Efficient Asymmetric Synthesis of Pumiliotoxin C *via* Intramolecular [4 + 2] Cycloaddition

by **Wolfgang Oppolzer**[1]), **Elmar Flaskamp**, and **Lothar W. Bieber***[2])

Département de Chimie Organique, Université de Genève, CH-1211 Genève 4

An efficient asymmetric synthesis in nine steps of natural (−)-pumiliotoxin C (**1**), a decahydroquinoline alkaloid found in the skin of Central American frog species, is presented. The enantiomerically pure starting material (*S*)-norvalinol (**3**), obtained from commercial (*S*)-norvaline, was cyclized in a one-pot procedure to the tosylated aziridine **5**. Ring opening with propargylmagnesium bromide led to the acetylenic sulfonamide tosylamide **6**, free of the allenic isomer. Compound **6** was methylated on the acetylenic C-atom, reduced, and deprotected with Na in liquid NH_3 to give the (*E*)-configured unsaturated amine **8**, which was condensed with crotonaldehyde to the imine **9** and *N*-acylated with isobutanoyl chloride to the key intermediate **2**. Intramolecular *Diels-Alder* reaction furnished a diastereoisomeric mixture of *N*-protected octahydroquinolines **10**. After catalytic hydrogenation and cleavage of the amide, natural **1** was obtained as the main product in 25% overall yield; 3.2% of its isomer **11** with the inverse configurations in position 4a, 5, and 8a was also isolated.

1. Introduction. – Since the isolation of the first 2,5-substituted decahydroquinoline, pumiliotoxin C (**1**), from the skin secretions of *Dendrobates pumilio* in 1969 [1], more than 30 different alkaloids of this structural class have been described [2]. In spite of their highly interesting neurological properties, the trace amounts present in the skin of amphibians and the difficult isolation have restricted more detailed pharmacological studies. So it is not surprising that **1** has attracted the attention of synthetic chemists and has been object of *ca.* 50 publications over the last quarter of century, 11 of these dealing with asymmetric approaches [3]. Of the last group, only five strategies involve fewer than 10 steps with preparatively interesting yields [3a,g,h,j,k]. Our approach, presented in 1977 [3k], has allowed the stereoselective construction of **1** in 9 steps starting from (*S*)-norvalinol (**3**) and has resulted in the revision of the absolute configuration of natural pumiliotoxin C (**1**). The key step of the strategy has been the intramolecular *Diels-Alder* reaction of the aminobutadiene **2** (*Scheme 1*) that provided selectively the *cis*-octahydroquinoline system [4]; the correct configuration was induced by the only pre-existing stereogenic C-atom and the (*E*)-configured dienophile. The inherent chiral economy of our strategy and the possibility to obtain structural analogues by simple variation of substituents, configuration of the stereogenic C-atom, and configuration of the C=C bond of aminobutadienes of type **2** are important advantages in comparison with most other syntheses that require complex chiral starting materials [3g,j], sometimes obtained by tedious resolution of racemates [3a]. Nevertheless, low yields in several steps prior to the crucial cyclization have

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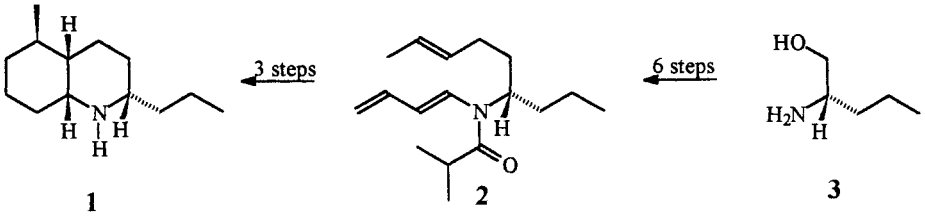
[1]) Deceased 15th March 1996.

[2]) Present address: Departamento de Química Fundamental, Universidade Federal de Pernambuco, Cidade Universitária, 50670-901 Recife-PE, Brazil (fax: (55 81) 2 71 84 48; e-mail: lothar.bieber@dqfex.ufpe.br).

initially limited the preparative usefulness. The continuous interest in the biological properties of **1** and related *cis*- and *trans*-decahydroquinolines prompted us to report here a substantial improvement of the original synthesis.

