50. Synthesis of the Enantiomerically Enriched Macrocyclic Lactones (+)-(*S*)- and (–)-(*R*)-Phoracantholide I and (+)-(*S*)-Tetradecan-13-olide

by **Stephan Stanchev**[1]) and **Manfred Hesse***

Organisch-chemisches Institut der Universität Zürich, Winterthurerstrasse 190, CH–8057 Zürich

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Synthesis of two naturally occurring macrocyclic lactones is described. (–)-(*R*)-Phoracantholide I ((–)-**1**; *Scheme 2*) was synthesized by asymmetric and chemoselective reduction of the side-chain C=O group of (–)-4-(1-nitro-2-oxocyclohexyl)butan-2-one ((–)-**6**) with (*R*)-*Alpine-Hydride* (47% ee). It was shown that the formation of only one diastereoisomer of the hemiacetal **5**, by methylation with $(i\text{-PrO})_2TiMe_2$, of ketoaldehyde (–)-**2** is thermodynamically controlled. (+)-(*S*)-Tetradecan-13-olide ((+)-**10**) was obtained by reduction of diketone (±)-**11** with optically active borohydrides followed by denitration (*Scheme 3*).

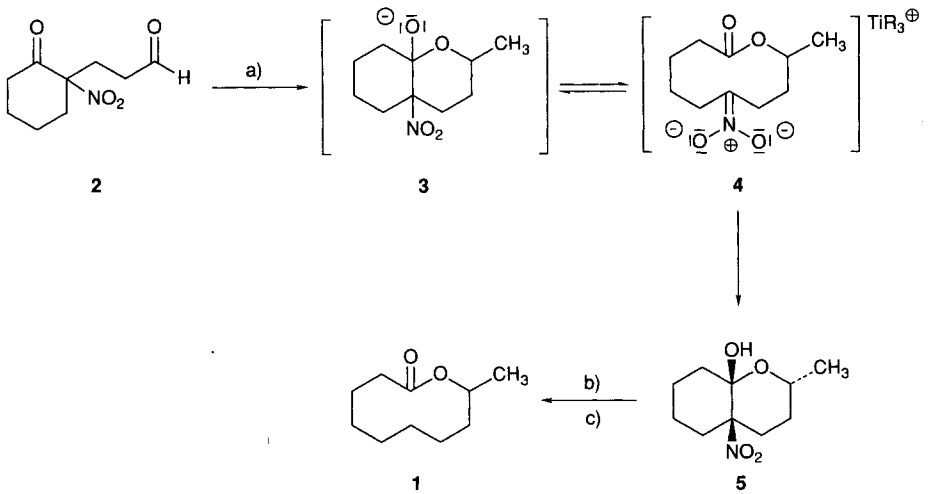
1. Synthesis of (+)-(*S*)- and (–)-(*R*)-Phoracantholide I. – The ten-membered lactone (–)-(*R*)-phoracantholide I ((–)-**1**) [1] was isolated as a defensive secretion from the metasternal gland of the eucalypt longicorn *Phoracantha synonyma* NEWMAN [2]. Several synthetic methods were reported for racemic **1** [3] [4]. Optically active phoracantholide I was synthesized by *Kitahara et al.* [1], starting from ethyl (*S*)-3-hydroxybutyrate; by *Naoshima* and *Hasegawa* [5a] with a key-step asymmetric reduction of 9-oxononanoic acid using immobilyzed baker's yeast, and by *Fouque* and *Rousseau* [5b] using horse-liver-esterase hydrolysis of (±)-**1**.

Now, we wish to report the synthesis of the enantiomerically enriched (–)-(*R*)-phoracantholide I ((–)-**1**) as well as of the not naturally occurring enantiomer (+)-**1** by a ring-enlargement reaction.

The central step in our earlier synthesis of (±)-**1** is the methylation of the aldehyde **2** with $(i\text{-PrO})_2TiMe_2$ [4] (*Scheme 1*). From the reaction mixture, only the hemiacetal (±)-**5** was isolated. The formation of only one diastereoisomer of **5** was surprising, and two explanations were proposed: firstly, the stereoselective methylation of the aldehyde (*cis*- or *trans*-oriented to the NO_2 group), and secondly, the possibility of an equilibrium between hemiacetal **3** and lactone **4** under the influence of the Ti complex or during workup. The most stable isomer crystallized from the solution. It was thought that the repetition of the methylation with the optically resolved aldehyde **2** would distinguish between these possibilities, and eventually open the way to (+)- or (–)-**1**.

[1]) Part of the thesis of *St. St.*, Bulgarian Academy of Sciences, Sofia, Bulgaria; guest of the Institute of Organic Chemistry, University of Zürich.

Scheme 1



2 **3** **4** **1** **5**

a) $(i\text{-PrO})_2TiMe_2$, Et_2O/H_2O. b) Bu_4NF, THF. c) $TiCl_3/NH_4OAc$; $(CH_2SH)_2$, BF_3, Et_2O; *Ra*-Ni, MeOH.

