7. A New Total Synthesis of *dl*-Pumiliotoxin-C *via* an Indanone[1])

by **Wolfgang Oppolzer, Charles Fehr** and **Jochen Warneke**
Département de Chimie Organique, Université de Genève, CH-1211, Genève 4

(17. XI. 76)

Summary

dl-Pumiliotoxin-C (**4**) was synthesized in a practical manner from *trans*-4-hexenal (**9**). The key step **14** → **15** (*Scheme 3*) involves an intramolecular *Diels-Alder* reaction giving mainly the *cis*-fused indanols **15a**, which were converted to the *cis*-fused ketone **16**. After *Beckmann*-rearrangement of **16** the octahydroquinolinone **7** was transformed to the lactim-ether **23**. (*Scheme 7*). Reaction of **23** with propylmagnesium bromide followed by hydrogenation furnished *dl*-**4** in a highly stereoselective fashion.

1. Introduction. – Pumiliotoxin-C (**4**) occurs in minor quantities in the skin of the frogs *Dendrobates pumilio* [1] and *D. auratus* [2]. The complex stereochemical features[2]) and the paucity of this physiologically active alkaloid provide a considerable challenge to the synthetic chemist [3–6]. We have recently met this challenge by using the intramolecular *Diels-Alder* reaction **2** → **3** as the crucial step in the synthesis outlined below[3]) (*Scheme 1*); one of its key features is that during the conversion of **1** to **4** the original chiral center of the amine **1** controls to a major extent the configuration of the other chiral centers which are formed simultaneously in the cycloaddition process.

We now wish to report an alternative synthetic scheme (**5** → **6** → **7** → **4**) following a different stereochemical strategy in which center C(2) is induced by the other three chiral centers[4]) during the transformation **7** → **4**; for their assembly an intramolecular cycloaddition **5** → **6** was envisaged. Since both *trans*-dienes **5a**, as well as the corresponding *cis*-dienes (**5b**) may be considered as leading selectively to the required *cis*-junction of **6** the two isomeric trienols **11** and **12** were separately prepared from the dienynol **10** in a stereocontrolled manner.

2. Preparation of the trans- and cis-Trienols 11 and 12 (see *Scheme 2*). – The common precursor **10** was readily available by addition of vinylacetylene magnesium bromide [8] to the aldehyde **9**, obtained from 3-buten-2-ol (**8**) *via* a *Claisen-Cope* rearrangement of its vinyl ether [9]. Reduction of **10** with lithium aluminium hydride/sodium methanolate in THF [10] furnished exlusively the *trans*-trienol **11** (87% yield).

---

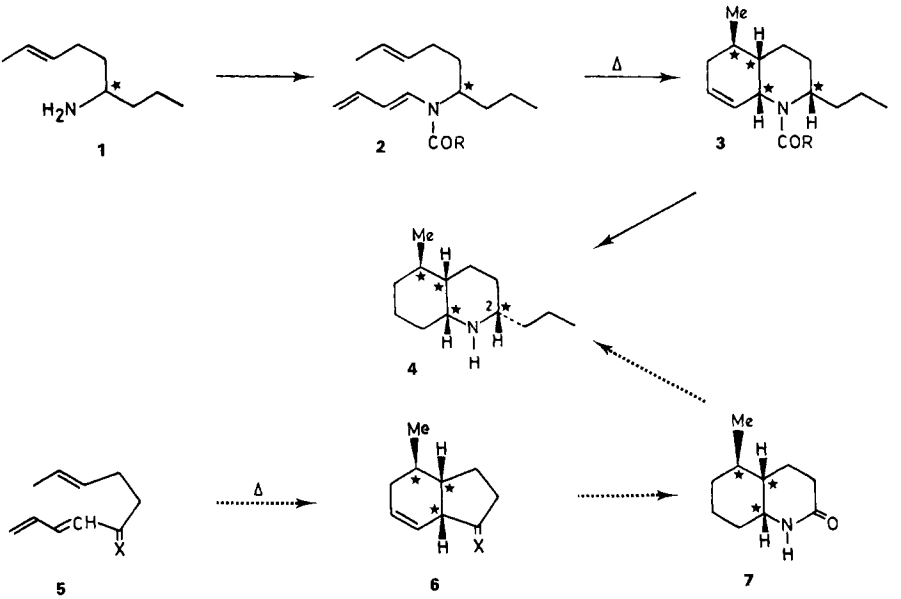
[1]) Presented by one of us (*W. O.*) at the 4th Intern. Symposium 'Synthesis in Organic Chemistry', Cambridge (England), July 1975.

[2]) Determined by X-ray analysis of the hydrochloride [1].

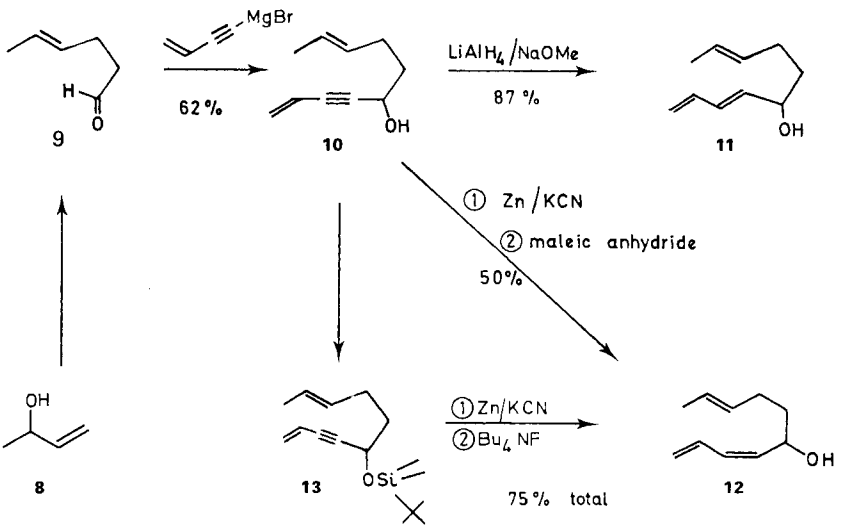
[3]) We have very recently improved considerably the yield and stereoselectivity of our reported synthesis [3]. Furthermore, each enantiomer of **4** has been prepared from enantiomerically pure (*R*)- and (*S*)-amine **1**, respectively [7].