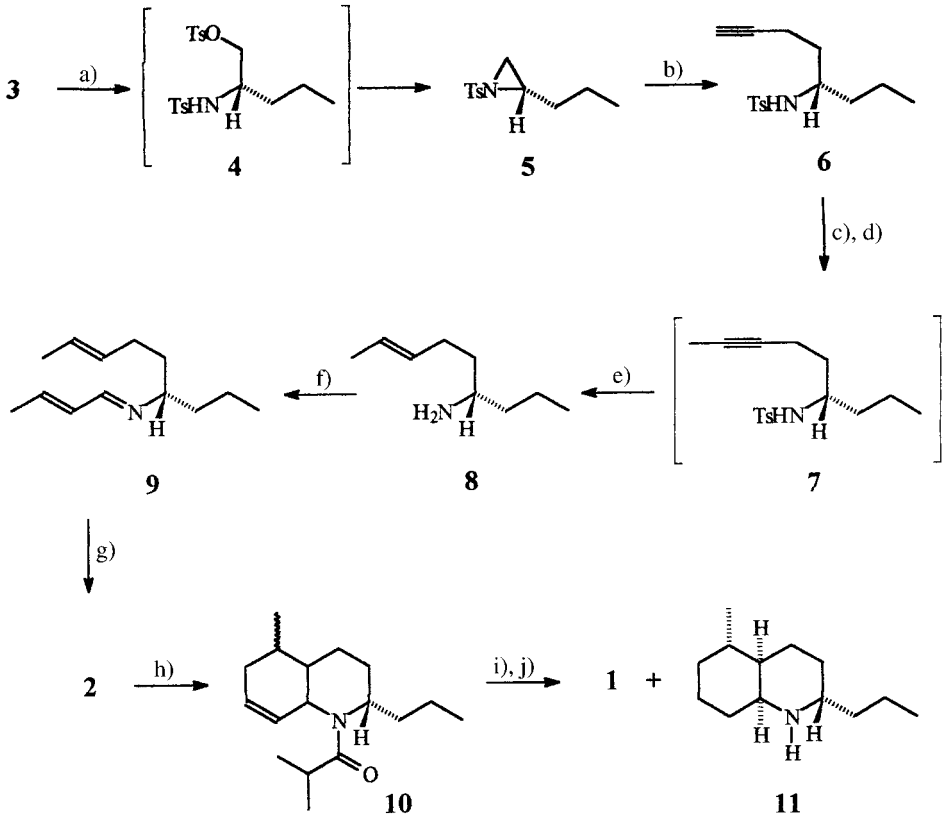
Scheme 1



Results. – As reported in our preliminary communication [3k], the asymmetric starting material was the amino alcohol **3**, easily obtained by reduction of commercially available (*S*)-norvalin [5]. To avoid the unstable intermediate **4**, which was described previously [3k], **3** was treated with excess TsCl and NaH in THF to lead directly and in high yield to aziridine **5** as a distillable colorless liquid, which is stable at low temperature for months (*Scheme 2*). In the next step, nucleophilic ring opening of **5**, originally the *Grignard* reagent derived from 1-bromobut-2-yne has been used to produce, as the main product, not the desired acetylenic sulfonamide **7** but its allenic isomer. The low yield of **7** and its tedious chromatographic separation could be circumvented by the use of propargylmagnesium bromide, which gave the crystalline acetylenic compound **6** as the only product [6]. Alkylation of **6** with $LiNH_2$ and MeI in liquid NH_3 then produced **7**, which could be hydrogenated and deprotected immediately to the (*E*)-configured amine **8** by metallic Na by a one-pot procedure and in high yield. Condensation with crotonaldehyde furnished the imine **9** as described before [3k]. The following *N*-acylation was improved by the use of Et_3N in CH_2Cl_2 [7] and led to the isobutyramide **2** in 95% yield. Intramolecular cyclization at 230–240° in toluene led to the octahydroquinoline **10** as a diastereoisomeric mixture, which was not separated at this stage. Catalytic hydrogenation of **10** and deprotection with BuLi gave a mixture of three isomeric decahydroquinolines in a ratio of 62:1:37, as indicated by GC/MS analysis. The main product, pumiliotoxin C (**1**), could be isolated as the hydrochloride by crystallization in 57% yield; its physical and spectroscopic properties were identical in all respects with those of the natural and synthetic products obtained previously [1][3k]. Chromatography of the free bases obtained from the mother liquor gave a second amount of **1** (3.5%) and a more-polar fraction isolated as the hydrochloride in 14% yield. The structure of the latter was deduced on the basis of the ^{1}H-NMR spectrum of the free base [8] and by comparison with literature data of the racemic compound [9] to be the isomer **11**, which has the inverse absolute configurations at C(4a), C(5), and C(8a). The third isomer present in the crude mixture could not be obtained in pure form.

