Synthesis of 15-Cyano-12-oxopentadecano-15-lactone and 15-Cyano-12-oxopentadecano-15-lactam

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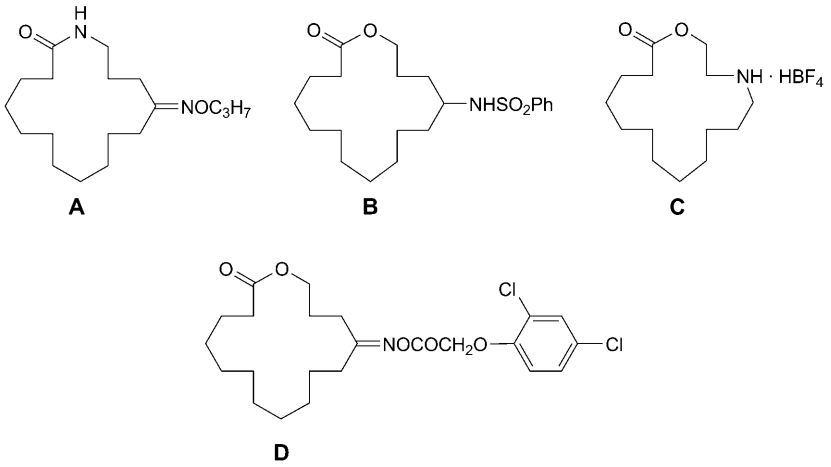
15-Cyano-12-oxopentadecano-15-lactone was synthesized in 59% total yield starting from 2-nitrocyclododecanone by *Michael* addition to acrylaldehyde, followed by reaction with trimethylsilylcyanide, hydrolysis, ring-expansion, and *Nef* reaction. A two-step, one-pot synthesis of intermediate 2-hydroxy-4-(1-nitro-2-oxycyclododecyl)butanenitrile from 3-(1-nitro-2-oxocyclododecyl)propanal was developed and the conditions for the *Nef* reaction were studied. 15-Cyano-12-oxopentadecano-15-lactam was synthesized in 40% total yield starting from 2-nitrocyclododecanone by *Michael* addition to acrylaldehyde, followed by *Strecker* reaction, ring-expansion, and *Nef* reaction. The conditions for the *Strecker* and *Nef* reactions were studied. The structures of the target compounds, intermediates, and by-product were characterized by IR, ^{1}H- and ^{13}C-NMR, and elemental analysis or MS.

Introduction. – In search of potential pesticides, more than ten series of macrolactone and macrolactam derivatives have been synthesized, and their biological activities have been evaluated in our laboratory. Among them, compound **A** has a broad spectrum of fungicidal activity [1], and especially has excellent fungicidal activity against *Alternaria kikuchiana* and *Phyllosticta physaleos* SACC. Compounds **B** and **C** display excellent fungicidal activity [2] against *Rhizoctonia solani* KÜHN and were comparable with the commercial fungicide carbendazim. Compound **D** exhibits good-to-excellent herbicidal activity against both dicotyledons and monocotyledons [3].

In continuation of our work on potential pesticides, we planned to introduce a CN group into the above-mentioned macrolactone and macrolactam skeletons to improve their fungicidal activity, for it has been used in pesticide and medicine as an effective active group [4]. For example, azoxystrobin [5] containing a CN group is the first commercialized strobilurin fungicide. A series of *N*-alkyl- and *N*-aryl-piperazine derivatives containing a CN group were synthesized and screened for their antibacterial and antifungal activity by *Chaudhary* and co-workers [6]. Three of them showed potent antibacterial activity against pathogenic strains of *Aspergillus fumigatus* (ITCC 4517), *Aspergillus flavus* (ITCC 5192), and *Aspergillus niger* (ITCC 5405).

The compounds **A**, **B**, and **D** were synthesized by means of ring-enlargement reactions from 2-nitrocyclododecanone. The synthesis of macrolactams by ring enlargement was previously reported by *Hesse* and co-workers [7] and macrolactones by *Cookson et al.* [8]. Subsequently, the synthesis of macrocyclic compounds by ring enlargement were broadly investigated by *Hesse* and *Stach* [9]. In this article we would