Several transformations, necessary for an optical resolution of **2**, were tried without success: oxidation of **2** with $KMnO_4$ gave the corresponding acid, which could be crystallized as its brucine salt. Hovever, during recrystallization, the salt was hydrolyzed to 4-oxononanedioic acid [6]. In another attempt, the acetal was formed from the ketone C=O group of **2** and (–)-butane-2,3-diol. The product was optically resolved, but after its hydrolysis, the protecting group and the C(1)–C(2) bond were cleaved. The C(1)–C(2) bond in an activated cycloalkanone such as **2** is unstable in the presence of aqueous acids and bases as well as of nucleophiles. Transformations of one of the two C=O groups of **2** into other functions, would, therefore, seem to be difficult.

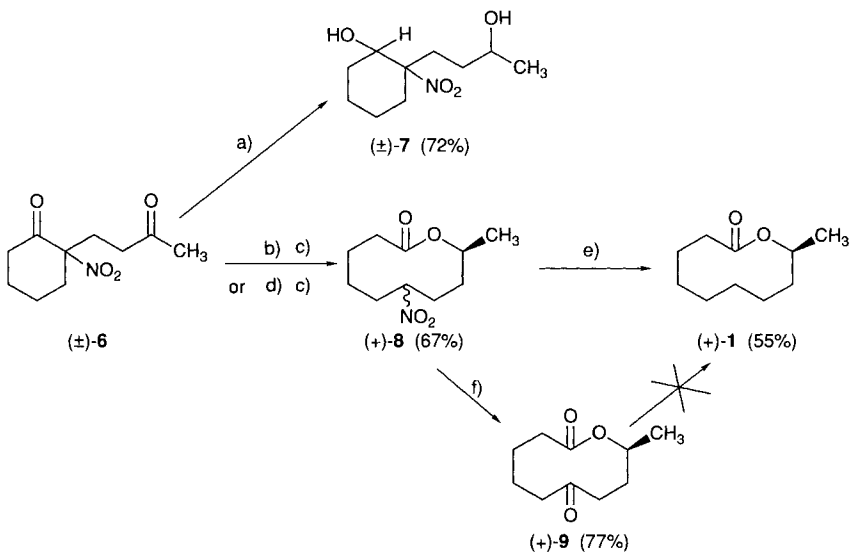
Optically active (–)-**2** (50% ee) was finally prepared by an asymmetric *Michael* addition of 2-nitrocyclohexanone to acrylaldehyde [7b], but only racemic methylation products were observed, when (–)-**2** was reacted with $(i\text{-PrO})_2TiMe_2$ (see *Exper. Part*). From this experiment, it can be concluded that no stereoselective methylation took place with the optically inactive Ti reagent, and that the formation of only one diastereoisomer of **5** is best explained by thermodynamic control.

Optically active phoracantholide I ((+)- and (–)-**1**) was prepared by an asymmetric reduction from 4-(1-nitro-2-oxocyclohexyl)butan-2-one ((±)-**6**; *Scheme 2*). The starting material (±)-**6** was synthesized from 2-nitrocyclohexanone and methyl vinyl ketone. In contrast to the corresponding twelve-membered-ring derivative [7a], the reduction of (±)-**6** with $NaBH_4$ was not chemoselective. Both C=O groups were reduced leading to (±)-2-(3-hydroxybutyl)-2-nitrocyclohexan-1-ol ((±)-**7**; 72%). Reduction of (±)-**6** with optically active borohydrides ((*S*)- and (*R*)-*Alpine-Hydride* as well as *NB-Enantride*)[2]) gave the optically active ring-enlargement products (+)-**8** directly, and reduction of

[2]) *NB-Enantride*™ and (*S*)- and (*R*)-*Alpine-Hydride*® are trade names given by the *Aldrich Chemical Company*.

nitrolactone (+)-**8** with $Bu_3SnH/\alpha,\alpha'$-azobis(isobutyronitrile) (= 2,2'-dimethyl-2,2'-azobis-(propanenitrile); AIBN)[3]) afforded (+)-**1** in 37% overall yield from (±)-**6** (see *Scheme 2* and *Table 1*). It is known [8] that (–)-(*R*)-butan-2-ol is formed by reduction of butan-2-one with (*R*)-*Alpine-Hydride* and (+)-(*S*)-butan-2-ol with *NB-Enantride*. This is in contrast to the formation of (+)-**1** from (±)-**6** with (*S*)-*Alpine-Hydride* and with *NB-Enantride* (24 and 39% ee, respectively).

Scheme 2



a) $NaBH_4$, MeOH, 1.5 h, 0°. b) (*S*)-*Alpine-Hydride*, THF, 2 h, –78°. c) $NH_2CH_2CH_2OH$, 1 h, 20°. d) *NB-Enantride*, THF/Et_2O/pentane 4:1:1, 1 h, –100°. e) Bu_3SnH, AIBN, toluene, reflux. f) NaOMe, MeOH, 15 min, 20°; NaOAc, $TiCl_3$, 1.5 h, 20°.