[4]) In the course of this work and after its completion two different syntheses, using the lactam **7** as a key intermediate, were reported ([4a] resp. [6]).

Scheme 1



Scheme 2



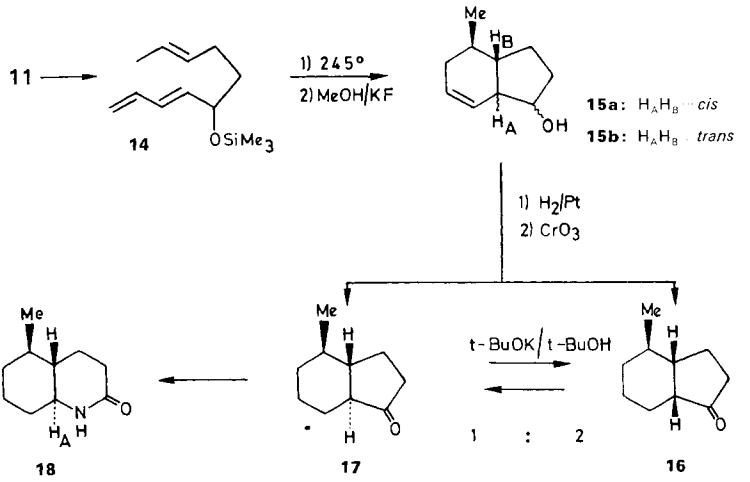
On the other hand, reaction of the acetylene **10** with zinc metal in presence of KCN at 0° [11][5]) afforded a (1:2)-mixture of **11** and **12**. In order to obtain the pure *cis*-alcohol **12** this mixture was treated with maleic anhydride; distillation then gave

[5]) On attempting the partial hydrogenation of **10** in the presence of *Lindlar* catalyst, over-reduction could not be avoided; see for example [12].

unreacted **11** in 50% yield (from **9**). A much more selective pathway to **12** (78% yield from **9**) was achieved by successive reduction of the dimethyl(*t*-butyl)silyl ether **13** with Zn/KCN and Si–O-cleavage with tetrabutylammonium fluoride [13].

3. Conversion of the Trienols 11 and 12 to the Hexahydro-indanones 16 and 17 (*Scheme 3*). – No reaction took place below 240°, on attempting the intramolecular cycloaddition of the trienol **11**, whereas at higher temperature dehydration products were obtained together with minor quantities (10%) of the indanols **15**. The thermolysis of the unstable trienone **5b** (X=O), prepared by oxidation of **11** with MnO_2, looked even less encouraging since it gave a complex mixture of nonidentified products. However, the undesired elimination processes, during the intramolecular cycloaddition of the trienol **11** became less important on heating the corresponding

Scheme 3

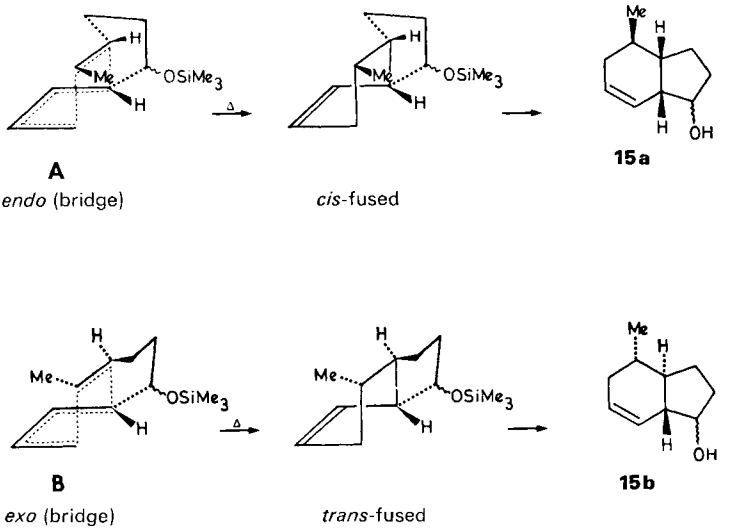


trimethylsilylether **14** to 245°; after hydrolysis the indanols **15** were obtained in 51% overall yield (from **11**). Catalytic hydrogenation of this stereoisomeric mixture followed by oxidation with *Jones'* reagent under nonequilibrating conditions furnished a (2:1)-mixture of *cis*- and *trans*-fused indanones **16** and **17**.

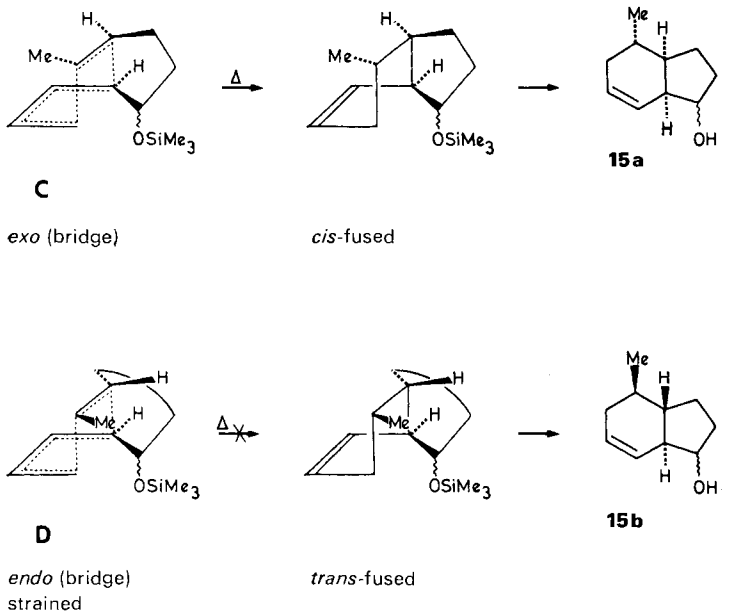
Assuming that the cycloaddition of **14** is kinetically controlled it thus follows that the desired *endo*-transition state **A** (*Scheme 4*) is favored by only 0.6 kcal over the *exo*-orientation **B**. In fact, examination of models reveals that both transition states **A** and **B** are perfectly attainable without the development of significant angle strain; thus, any discrimination between **A** and **B** seems to be subject to less predictable conformational factors. In contrast, the analogous addition of the *cis*-diene **19** can only proceed by way of the *exo*-orientation **C** (*Scheme 5*), the alternative *endo*-transition state **D** being severely strained; accordingly, *cis*-fused adducts should be obtained from **19** in a highly stereocontrolled manner[6]).