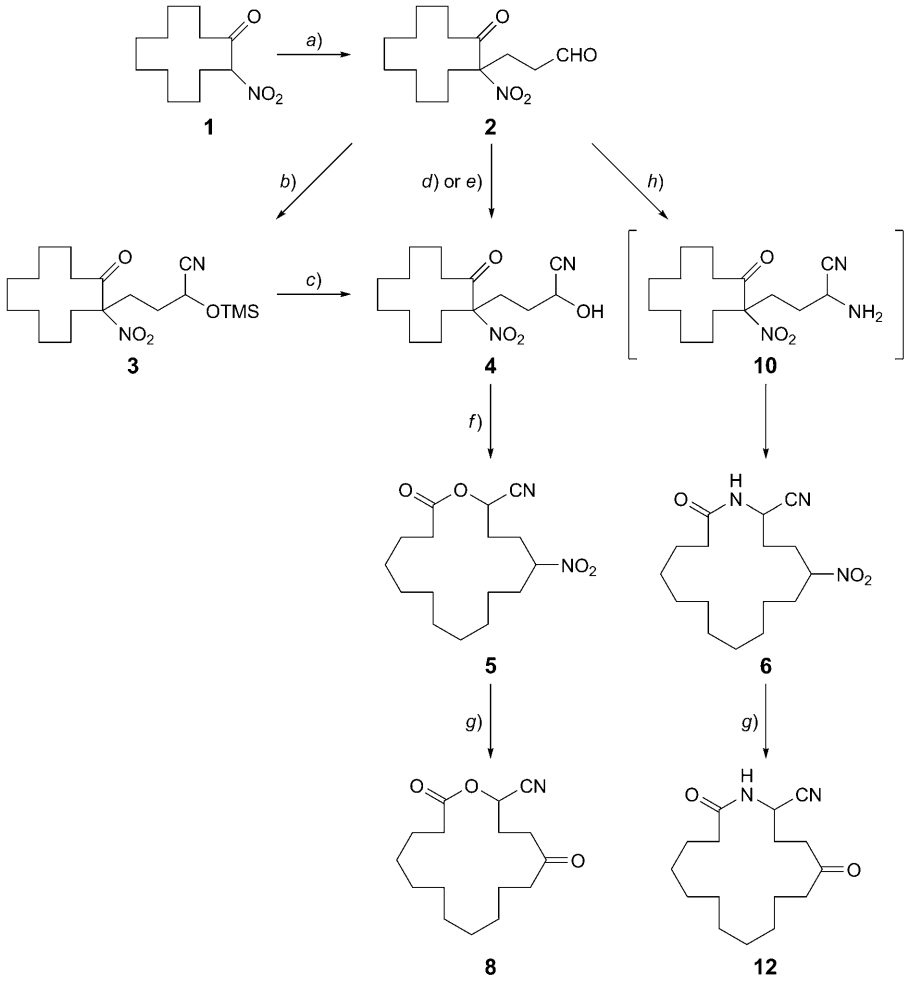


like to report the synthesis of 15-cyano-12-oxopentadecano-15-lactone and 15-cyano-12-oxopentadecano-15-lactam, from which many macrolactone and macrolactam derivatives containing a cyano group can be prepared. So far no report for their preparation from readily available twelve-membered cyclic compounds is available. The main methods for the introduction of a CN group into a molecule include oxidation of amines [10], dehydration of aldoximes and amides [11], and the reaction of halohydrocarbons with metal cyanides [12]. But it is difficult to introduce a CN group into the molecular skeleton of macrocyclic compounds through the methods mentioned above. Thus, we developed a strategy for the synthesis of 15-cyano-12-oxopentadecano-15-lactone and 15-cyano-12-oxopentadecano-15-lactam that introduced the '$CH_2CH_2CH(CN)OH$' and '$CH_2CH_2CH(CN)NH_2$' units into 2-nitrocyclododecanone by nucleophilic addition of TMSCN and *Strecker* reaction, respectively. The routes of the synthesis of 15-cyano-12-oxopentadecano-15-lactone and 15-cyano-12-oxopentadecano-15-lactam are shown in *Scheme 1*.

Results and Discussion. – It has been reported that 2-nitrocyclododecanone (**1**) easily undergoes a *Michael* addition reaction with acrylaldehyde [13] in high yield. The addition of Me_3SiCN (TMSCN) to the aldehydes (or ketones) catalyzed by *Lewis* acid [14] and *Lewis* base [15] has been reported hundreds of times. Herein we chose I_2, which acts as a mild *Lewis* acid, and might be a useful and inexpensive catalyst for the addition of TMSCN to **2**. The experiment results showed that **3** was obtained in excellent yield in the presence of I_2 (*Table 1*). The mixtures of **3** contained two pairs of enantiomers, each is an epimer of the other, as shown by HPLC-MS: HPLC showed two peaks and the MS showed their $[M + Na]^+$ peaks all at m/z 405.3. The compounds **4**, **5**, and **6** also contained two pairs of enantiomers. This could be determined by HPLC-MS as well.

