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Total Synthesis of (–)-Pumiliotoxin C by Aqueous Intramolecular Acylnitroso Diels–Alder Approach

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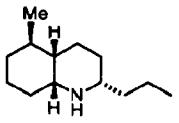
Abstract: A chiral approach to (–)-pumiliotoxin C via a stereoselective intramolecular hetero Diels–Alder reaction of a chiral acylnitroso compound performed in an aqueous medium is described.

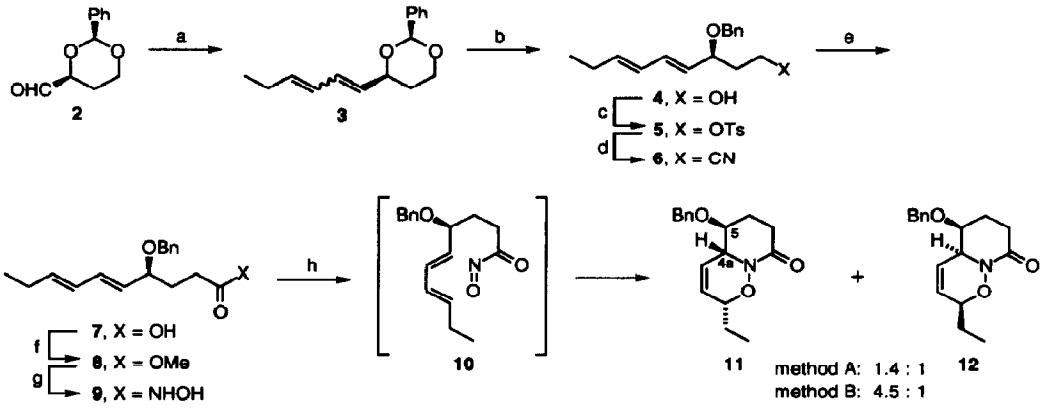
Recently we reported that, in aqueous media, intramolecular hetero Diels–Alder cycloadditions of the chiral acylnitroso compounds show a pronounced enhancement of the diastereoselectivity compared with the reaction under conventional nonaqueous conditions,[1] and described an application of this reaction to an enantioselective synthesis of (–)-swainsonine.[2] Our interest in this area led us to investigate a further application of this strategy for the chiral preparation of natural products, and we now wish to report the enantioselective synthesis of (–)-pumiliotoxin C (decahydroquinoline *cis*-**195A**) (**1**),[3, 4] isolated from skin extracts of the Panamanian poison-frog *Dendrobates pumilio*[5] as the first member of one major class of dendrobatid alkaloids.[6]



(–)-Pumiliotoxin C (**1**)

Wittig reaction of (2*S*,4*S*)-4-formyl-2-phenyl-1,3-dioxane (**2**), available from L-malic acid,[7] with *trans*-2-pentenyltriphenylphosphonium bromide (*t*-BuOK, THF) proceeded without epimerization to give a mixture of (*E*)- and (*Z*)-dienes **3** in 95% combined yield (Scheme 1). Ring-opening of the benzylidene acetal with DIBALH gave an *E*/*Z* mixture of the alcohol **4** (86%), which underwent photoisomerization in benzene in the presence of iodine to generate the geometrically pure (4*E*)-diene **4** in 69% overall yield. This compound was converted to the ester **8** by standard procedures involving sequential tosylation, cyanation, alkaline hydrolysis, and then diazomethane esterification. Treatment of the ester **8** with hyroxylamine under basic conditions (methanolic KOH) afforded the hydroxamic acid **9** (89%). Subsequent periodate oxidation of **9** under nonaqueous conditions (method A: Pr_4NIO_4, $CHCl_3$, 0 °C) resulted in in situ generation of the intermediacy acylnitroso diene **10**, which spontaneously underwent intramolecular cycloaddition to produce poor diastereoselectivity (1.4:1) of the *trans* (with respect to 4a–H and 5-H) vs. *cis* adducts (**11** and **12**). However, the use of an aqueous solvent system (method B: H_2O–MeOH, 6:1) instead of $CHCl_3$ significantly enhanced the trans isomer ratio up to 4.5:1.