Applying modified *Nef*-reaction conditions to (+)-**8** afforded (+)-**9** in 77% yield. Attempts to reduce the oxolactone under conditions other than those mentioned in *Scheme 1* [4] failed. Neither the reduction from the corresponding tosylhydrazone with $(Ph_3P)_2CuBH_4$ nor direct reduction of the C=O group with $Zn/Et_2O/HCl$[4]) gave the expected product.

Natural (–)-(*R*)-phoracantholide I ((–)-**1**) was synthesized in 47% ee and 20% overall yield from (–)-**6** [7b] by reduction with (*R*)-*Alpine-Hydride via* denitration of the ring-enlargement product (–)-**8**, as described for (+)-**1** (see *Table 1*). Similar to the reduction of (+)-4-(1-nitro-2-oxocyclododecyl)butan-2-one (see below, (+)-**14**) [7a], the asymmetric reduction of diketone (–)-**6** is strongly influenced by the complex formation between the NO_2 group and the B-atom of the reducing reagent.

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[3]) Although the chemical yield is lower than with other processes [5], the denitration with Bu_3SnH/AIBN/toluene under reflux was used to reduce the number of reaction steps.

[4]) In this experiment, only small quantities of **1**, the product of H_2O elimination, and starting material (±)-**9** were observed.

Table 1. *Chemical Yields and Enantiomeric Excess* (ee) *of Phoracantholide I* (**1**) *Obtained by Asymmetric Reduction of Diketone* **6**

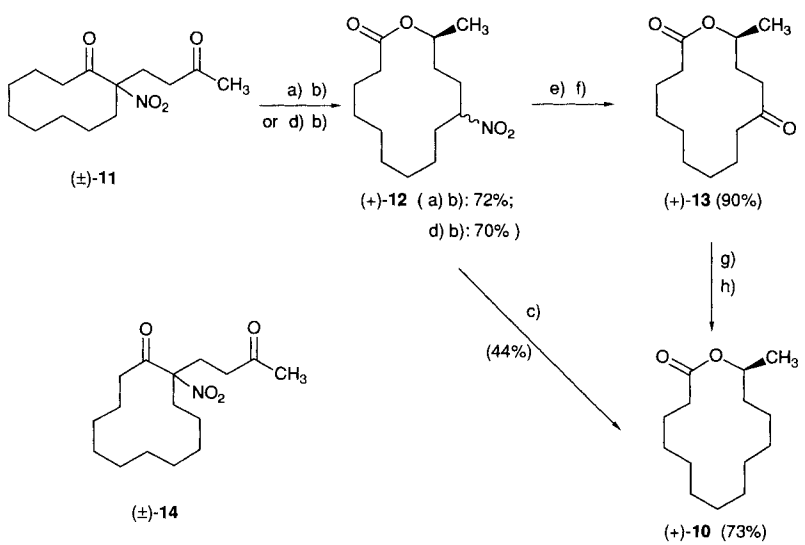
Starting material	Reducing agent	**1**		
		Chemical yield [%]	$[\alpha]_D^{22}$	ee [%][a]
(±)-**6**	*(S)-Alpine-Hydride*	37	+9.4	24
	NB-Enantride	37	+14.4	39
(–)-**6**	*(R)-Alpine-Hydride*	20	–18.5	47

[a]) The ee values were determined by comparison of the $[\alpha]_D$ value of the product with that of the optically pure (–)-**1** ($[\alpha]_D^{22} = -39.4$).

2. Synthesis of (+)-(*S*)-Tetradecan-13-olide ((+)-10). – Besides other macrocyclic compounds, (–)-tetradecan-13-olide ((–)-**10**; $[\alpha]_D^{22} = -34.5$ ($CHCl_3$)) was isolated from *Galbanum* oleo-gum-resin, a commercial product which is obtained from *Ferula galbaniflua* BOISSIER *et* BUHSE and *F. rubicaulis* BOISSIER [9]. Several synthetic methods have been reported for the racemic **10** [9] [10]. The first synthesis of optically active **10** has recently been achieved by *Voss* and *Gerlach* [11] and the (–)-(*R*)-enantiomer confirmed to be the naturally occurring compound.