The adduct **3** can be easily hydrolyzed with 1N HCl to afford **4**. On the other hand, **4** was obtained from **2** in 81% (step *d*) or 84% (step *e*) yield in a one-pot, two-step procedure. As usual, **4** was converted into **5** in 86% yield by a ring-expansion using

Scheme 1. *Synthesis of 15-Cyano-12-oxopentadecano-15-lactone and 15-Cyano-12-oxopentadecano-15-lactam*



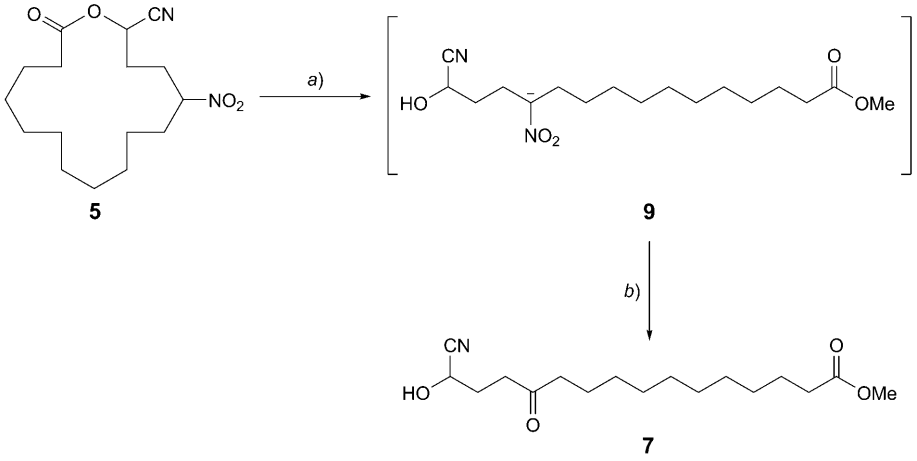
a) CH_2=CHCHO, THF, 0°, 2 h; 95%. *b*) TMSCN, I_2, CH_2Cl_2, r.t., 30 min; 92%. *c*) 1N HCl, THF, r.t., 1 h; 85%. *d*) TMSCN, I_2, CH_2Cl_2, 30 min, then 1N HCl, 1 h, r.t.; 81%. *e*) TMSCN, MeOH, r.t., 5 h; 84%. *f*) TBAF, THF, r.t., 1 h; 86%. *g*) $NaNO_2$ (2 equiv.), H_2O/DMSO 1:7 (*v*/*v*), 65°, 28 h; 86% (**8**), 88% (**12**). *h*) TMSCN, NH_3 (1M in MeCN), NH_2SO_3H (10 mol-%), MeCN, 0°, 1 h, r.t., 20 h; 48%.

Table 1. *Nucleophilic Addition of TMSCN to* **2**

Entry	I_2 (equiv.)	Solvent	Temperature	Time	Yield [%]
1	0	MeCN	r.t.	10 h	55
2	0.05	MeCN	r.t.	30 min	86
3	0	CH_2Cl_2	r.t.	10 h	69
4	0.05	CH_2Cl_2	r.t.	30 min	92

^{t}BuNF (TBAF) as a catalyst. However, **7** was obtained from **5** in 81% yield rather than **8** under the conditions [16] that converted 12-nitropentadecano-15-lactone into 12-oxopentadecano-15-lactone. Based on the fact that the solution of **5** and NaOMe in MeOH was stirred for 30 min at 0° and then an excess of HCl was added to give **7**, we suggest that due to the strong electron-withdrawing inductive effect of the CN group, transesterification of **5** with MeOH in the presence of MeONa produced intermediate **9**, which was converted into **7** in the presence of the excess of HCl in a *Nef* reaction (*Scheme 2*).

Scheme 2. *Transesterification of* **5** *and Subsequent* Nef *Reaction*



a) MeONa, MeOH, 0°, 30 min; *b*) 4M HCl, 0°, 20 min; 81%.

Subsequently, we used an improved *Nef* reaction, namely the $NaNO_2$-mediated transformation of aliphatic secondary nitroalkanes into ketones [17] to obtain **8** from **5**. The reaction conditions were optimized (*Table 2*).

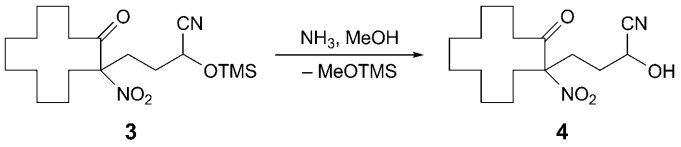
Table 2. Nef *Reaction of* **5** *and* **6** *in DMSO*

Entry	H^+ donor (equiv.)	Time [h]	Temp [°]	**8** [%]	**12** [%]
1	MeCOOH (1.2)	36	45	73	74
2	H_2O (excess)	36	45	75	78
3	MeCOOH (1.2)	28	65	80	81
4	H_2O (excess)	28	65	86	88

We planned to prepare intermediate **10** by a *Strecker* reaction of **2**. The *Strecker* reaction in a broad sense has been considerably extended by employment of various catalysts in different solvents and sources of amino and cyano groups [18]. Among cyanide ion equivalents, TMSCN is more efficient in preparation of α-amino nitriles and safer in handling [19]. In the *Strecker*-type reactions, *Lewis* acids [20], *Lewis* bases [21], and *Lewis* acid–*Lewis* base bifunctional catalysts [22] have been employed to promote the transformations. We chose TMSCN as a source of the cyano group and

studied the reaction of NH_3 with **3** in MeOH [23] to obtain intermediate **10**. To our surprise, we obtained **4** rather than **10**. It is clear that solvolysis of **3** took place in MeOH (*Scheme 3*).