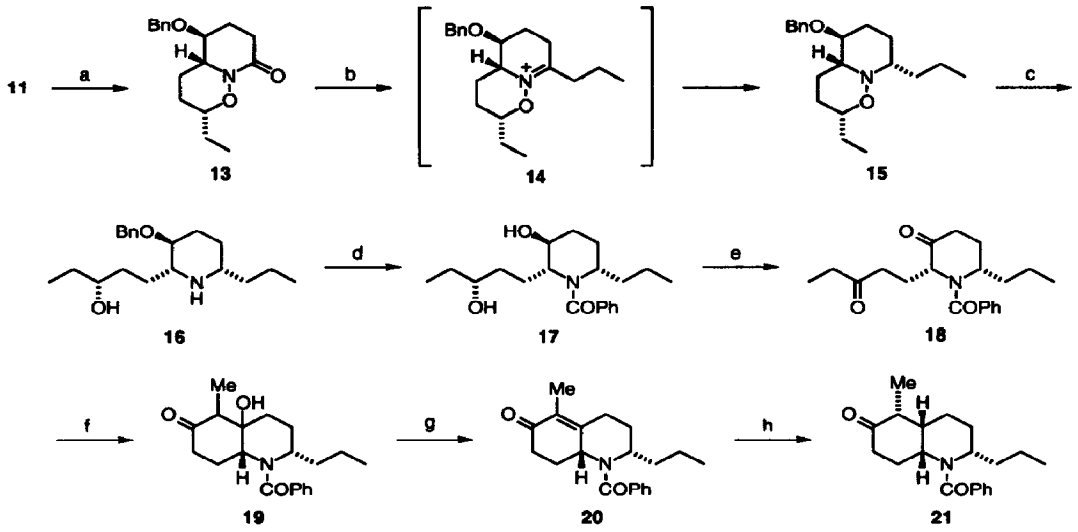
Scheme 1



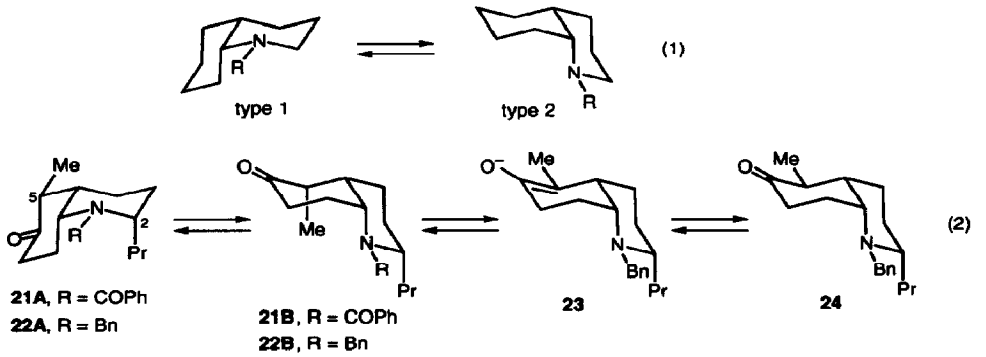
(a) EtCH=CH(*trans*)CH_2PPh_3Br, *t*-BuOK, THF, r.t. (95%); (b) i, DIBALH, CH_2Cl_2, 0 °C (86%); ii, hv, I_2, benzene, r.t. (80%); (c) TsCl, pyridine, 0 °C (95%); (d) NaCN, DMSO, r.t. → 50 °C (93%); (e) aq. NaOH, MeOH, r.t. (84%); (f) CH_2N_2, Et_2O, 0 °C (88%); (g) NH_2OH•HCl, KOH, MeOH, 0 °C (89%); (h) method A: Pr_4NIO_4, $CHCl_3$, 0 °C (87%); method B: Pr_4NIO_4, H_2O–MeOH (6:1), 0 °C (73%).