The synthesis of the (+)-tetradecan-13-olide ((+)-**10**) *via* ring-enlargement reaction is outlined in *Scheme 3*. Reduction of (±)-**11** with *(S)-Alpine-Hydride* at –78° in THF gave

Scheme 3



a) *(S)-Alpine-Hydride*, THF, 2 h, –78°. b) $NH_2CH_2CH_2OH$, 1 h, 20°. c) Bu_3SnH, AIBN, toluene, reflux. d) *NB-Enantride*, THF/Et_2O/ pentane 4:1:1, 1 h, –100°. e) NaOMe, MeOH, 15 min, 20°. f) NaOAc, $TiCl_3$, 1.5 h, 20°. g) $TsNHNH_2$, MeOH, 1 h, reflux. h) $(Ph_3P)_2CuBH_4$, $CHCl_3$, reflux.

the nitrolactone (+)-**12** (72%). After conversion of the NO_2 to the C=O group by a modified *Nef* reaction (→ **13**; 90%), the C=O group was removed by standard procedures (Bu_3SnH/AIBN) to give (+)-(*S*)-tetradecan-13-olide ((+)-**10**) in 47% overall yield and 12.5% ee. Treatment of (±)-**11** with *NB-Enantride* at –100° gave the ring-enlarged (+)-**12** in 70% yield. The NO_2 group was removed by the Bu_3SnH method, giving (+)-(*S*)-**11** in 44% yield and 3% ee.

In *Table 2*, the results of reductions of different 4-(1-nitro-2-oxocycloalkyl)butan-2-ones by two optically active borohydride reagents are summarized. The enantiomeric excess is strongly dependent on the ring size of the diketone and on the reducing reagent, the ten- and twelve-membered-ring derivatives showing significantly lower ee values than those of the six-membered one. Treatment of butan-2-one with *(R)-Alpine-Hydride* gave (–)-(*R*)-butan-2-ol (29% ee) and with *NB-Enantride* (+)-(*S*)-butan-2-ol (76% ee).

Table 2. *Chemical Yields and Enantiomeric Excess of Asymetric Reductions of* (±)-**6**), (±)-**11**), (±)-**14**), *and Butan-2-one*

Ketone	Product	*(S)-Alpine-Hydride*		*NB-Enantride*	
		Yield [%]	ee [%][a])	Yield [%]	ee [%][a])
(±)-**6**	(+)-**8**	67	24	67	39
(±)-**11**	(+)-**12**	72	12	70	3
(±)-**14**	(+)-12-Nitrohexadecan-15-olide	82	15	85	10
Butan-2-one	(+)- or (–)-Butan-2-ol	75	29	72	76

[a]) Because of the diastereoisomeric nature of the nitrolactones obtained, they were converted to the corresponding lactones (+)-**1**, (+)-**10**, and (+)-hexadecan-15-olide, respectively. The ee values were determined by comparison of the [α] values of the products with those of the optically pure (–)-**1**, (–)-**10**, and (–)-hexadecan-15-olide.

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Experimental Part

General. All solvents and reagents are from *Fluka*, except (*S*)- and (*R*)-*Alpine-Hydride*, (= (*R*)-lithium β-isopinocamphenyl-9-borabicyclo[3.3.1]nonyl hydride) as 0.5M soln. in THF and *NB-Enantride*™ (= lithium 9-borabicyclo[3.3.1]nonyl hydride nopol benzyl ether adduct, *Aldrich Chemical Co.*) as 0.5M soln. in THF, and were used without further purification. All reactions involving air-sensitive reagents or organometallics were conducted under N_2. Glassware for reactions was dried in an oven overnight at 125° and cooled under a stream of N_2. Solns. were dried over anh. $MgSO_4$. All isolated compounds were identified by GC and TLC comparison with authentic samples [4][7]. TLC: silica gel alu foils (*60 F_{254}, Merck*). FC (flash chromatography): silica gel *60 PF_{254}* (*Merck*). CC (column chromatography): *Merck Lobar* pre-packed column, size *B* (310–25) *LiChroprep®*, *Si 60* (40–63 μm). M.p.: *Mettler FP-5*; uncorrected. Optical rotation: *Perkin-Elmer 241* polarimeter in $CHCl_3$. IR spectra: *Perkin-Elmer* 297; $CHCl_3$ soln. unless otherwise specified; in cm^{-1}. ^1H- (200 MHz) and ^{13}C-NMR (50 MHz): *Varian XL-200*; $CDCl_3$ soln.; chemical shifts (δ) in ppm, coupling constants *J* in Hz. CI-MS: *MAT 112S*, reactant gas 2-methylpropane.

General Procedures. A. *Reduction with* (S)- *or* (R)-Alpine-Hydride. To a stirred soln. of 1 mmol of 4-(1-nitro-2-oxocycloalkyl)butan-2-one in 10 ml of 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 was destroyed by addition of 0.1 ml EtOH and, at 0°, of 1.5 mmol of $NH_2CH_2CH_2OH$. The resulting mixture was stirred for 1 h at 20° and evaporated, and the residue purified (FC and CC).

B. *Reduction with* NB-Enantride. To a stirred soln. of 1 mmol of the corresponding diketone in 24 ml of THF/Et_2O/pentane 4:1:1 at –100°, 2.2 ml (1.1 mmol) of *NB-Enantride* (0.5M soln. in THF, cooled to –80° for 10 min) were added. The mixture was stirred at –100° for 1 h. At 0°, 0.1 ml EtOH were added, followed by 1.5 mmol of $NH_2CH_2CH_2OH$. Stirring was continued at 20° for 1 h, the solvent evaporated, and the crude product was chromatographed.