[6]) This reasoning is supported by the regio- and stereoselective formation of a *cis*-fused hydrindane on thermolysis of *cis,trans*-methyl-2,6,8-nonatrienoate [14]. For a recent review article on stereochemical and synthetic aspects of intramolecular cycloaddition reactions see [15].

Scheme 4. *Transition states for the intramolecular cycloaddition of the* trans-*diene* **14**



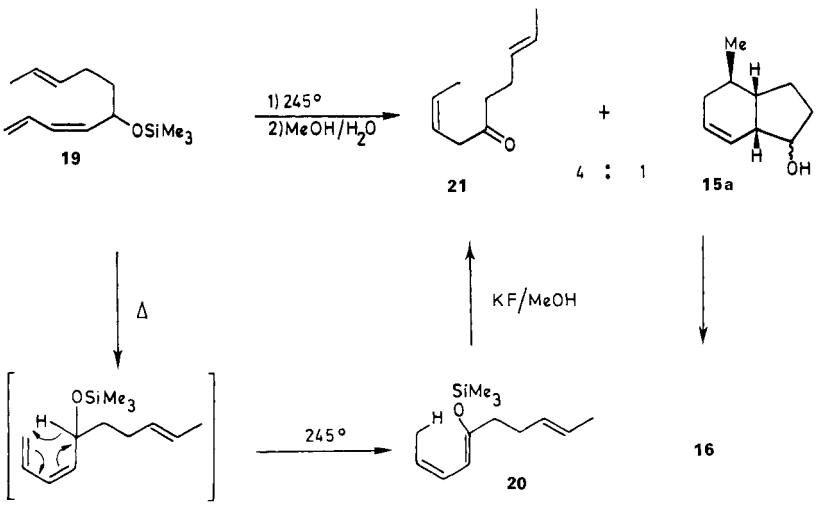
Scheme 5. *Transition states for the intramolecular cycloaddition of the* cis-*diene* **19**



Thus, the *cis*-diene **19** was heated to 245° for 16 h; (*Scheme 6*) subsequent Si–O-cleavage of the reaction mixture with KF/methanol and oxidation, as previously described, indeed furnished the stereochemically pure *cis*-fused indanone **16**, but in only 15% yield.

Chromatography of the hydrolysed thermolysis mixture gave the ketone **21** as the main product. This shows that the low yield of the cycloadduct **16** is the result

Scheme 6



of a competitive 1,5-hydrogensshift **19** → **20**[7]). Hence it appears that this 1,5-shift becomes dominant at the high temperature (245°) needed for the cycloaddition of **19**, involving a nonactivated dienophile unit; in contrast, the previously reported intramolecular *Diels-Alder* addition of an activated dienophile [14] proceeds cleanly at 135°.

4. Transformation of the Indanols 15 to *dl*-Pumiliotoxin-C (4) (*Scheme 7*). – In view of the above result it seemed preferable to base our synthetic scheme on the thermolysis of the *trans*-diene **14** (*Scheme 3*). Hydrogenation of the crude reaction mixture with PtO_2 in methanol[8]), followed by oxidation with *Jones'* reagent gave directly a (2:1)-mixture of the indanones **16** and **17** in 51% overall yield (from **11**). After chromatographic separation the minor *trans*-fused isomer **17** could be recycled to **16** by epimerization with potassium *t*-butoxide to give a separable (3:2)-equilibrium mixture of **16** and **17**[9]). However, having observed that the *trans*-indanone **17** reacts

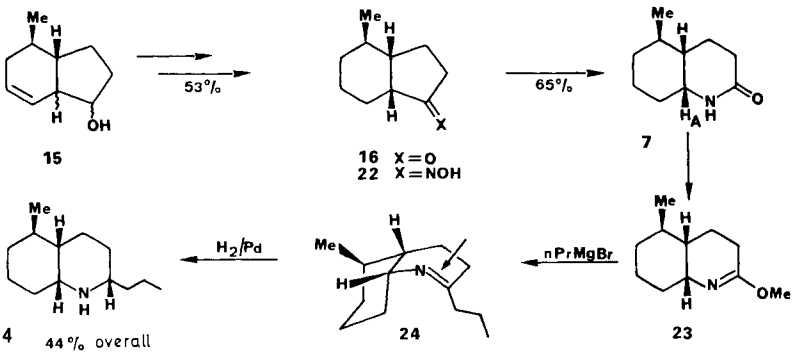
[7]) For a synthetic application of a related sigmatropic 1,5-H-shift see [16]. Examples of 1,5-hydrogen migrations which compete with intramolecular *Diels-Alder* reactions of cyclopentadiene and cyclohexadiene derivatives have been described [17–19].

[8]) For the cleavage of silylethers by catalytic hydrogenation see [20].

[9]) The same (3:2)-mixture was obtained by epimerization of **16**. For equilibrium ratios between *cis*- and *trans*-indanones see [21].

faster with hydroxylamine than its *cis*-isomer **16** it was more convenient to treat the crude indanones with a stoichiometric amount (relative to **17**) of hydroxylamine hydrochloride and sodium acetate in ethanol; simple crystallization and distillation of the reaction mixture gave the pure *cis*-fused indanone **16** in 51% yield (from **15**). Oximation of **16** with an excess of hydroxylamine, followed by *Beckmann* rearrangement with *p*-toluenesulfonyl chloride in aqu. NaOH/dioxane [22] furnished the *cis*-fused lactam **7** (*Scheme 7*).

Scheme 7



The configuration of the lactams **7** and **18** (*Scheme 3* and *7*) could be readily assigned on the basis of their NMR. spectra: The spectrum of **7** indicates an equatorial H_A, which appears as a narrow multiplett (half-height width = 7 Hz) at $\delta = 3.64$ ppm; the axial H_A of the *trans*-fused isomer **18** gives rise to a broad signal (half-height width = 22 Hz) at higher field ($\delta = 3.0$ ppm) [23]. This assignment was confirmed by comparison of **7** with a sample provided by *Inubushi*, as well as by its conversion to *dl*-pumiliotoxin-C.

