.411): C 75.53, H 11.88; found: C 75.30, H 11.63.

2.7.2. To a stirred soln. of 268 mg (1 mmol) of (+)-**7** ($[\alpha]_D^{22} = +1.60$) in 20 ml of Et_2O/HCl (sat. at 0°) [20a], 3 g of activated Zn [20b] were added at 0° for 1 h, and the mixture was stirred at 0° for additional 1.5 h. Then it was poured into ice/H_2O, extracted with Et_2O, the combined org. layer washed with cold 1% $NaHCO_3$ soln. and brine, dried, and evaporated, and the crude product purified on a *Lobar* column (hexane/Et_2O 99.5:0.5): 220 mg (86%) of (+)-**1** as colourless oil. $[\alpha]_D^{22} = +1.74$ ($c = 2.08$); 10% ee. Anal. calc. for $C_{16}H_{30}O_2$ (254.411): C 75.53, H 11.88; found: C 75.68, H 12.14.

2.7.3. To a refluxing soln. of 0.8 ml (3.0 mmol) of Bu_3SnH in 2 ml of toluene, 81 mg (0.48 mmol) of AIBN and 180 mg (0.6 mmol) of (+)-**5** from *2.3.5* ($[\alpha]_D^{22} = +8.86$) in 5 ml toluene were added within 30 min. The mixture was refluxed for additional 10 min, then passed through a short silica-gel column, and the solvent evaporated. The

crude product was purified on a *Lobar* column (hexane/Et_2O 99:1): 75 mg (49%) of (+)-**1** as colourless oil. $[\alpha]_D^{22} = +12.21$ ($c = 0.82$); 74.0% ee.

Under the same conditions as in *2.7.3*, 114 mg (0.38 mmol) of (+)-**5** from *2.3.6* ($[\alpha]_D^{22} = +5.34$) were reduced to 42 mg (44%) of (+)-**1**, colourless oil. $[\alpha]_D^{22} = +7.35$ ($c = 1.02$); 44.6% ee.

3. *(−)-(R)-15-Hexadecanolide* ((−)-**1**). Following the denitration procedure *2.7.3*, 374 mg (1.25 mmol) of (−)-**5** ($[\alpha]_D^{22} = -3.62$) were reduced to 150 mg (47%) of (−)-**1**. $[\alpha]_D^{22} = -4.00$ ($c = 2.42$); 24% ee. By ^{1}H-NMR: 18.8% ee.

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