Scheme 3. *Solvolysis of* **3**

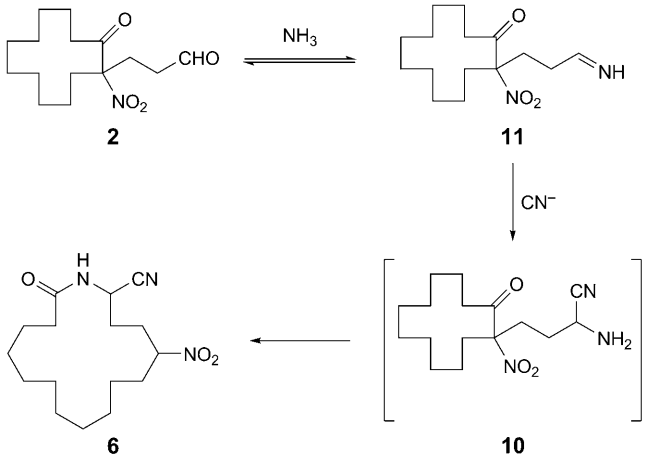


3 **4**

Thus we planned to prepare **10** from **2** by reaction of **2** with NH_3, followed by addition of TMSCN. But **4** was still obtained as the main product whether a catalyst was present or not. The result showed that the main course of this reaction was the addition of TMSCN to **2**, followed by the solvolysis of **3** in MeOH. To avoid this, we developed a simple and efficient one-pot procedure for the synthesis of **4**, and it was obtained in 84% yield by the reaction of **2** with TMSCN in MeOH at r.t. (step *e* in *Scheme 1*).

On the other hand, we studied the reaction of **2** with NH_3 and TMSCN in anhydrous MeCN to obtain **10** or the target product **6**. As a result, a mixture of **6** and **3** was obtained, which showed that the cyanide ion may attack either the intermediate imine **11** followed by a ring expansion *in situ* to give **6**, or compound **2** to give **3** (*Scheme 4*).

Scheme 4. Strecker *Reaction of* **2** *and Ring-Expansion Reaction*



2 **11** **6** **10**

Many types of *Lewis* acids are effective catalysts in the *Strecker* reaction. In this work, we chose I_2 [24], NH_2SO_3H [25], and ZnI_2 [26], and compared their effect in the reaction of **2** with NH_3 and TMSCN in anhydrous MeCN (*Table 3*).

It can be seen from *Table 3* that the yield of **6** was improved in the presence of the catalysts. Among the three catalysts, NH_2SO_3H showed more active than the others. The influence of the amount of NH_2SO_3H was also studied (*Table 4*), and **6** was

Table 3. *The Effect of Catalyst in the* Strecker *Reaction*

Entry	Catalyst	Catalyst load [mol-%]	Time [h]	**6** [%]	**3** [%]
1	no		20	20	51
2	I_2	10	20	42	32
3	NH_2SO_3H	10	20	48	28
4	ZnI_2	10	20	36	37

Table 4. *Influence of the Amount of NH_2SO_3H in the* Strecker *Reaction* (time: 20 h)

Entry	NH_2SO_3H [mol-%]	**6** [%]	**3** [%]
1	5	30	42
2	10	48	28
3	15	35	36
4	20	23	45

obtained in 48% yield in the presence of 10 mol-% NH_2SO_3H. The desired product **12** was obtained in 88% yield *via Nef* reaction of **6**, after optimization of the reaction conditions (*Table 2*).

Experimental Part

General. The solvents and reagents were used as received or were dried prior to use as needed. M.p.: *Yanagimoto* micro-melting point apparatus; uncorrected. IR Spectra: in KBr or as films on a *Shimadzu IR-435* spectrophotometer. NMR Spectra: in $CDCl_3$ and $(D)_6MSO$, with a *Bruker DPX300* spectrometer (^1H: 300 MHz, ^{13}C: 75 MHz); TMS as an internal standard. MS: *Agilent 1100* series *LC/MSD Trap.A AICHROM* with *C18,* 5 μm, 250-mm column (mobile phase: MeCN/H_2O, 70:30, *v/v*). Elemental analyses were performed at the analytical center in Peking University (Beijing).