For this purpose the previously described multistep transformation **7** → **4** [4] seemed not to be reproducible in our hands. We also have studied independently the thermal rearrangement of the corresponding *N*-propionyllactam with CaO [6] [24]. However, the reaction of the lactim-ether **23**[10]), prepared from **7** using trimethyloxoniumtetrafluoroborate, with propylmagnesium bromide in benzene under reflux [26] appeared to be much more efficient and reliable. Hydrogenation of the so obtained crude imine **24** proceeded, as expected, selectively from the *exo*-side, to give *dl*-pumiliotoxin-C (**4**) in 44% yield (from **7**). The free base is indistinguishable by GC. from natural **4**. The synthetic hydrochloride, m.p. 238–242° shows the same ^{1}H-NMR.-, IR.- and mass spectra to be identical with a sample, synthesized by an independent route [3].

We are grateful to Prof. *Y. Inubushi* and to Prof. *B. Witkop* for kindly providing samples of the *dl*-lactam **7** and of natural pumiliotoxin-C. We thank the *Fonds National Suisse de la Recherche Scientifique*, *Sandoz Ltd*, Basel and *Givaudan SA*, Vernier for financial support of this work.

[10]) For a review article on lactim-ethers see [25].

Experimental Part

General Remarks. – *Preparative chromatography* was carried out on silica gel (*Merck*, 0.05–0.20 mm). *Gas chromatograms* (GC.): steel column (2mm/4m), 5% FFAP on Chromosorb W, 2.5 atm N_2 unless specified otherwise; retention time in min. *Melting points* (m.p.) are not corrected. *UV. spectra*: λ_{max} in nm, log ε in parantheses. *IR. spectra*: in $CHCl_3$ unless specified otherwise; $\tilde{\nu}_{max}$ in cm^{-1}. *^{1}H-NMR. spectra*: in $CDCl_3$, internal standard tetramethylsilane ($\delta = 0$ ppm); abbreviations: *s* = singlet, *d* = doublet, *t* = triplet, *m* = multiplet, *J* = spin-spin coupling constant (Hz). *Mass spectra* (MS.): *m/e*, relative peak intensity in % in parantheses.

Preparation of the Stereoisomeric Trienols 11 and 12 (*Scheme 2*). – trans-*1,8-Decadien-3-yne-5-ol* (**10**). A stream of vinylacetylene [8] (8.1 g, 156 mmol) was passed slowly at 0° into a stirred solution of ethyl magnesium bromide, freshly prepared from ethylbromide (15.9 g, 146 mmol) and magnesium (3.5 g, 146 mmol), in ether (300 ml). The mixture was stirred at RT. for 16 h and then heated under reflux for 1 h. After addition of *trans*-4-hexenal (**9**) [9] (13,6 g, 139 mmol, calculated from GC.-analysis of the crude mixture obtained from 1-buten-3-ol) to the so prepared solution of vinylacetylenemagnesium bromide at −5° the reaction was stirred at 0° for 2 h, decomposed with ice/NH_4Cl, and extracted with ether. The washed (sat. aqu. NaCl), dried ($MgSO_4$) and evaporated extracts gave, on distillation, the acetylenic alcohol **10** as a colourless oil (13.0 g, 66%), b.p. 74°/0.1 Torr. GC. (200°): retention time 10.4. – IR.: 3590, 3400br., 980, 935. – ^{1}H-NMR. (90 MHz): 1.6–2.4 (8H); 4.50 (*d* × *t*, *J* = 1 and 6.5, 1H); 5.2–6.1 (5H). – MS.: 149 ($C_{10}H_{14}O-1^+$, 3), 135 (15), 131 (17), 117 (85), 107 (29), 106 (21), 105 (17), 103 (22), 95 (19), 94 (45), 93 (22), 91 (59), 81 (100).

trans,trans-*1,3-8-Decatrien-5-ol* (**11**). A suspension of $LiAlH_4$ (290 mg, 7.5 mmol) and $NaOCH_3$ (810 mg, 15 mmol) in dry THF (50 ml) was added at 0° to a stirred solution of the acetylenic alcohol **10** (1.50 g, 10 mmol) in THF (10 ml). The reaction mixture was stirred at 25° for 2 h, decomposed with sat. aqu. Na_2SO_4, filtered, evaporated and distilled to afford the pure *trans,trans*-trienol **11** (225 mg, 87%), b.p. 70°/0.2 Torr. – GC. (200°): retention time 8.1. – UV. (cyclohexane): 226 (3.3). – IR.: 3600, 3400br., 1010, 970, 910. – ^{1}H-NMR. (100 MHz): 1.3–1.8 (4H); 1.8–2.3 (4H); 4,18 (*q*, *J* = 6.5, 1 H); 4.9–5.5 (4H); 5.8 (*d* × *d*, *J* = 6.5 and 15, 1H, irradiation at 4.18 → *d*, *J* = 15); 6.0–6.6 (2H). – MS.: 152 ($C_{10}H_{16}O^+$, 5), 97 (37), 92 (38), 91 (52), 83 (100), 69 (46), 55 (100).

cis,trans-*1,3,8-Decatrien-5-ol* (**12**). a) Zinc powder (10 g) and KCN (1,0 g) was added in one portion at 25° to a stirred solution of the acetylenic alcohol **10** (190 mg, 1.36 mmol) in 2-propanol/water 1:1 (30 ml). 5 min later, after the addition of another portion of zinc powder (5 g) the mixture was stirred for 30 min and separated into two liquid phases by addition of benzene (20 ml). Filtration of the organic phase through SiO_2 (3 g) and evaporation of the filtrate furnished a (1:2)-mixture (GC., 200°) of the trienols **11** and **12** (190 mg, 99%) which was heated for 3 h under reflux in toluene (3 ml) with maleic anhydride (60 mg, 0.61 mmol) and a trace of hydroquinone. Bulb-to-bulb distillation of the evaporated mixture gave the pure *cis,trans*-trienol **12** (96 mg, 50%), b.p. (bath) 90°/0.2 Torr. – GC. (200°): retention time 7.48. – UV. (cyclohexane): 228 (3.27). – IR.: 3600, 3400br., 1050, 1007, 970, 920. – ^{1}H-NMR. (60 MHz): 1.4–2.2 (7H); 3.0 (br., 1H); 4.50 (*d* × *t*, *J* = 13 and 6.5, 1H); 4.8–5.3 (5H); 5.9 (*t*, *J* = 10.5, 1H); 6.5 (*d* × *t*, *J* = 16.5 and 10.5, 1H). – MS.: 152 ($C_{10}H_{16}O^+$, 6), 123 (13), 97 (38), 83 (100), 69 (45), 55 (74).