Discussion. – The modified sequence described here improved the overall yield to 25%, *ca.* 20 times that of the original procedure, providing thus an efficient synthetic access to natural pumiliotoxin C (**1**). The total number of steps remained the same, but

Scheme 2



a) NaH, TsCl, THF; 94%. b) $HCCCH_2MgBr$, Et_2O, 75%. c) BuLi, liq. NH_3. d) MeI. e) Na, liq. NH_3, 80%. f) MeCH=CHCHO, mol. sieves; 86%. g) $Me_2CHCOCl$, Et_3N, CH_2Cl_2; 95%. h) 230–240°, 20 h, toluene (90%). i) H_2/Pd, MeOH. j) BuLi, THF; 60.5 + 14%.

the original first two steps could be performed in a one-pot reaction with considerable advantages in yield and experimental simplicity. On the other hand, the subsequent organometallic reaction was split into two steps with improved regioselectivity and yield. Further modifications were introduced in the experimental procedure for the aminobutadiene **2** and in the final hydrolysis. In view of the remarkable stereoselection induced by one asymmetric C-atom in the starting material **3** and the geometry of the C=C bond in the key intermediate **2**, this synthetic strategy should be suitable also for the preparation of related natural *cis*-decahydroquinolines, their unnatural enantiomers and analogues [2] by simple variation of the starting amino alcohol and the nature of the dienophilic side chain, thus providing the basis for a better pharmacological evaluation and the study of structure/activity relationships.

Experimental Part

General. Moisture and O_2-sensitive manipulations were carried out under purified Ar. THF and Et_2O were dried and distilled from Na/K alloy under N_2 before use; CH_2Cl_2 was distilled from CaH_2. (*S*)-Norvalinol (**3**) was obtained from commercial (*S*)-norvaline (*Aldrich*) according to the procedure in [5]. All other reagents were purchased from commercial suppliers (*Aldrich* and *Fluka*). Compounds **1**, **2**, **5**, **7**, **8**, and **9** have been described previously [3k]; only unpublished spectroscopic and physical data are described here.

*(*S*)-1-[(4-Methylphenyl)sulfonyl]-2-propylaziridin* (**5**). A soln. of 3.88 g (37.7 mmol) of (*S*)-*norvalinol* (**3**) [5] in 10 ml of dry THF was added, at 0° over a period of 15 min, to a suspension of 3.6 g (0.15 mol) of NaH in 100 ml of THF, followed by a soln. of 16.7 g (85 mmol) of TsCl in 20 ml of THF. After stirring for 20 h at r.t., gas evolution ended, and 150 ml of hexanes and 20 g of *Celite* were added. Stirring was continued for 1 h, then the insoluble material was filtered off under Ar and washed with 100 ml of dry Et_2O. The filtrate was concentrated under vacuum, and the remaining brownish oil was purified by column chromatography (CC) (200 g of SiO_2; $CHCl_3$): 8.45 g (94%) of **5** as a colorless liquid, which crystallized at −30° and could be stored at this temp. for months; at r.t., it undergoes slow polymerization. The product can be distilled under vacuum (b.p. 112–115°/10^{-3} mm), but was used directly in the following step. $[\alpha]_D = +12.9$; $[\alpha]_{578} = +13.2$; $[\alpha]_{546} = +14.6$; $[\alpha]_{436} = +21.0$; $[\alpha]_{365} = +24.0$ (c = 1, MeOH, 20°).

