Experiment 2.7.1–2.7.3. 16,81 mg (0,0756 mmol, 32,0 mCi/mmol) (2*E*,6*Z*)-11′,12-^{3}H-**2** wurden gemischt mit 11,80 mg (0,0532 mmol, 1,9 mCi/mmol) (*E*,*E*)-4-^{14}C-**2**[7]), bei 120°/0,01 Torr destilliert und ^{3}H/^{14}C: 23,7 ± 0,3 bestimmt.

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229. A New Synthetic Route to (±)-Perhydrohistrionicotoxin[1])

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(22. VIII. 77)

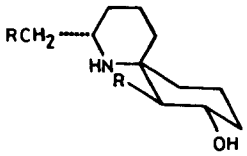
Summary

Starting from ethyl 2-cyclohexen-1-carboxylate (**3**) the total synthesis of the perhydrohistrionicotoxin intermediate **23** was achieved in 25% overall-yield. The two key steps involve a positionally specific addition of HOBr to the oxime-olefin **7** and the alkylation of bromooxime **17** with 1-lithio-1-butyne. The latter represents a novel method for stereospecific and position-specific introduction of a nucleophilic butyl equivalent in α-position to a ketonic carbonyl group.

The perhydro derivative **1** of histrionicotoxin **(2)** known to exhibit unique neurotoxic properties [2] was first synthesized in these laboratories [3] [4] and in this publication we now wish to present a new route to (±)-perhydrohistrionicotoxin (**1**) *via* the intermediate **23** of our original synthesis (*Scheme 1*). To build up the basic spirocyclic skeleton of the molecule ethyl 2-cyclohexen-1-carboxylate (**3**)[2]) was

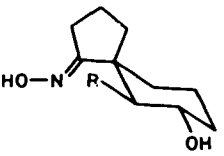
[1]) For a preliminary account of this work see [1].
[2]) Reduction of benzoic acid by lithium in liquid ammonia gave the 1,4-dihydro derivative which was converted to cyclohexadien-1,3-carboxylic acid during isolation. Further reduction by liquid ammonia and esterification furnished **3**. For similar transformations see [5].

Scheme 1



1 R= $(CH_2)_3CH_3$

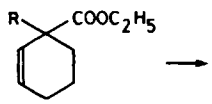
2 R= $CH\overset{cis}{=}CHC\equiv CH$



23 R= $(CH_2)_3CH_3$

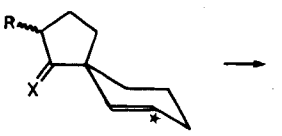
alkylated with ethyl 4-bromobutyrate following the procedure of *Schlessinger et al.* [6] to afford the unsaturated diester **4** which when subjected to the conditions of a *Dieckmann* condensation using sodium hydride as a base cleanly cyclized to the spirocyclic β-ketoester **5**. Subsequent hydrolysis-decarboxylation gave after distillation spiro[4,5]dec-6-en-1-one (**6**) in 66% yield from **3** (*Scheme 2*). The ketone **6**

Scheme 2



3 R= H

4 R= $(CH_2)_3COOC_2H_5$

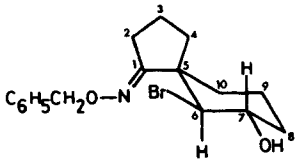


5 X= O, R= $COOC_2H_5$

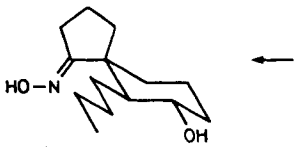
6 X= O, R= H

7 X= NOH, R= H

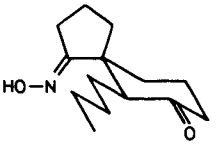
8 X= $NOCH_2C_6H_5$, R= H



9



23



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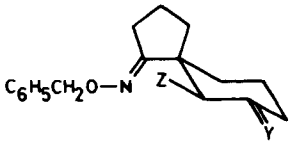


12 Y= O, Z= Br

17 Y= NOH, Z= Br

19 Y= NOH, Z= $C\equiv CC_2H_5$

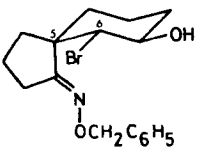
20 Y= NOH, Z= $n\text{-}C_4H_9$

21 Y= O, Z= $n\text{-}C_4H_9$

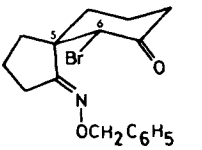
upon treatment with hydroxylamine hydrochloride and pyridine in absolute ethanol furnished as anticipated exclusively the *E*-isomer of the oxime derivative **7** (83%), *i.e.* the isomer corresponding to that hydroxy hydroxylamine precursor which is sterically less crowded. To protect the oxime function it was further transformed into