b) A mixture of the acetylenic alcohol **10** (800 mg, 5.33 mmol), *t*-butyl-dimethyl-chlorosilane (1.0 g, 6.68 mmol) and imidazol (1.0 g, 14.7 mmol) in dry DMF (2 ml) was stirred at 35° for 15 h, then diluted with water (10 ml) and extracted with pentane (2 × 10 ml). The extracts were washed, dried and evaporated to give a viscous residue which after filtration through SiO_2 (10 g, benzene) furnished the pure silylether **13** (1.33 g, 94%), b.p. 90°/0.2 Torr. – GC. (160°): retention time 11.38 min. – IR.: no OH, 2870, 1260, 1095, 1080, 973, 840. – ^{1}H-NMR. (60 MHz, CCl_4): 0.02 (*s*, 6H); 0.85 (*s*, 9H); 1.5–2.3 (7H); 4.41 (*t*, *J* = 6, 1H); 5.3–5.8 (5H). – MS.: no $C_{16}H_{28}OSi^+$-peak, 207 (24), 189 (42), 147 (97), 109 (24), 75 (100), 73 (34).

Zinc powder (30 g) and KCN (5.0 g) were added at 25° to a stirred solution of the acetylenic silylether **13** (1.32 g, 5.0 mmol) in 2-propanol/water 1:1 (120 ml). After addition of another portion

of zinc powder (10 g) the mixture was stirred at 25° for 15 h and worked up as described above to give a viscous residue (1.35 g) which on distillation afforded the pure *t*-butyl-dimethylsilyl ether of **12** (1.125 g, 79% from **10**), b.p. 90° (bath)/0.2 Torr. – GC.: (160°): retention time 9.06. – UV. (cyclohexane): 229 (3.32). – IR. (film): no OH, 2870, 1263, 1090, 1080, 970, 840, 780. – ^{1}H-NMR. (100 MHz): 0.03 (*s*, 6H); 0.90 (*s*, 9H); 1.3–2.2 (7H); 4.59 (*d*×*t*, *J*=9 and 6.5, 1H, irradation at 1.8 → *d*, *J*=9); 5.0–5.6 (5H); 5.98 (*t*, *J*=11, 1H); 6.6 (*d*×*t*, *J*=16.5 and 11, 1H). – MS.: 266 ($C_{16}H_{30}OSi^+$, 1), 209 (47), 189 (24), 147 (81), 75 (100).

Tetrabutylammonium fluoride (150 mg, 0,174 mmol) was added to a solution of the *t*-butyl-dimethylsilyl ether of **12** (50 mg, 0.19 mmol) in THF (1 ml). After 20 min at 25° the homogemeous solution was evaporated. Filtration of the residue through SiO_2 (500 mg, CH_2Cl_2), followed by distillation of the evaporated filtrate furnished the pure *cis,trans*-trienol **12** (25 mg, 88%), identical in all respects, by spectral comparison, to the authentic material prepared by method a).

Conversion of the Trienols 11 and 12 to the Hexahydroindan-1-ones 16 and 17. – *Thermolysis of the* trans,trans-*trienol* **11**. A solution of **11** (1 g, 6.6 mmol) in toluene (25 ml) was heated under argon in a sealed tube to 250° for 16 h. Chromatography of the evaporated mixture (C_6H_6/EtOAc 19:1) furnished (apart from less polar products) the indenols **15** (100 mg, 10%) as a mixture of stereoisomers. – IR.: 3600, 3420br., 835. – ^{1}H-NMR. (100 MHz): 0.93 (*d*, *J*=6, 3H); 1.1–2.6 (10H); 3.9 (*m*, 1H); 5.6–5.9 (2H). – MS.: 152 ($C_{10}H_{16}O^+$, 8), 134 (56), 119 (42), 108 (42), 93 (100).

The yield of **15** could not be improved when the thermolysis of **11** was carried out either by flash pyrolysis or in solution (toluene) after addition of potassium *t*-butoxide (5 mol%) or triethylamine.

Preparation and Thermolysis of trans,trans-*1,3,8-Decatrien-5-one* (**5b**, X=0). Activated MnO_2 (10 × 100 mg) was added portionwise over 3 h to a stirred solution of the trienol **11** (100 mg) in benzene (2 ml) until no more **11** could be detected by GC. analysis. Filtration, evaporation and distillation of the mixture afforded the trienone **5b** (X=0, 60 mg, 61%), b.p. 75° (bath)/0.2 Torr. – GC. (200°): retention time 6.92. – UV. (cyclohexane): 262 (3.4). – IR.: no OH, 1690, 1665, 1625, 1597, 1010, 970, 930. – ^{1}H-NMR. (60 MHz): 1.7 (*m*, 3H); 2.0–3.0 (4H); 5.3–6.9 (6H); 7.23 (*d*×*d*, *J*=7.5 and 11.5, 1H).

The trienone **5b** (X=0, 55 mg) was heated in either toluene or heptane (20 ml) in the presence or absence of 2,6-dimethylphenol (10 mg) in a sealed ampoule under argon for 16 h. Below 180° no reaction took place, whereas higher temperatures furnished a complex mixture of products (TLC., GC.) the ^{1}H-NMR. spectrum of which shows no doublet at $\delta \simeq 1$.