3-(1-Nitro-2-oxocyclododecyl)propanal (**2**). Compound **2** was synthesized from 2-nitrocyclododecanone according to the method described in [13b].

4-(1-Nitro-2-oxocylododecyl)-2-[(trimethylsilyl)oxy]butanenitrile (**3**). A mixture of **2** (566 mg, 2 mmol) and TMSCN (250 mg, 2.5 mmol) in dry CH_2Cl_2 (5 ml) was stirred at r.t. in the presence of I_2 (25 mg, 0.1 mmol). After 30 min, H_2O (5 ml) was added, and the aq. phase was extracted with CH_2C1_2 (2×10 ml). The combined org. phases were washed with H_2O, dried ($MgSO_4$), and concentrated in vacuum to afford the crude product, which was purified by recrystallization (AcOEt/petroleum ether (PE) 1:10 (*v/v*)) to give **3** as a white solid (mixture of diastereoisomers, 750 mg, 92%). M.p. 76–77°. IR (KBr): 3432, 2935, 2868, 2360, 1725, 1652, 1539, 1412, 1255, 1115, 844, 749. ^1H-NMR ($CDCl_3$): 4.39–4.43 (*m*, 1 H); 2.80–2.87 (*m*, 1 H); 2.24–2.40 (*m*, 4 H); 2.08–2.17 (*m*, 2 H); 1.72–1.77 (*m*, 1 H); 1.50–1.59 (*m*, 1 H); 1.24–1.43 (*m*, 13 H); 0.89–1.05 (*m*, 2 H); 0.19–0.23 (*m*, 9 H). HPLC-MS: diastereoisomer 1: 405.3 ($[M+Na]^+$); diastereoisomer 2: 405.3 ($[M+Na]^+$).

2-Hydroxy-4-(1-nitro-2-oxocyclododecyl)butanenitrile (**4**). *Method A* (from **3**). Compound **3** (382 mg, 1mmol) was dissolved in THF (2 ml), and 1N HCl (1 ml) was slowly added to the mixture. After stirring at r.t. for 1 h, the mixture was diluted with AcOEt (5 ml) and washed with brine. The org. phase was dried ($MgSO_4$) and concentrated *i.v.* to afford crude product, which was purified by recrystallization (AcOEt/PE 2:5, *v/v*), to give **4** as a white solid (mixture of diastereoisomers; 263 mg, 85%). M.p. 99–100°. IR (KBr): 3429, 2935, 2869, 2360, 1725, 1652, 1539, 1448, 1255, 1107, 844, 748. ^1H-NMR ($CDCl_3$): 4.47–4.53 (*m*, 1 H); 2.81–2.86 (*m*, 1 H); 2.65 (br. *s*, 1 H); 2.25–2.43 (*m*, 4 H); 2.08–2.20 (*m*, 2 H); 1.74–1.90 (*m*, 1 H); 1.64–1.66 (*m*, 2 H); 1.25–1.44 (*m*, 12 H); 0.97–1.11 (*m*, 2 H). HPLC-MS: diastereoisomer 1: 333.3 ($[M+Na]^+$); diastereoisomer 2: 333.3 ($[M+Na]^+$).

Method B (two-step, one-pot procedure from **2**). A mixture of **2** (566 mg, 2 mmol), and TMSCN (250mg, 2.5 mmol) in dry CH_2Cl_2 (5 ml) was stirred at r.t. in the presence of I_2 (25 mg, 0.1 mmol). After 30 min, 1N HCl (1 ml) was slowly added to the mixture, and the mixture was stirred at r.t. for 1 h, diluted with AcOEt (5 ml) and washed with brine. The org. phase was dried ($MgSO_4$) and concentrated *i.v.* to afford crude product, which was purified by recrystallization (AcOEt/PE 2:5, *v*/*v*), to give **4** as a white solid (mixture of diastereoisomers, 251 mg, 81%).

Method C (two-step, one-pot procedure from **2**). To a soln. of **2** (566 mg, 2 mmol) in MeOH (5 ml) was added TMSCN (250mg, 2.5 mmol), and the mixture was stirred for 5 h. Then H_2O (10 ml) was added, and the mixture was extracted with CH_2C1_2 (2 × 10 ml). The combined org. phase was dried ($MgSO_4$) and concentrated *i.v.* to afford crude product, which was purified by recrystallization (AcOEt/PE 2:5, *v*/*v*), to give **4** as a white solid (mixture of diastereoisomers, 260 mg, 84%).