1. *Methylation of (–)-3-(1-Nitro-2-oxocyclohexyl)propanal* ((–)-**2**) *with (i-PrO)$_2$TiMe$_2$.* To a stirred Et_2O soln. of (i-PrO)$_2$TiMe$_2$ (16 mmol; synthesized by addition of 0.88 ml (8 mmol) of $TiCl_4$ to 2.4 ml (8 mmol) of (i-PrO)$_4$Ti in 10 ml of Et_2O at 0°, after stirring for 20 min at 20°, and addition of 20 ml (32 mmol) of MeLi (*ca.* 1.6M soln. in Et_2O) at –70°), 800 mg (4 mmol) of (–)-**2** [7b] in 10 ml of Et_2O were added at –78° within 10 min and stirred for 6 h (until 20° was reached). Then, the mixture was hydrolyzed with 10% aq. KF soln., the org. phase separated, and the aq. phase acidified (pH *ca.* 1) with 1% HCl soln. and extracted with CH_2Cl_2. The combined org. layers were washed with cold 1% $NaHCO_3$ soln., brine, dried, and evaporated. FC (hexane/Et_2O 19:1) gave *(±)-6-nitrodecan-9-olide* ((±)-**8**; 56 mg, 6.7%; $[\alpha]_D^{22} = \pm 0$ (c = 1.95)), *(±)-t-3-methyl-c-6-nitro-2-oxabicyclo[4.4.0]decan-r-1-ol* ((±)-**5**; 166 mg, 19%; $[\alpha]_D^{22} = \pm 0$ (c = 0.98); m. p. 114–116°; anal. calc. for $C_{10}H_{17}NO_4$ (215.248): C 55.80, H 7.96, N 6.50; found: C 55.71, H 7.92, N 6.40; all spectral data identical with those published in [4]), and *(±)-6-(hydroxyamino)decan-9-olide* (352 mg, 44%; $[\alpha]_D^{22} = \pm 0$ (c = 0.92)).

Data of (±)-6-(Hydroxyamino)decan-9-olide. M. p. 140.8–142.8° ($CHCl_3$/hexane) ([4]: 135.7–137.2°). IR: 3590, 3270, 2930, 2860, 1715, 1448, 1280, 1265, 1240, 1070, 1055, 962. IR (KBr): 3410, 3250, 2980, 2860, 1718, 1672, 1450, 1278, 1264, 1235, 1065, 972. ^{1}H-NMR: 8.85 (br. *s*, OH, exchangeable with D_2O); 5.08–4.87 (*m*, H–C(9)); 3.04 (*ddd*, J = 2.8, 6.8, 13.2, H–C(2)); 2.69–1.16 (*m*, 14 H), therein at 1.25 (*d*, J = 6.2, CH_3). ^{13}C-NMR (diastereoisomeric mixture): 173.6, 173.0 (2 *s*, C(1)); 159.5 (*s*, C(6)); 72.3, 71.7 (2 *d*, C(3)); 40.2 (2 C); 35.0, 34.5, 33.8, 32.3, 28.3, 24.4, 22.6, 20.3 (9 *t*); 20.2, 19.6 (2 *q*, CH_3). CI-MS: 200 ([M + 1]$^+$). Anal. calc. for $C_{10}H_{17}NO_3$ (199.254): C 60.28, H 8.60, N 7.03; found: C 60.32, H 8.67, N 7.10.

2. *(+)-(S)-Phoracantholide I* ((+)-**1**). 2.1. *(±)-4-(1-Nitro-2-oxocyclohexyl)butan-2-one* ((±)-**6**). According to [12], (±)-**6** was synthesized from 2-nitrocyclohexanone and methyl vinyl ketone. Pale yellow oil (95%). B.p. 115°/0.02 Torr. IR: 2950, 2870, 1725, 1550, 1435, 1360, 1170. IR (film): 2940, 2870, 1720, 1545, 1430, 1360, 1170. ^{1}H-NMR: 2.92–1.44 (*m*, 15 H), therein at 2.15 (*s*, CH_3). ^{13}C-NMR: 206.1 (*s*, C(2')); 200.6 (*s*, C(2)); 96.2 (*s*, C(1')); 39.6, 37.6, 37.2, (3 *t*); 29.8 (*q*, CH_3); 28.9, 26.6, 21.4 (3 *t*). CI-MS: 214 ([M + 1]$^+$). Anal. calc. for $C_{10}H_{15}NO_4$ (213.238): C 56.33, H 7.09, N 6.57; found: C 56.77, H 7.30, N 6.65.