Conversion of **11** *to the 4-Methyl-hexahydroindan-1-ones* **16** *and* **17** via *Thermolysis of the* trans, trans-*Trienolsilylether* **14**. A mixture of the *trans,trans*-trienol **11** (526 mg, 3.46 mmol), trimethylsilylacetamide (500 mg, 3.80 mmol) and hexane (3 ml) was heated 1 h under reflux, then allowed to stand at +5° for 16 h. The filtrated and evaporated mixture furnished on distillation the pure *trans,trans*-silylether **14** (668 mg, 86%), b.p. 64°/0.4 Torr. – GC. (130°): retention time 7.81. – IR. (CCl_4): no OH, 2870, 1610, 1260, 1080, 1005, 970, 905. – ^{1}H-NMR. (60 MHz): 0.05 (*s*, 9H); 1.1–2.3 (7H); 4.07 (*m*, 1H); 4.8–6.6 (7H). A solution of the *trans,trans*-silylether **14** (668 mg, 2.98 mmol) in dry toluene (30 ml) was heated in a silylated (the tube was pre-treated with a 1% solution of bis(trimethylsilyl)acetamide in pentane for 5 min) and sealed pyrex tube to 245 to 250° for 16 h and then evaporated to give a viscous residue (680 mg) which was converted to the ketones **16** and **17** either by method a) or by method b).

a) A solution of the crude thermolysis mixture (340 mg) and KF (180 mg, 3.1 mmol) in methanol (5 ml) was stirred at 25° for 4 h and then filtered through SiO_2 (200 mg). The evaporated filtrate gave on chromatography (SiO_2, 1 g; CH_2Cl_2/EtOAc 9:1) the pure alcohols **15** (116 mg, 51% from **11**) identical with the alcohols **15** obtained by direct pyrolysis of **11**. A solution of **15** (1.05 g, 6.90 mmol) in methanol (20 ml) was stirred with PtO_2 (50 mg) under H_2 for 3 h, filtered through *Celite* and evaporated to give a viscous residue (1.049 g) [^{1}H-NMR. (60 MHz): 0.5–2.7 (17H); 4.13 (*m*, 1H)], which was oxidized at 0° to 10° in acetone (40 ml) with *Jones'* reagent (6 ml of a solution of 5.3 g CrO_3 + 8 g H_2SO_4 in 40 ml of water). After addition of pentane (150 ml) the organic phase was shaken with sat. aq. $NaHCO_3$ (2 ×), dried and evaporated. The residue was filtered through SiO_2 (5 g, CH_2Cl_2 to give, after evaporation, a (2:1)-mixture (GC.) of the ketones **16** and **17** (945 mg, 90% from **15**).

b) A solution of the crude mixture, obtained by thermolysis of **14** (340 mg), in methanol (15 ml) was stirred with PtO_2 (30 mg) under H_2 for 3 h. Filtration and evaporation of the filtrate afforded a viscous residue (280 mg) which was oxidized in acetone (10 ml) with *Jones'* reagent (0.75 ml). Work-up and purification as in methode a) gave a (2:1)-mixture (GC.) of **16** and **17** (134 mg, 51% from **11**). The same stereoisomeric ratio of **16** and **17** was obtained when the oxidation was carried out with chromic acid in a 2-phase system or with CrO_3/pyridine[11]).

Thermolysis of the cis, trans-*Trienolsilylether* **19**.a) *Preparation of the* cis-*fused Hexahydroindan-1-one* (**16**). The *cis,trans*-trienol **12** (90 mg, 0.59 mmol) was silylated (as described for the conversion **11** → **14**) to give the pure distilled silylether **19** (109 mg, 82%), which was heated under the same conditions as used for its stereoisomer **14**. Following the experimental conditions outlined above the crude thermolysis mixture was successively hydrogenated (PtO_2/H_2) and oxidized (*Jones'* reagent) to give, after chromatography, **16** (13 mg, 15% from **12**), which contains less than 0.8% of its *trans*-isomer **17** (GC.-analysis).

b) *Formation of 2,8-Decadien-5-one* (**21**). The crude mixture (150 mg) obtained by thermolysis (245°) of the silylether **19** (150 mg, 0.67 mmol) was treated with KF in methanol as described earlier to afford, after work-up, a viscous residue, which on chromatography (SiO_2, 2 g, benzene) furnished the pure dienone **21** (33 mg, 32%), IR. (CCl_4): no OH, 1720. – ^{1}H-NMR. (100 MHz): 1.5–1.8 (6H); 2.1–2.7 (4H); 3.0–3.3 (2H); 5.2–5.9 (4H).

Chromatographic Separation and Characterization of the Hexahydro-indan-1-ones **16** *and* **17**. The (2:1)-mixture of **16** and **17** (60 mg, 0.4 mmol) was chromatographed (SiO_2, 6 g; toluene) to afford the less polar *cis*-fused hexahydroindanone **16** (33 mg, 0.22 mmol) [B.p. 75° (bath)/0.1 Torr. – GC. (steel capillary column, 150 ft/0.01 inch *Perkin Elmer*, K – 20 M, 160°, 3 atm N_2): retention time 14.54. – IR.: 1735. – ^{1}H-NMR. (100 MHz): 0.95 (*d*, J = 7, 3H); 0.8–2.7 (13H). – MS.: 152 ($C_{10}H_{16}O^+$, 69), 137 (6), 134 (8), 123 (12), 110 (18), 108 (23), 95 (23), 92 (89), 91 (100), 83 (65), 81 (38).], followed by a fraction containing **16** and **17** (5 mg), and finally the pure *trans*-indanone **17** (16 mg, 0.1 mmol) [B.p. 75° (bath)/0.1 Torr. – GC. (steel capillary column, 150/0.01, *Perkin Elmer* K – 20 M, 160°, 3 atm N_2): retention time 14.13. – IR.: 1735. – ^{1}H-NMR .(100 MHz): 0.95 (*d*, J = 7, 3H); 0.8–2.7 (13H). – MS.: 152 ($C_{10}H_{16}O^+$, 92), 137 (10), 134 (10), 123 (15), 110 (27), 108 (40), 95 (38), 83 (100), 81 (58)]. The stereochemical assignment of the ketones **16** and **17** is based on the properties of the corresponding lactams **7** and **18**, respectively.