the oily *O*-benzyl derivative **8** (98%) by reaction of the potassium salt with benzyl bromide in dimethoxyethane. The subsequent reaction of **8** with *N*-bromosuccinimide in wet dimethoxyethane at $-20°$ proceeded with high positional specificity in the desired direction, *i.e.* attachment of oxygen to the starred carbon atom of the double bond. The major product (72% isolated yield) was the bromohydrin **9**, which was crystallyzing directly from the product mixture (m.p. 106–107.5°). The remaining two by-products, bromohydrin **10** and bromoketone **11**, were each formed to the extent of *ca.* 10% and could be separated chromatographically (*Scheme 3*). Identicality

Scheme 3



10



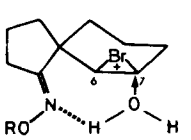
11

of the stereorelationship between C(5) and C(6) in **10** and **11** could be shown by transformation of bromohydrin **10** to bromoketone **11** by *Jones* oxidation. Analogous oxidation of bromohydrin **9** with *Jones* reagent afforded the isomeric bromoketone **12** (99%) as a chromatographically homogeneous, colorless oil. The location of bromine and carbonyl groups in the bromoketones **11** and **12** was confirmed by the appearance in the NMR. spectra of a sharp singlet due to the proton at C(6) at δ 4.71 and δ 4.32 ppm, respectively. In each case the conformation of the six-membered ring is such as to place the bromine substituent in an equatorial arrangement as shown by the occurrence of carbonyl absorption in the IR. spectra of **11** and **12** at 1739 cm^{-1} and 1730 cm^{-1}, respectively [7].

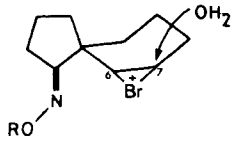
The direction of addition of HOBr to the double bond of **8** was also clear from analysis of the NMR. spectra of the isomeric bromohydrins **9** and **10** which exhibit sharp doublets due to the C(6) proton at δ 4.35 ppm (J = 10 Hz) and δ 3.87 ppm (J = 10 Hz), respectively (essentially unshifted in the corresponding acetate esters), and multiplets for the C(7) proton, centered at δ 3.66 and 4.43 ppm, respectively (each shifted downfield by *ca.* 1.3 ppm by acetylation). The assignement of complete stereochemistry to the two bromohydrins, each of which must have a diequatorial arrangement of HO- and Br-groups in view of J = 10 Hz observed for the C(6) proton, is also clear from the NMR. spectra. The C(6) proton doublet is *downfield* (by 0.5 ppm) in **9** relative to **10** whereas the C(7) proton multiplet is *upfield* (by *ca.* 0.8 ppm) in **9** relative to **10**. These shifts are readily understood in terms of the stereoformulas shown for **9** and **10** in which the C=N group should strongly deshield the C(6) proton in **9** and the C(7) proton in **10**.

The predominant formation of bromohydrin **9** may be due to oxime-assisted bromonium ion formation and/or reaction as expressed in **13** whereby attack of water at C(7) also constitutes the diaxial mode of opening from this conformation (*Scheme 4*). The diastereomeric bromonium ion having Br on the opposite side of the ring relative to ion **13** may be expected to prefer conformation **14**. From this confor-

Scheme 4



13

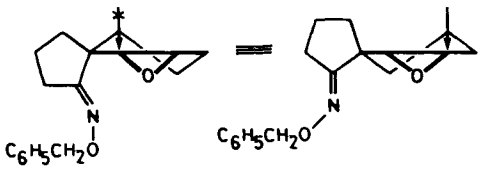


14

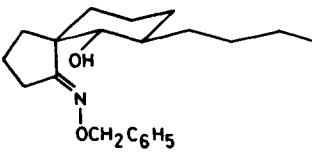
mation diaxial opening would restrict attack of water to C(7) thereby eventuating in bromohydrin **10** and the corresponding ketone **11**. In agreement with this hypothesis is the fact that considerably less of bromohydrin **9** and *vice versa* more of bromohydrin **10** and bromoketone **11** was formed if the solvent system of the reaction was modified in such a way that relatively less water with respect to dimethoxyethane was present.