4-Methyl-N-*[(*S*)-1-propylpent-4-ynyl]benzenesulfonamide* (**6**). A *Grignard* reagent was prepared from 11.9 g (0.1 mol) of propargyl bromide and 2.9 g (0.12 mol) of Mg turnings in 100 ml of dry Et_2O and added dropwise, at 0°, to a soln. of 7.89 g (33.0 mmol) of **5** in 100 ml of the same solvent. After stirring at r.t. overnight, the mixture was hydrolyzed with NH_4Cl soln. and extracted with Et_2O. The dried extracts were concentrated under vacuum, and the residue was purified by CC (100 g of SiO_2; $CHCl_3$). Crystallization from hexanes/benzene yielded 6.90 g (75%) of **6**. Colorless crystals. M.p. 48–50°. $[\alpha]_D = +3.15$; $[\alpha]_{578} = +3.15$; $[\alpha]_{546} = +3.64$; $[\alpha]_{436} = +5.31$; $[\alpha]_{365} = +5.45$ ($c = 1$, $CHCl_3$, 20°). IR (CCl_4): 3305, 3265, 2120, 1602, 1332, 1163, 1097. ^{1}H-NMR ($CDCl_3$, 100 MHz): 0.77 (*t*, *J* = 7.0, 3 H); 1.00–1.86 (*m*, 6 H); 1.93 (*t*, *J* = 2.5, 1 H); 2.15 (*td*, *J* = 7.0, 2.5, 2 H); 2.43 (*s*, 3 H); 3.37 (br. *m*, 1 H); 4.86 (*d*, *J* = 9.0, NH); 7.56 (*AA′BB′*, 4 H). EI-MS (70 eV): 279 (M^+), 278, 236, 226, 215, 172, 155, 91 (100), 80, 65. Anal. calc. for $C_{15}H_{21}NO_2S$ (279.40): C 64.48, H 7.58, N 5.01, S 11.48; found: C 64.18, H 7.65, N 5.07, S 11.21.

*(1*S*,4*E*)-1-Propylhex-4-enamine* (**8**). To 120 ml of liq. NH_3 at −78° BuLi (29 ml 1.74N in hexanes) was added. After 5 min, a soln. of 3.63 g (13.0 mmol) of **6** in 15 ml of dry Et_2O was added, the mixture was allowed to warm to −30° and cooled again to −78°. MeI (1.98 g, 14.0 mmol) was added, and the soln. was stirred at −30° for 3 h. Then, 2.30 g (0.1 mol) of Na metal was added in small pieces, and the solvent was evaporated overnight. The residue was suspended in 50 ml of Et_2O and hydrolyzed carefully under Ar with 50 ml of H_2O. The mixture was extracted with Et_2O, the extracts were dried (KOH pellets), concentrated, and distilled under vacuum, yielding 145.6 mg (80%) of **8**. Colorless liquid, b.p. 65–70°/15 Torr. $[\alpha]_D = +9.9$; $[\alpha]_{578} = +10.3$; $[\alpha]_{546} = +11.6$; $[\alpha]_{436} = +20.5$; $[\alpha]_{365} = +33.2$ (**8**·HCl, $c = 1$, $CHCl_3$, 20°).

*(1*S*,4*E*)*-N-*(But-2-enylidene)-1-propylhex-4-enamine* (**9**). To a suspension of 10 g of dry molecular sieves (4 Å) in 20 ml of dry Et_2O at 0°, 2.82 g (20 mmol) **8** and 1.54 g (22 mmol) crotonaldehyde were added. After standing at r.t. overnight, the molecular sieves were filtered off under Ar and washed with 20 ml of Et_2O. The filtrate was evaporated and distilled under vacuum, yielding 3.33 g (86%) of **9**. Colorless oil, b.p. 56–58°/10^{-2} Torr. $[\alpha]_D = +8.2$; $[\alpha]_{578} = +8.5$; $[\alpha]_{546} = +9.9$; $[\alpha]_{436} = +19.6$ ($c = 1$, $CHCl_3$, 20°). IR (neat): 3020, 1660, 1627, 1455, 1385, 982, 968. ^{1}H-NMR ($CDCl_3$, 100 MHz): 0.87 (*t*, *J* = 7.3, 3 H); 1.00–2.10 (*m*, 15 H); 2.90 (*quint.*, *J* = 6.3, 1 H); 5.41 (*m*, 2 H); 6.22 (*m*, 2 H); 7.78 (*d*, *J* = 8.0, 1 H). EI-MS (70 eV): 193 (M^+), 192, 178, 150 (100).

N-*(Buta-1,3-dienyl)-2-methyl*-N-*[(1*S*,4*E*)-1-propylhex-4-enyl]propanamide* (**2**). To a soln. of 745 mg (7.0 mmol) of isobutyryl chloride in 20 ml of dry CH_2Cl_2 at −78°, 1.20 g (12 mmol) Et_3N and 1.15 g (6.0 mmol) of **9** were added. The soln. was allowed to warm overnight to +5°, poured directly in the cold (5°) on the top of a column of 50 g of SiO_2 and eluted with $CHCl_3$. After evaporation of the solvent, 1.50 g (95%) of **2** were obtained as yellowish oil. $[\alpha]_D = -4.0$; $[\alpha]_{578} = -4.3$; $[\alpha]_{546} = -5.3$; $[\alpha]_{436} = -14.2$; $[\alpha]_{365} = -37.8$ ($c = 1$, $CHCl_3$, 20°).