5-Nitro-16-oxo-1-oxacyclohexadecane-2-carbonitrile (**5**). Compound **4** (310 mg, 1 mmol) was dissolved in THF (2 ml), and stirred at r.t. in the presence of a cat. amount TBAF. After 1 h, H_2O (2 ml) was added, the mixture was extracted with CH_2C1_2 (2 × 5 ml). The combined org. phase was dried ($MgSO_4$), and concentrated *i.v.* to afford crude product, which was purified by chromatography on SiO_2 (AcOEt/PE 1:10 (*v*/*v*)) to give **5** as a colorless liquid (mixture of diastereoisomers, 266 mg, 86%). IR (neat): 2931, 2880, 1751, 1549, 1445, 1366, 1219, 1136. ^{1}H-NMR ($CDCl_3$): 5.52–5.55, 5.38–5.42 (2*m*, 1 H, –O–C*H*–CN of two pairs of enantiomer); 4.52–4.66 (*m*, 1 H); 2.44–2.49 (*m*, 2 H); 2.18–2.34 (*m*, 1 H); 1.88–2.10 (*m*, 5 H); 1.60–1.74 (*m*, 2 H); 1.32–1.47 (*m*, 14 H). HPLC-MS: diastereoisomer 1: 333.2 ($[M+Na]^+$); diastereoisomer 2: 333.3 ($[M+Na]^+$).

5,16-Dioxo-1-oxacyclohexadecane-2-carbonitrile (**8**). A soln. of compound **5** (310 mg, 1 mmol), and $NaNO_2$ (138 mg, 2 mmol), in DMSO/H_2O (7:1, *v*/*v*, 4 ml) was stirred at 65° for 28 h. An equal volume of H_2O was then added and the mixture was extracted with Et_2O (2 × 10 ml). The combined org. layer was dried (Na_2SO_4) and concentrated *i.v.* to afford crude product, which was purified by CC on SiO_2 (AcOEt/PE 1:5 (*v*/*v*)) to give **8** as a white solid (240 mg, 86%). M.p. 55–56°. IR (KBr): 2933, 2863, 2362, 1742, 1707, 1423, 1229, 1174. ^{1}H-NMR ($CDCl_3$): 5.52 (*dd*, *J* = 3.66, 7.59, 1 H); 2.65–2.73 (*m*, 2 H); 2.47–2.52 (*m*, 1 H); 2.31–2.43 (*m*, 4 H); 2.12–2.17 (*m*, 1 H); 1.72–1.75 (*m*, 2 H); 1.57–1.63 (*m*, 2 H); 1.29–1.38 (*m*, 12 H). ^{13}C-NMR ($CDCl_3$): 208.8; 171.6; 116.6; 59.6; 41.8; 36.5; 33.2; 27.3; 26.7; 26.4; 26.3; 26.2; 26.1; 26.0; 24.0; 23.4. Anal. calc. for $C_{16}H_{25}NO_2$ (279.4): C 68.79, H 9.02, N 5.01; found: C 68.75, H 8.96, N 5.09.

5-Nitro-16-oxo-1-azacyclohexadecane-2-carbonitrile (**6**). A mixture of **2** (566 mg, 2 mmol), NH_3 (2 ml, 1M in MeCN), NH_2SO_3H (20 mg, 0.2 mmol), and molecular sieve powder (1.50 g) in dry MeCN (5 ml) was stirred under N_2 for 1 h and cooled to 0°, TMSCN (220 mg, 2.2 mmol) was added slowly and stirred at r.t. for 20 h. The molecular sieve powder was filtered out, and H_2O (10 ml) was added. The mixture was extracted with CH_2Cl_2 (2 × 20 ml). The combined org. layer was dried (Na_2SO_4) and the solvent was evaporated *i.v.* The residue was purified by CC using AcOEt/PE 2:5 (*v*/*v*) as eluent to provide **6** as a white solid (mixture of diastereoisomers, 300 mg, 48%). M.p. 116–118°. IR (KBr): 3269, 2934, 2858, 2359, 1653, 1546, 1448, 1409, 1368, 1284, 682. ^{1}H-NMR ((D$_6$)DMSO): 8.76 (*d*, *J* = 8.67); 8.64 (*d*, *J* = 8.31, 1 H, NH of two pairs of enantiomers); 5.04 (*ddd*, *J* = 8.4, 8.4, 4.75); 4.84 (*ddd*, *J* = 8.4, 8.4, 4.56, 1 H, N–C*H*–*C*N of two pairs of enantiomers); 4.67–4.72 (*m*); 4.55–4.62 (*m*, 1 H, –C*H*NO$_2$– of two pairs of enantiomers); 2.12–2.18 (*m*, 2 H); 1.79–1.86 (*m*, 6 H); 1.54–1.59 (*m*, 2 H); 1.17–1.22 (*m*, 14 H). HPLC-MS: diastereoisomer 1: 333.3 ($[M+Na]^+$); diastereoisomer 2: 333.3 ($[M+Na]^+$).