Having the pure bromohydrin **9** in hand a very attractive approach to introduce the butyl side chain and the hydroxy group at C(7) both with the correct configuration would be the opening of epoxide **15**, which can be obtained in high yield by treatment of **9** with sodium 2-propoxide in 2-propanol at ambient temperature, with a nucleophilic butyl equivalent (*Scheme 5*). However reaction of epoxide **15** with a

Scheme 5



15



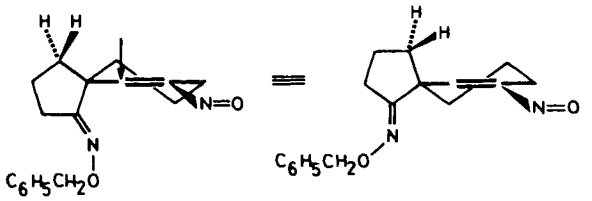
16

mixed cuprate reagent R^1R^2CuLi (R^1 = butyl, R^2 = 1-pentynyl [8]) in ether at $-45°$ in the presence of two equivalents of hexamethylphosphorous triamide afforded exclusively alcohol **16**.

Another strategy was required in order to complete the synthesis and accordingly we prepared the oxime **17** (quantitatively) by reaction of bromoketone **12** with hydroxylamine hydrochloride and sodium acetate in acetic acid at 25°. It is noteworthy that under identical conditions the epimeric bromoketone **11** remained unchanged. If the reaction temperature was raised to 100° oxime formation as well as its decomposition took place. The bromooxime **17** was then utilized according to a recently described strategy for attaching a nucleophilic carbon reagent α to carbonyl [9]. Exposure of the bromooxime to excess 1-lithio-1-butyne in tetrahydrofuran at $-78°$ led to formation of a blue color, due to the nitroso-ene intermediate **18**. As the temperature of the reaction mixture was raised, the color began to fade (at *ca.* $-20°$) and then disappeared (at *ca.* $-10°$). Rapid isolation of product gave the acetylenic oxime **19** which immediately and without purification was hydrogenated over 10% Pd/C in ethyl acetate to furnish the tetrahydro derivative **20** (77% overall from **12**).

The reason for the complete stereospecificity of the alkylation of the nitroso-ene intermediate **18** is not quite certain. However examination of models of the two conformations of **18** which presumably are in equilibrium reveal that out of the four possible approaches for the 1-lithio-1-butyne to the electrophilic carbon atom of the double bond the one indicated by an arrow in the formula seems to involve the least sterical interaction and furthermore in an axial mode (*Scheme 6*). In this regard it should be noted that the direct butylation of the oxime **17** by di-*n*-butylcopperlithium

Scheme 6



18

or by *n*-butyllithium (*cf.* [9]) did not proceed in the desired sense, presumably for steric reasons.

Cleavage of the free oxime function in **20** with aqueous titanium trichloride [10] in methanol at pH 6 afforded ketone **21** (95%) which was debenzylated by hydrogenation in ethanol over 10% Pd/C to form **22** in 98% yield. Reduction of the ketone **22** using excess sodium in liquid ammonia/tetrahydrofuran at $-78°$ with 2-propanol as a proton source proceeded stereospecifically to form the desired hydroxyoxime **23** (92%), identical chromatographically and spectroscopically with a sample synthesized as previously described [3]. The intermediate **23** is convertible to perhydrohistrionicotoxin **(1)** in a straightforward way [3] [4].

The synthetic route outlined here represents a practical method of synthesis of (±)-perhydrohistrionicotoxin. It also illustrates some interesting new chemistry including the functionalgroup induced, positionally specific addition of HOBr[3]) to the oxime-olefin **8** and a novel method for stereospecific and positionspecific introduction of a nucleophilic butyl equivalent α to ketonic carbonyl (or alternatively of generating the electrophilic counterpart of a nucleophilic enolate for alkylation) [9].

This work was assisted by a grant from the *U.S. National Science Foundation* and a Fellowship to *M. P.* from the *Swiss National Science Foundation.*

Experimental Part

General remarks. Melting points (m.p.) and boiling points (b.p.) are not corrected. IR. spectra are recorded in cm^{-1}. The chemical shift in NMR. spectra is given in ppm relative to tetramethylsilane as internal standard ($\delta = 0$). Multiplicities are expressed as singlet (*s*), doublet (*d*), triplet (*t*), quartet (*qa*), multiplet (*m*), doublet of triplet (*d* × *t*) *etc.* Spin-spin coupling constants are given in Hertz (Hz). Silica gel PF_{254} *Merck* was used for preparative thick-layer chromatography (prep. TLC.). Abbreviations: THF = tetrahydrofuran, DME = dimethoxyethane, ∅ = diameter, L = length, i.V. = *in vacuo*, RV. = rotary evaporator.

[3]) For another interesting case of positionally specific HOBr addition to –CH=CH– see [11].