Cyclization of **2**. Compound **2** (620 mg, 2.36 mmol) and 0.6 ml of *N,O*-bis(trimethylsilyl)acetamide were placed in a *Pyrex* tube and connected to a vacuum line. Toluene (50 ml), dried over $LiAlH_4$, was condensed into the reagents, the tube was degassed by several freeze/thaw cycles and sealed. After 20 h at 230–240°, the colorless soln. was concentrated under vacuum, and the oily residue was purified by CC (20 g SiO_2; $CHCl_3$) to yield 60 mg (10%) of unreacted **2** and 505 mg (90% based on reacted **2**) of the diastereoisomeric mixture **10**. B.p. 105–110°/10^{-2} Torr. ^{1}H NMR (CCl_4, 60 MHz): 0.60–2.30 (*m*), 1.03 (*d*, *J* = 7.0), 1.07 (*d*, *J* = 7.0) (total 24 H); 2.60 (*sept.*, *J* = 7.0, 1 H); 3.46, 3.76, 4.40 (br. *m*, total 2 H); 5.47 (*m*, 1 H); 5.55 (*m*, 1 H). EI-MS (70 eV): 263 (M^+), 248, 220, 192, 150 (100).

(−)-Pumiliotoxin C (= *[2*S*-(2α,4aβ,5β,8aβ)]-Decahydro-5-methyl-2-propylquinoline*; **1**). The cyclization product **10** (340 mg, 1.28 mmol) was dissolved in 50 ml of MeOH and stirred with 30 mg of Pd/C (10%) under H_2 for 15 h at r.t. After filtration, the solvent was removed under vacuum, and the residue was dissolved in 10 ml of dry THF. At −78°, BuLi (4.0 ml 1.7N) was added, and the soln. was allowed to warm overnight. The mixture was hydrolyzed with 20 ml of 10% aq. NaOH and extracted with Et_2O. The extracts were dried (K_2CO_3) and submitted to GC (*Carbowax 4000*, 3% KOH, 160°): isomer ratio 62 : 1 : 37. The filtered soln. was saturated with HCl gas and evaporated. Crystallization from i-PrOH gave 170 mg (57%) of pure **1**, m.p. 290–2° (sealed capillary), identical in all respects to the natural alkaloid [1][3k]. $[\alpha]_D = -17.7$; $[\alpha]_{578} = -18.9$; $[\alpha]_{546} = -21.2$; $[\alpha]_{436} = -36.0$; $[\alpha]_{365} = -54.7$ (**1** · HCl, $c = 1$, MeOH, 20°). ^{13}C-NMR (free base, $CDCl_3$, 25.4 MHz): 14.24 (Me); 19.09 (CH_2); 19.84 (Me): 21.33 (CH_2); 27.18 (CH_2); 27.43 (CH_2, CH); 33.63 (CH_2); 36.12 (CH_2); 39.83 (CH_2); 42.83 (CH): 55.95 (CH); 57.65 (CH).

(−)-4a,5,8a-Epipumiliotoxin C (= *[2*S*-(4aα,5α,8aα)]-Dehydro-5-methyl-2-propylquinoline*; **11**). The mother liquors of the crystallization of **1** were alkalinized and extracted with Et_2O. CC (10 g of SiO_2, hexanes/AcOEt/$PrNH_2$ 90 : 10 : 3) yielded a further amount of **1** (3.5%) and 40.6 mg (14%) of **11** · HCl, m.p. 263–5° (i-PrOH/Et_2O, sealed cap.). The spectroscopic properties are in good agreement with those published for racemic **11**. $[\alpha]_D = -33.4$; $[\alpha]_{578} = -35.0$; $[\alpha]_{546} = -39.7$; $[\alpha]_{436} = -66.3$; $[\alpha]_{365} = -101.0$ (**11** · HCl, $c = 1$, MeOH, 20°). ^{13}C-NMR (free base, $CDCl_3$, 25.4 MHz): 14.19 (Me); 19.30 (CH_2); 19.44 (Me); 20.68 (CH_2); 25.39 (CH_2); 28.78 (CH_2); 28.97 (CH_2); 31.34 (CH_2); 32.50 (CH); 38.39 (CH_2); 42.28 (CH); 49.71 (CH); 49.90 (CH). Anal. calc. for $C_{13}H_{26}ClN$ (231.81): C 67.36, H 11.31, N 6.04; found: C 67.21, H 11.38, N 5.93.

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