5,16-Dioxo-1-azacyclohexadecane-2-carbonitrile (**12**). A soln. of compound **6** (309 mg, 1 mmol), and $NaNO_2$ (138 mg, 2 mmol), in DMSO/H_2O (7:1, *v*/*v*, 4 ml) was stirred at 65° for 28 h. An equal volume of H_2O was then added and the mixture was extracted with Et_2O (2 × 10 ml). The combined org. layer was dried (Na_2SO_4), concentrated *i.v.*, and the resulting crude product was purified by recrystallization (AcOEt/PE 5:1 (*v*/*v*)) to give **12** as a white solid (245 mg, 88%). M.p. 128–129°. IR (KBr): 3281, 2929, 2855, 2360, 1707, 1654, 1408. ^{1}H-NMR ((D$_6$)DMSO): 8.62 (*d*, *J* = 8.31, 1 H); 4.78–4.85 (*m*, 1 H); 2.52–2.58 (*m*, 2 H); 2.29–2.36 (*m*, 2 H); 2.13–2.17 (*m*, 2 H); 1.90–1.98 (*m*, 2 H); 1.18–1.61 (*m*, 16 H). ^{13}C-NMR ((D$_6$)DMSO): 209.8; 172.6; 119.7; 41.5; 38.2; 36.7; 34.7; 27.1; 26.7; 26.6; 26.5; 26.3; 25.7; 25.6; 24.6; 22.9. Anal. calc. for $C_{16}H_{26}N_2O_2$ (278.4): C 69.03, H 9.41, N 10.06; found: C 68.93, H 9.32, N 10.07.

Methyl 15-Cyano-15-hydroxy-12-oxopentadecanoate (**7**). A soln. of MeONa (108 mg, 2 mmol) in MeOH (10 ml) was added to the soln. of **5** (620 mg, 2 mmol) in MeOH (10 ml) at 0°, and the mixture was stirred at this temp. for 30 min. Then 4N HCl (20 ml) was added and the mixture was stirred for further

30 min. The mixture was neutralized with sat. $NaHCO_3$ and then extracted with AcOEt (3×20 ml). The combined org. phase was washed with brine and dried (Na_2SO_4). After filtration, the solvent was removed to give the crude product, which was purified by recrystallization (AcOEt/PE 3:5 (*v*/*v*)) to afford **7** (504 mg, 81%). M.p. 71–72°. IR (KBr): 3399, 2914, 2850, 1721, 1706, 1415, 1200, 1080. ^{1}H-NMR ($CDCl_3$): 4.62 (*ddd*, $J = 4.9, 6.6, 6.6$, 1 H); 4.03 (*d*, $J = 6.78$, 1 H); 3.67 (*s*, 3 H); 2.78–2.85 (*m*, 2 H); 2.46–2.51 (*m*, 2 H); 2.31 (*t*, $J = 7.4$, 2 H); 2.08–2.16 (*m*, 2 H); 1.57–1.64 (*m*, 5 H); 1.23–1.36 (*m*, 12 H). ^{13}C-NMR ($CDCl_3$): 211.7; 174.5; 119.4; 60.7; 51.5; 42.8; 38.0; 34.1; 29.2; 29.1; 29.0; 28.8; 24.9; 23.8. MS-FAB: 334.3 ($[M + Na]^+$).