Alkylation of ethyl 2-cyclohexen-1-carboxylate (**3**). To a chilled solution (0°) of 10.0 ml (71.4 mmol) of diisopropylamine in 42 ml of dry THF was added 30.0 ml (71.4 mmol) of a 2.38 M solution (in hexane) of butyllithium over 8 min and stirred for an additional 10 min at 0°. After cooling the reaction mixture to −78° 13.7 ml (1.1 mol-equiv.) of dry hexamethylphosphoramide was introduced followed (after stirring for 30 min) by 10.93 g (70.9 mmol) of ethyl 2-cyclohexen-1-carboxylate (**3**) (over 10 min). The reaction mixture was stirred for 10 min before 13.95 g (85.7 mmol) of ethyl 4-bromobutyrate were added over 5 min. The temperature was then allowed to rise to −20° over a period of 1 h and was maintained there for 2 h. Quenching the reaction mixture with sat. aqueous ammonium chloride, extraction of the product with petroleum ether (500 ml), washing the organic layers with 50% sat. brine and drying over magnesium sulfate afforded after evaporation of the solvents 17.69 g (93%) of crude diester **4**. This material was used for the following *Dieckmann* condensation without further purification. A purified analytical sample exhibited the following spectral data: – IR. (liq. film): 3030, 2980, 2940, 2870, 2840, 1731, 1450, 1373, 1345, 1302, 1182, 1155, 1120, 1097, 1029, 930, 854, 730. – NMR. ($CDCl_3$, 100 MHz): 1.14–2.40 (br. *m* with *t*, *J* = 7, at 1.24, 24 H, aliphatic protons, 2 CH_3); 4.12 and 4.14 (2 *qa*, *J* = 7, 4 H, O–CH_2); 5.65–5.81 (*m*, 2 H, CH=CH). – MS.: 268 (M^+), 236, 223, 222, 210, 195 (100%), 194, 149, 147, 131, 107 ($C_{15}H_{24}O_4$).

Dieckmann condensation of diester **4**. To a suspension of 2.91 g (121 mmol, 2.4 mol-equiv.) of sodium hydride in 200 ml of dry THF was added one half (6.76 g/25.2 mmol) of the crude diester **4** together with 0.1 ml of abs. ethanol. After stirring the reaction mixture for 3 h at ambient temperature the second half of **4** was added. Additional stirring for 20 h at 25° and 30 min at reflux caused the reaction mixture to turn dark brown. It was carefully quenched with ice chips and then acidified with 6 N HCl. The product was extracted with petroleum ether/methylene chloride 4:5 (900 ml), the organic layers washed with 50% sat. brine (4 × 1000 ml) and dried over magnesium sulfate furnishing after concentration i.V. 10.73 g (96%) of crude β-ketoester **5**. For the following decarboxylation this material was used without further purification. A purified analytical sample exhibited the following spectral data: – IR. (liq. film): 3025, 2980, 2940, 2870, 2840, 1751, 1728, 1659, 1620, 1450, 1372, 1337, 1303, 1247, 1190, 1153, 1130, 1048, 957, 942, 900, 732. – NMR. ($CDCl_3$, 100 MHz): 1.08–2.52 (*br. m* with *t*, *J* = 7, at 1.25, 13 H, aliphatic protons, CH_3); 3,25 (*t*, *J* = 9.5, 1 H, CO–CH–COO); 4.19 (*qa*, *J* = 7, 2 H, O–CH_2); 5.30 and 5.47 (2 *d* × *t*, *J* = 10 and 2, 1 H, C–CH=C); 5.87 and 5.97 (2 *m*, 1 H, C=CH–C). – MS.: 222 (M^+), 204, 177, 176, 148, 131, 120, 94 (100%), 79 ($C_{13}H_{18}O_3$).

Spiro[4,5]dec-6-en-1-one (**6**). 1.48 g (6.67 mmol) of crude spiro-β-ketoester **5** were dissolved in 40 ml of THF, 10 ml of water and 5 ml of conc. sulfuric acid and the reaction mixture was heated under reflux for 4 h. The bulk of THF was removed on a RV., the residue extracted with pentane (3 × 50 ml) and the organic layers washed with 50% sat. brine (3 × 50) ml). Drying over sodium sulfate and removal of the solvent afforded 1.08 g of a yellow oil, which upon Kugelrohrdistillation (65–80°/0.6–0.7 Torr) yielded 737 mg (66% overall from **2**) of a colorless liquid, homogeneous by TLC. – IR. (liq. film): 3020, 2930, 2860, 2840, 1736, 1640, 1448, 1408, 1343, 1312, 1269, 1179, 1161, 1146, 1132, 1060, 1028, 941, 917, 877, 731, 689. – NMR. ($CDCl_3$, 100 MHz): 1.12–2.47 (br. *m*, 12 H); 5.35 (*d* × *t*, *J* = 10 and 1.5, 1 H, C–CH=C); 5.91 (*d* × *t*, *J* = 10 and 4, 1 H, C=CH–C). – MS.: 150 (M^+), 132, 94, 79 (100%) ($C_{10}H_{14}O$).