2.2. *Reduction of (±)-6 with NaBH$_4$.* To a stirred soln. of 213 mg (1 mmol) of (±)-**6** in 20 ml of MeOH at 0°, 26 mg (0.68 mmol) of $NaBH_4$ were added in small portions within 1 h. After 1 h stirring at 0°, 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 residue was purified by FC (hexane/Et_2O 1:2): 156 mg (72%) of *(±)-2-(3-hydroxybutyl)-2-nitrocyclohexan-1-ol* ((±)-**7**) as colorless crystals. M. p. 93–95°. IR: 3610, 2945, 2870, 1538, 1450, 1125. IR (KBr): 3360, 2940, 2870, 1530, 1460, 990. ^{1}H-NMR: 4.00 (br. *s*, H–C(1)); 3.90–3.64 (*m*, H–C(3')); 2.84 (br. *s*, HO–C(1), exchangeable with D_2O); 2.44–1.16 (*m*, 16 H), therein at 2.16 (*s*, HO–C(3'), exchangeable with D_2O) and at 1.19 (*d*, J = 6.2, CH_3). ^{13}C-NMR (diastereoisomeric mixture): 94.6, 94.5 (2 *s*, C(2)); 72.3, 72.0 (2 *d*, C(1)); 67.4, 67.3 (2 *d*, C(3')); 32.5 (2 C); 32.0, 31.9, 30.5 (2 C); 29.0, 28.6 (6 *t*); 29.0, 28.6 (2 *q*, CH_3); 21.7, 21.6, 20.8 (3 *t*). CI-MS: 218 ([M + 1]$^+$).

2.3. *Reduction of (±)-6 with Optically Active Borohydrides.* 2.3.1. *Reduction of (±)-6 with (S)*-Alpine-Hydride. Following *General Procedure A*, 713 mg (3.40 mmol) of (±)-**6** gave, after FC (hexane/Et_2O 6:1) and CC (hexane/Et_2O 15:1), 516 mg (67%) of (+)-**8** as colorless oil. B.p. 125°/0.015 Torr. $[\alpha]_D^{22} = +3.65$ (c = 1.37). IR: 2940, 2870, 1725, 1550, 1455, 1380, 1260. ^{1}H-NMR (diastereoisomeric mixture): 5.14–4.87 (*m*, 2 H); 2.48–1.18 (*m*, 15 H), therein at 1.33 (*d*, J = 6.6, CH_3). ^{13}C-NMR (diastereoisomeric mixture): 172.6 (*s*, C(1)); 85.2, 85.0 (2 *d*, C(6)); 71.8, 71.4 (2 *d*, C(9)); 34.8, 34.6, 30.2, 29.6, 29.1, 28.9, 28.2, 27.8, 24.9, 23.3, 22.6 (11 *t*); 20.7 (*q*, CH_3); 19.8 (*t*); 18.6 (*q*, CH_3). CI-MS: 216 ([M + 1]$^+$). Anal. calc. for. $C_{10}H_{17}NO_4$ (215.254): C 55.80, H 7.96, N 6.51; found: C 57.30, H 8.17, N 6.19.

2.3.2. *Reduction of (±)-6 with* NB-Enantride. Following *General Procedure B*, from 385 mg (1.18 mmol) of (±)-**6**, after chromatographic purification (see above), 260 mg (67%) of (+)-**8** were obtained. $[\alpha]_D^{22} = +5.62$ (c = 0.76).

2.3.3. *Reduction of (–)-6 with (R)*-Alpine-Hydride. According to *General Procedure A*, 213 mg (1 mmol) of (–)-**6** [7b] gave 109 mg of (–)-**8** (50%). $[\alpha]_D^{22} = -6.69$ (c = 3.05).

2.4. *(+)-(S)-Phoracantholide I* ((+)-**1**). To a refluxing soln. of 1.33 ml (5 mmol) of Bu_3SnH in 2 ml of toluene were added 135 mg (0.8 mmol) of AIBN and 215 mg (1 mmol) of (+)-**8** ($[\alpha]_D^{22}$ = +3.65) in 5 ml of toluene within 30 min. The mixture was refluxed for additional 10 min, then passed through a short silica-gel column, and evaporated. The crude product was purified by CC (hexane/Et_2O 99:1) and bulb-to-bulb distillation: 95 mg (55%) of (+)-**1** as pale-yellow oil. B.p. 90°/12 Torr. ([5]: 60°/0.8 Torr). $[\alpha]_D^{22}$ = +9.39 (*c* = 2.17; 24% ee). Natural product *(–)-(R)-phoracantholide I* ((–)-**1**): $[\alpha]_D^{22}$ = –39.4 (*c* = 1.77) [1]; $[\alpha]_D^{22}$ = –37.4 (*c* = 0.02; *ca.* 95% ee) [5a]. (+)-**1**: IR: 2940, 2870, 1715, 1265, 1240. IR (film): 2935, 2870, 1730, 1255, 1240. ^{1}H-NMR: 4.93 (*dt*, *J* = 8.0, 3.0, H–C(9)); 2.52–1.06 (*m*, 17 H), therein at 1.20 (*d*, *J* = 6.6, CH_3). ^{13}C-NMR: 173.8 (*s*, C(1)); 72.4 (*d*, C(9)); 35.1, 31.3, 27.0, 24.1, 23.9, 23.3, 20.5 (7 *t*); 19.3 (*q*, CH_3). CI-MS: 171 ($[M + 1]^+$). Anal. calc. for $C_{10}H_{18}O_2$ (170.250): C 70.54, H 10.65; found: C 69.90, H 10.88.