Interconversion of the Hexahydroindanones **16** *and* **17**. A solution of the *trans*-ketone **17** (180 mg, 1.2 mmol) in 0.2 N potassium *t*-butoxide/*t*-butylalkohol (1 ml) was stirred at 50° for 1 h. After addition of ether (20 ml) the mixture was shaken with 5% aqu. citric acid and with sat. aqu. $NaHCO_3$, dried and evaporated to give a (3:2)-mixture (GC.) of **16** and **17** (155 mg, 86%). The same (3:2)-equilibrium mixture of **16** and **17** was obtained from the *cis*-fused ketone **16** using identical conditions.

Separation of the cis-*fused Hexahydroindanone* **16** *from* **17** *by selective Oximation of* **17**. a) Hydroxylamine hydrochloride (143 mg, 2.06 mmol) was added to a solution of a (2:1)-mixture of **16** and **17** (945 mg, 6.2 mmol) and NaOAc (129 mg, 2.06 mmol) in methanol (5 ml). The reaction mixture was stirred at 25° for 45 min and then evaporated. The residue was transferred to a SiO_2 column (6 g). Elution with benzene (200 ml) furnished the unchanged pure *cis*-isomer **16** (560 mg, 53% from **15**), whereas the more polar oxime of the *trans*-isomer **17** remained on the column.

b) A (2:1)-mixture of **16** and **17** (63 mg, 0.41 mmol) was reacted with a stoichiometric amount (corresponding to **17**) of hydroxylamine as described above. The crude evaporated mixture was shaken with water/ether and the dried ether layer evaporated. Crystallisation of the residue from pentane (to remove a part of the oxime of **17**), followed by distillation of the evaporated mother liquor at 75°/0.1 Torr afforded the pure *cis*-isomer **16** (37 mg) as a colourless oil.

Preparation of the Lactams 7 and 18 (*Schemes 3* and *7*). – (*4aR*,5S*,8aS**) *5-Methyl-decahydroquinolin-2-one* (**7**). A mixture of the *cis*-fused hexahydroindanone **16** (560 mg, 3.68 mmol), hydroxylamine hydrochloride (383 mg, 5.5 mmol), NaOAc (492 mg, 6.0 mmol) and methanol (8 ml) was

---

11) Under these conditions ketones are not epimerized in α-position to the carbonyl [27].

stirred at 25° for 45 min and then evaporated. The residue was shaken with ether/water and the aqueous phase extracted with ether (3 × 10 ml). The combined dried ether extracts afforded on evaporation the crude oxime **22** (640 mg, m.p. 110–111°, ether/pentane). *p*-Toluenesulfonylchloride (1.41 g, 7.40 mmol) was added portionwise over 30 min to a stirred solution of the crude oxime **22** (640 mg), and NaOH (675 mg, 17 mmol) in 70 ml dioxane/water 3:4 at 5°. The mixture was stirred at 25° for 15 h, evaporated and shaken with conc. aqu. $NaCl/CH_2Cl_2$. The dried organic layer gave, after evaporation and crystallization (ether), the pure *cis*-fused lactam **7** (280 mg). The mother liquor was transferred to a small column of SiO_2 (500 mg), and an apolar impurity was removed by elution with benzene. Elution with EtOAc, followed by sublimation of the evaporated eluate at 100°/0.01 Torr furnished another crop (120 mg) of crystalline lactam **7** (total yield: 400 mg, 65% from **16**), m.p. 150–152°. – GC. (steel column (2 mm/2 m) 5% OV225 on Chromosorb W, 200°, 2.5 atm N_2): retention time 26.05. – IR.: 3395, 3290, 3200, 1660. – ^{1}H-NMR. (100 MHz): 0.94 (*d*, *J*=6, 3H); 1.3–2.6 (12H); 3.64 (*m*, half-height width=7, 1H); 6.54 (*s*, br., 1H). – MS.: 167 ($C_{10}H_{17}NO^+$, 28), 125 (10), 124 (100). The lactam **7** was shown to be identical with a sample provided by *Inubushi* on the basis of a mixed m.p. and by comparison of their GC., IR. and ^{1}H-NMR. spectra.

(*4aR*,5S*,8aR**)-*Decahydro-5-methyl-quinolin-2-one* (**18**). The *trans*-fused indanone **17** (87 mg, 0.57 mmol) was transformed to its oxime, which, subjected to a *Beckmann* rearrangement as described above, gave the *trans*-fused lactam **18** (55 mg, 58%), m.p. 161° (acetone). – GC. (steel column, 2 mm, 2 m, 5% OV225 on Chromosorb W, 200°, 2.5 atm N_2): retention time 24.95. – IR.: 3400, 3280, 3210, 1660. – ^{1}H-NMR. (100 MHz): 0.96 (*d*, *J*=5.5, 3H); 0.8–2.75 (12H); 3.0 (*m*, half-height width=22, 1H); 6.5 (*s*, br., 1H). – MS.: 167 ($C_{10}H_{17}NO^+$, 25); 124 (100).

Conversion of the Lactam 7 to *dl*-Pumiliotoxin-C (4) (*Scheme 7*). – (*4aR*,5S*,8aS**)-*2-Methoxy-3,4,4a,5,6,7,8,8a-octahydroquinoline* (**23**). The lactam **7** (268 mg, 1.60 mmol) was added to a stirred mixture of trimethyloxonium tetrafluoroborate (453 mg, 3.0 mmol), *N*-ethyl-diisopropylamine (1 drop) and CH_2Cl_2 (2 ml) at 10° under argon. The mixture was stirred at 25° for 1 h, diluted with CH_2Cl_2, shaken with sat. aqu. $NaHCO_3$ at 0°, dried and evaporated to give the crude lactim-ether **23** (314 mg). – IR.: no NH, 1663. – ^{1}H-NMR. (60 MHz): 0.95 (*d*, *J*=6, 3H); 0.8–2.5 (12H); 3.50 (*m*, 1H); 3.54 (*s*, 3H). The unstable lactim-ether **23** was immediately transformed to *dl*-pumiliotoxin-C (**4**) as described below.