Spiro[4,5]dec-6-en-1-one oxime (**7**). To a solution of 6.24 g (41.6 mmol) of the spiro[4,5]dec-6-en-1-one (**6**) and 16.9 ml (5 mol-equiv.) of pyridine in 12 ml of abs. ethanol was added 3.47 g (1.2 mol-equiv.) of hydroxylamine hydrochloride and the reaction mixture was stirred for 18 h at ambient temperature. Chilling the mixture in an ice bath followed by slow addition of 75 ml of water precipitated the oxime derivative **7**. Filtration and washing with water afforded after drying i.V. overnight 5.71 g (83%) of colorless crystals, homogeneous by TLC. (m.p. 118–120°). – IR. ($CHCl_3$): 3580, 3265, 2995, 2935, 2860, 2840, 1665 br, 1443, 1420, 1352, 1178, 950, 926, 906, 869. – NMR. ($CDCl_3$, 100 MHz): 1.40 (br. *m*, 10 H); 2.40–2.71 (*m*, 2 H, CH_2–C=N); 5.42 (*d* × *t*, *J* = 10 and 1.5, 1 H, C–CH=C); 5.84 (*d* × *t*, *J* = 10 and 4, 1 H, C=CH–C). – MS.: 165 (M^+), 148, 146, 133, 131, 120, 119, 107, 91, 79 (100%), 77, 70 ($C_{10}H_{15}NO$).

O-*Benzylation of spiro[4,5]dec-6-en-1-one oxime* (**7**). To a suspension of 229 mg (1.2 mol-equiv.) of KH in 20 ml of dry DME at 0° was added a solution of 785 mg (4.76 mmol) of spiro[4,5]dec-6-en-1-one oxime (**7**) in 10 ml of dry DME. After stirring the reaction mixture for 15 min at 0° (evolution of hydrogen had stopped) 0.68 ml (1.2 mol-equiv.) of benzylbromide were added. The ice bath was removed and the reaction mixture stirred for an additional 1.5 h. After removal of the bulk of DME

i.V. the residue was taken up in petroleum ether (3 × 50 ml) and washed with 50% sat. brine (3 × 40 ml). Drying the combined organic layers over magnesium sulfate and evaporation of the solvents furnished 1.35 g of a colorless oil, which according to TLC.-analysis contained some benzylbromide. Purification by chromatography on 45 g of silica gel (⌀ = 30 mm, L = 12 cm) with benzene afforded 1.19 g (98%) of a colorless liquid, homogeneous by TLC. – IR. (liq. film): 3095, 3070, 3030, 2945, 2870, 1640, 1490, 1450, 1359, 1258, 1200, 1173, 1018, 909, 888, 857, 794, 721, 689. – NMR. ($CDCl_3$, 100 MHz): 1.36–2.16 (br. *m*, 10H); 2.39–2.64 (*m*, 2H, CH_2–C=N); 5.08 (*s*, 2H, O–CH_2); 5.45 (*d* × *t*, *J* = 10 and 1.5, 1H, C–CH=C); 5.76 (*d* × *t*, *J* = 10 and 4, 1H, C=CH–C); 7.28 (*s*, 5H, arom. H). – MS.: 255 (M^+), 238, 164, 146, 133, 120, 107, 105, 91 (100%), 79, 77 ($C_{17}H_{21}NO$).

Formation of bromohydrin **9** *from* **8**. A solution of 1.06 g (4.16 mmol) of the *O*-benzylether of spiro[4,5]dec-6-en-1-one oxime **8** in 100 ml of DME and 50 ml of water was treated with 1.11 g (1.5 mol-equiv.) of *N*-bromosuccinimide at −20°. After stirring the reaction mixture for 1.25 h at −20° the bulk of DME was removed on a RV. The residue was taken up in ether/methylene chloride 3:1 (3 × 50 ml), treated with 5% aqueous sodium hydrogensulfite (50 ml) until the organic layer was colorless and washed with 50% sat. brine (2 × 50 ml). Drying the organic phase over magnesium sulfate and evaporation of solvents furnished a viscous oil, which on standing crystallized. Trituration with pentane (2 × 10 ml) gave 1.05 g of crystalline material, which upon recrystallization from ether/pentane in the cold afforded 879 mg (60%) of TLC. pure bromohydrin **9** (m.p. 106–107.5°). The remaining mother liquors were combined (3 spots on TLC.) and purified by prep. TLC. with hexane/THF 9:1 (3 elutions) yielding 127 mg (9%) of bromoketone **11** and 330 mg of a mixture of the desired bromohydrin **9** and a stereoisomeric bromohydrin **10**. Separation between **9** and **10** was effected by another purification by prep. TLC. with benzene/THF 15:1 (2 elutions) affording 175 mg (12%) of **9** and 140 mg (10%) of **10**. The mass recovery thus was 91% and the total yield of the desired bromohydrin **9** 72%.