Under the same conditions, 215 mg of (+)-**8** from *2.3.2* ($[\alpha]_D^{22}$ = +5.62 (*c* = 0.76) were transformed to 95 mg (55%) of (+)-**1**. $[\alpha]_D^{22}$ = +14.4 (*c* = 0.95; 38.8% ee).

3. *(–)-(R)-Phoracantholide I* ((–)-**1**). Following *Exper. 2.4*, 86 mg (0.4 mmol) of (–)-**8** with $[\alpha]_D^{22}$ = –6.69 were reduced to 28 mg (41%) of (–)-**1**. $[\alpha]_D^{22}$ = –18.52 (*c* = 0.45); 47% ee. CD ($2.09 \cdot 10^{-3}$ M in MeCN): 202 (0.00), 216 (–1.45), 251 (0.00).

4. *(+)-(S)-Tetradecan-13-olide* ((+)-**10**). 4.1. *(±)-4-(1-Nitro-2-oxocyclodecyl)butan-2-one* ((±)-**11**). To a soln. of 2.10 g (10.6 mmol) of 2-nitrocyclodecanone and 1.08 ml (13.2 mmol) of methyl vinyl ketone in 25 ml of THF at 20°, 0.30 g (1.14 mmol) of Ph_3P (10% soln. in THF) were added dropwise within 10 min. After 1.5 h stirring, the reaction was stopped by adding 2 ml of MeI. The solvent was evaporated, the residue dissolved in CH_2Cl_2, the soln. washed with H_2O, dried, and evaporated. The crude product was chromatographed (hexane/Et_2O 5:1): 2.48 g (88%) of (±)-**11** as colorless crystals. M. p. 79.3–79.7° (EtOH; with sublimation at 38–44°). IR: 2930, 2880, 2860, 1720, 1545, 1475, 1360, 1170. IR (KBr): 2940, 2900, 2860, 1730, 1715, 1540, 1480, 1165. ^{1}H-NMR: 2.94–1.98 (*m*, 12 H), therein at 2.14 (*s*, CH_3); 1.78–1.22 (*m*, 11 H). ^{13}C-NMR: 205.9 (*s*, C(2')); 202.3 (*s*, C(2)); 100.3 (*s*, C(1')); 37.6, 35.4, 30.8 (3 *t*); 29.9 (*q*, CH_3); 28.2, 25.2, 25.2, 24.4, 22.8, 19.9 (6 *t*). CI-MS: 270 ($[M + 1]^+$). Anal. calc. for $C_{14}H_{23}NO_4$ (269.350): C 62.43, H 8.61, N 5.20; found: C 62.71, H 8.47, N 5.14.

4.2. *(+)-(13S)-10-Nitrotetradecan-13-olide* ((+)-**12**). 4.2.1. *Reduction of (±)-***11** *with (S)-*Alpine-Hydride. Following *General Procedure A*, from 1.21 g (4.5 mmol) of (±)-**11** were obtained, after FC (toluene/hexane 30:1) and CC (hexane/Et_2O 19:1), 880 mg (72%) of (+)-**12** as colorless crystals. M.p. 29.6–30.6°. $[\alpha]_D^{22}$ = +2.67 (*c* = 1.50). IR: 2935, 2860, 1725, 1550, 1460, 1450, 1370. IR (KBr): 2920, 2860, 1715, 1550, 1465, 1445, 1375, 1220, 1180. ^{1}H-NMR (*ca.* 2:1 diastereoisomeric mixture): 5.14–4.97 (*m*, H–C(10)); 4.66–4.42 (*m*, H–C(13)); 2.52–2.23 (*m*, 2 H–C(2)); 2.12–1.66 (*m*, 21 H), therein at 1.24, 1.23 (2 *d*, *J* = 6.2, CH_3). ^{13}C-NMR (diastereoisomeric mixture): 173.4, 173.1 (2 *s*, C(1)); 87.5, 85.1 (2 *d*, C(10)); 70.1, 68.3 (2 *d*, C(13)); 34.1, 34.0, 31.8, 31.7, 31.4, 30.6, 27.0, 26.0, 25.8, 25.7, 25.4, 25.3, 25.1, 25.0, 24.7, 24.2, 23.5, 22.4, 22.3 (19 *t*); 20.2, 19.7 (2 *q*, CH_3). CI-MS: 272 ($[M + 1]^+$). Anal. calc. for $C_{14}H_{25}NO_4$ (271.354): C 61.97, H 9.29, N 5.16; found: C 62.06, H 9.25, N 5.20.