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REFERENCES

[1] J.-X. Huang, Y.-M. Jia, X.-M. Liang, W.-J. Zhu, J.-J. Zhang, Y.-H. Dong, H.-Z. Yuan, S.-H. Qi, J.-P. Wu, F.-H. Chen, D.-Q. Wang, *J. Agric. Food. Chem*. **2007**, *55*, 10857.
[2] W.-J. Zhu, P. Wu, X.-M. Liang, Y.-H. Dong, J.-J. Zhang, H.-Z. Yuan, S.-H. Qi, X.-Q. Meng, J.-P. Wu, F.-H. Chen, D.-Q. Wang, *J. Agric. Food. Chem*. **2008**, *56*, 6547.
[3] X.-Q. Meng, J.-J. Zhang, X.-M. Liang, W.-J. Zhu, Y.-H. Dong, X.-M. Wu, J.-X. Huang, C.-H. Rui, X.-L. Fan, F.-H. Chen, D.-Q. Wang, *J. Agric. Food. Chem*. **2009**, *57*, 610.
[4] B. Melichar, M. Konopleva, W. Hu, K. Melicharova, M. Andreeff, R. S. Freedman, *Gynecol. Oncol.* **2004**, *93*, 149; P. G. Baraldi, M. G. Pavani, M. del Carmen Nuñez, P. Brigidi, B. Vitali, R. Gambari, R. Romagnoli, *Bioorg. Med. Chem*. **2002**, *10*, 449; S. H. Abdel-Hafez, *Eur. J. Med. Chem*. **2008**, *43*, 1971; A. R. Gholap, K. S. Toti, F. Shirazi, R. Kumari, M. K. Bhat, M. V. Deshpande, K. V. Srinivasan, *Bioorg. Med. Chem*. **2007**, *15*, 6705.
[5] J. M. Clough, C. R. A. Godfrey, I. T. Streeting, R. Cheetham, Eur. Pat. Appl. 1990, [P]. EP:0382375.
[6] P. Chaudhary, S. Nimesh, V. Yadav, A. K. Verma, R. Kumar, *Eur. J. Med. Chem*. **2007**, *42*, 471.
[7] R. Wälchli, M. Hesse, *Helv. Chim. Acta* **1982**, *65*, 2299; R. Wälchli, S. Bienz, M. Hesse, *Helv. Chim. Acta* **1985**, *68*, 484.
[8] R. C. Cookson, P. S. Ray, *Tetrahedron Lett*. **1982**, *23*, 3521.
[9] H. Stach, M. Hesse, *Tetrahedron* **1988**, *44*, 1573.
[10] K. Nakagawa, T. Tsuji, *Chem. Pharm. Bull*. **1963**, *11*, 296; Q. Zheng, C. Huang, G. Xie, C. Xu, Y. Chen, *Synth. Commum*. **1999**, *29*, 2349; R. J. Card, J. L. Schmitt, *J. Org. Chem*. **1981**, *46*, 754.
[11] H. Gross, J. Gloede, *Chem. Ber.* **1963**, *96*, 1387; M. F. Browne, R. L. Shriner, *J. Org. Chem*. **1957**, *22*, 1320.
[12] F. H. Allen, *Org. Synth*. **1928**, *8*, 52.
[13] a) H. Stach, M. Hesse, *Helv. Chim. Acta* **1987**, *70*, 315; b) J. J. Zhang, Y. H. Dong, X. M. Liang, D. Q. Wang, *Chem. J. Chin. Univ*. **2003**, *24*, 1604.
[14] D. A. Evans, G. L. Carroll, L. K. Truesdale, *J. Org. Chem*. **1974**, *39*, 914.
[15] S. E. Denmark, W.-J. Chung, *J. Org. Chem*. **2006**, *71*, 4002.
[16] B. Milenkov, A. Guggisberg, M. Hesse, *Helv. Chim. Acta* **1987**, *70*, 760.
[17] A. Gissot, S. N'Gouela, C. Matt, A. Wagner, C. Mioskowski, *J. Org. Chem*. **2004**, *69*, 8997.
[18] H. Gröger, *Chem. Rev*. **2003**, *103*, 2795; D. Enders, J. P. Shilvock, *Chem. Soc. Rev*. **2000**, *29*, 359.
[19] Y. Mori, M. Kimura, M. Seki, *Synthesis* **2003**, 2311; K. Matsumoto, J. C. Kim, N. Hayashi, G. Jenner, *Tetrahedron Lett*. **2002**, *43*, 9167; S. Kobayashi, T. Busujima, *Chem. Commun*. **1998**, 981.
[20] B. Das, R. Ramu, B. Ravikanth, K. R. Reddy, *Synthesis* **2006**, 1419; K. De Surya, R. A. Gibbs, *Synth. Commun*. **2005**, *35*, 961; J. S. Yadav, B. V. Subba Reddy, B. Eeshwaraiah, M. Srinivas, *Tetrahedron* **2004**, *60*, 1767; B. C. Ranu, S. S. Dey, A. Hajra, *Tetrahedron* **2002**, *58*, 2529; A. Heydari, P. Fatemi, A.-A. Alizadeh, *Tetrahedron Lett*. **1998**, *39*, 3049.
[21] S. A. Paraskar, A. Sudalai, *Tetrahedron Lett*. **2006**, *47*, 5759; B. M. Fetterly, N. K. Jana, J. G. Verkade, *Tetrahedron* **2006**, *62*, 440.
[22] Y. Hoashi, T. Okino, Y. Takemoto, *Angew. Chem., Int. Ed*. **2005**, *44*, 4032; S. B. Tsogoeva, M. J. Hateley, D. A. Yalalov, K. Meindl, C. Weckbecker, K. Huthmacher, *Bioorg. Med. Chem*. **2005**, *13*, 5680; H. Gröger, *Chem. – Eur. J.* **2001**, *7*, 5246.

[23] K. Mai, G. Patil, *Tetrahedron Lett*. **1984**, *25*, 4583.
[24] L. Royer, S. K. De, R. A. Gibbs, *Tetrahedron Lett*. **2005**, *46*, 4595.
[25] Z. Li, Y. Sun, X. Ren, P. Wei, Y. Shi, P. Ouyang, *Synlett* **2007**, *5*, 803.
[26] G. Cainelli, D. Giacomini, A. Treré, P. Galletti, *Tetrahedron: Asymmetry* **1995**, *6*, 1593.

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