Analytical data of **9**. – IR. ($CHCl_3$): 3560, 3290, 3090, 3065, 3035, 3010, 2945, 2875, 1655, 1500, 1473, 1455, 1424, 1369, 1337, 1323, 1282, 1252, 1182, 1159, 1120, 1080, 1057, 1018, 990, 969, 940, 920, 905, 898, 880, 843, 729, 698. – NMR. ($CDCl_3$, 100 MHz): 1.20–2.90 (br. *m*, 11H); 3.48–3.85 (*m*, 1H, CH–O); 4.35 (*d*, *J* = 10, 1H, CH–Br); 5.10 (*s*, 2H, O–CH_2); 7.31 (*s*, 5H, arom. H). – MS.: 273 ($M^+ - Br$), 255, 226, 91 (100%) ($C_{17}H_{22}BrNO_2$).

Analytical data of **10**. – NMR. ($CDCl_3$, 100 MHz): 1.09–2.99 (br. *m*, 11H); 3.87 (*d*, *J* = 10, 1H, CH–Br); 4.27–4.59 (*m*, 1H, CH–O); 5.09 (*s*, 2H, CH_2–O); 7.30 (br. *s*, 5H, arom. H).

Analytical data of **11**. – IR. (CCl_4): 3090, 3065, 3035, 2940, 2875, 1739, 1635, 1498, 1470, 1455, 1442, 1432, 1410, 1368, 1322, 1288, 1272, 1201, 1184, 1165, 1128, 1110, 1016, 948, 917, 867, 698, 662. – NMR. ($CDCl_3$, 100 MHz): 4.71 (*s*, 1H, CH–Br); 5.14 (*s*, 2H, O–CH_2); 7.33 (*s*, 5H, arom. H). – MS.: 351 and 349 (M^+), 273, 271, 255, 253, 179, 162, 149, 131, 105, 92, 91 (100%) ($C_{17}H_{20}BrNO_2$).

Oxidation of **9** *to* **12**. To a solution of 507 mg (1.44 mmol) of bromohydrin **9** in 60 ml of acetone was added 1.62 ml (3 mol-equiv.) of a 2.67 M solution of *Jones* reagent at 0°. After stirring the reaction mixture for 1.5 h at 0° and 30 min at 25° it was quenched with 5% aqueous sodium hydrogensulfite (50 ml) and the bulk of acetone was removed at reduced pressure. Extraction with ether (3 × 80 ml) and washing the organic layers with 50% sat. brine (2 × 60 ml) afforded after drying over magnesium sulfate and evaporation of the solvent i.V. 499 mg (99%) of bromoketone **12** as a colorless oil, homogeneous by TLC. – IR. (CCl_4): 3090, 3065, 3035, 2960, 2875, 1730, 1657, 1498, 1457, 1443, 1422, 1377, 1320, 1278, 1228, 1209, 1173, 1157, 1129, 1102, 1007, 997, 981, 948, 939, 918, 882, 869, 698, 675. – NMR. ($CDCl_3$, 100 MHz): 1.56–3.08 (br. *m*, 12H); 4.32 (*s*, 1H, CH–Br); 5.00 (*s*, 2H, O–CH_2); 7.31 (*s*, 5H, arom. H). – MS.: 351 and 349 (M^+), 271, 270 (100%), 242, 216, 214, 92, 91 (100%) ($C_{17}H_{20}BrNO_2$).

In an analogous experiment the stereoisomeric bromohydrin **10** could be converted to the epimeric bromoketone **11** in quantitative yield. For analytical data see above.