4.2.2. *Reduction of (±)-***11** *with* NB-Enantride. According to *General Procedure B*, from 673 mg (2.5 mmol) of (±)-**11**, after purification, 477 mg (70%) of (+)-**12** were obtained as colorless crystals. M.p. 29–30°. $[\alpha]_D^{22}$ = +0.7 (*c* = 1.74). CI-MS: 272 ($[M + 1]^+$).

4.3. *(+)-(S)-10-Oxotetradecan-13-olide* ((+)-**13**). To a soln. of 542 mg (2 mmol) of (+)-**12** ($[\alpha]_D^{22}$ = + 2.67) in 5 ml of MeOH, 4.4 ml (2.2 mmol) of 0.5M NaOMe in MeOH were added. 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) and 6 ml of aq. $TiCl_3$ soln. (1.74 g, 11.8 mmol) were added. The mixture was stirred for 1.5 h at 20°, acidified with conc. HCl soln. (pH *ca.* 1), and extracted several times with CH_2Cl_2. The org. layers were washed with 5% $NaHCO_3$ soln., brine, dried, and evaporated. The crude product was chromatographed (hexane/Et_2O 4:1): 432 mg (90%) of (+)-**13**, as colorless crystals. M.p. 37.5–38.5°. $[\alpha]_D^{22}$ = +3.10 (*c* = 1.5). IR: 2935, 2860, 1725, 1460. IR (KBr): 2925, 2860, 1715, 1695, 1465. ^{1}H-NMR: 5.06-4.92 (*m*, H–C(13)); 2.78–2.17 (*m*, 6 H); 2.04–1.08 (*m*, 17 H), therein at 1.25 (*d*, *J* = 6.2, CH_3). ^{13}C-NMR: 211.3 (*s*, C(10)); 173.2 (*s*, C(1)); 69.7 (*d*, C(13)); 42.1, 36.3, 34.6, 29.0, 26.0, 25.9, 25.8, 25.5, 24.5, 23.8 (10 *t*); 20.2 (*q*, CH_3). CI-MS: 241 ($[M + 1]^+$). Anal. calc. for $C_{14}H_{24}O_3$ (240.346): C 69.96, H 10.06; found: C 70.20, H 10.05.

4.4. *(+)-(S)-Tetradecan-13-olide* ((+)-**10**). 4.4.1. To a stirred soln. of 280 mg (1.17 mmol) of (+)-**13** ($[\alpha]_D^{22}$ = +3.10) in 3 ml of MeOH, 240 mg (1.23 mmol) of $TsNHNH_2$ were added and refluxed for 1 h. The solvent was

removed and the residue dried (3 h, 0.005 Torr) and dissolved in 12 ml of $CHCl_3$. Then, 762 mg (1.32 mmol) of $(Ph_3P)_2CuBH_4$ were added, and the mixture was refluxed for 4 h. The solvent was evaporated, the residue extracted 6 × with hot hexane, the hexane evaporated, and the crude product purified by FC (hexane/Et_2O 30:1) and CC (hexane/Et_2O 197:1): 192 mg (73%) of (+)-**10** as colorless oil. B.p. 100°/0.04 Torr ([9]: 91°/0.005 Torr; [11]: 100°/0.05 Torr). $[\alpha]_D^{22}$= +4.21 (*c* = 1.78); 12.5% ee ([9]: $[\alpha]_D^{20}$= –33.8 (*c* = 1.035); [11]: $[\alpha]_D^{20}$= –34.5 (*c* = 1.64) for (–)-(*R*)-tetradecan-13-olide). IR: 2930, 2860, 1720, 1460. IR (film): 2930, 2860, 1730, 1460. ^{1}H-NMR: 5.10–4.92 (*m*, H–C(13)); 2.52–2.20 (*m*, H–C(2)); 1.87–1.01 (*m*, 23 H), therein at 1.22 (*d*, *J* = 6.4, CH_3). ^{13}C-NMR: 173.6 (*s*, C(1)); 69.9 (*d*, C(13)); 35.0, 34.5, 26.3, 26.2, 25.9, 25.5 (2 C); 24.8, 23.9, 23.8, 22.1 (10 *t*); 20.3 (*q*, CH_3). CI-MS: 227 ([*M* + 1]$^+$). Anal. calc. for $C_{14}H_{26}O_2$ (226.362): C 74.20, H 11.60; found: C 73.99, H 11.74.

4.4.2. Following the denitration procedure described in *Exper. 2.4*, 200 mg (0.74 mmol) of (+)-**12** ($[\alpha]_D^{22}$= +0.7) were reduced to 73 mg (44%) of (+)-**10**. Colorless oil. $[\alpha]_D^{22}$= + 0.91 (*c* = 1.56); 2.7% ee. CI-MS: 227 ([*M* + 1]$^+$).

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