dl-*Pumiliotoxin-C* (**4**). A solution of propylbromide (1.83 ml, 20 mmol) in ether (10 ml) was added dropwise to a suspension of magnesium turnings (500 mg, 20.8 mmol) in ether (5 ml). After stirring the *Grignard* solution at 25° for 30 min its molarity was 1.65 mol/l, as determined by *Gilman* titration [28]. Following the addition of dry benzene (5 ml) to the freshly prepared *Grignard* solution (3 ml, 5.0 mmol), and removal of ether at 80° using a stream of N_2, the crude lactim-ether **23** (314 mg, prepared from 268 mg of **7**) was added to the solution. The mixture was refluxed for 3 h, diluted with ether, washed with aqu. $NaHCO_3$ at 0°, dried and evaporated to give the crude imine **24** (292 mg) which, without purification, was hydrogenated in methanol (15 ml) in presence of 10% Pt/C (25 mg) for 3 h. Filtration of the mixture through *Celite*, evaporation of the oily residue (245 mg) and distillation furnished the more volatile unchanged lactam **7** (30 mg) and the free pumiliotoxin-C (**4**), b.p. 80° (bath)/0.01 Torr (214 mg, 45% from **7**). For the characterization of **4** its hydrochloride was prepared and crystallized from 2-propanol/ether to give colourless needles (81 mg), m.p. (sealed capillary) 238–242°. The mother liquor, after chromatography of the free base (SiO_2, 600 mg; benzene/methanol/sat aqu. NH_3 80:20:0.5) followed by crystallization of the hydrochloride furnished another crop of *dl*-pumiliotoxin-C hydrochloride (5 mg, total yield=86 mg), m.p. 238–242° (sealed capillary). – IR. (KBr): 3400 br., 2530, 1595, 1482, 1467, 1456, 1438, 1390, 1195, 1130, 982, 963, 760, 670. – ^{1}H-NMR. (100 MHz): 0.88 (*d*, *J*=6, 3H); 0.91 (*t*, *J*=6, 3H); 1.0–2.7 (16H); 2.96 (*m*, 1H); 3.32 (*m*, 1H); 8.35 (*m*, br., 1H); 9.55 (*m*, br., 1H). – GC. (free base, steel column 2 mm/2 m, 15% Carbowax 4000+3% KOH on Chromosorb W, 2.2 atm N_2, 160°): retention time 4.89 min. – MS. (free base): 195 ($C_{13}H_{25}N^+$, 5), 194 (3), 152 (100).

$C_{13}H_{26}ClN$ (231.8) Calc. C 67.4 H 11.3% Found C 67.5 H 11.3%

The synthetic **4**-hydrochloride showed the same ^{1}H-NMR., IR. and mass spectra as the hydrochloride of natural pumiliotoxin-C and showed no depression of its m.p. on admixture with *dl*-

pumiliotoxin-C–HCl which had been prepared by an independent route [3] and whose structure is confirmed by an X-ray analysis. The natural and synthetic free bases **4** were also indistinguishable by GC.

REFERENCES

[1] *J. W. Daly, T. Tokuyama, G. Habermehl, I. L. Karle & B. Witkop*, Liebigs Ann. Chem. *729*, 198 (1969).
[2] *W. Kissing*, Dissertation TH Darmstadt *1972*.
[3] *W. Oppolzer, W. Fröstl & H. P. Weber*, Helv. *58*, 593 (1975).
[4] a) *T. Ibuka, Y. Inubushi, I. Saji, K. Tanaka & N. Masaki*, Tetrahedron Letters *1975*, 323; Chem. pharm. Bull. (Japan) *23*, 2779 (1975).
[5] *G. Habermehl & H. Andres*, Naturwissenschaften *62*, 345 (1975); *G. Habermehl, H. Andres, K. Miyahara, B. Witkop & ú. W. Daly*, Liebigs Ann. Chem. *1976*, 1577.
[6] *T. Ibuka, Y. Mori & Y. Inubushi*, Tetrahedron Letters *1976*, 3169.
[7] *W. Oppolzer & E. Flaskamp*, Helv. *60*, 204 (1977).
[8] Org. Synth., Coll. Vol. IV, p. 683.
[9] *R. Marbet & G. Saucy*, Helv. *50*, 2095 (1967); *J. K. Crandall & C. F. Mayer*, J. org. Chemistry *35*, 3049 (1970).
[10] *K. Alder & H. v. Brachel*, Liebigs Ann. Chem. *608*, 195 (1957); *B. B. Molloy & K. L. Hauser*, Chem. Commun. *1968*, 1017.
[11] *F. Näf, R. Decorzant, W. Thommen, B. Willhalm & G. Ohloff*, Helv. *58*, 1016 (1975).
[12] *E. N. Marvell & T. Li*, Synthesis *1973*, 457.
[13] *E. J. Corey & B. B. Snider*, J. Amer. chem. Soc. *94*, 2549 (1972).
[14] *H. O. House & T. H. Cronin*, J. org. Chemistry *30*, 1061 (1965).
[15] *W. Oppolzer*, Angew. Chem. in press.
[16] *E. J. Corey & D. K. Herron*, Tetrahedron Letters *1971*, 1641.
[17] *G. Brieger*, J. Amer. chem. Soc. *85*, 3783 (1963).
[18] *E. J. Corey & R. S. Glass*, J. Amer. chem. Soc. *89*, 2600 (1967).
[19] *A. Krantz & C. Y. Lin*, J. Amer. chem. Soc. *95*, 5662 (1973).
[20] *E. J. Corey & A. Venkateswarlu*, J. Amer. chem. Soc. *94*, 6190 (1972).
[21] *H. O. House & G. H. Rasmusson*, J. org. Chemistry *28*, 31 (1963).
[22] *C. A. Grob, H. P. Fischer, H. Link & E. Renk*, Helv. *46*, 1190 (1963).
[23] *L. M. Jackman & S. Sternhell*, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Chemistry', 2nd ed., Pergamon Press 1969, p. 288.
[24] *B. P. Mundy & B. R. Larsen*, Synth. Commun. *2*, 197 (1972).
[25] *R. G. Glushkov & V. G. Granik*, 'Adv. in Heterocycl. Chem.' *12*, 185 (1970).
[26] *A. Etienne & Y. Correia*, Bull. Soc. chim. France *1969*, 3704.
[27] *H. C. Brown & C. P. Garg*, J. Amer. chem. Soc. *83*, 2952 (1961); *G. I. Poos, G. E. Arth, R. E. Beyler & L. H. Sarett*, ibid., *75*, 422 (1953).
[28] *H. Gilman*, Org. Reactions *6*, 352 (1951).