Formation of bromooxime **17** *from* **12**. To a solution of 499 mg (1.43 mmol) of bromoketone **12** and 212 mg (1.5 mol-equiv.) of potassium acetate in 2.90 ml of glacial acetic acid was added 150 mg (1.5 mol-equiv.) of hydroxylamine hydrochloride at 25°. After stirring for 2 h at 25° 50% sat. brine (60 ml) was added and the product was extracted with ether/methylene chloride 3:1 (3 × 70 ml). The organic layers were washed with 50% sat. brine (2 × 60 ml), dried over magnesium sulfate and concentrated i.V. Small amounts of acetic acid could be removed by taking up the resulting viscous oil in

10–20 ml of chloroform and reconcentrating it at reduced pressure for 2 or 3 times. By this procedure 519 mg (100%) of a very viscous oil were obtained, which according to NMR.-analysis consisted of a mixture of geometrically isomeric bromooximes ($E/Z = 1:2$) **17**. Unlike other α-halogenated oximes this compound is very stable and may be stored at ambient temperature for days without any noticeable decomposition. – IR. ($CHCl_3$): 3580, 3275, 3090, 3065, 3005, 2950, 2875, 1650, 1498, 1455, 1422, 1368, 1240, 1081, 1002, 960, 911, 872, 842, 697. – NMR. ($CDCl_3$, 100 MHz): 1.40–2.16 (br. *m*, 12H); 4.54 and 4.69 (2*s*, 1H, CH–Br); 4.96–5.00 (2 *s*, 2H, O–CH_2); 7.28 (*s*, 5H, arom. H).

Alkylation of **17** *and subsequent selective hydrogenation.* To a solution of 1.14 ml (10 mol-equiv.) of 1-butyne in 80 ml of dry THF at −78° was added 3.53 ml (6 mol-equiv.) of a 2.45M solution of butyllithium (in hexane). After stirring for an additional 15 min at −78° (clear colorless solution) a solution of 519 mg (1.42 mmol) of α-bromo-oxime **17** in 20 ml of dry THF was added at once whereby the reaction mixture turned immediately blue. After stirring for an additional 15 min at −78° the cooling bath was removed and the reaction mixture was allowed to warm up slowly (within 45 min) to 25°. At a temperature of −20° the blue color started to fade away and at −10° it had all disappeared. Brine (75 ml) was added and the product extracted with ether (3 × 70 ml). The organic layers were washed with brine (2 × 50 ml) and dried over magnesium sulfate to afford after concentration i.V. 500 mg of a yellow oil.

250 mg of this material were dissolved in 25 ml of ethyl acetate and treated with 125 mg (50% by weight) of 10% Pd/C. After stirring the heterogeneous mixture for 1 h under hydrogen (1 atm) at 25° another 63 mg (25% by weight) of 10% Pd/C were added and stirring was continued for 30 min. According to TLC.-analysis no more starting material was present. The catalyst was filtered off (through Celite), washed with acetone and the filtrate was concentrated i.V. The remaining viscous oil was purified by prep. TLC. with benzene/THF 15:1 (2 elutions) to afford 187 mg (77% overall from **17**) of oxime **20**, homogeneous by TLC. – IR. (CCl_4): 3600, 3290, 3090, 3065, 3035, 2960, 2940, 2865, 1655, 1498, 1468, 1455, 1422, 1368, 1213, 1080, 1042, 1018, 980, 957, 918, 900, 865, 840, 698. – NMR. ($CDCl_3$, 100 MHz): 0.60–1.88 (br. *m*, 5H, CH–CN–CH_2 and CH_2–C=N); 5.04 (*s*, 2H, O–CH_2); 7.28 (br. *s*, 5H, arom. H). – MS.: 342 (M^+), 326, 325, 286, 285, 269, 235, 229, 227, 202, 179, 163, 149, 91 (100%) ($C_{21}H_{30}N_2O_2$).

In a separate experiment the crude alkylation product was purified by prep. TLC. with benzene/THF 15:1 to furnish pure acetylene **19** in 85% yield (from **17**). – IR. (CCl_4): 3600, 3285, 3090, 3065, 3035, 2940, 2875, 1660, 1496, 1455, 1422, 1368, 1321, 1232, 1211, 1080, 1015, 998, 966, 918, 902, 870, 832, 698. – NMR. ($CDCl_3$, 100 MHz): 1.07 (*t*, $J = 7$, 3H, CH_3); 1.34–2.70 (br. *m*, 17H); 3.08–3.36 (*m*, 1H); 3.50 (*t*, $J = 2$, 1H, CH–C≡C); 5.11 (*s*, 2H, O–CH_2); 7.30 (br. *s*, 5H, arom. H). – MS.: 338 (M^+), 322, 321, 294, 293, 269, 231, 213, 203, 91 (100%) ($C_{21}H_{26}N_2O_2$).

Hydrolysis of the oxime **20** *to the ketone* **21**. To a solution of 72 mg (0.21 mmol) of **20** in 4 ml of methanol was added 0.95 ml (18 mol-equiv.) of a 4.14M aqueous ammonium acetate solution and 0.49 ml (6 mol-equiv.) of a 20% aqueous titanium trichloride solution. After stirring the black reaction mixture for 1.5 h at 25° it was quenched with 4 ml of 5% aqueous sodium hydrogencarbonate and transferred into a separatory funnel. Another 20 ml of 5% aqueous sodium hydrogencarbonate was added and the product extracted with ether (3 × 25 ml). The organic layers were washed with brine (2 × 25 ml), dried over magnesium sulfate and concentrated i.V. to afford 65 mg (95%) of **21** as a colorless oil, homogeneous by TLC. – IR. (CCl_4): 3090, 3065, 3035, 2960, 2930, 2875, 1710, 1498, 1469, 1457, 1432, 1422, 1367, 1310, 1210, 1190, 1079, 1040, 1018, 918, 900, 868, 845, 698. – NMR. ($CDCl_3$, 100 MHz): 0.68–2.10 (br. *m* with tripletoide *m* at 0.81, 18H, aliphatic H, CH_3); 2.10–2.78 (br. *m*, 5H, CH–CO–CH_2 and CH_2–C=N); 5.06 (*s*, 2H, O–CH_2); 7.29 (br. *s*, 5H, arom. H). – MS.: 327 (M^+), 310, 287, 284, 271, 270, 263, 259, 258 (100%), 236, 220, 202, 149, 91 ($C_{21}H_{29}NO_2$).

Removal of the benzyl protecting group of the O*-benzyl oxime* **21**. To a solution of 49 mg (0.15 mmol) of **21** in 5 ml of abs. ethanol was added 49 mg (100% by weight) of 10% Pd/C. After stirring the heterogeneous reaction mixture under hydrogen (1 atm) for 1 h at 25° the catalyst was filtered off (through Celite) and washed with acetone. Evaporation of the solvent at reduced pressure afforded 35 mg (98%) of the free oxime **22** as a colorless viscous oil, homogeneous by TLC. – IR. (CCl_4): 3600, 3310, 2960, 2940, 2880, 1710, 1470, 1455, 1435, 1425, 1381, 1356, 1312, 1278, 1249, 1208, 1190, 978, 918, 847. – NMR. ($CDCl_3$, 100 MHz): 0.83 (tripletoide *m*, 3H, CH_3); 0.95–2.10 (br. *m*, 15H); 2.12–2.74 (br. *m*, 5H, CH–CO–CH_2 and CH_2–C=N). – MS.: 237 (M^+), 220, 194, 192, 181, 167, 164, 153, 139, 138, 124, 122, 121, 119, 117 (100%), 112, 110 ($C_{14}H_{23}NO_2$).

Reduction of ketone **22** *to alcohol* **23**. 33 mg (1.43 mmol) of sodium was placed in a 50 ml flame dried 3-necked round bottomed flask, equipped with a glass-coated magnetic stirrer, a dry ice/acetone condenser, a septum capped inlet and a stopcock controlled tube, which was connected to a second identical apparatus wherein the ammonia was precondensed over sodium. All the following operations were performed under a static pressure of argon. Ammonia (10 ml) was distilled into the reaction flask and after stirring for 30 min at −78° a solution of 9.6 mg (0.040 mmol) of butyl ketone **22** and 0.11 ml (1.43 mmol) of 2-propanol in 2 ml of dry THF was added to the dark blue colored solution. The reaction mixture was stirred for an additional 2 min, quenched at −78° with 2 ml of sat. aqueous ammonium chloride solution, let warm up to 25° within 30 min and transferred into a separatory funnel. More sat. aqueous ammonium chloride solution (20 ml) was added and the product extracted with ether (3 × 25 ml). The organic layers were washed with brine (2 × 25 ml), dried over magnesium sulfate and concentrated i.V. furnishing 13,5 mg of colorless viscous oil, which according to TLC.-analysis contained some mineral oil as an impurity. Purification by prep. TLC. with benzene/THF 5:1 afforded 8.8 mg (92%) of butyl alcohol **23**, homogeneous by TLC., m.p. 129–131°. – IR. ($CHCl_3$): 3480, 3260 (shoulder), 3130, 2935, 1690, 1381, 1350, 1278, 1188, 1173, 1143, 1130, 1083, 1070, 1014, 990, 970, 950, 933, 909. – NMR. ($CDCl_3$, 100 MHz): 0.70–0.99 (tripletoide *m*, 3H, CH_3); 1.00–1.97 (br. *m*, 18H); 2.36–2.67 (*m*, 2H, CH_2–C=N); 3.62–3.86 (*m*, 1H, CH–O). – MS.: 239 (M^+), 222, 221, 204, 189, 182, 178, 168, 165, 164, 102 (100%), ($C_{14}H_{25}NO_2$).

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