After catalytic hydrogenation of the olefin moiety of the *trans* adduct **11**, introduction of the propyl side chain to the C-8 position of **13** was achieved in a completely stereoselective manner according to the two-step process previously reported from this laboratory.[8] Thus, **13** was subjected to Grignard reaction with PrMgBr followed by reduction of the resulting iminium salt **14** in an acidic medium (AcOH, THF) with $NaBH_3CN$ to provide **15** as a single diastereomer in 96% overall yield from **11**. Reductive N–O bond cleavage with Zn and aqueous AcOH followed by N-benzoylation of the resulting amino alcohol **16** gave **17** (89%). After hydrogenolysis over palladium on carbon, the resulting diol **17** was converted to the diketone **18** by PCC oxidation. Aldol cyclization of **18** (methanolic KOH, 0 °C) followed by dehydration ($KHSO_4$, MeOH, r.t.) yielded the bicyclic enone **20**. Subsequent catalytic hydrogenation of the C-4a–C-5 double bond exclusively occurred from the less hindered β-face to establish the cis-fused decahydroquinoline ring system **21**. In this transformation, however, the resulting methyl substitution at C-5 was of the incorrect α-configuration, which relates to 5-epipumiliotoxin C.[9] Booth[10] reported that conformationally mobile *cis*-decahydroquinoline itself has a strong preference for type 2 conformation, whereas the *N*-acyl derivatives prefer type 1 to avoid the $A^{1,3}$ type strain between the N-substituent and the C-8 methylene group (eq 1). This should hold even more so for the *N*-benzoyl-*cis*-decahydroquinolone **21**, which should exist preferentially in the conformation **21A** (type 1) with the 2-propyl and 5-methyl groups occupying pseudo-equatorial and axial positions, respectively (eq 2). The alternative conformation **21B** (type 2) is unlikely owing to the additional $A^{1,3}$ type strain between the *N*-benzoyl group and the propyl group at C-2. However, when the *N*-benzoyl group is replaced by the *N*-benzyl group as in **22**, it could lead to the absence of such allylic strain and should prefer the conformation **22B** (type 2) with the 2-propyl group equatorial, which avoids the 1,3-diaxial interaction between the axial 2-propyl group and the C-8 ring methylene group. However, a steric interaction due to the pseudo-axial methyl group at C-5 is present in **22B**; hence, upon isomerization through its enolate **23**, **22B** would as shown in eq 2 be converted to thermodynamically more stable **24** in which the C-5 methyl substitution is equatorial with the desired β-configuration.

Scheme 2



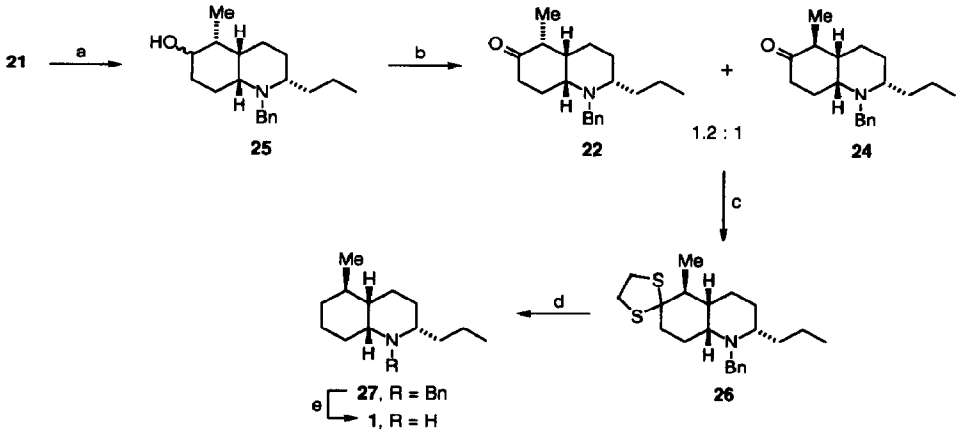
(a) H_2, 10% Pd–C, THF, r.t. (100%); (b) PrMgBr, THF, 0 °C, then $NaBH_3CN$, AcOH, THF, 0 °C (96%); (c) Zn, 85% aq. AcOH, 60 °C (91%); (d) i, PhCOCl, CH_2Cl_2 10% aq. K_2CO_3, then KOH (98%); ii, H_2, 10% Pd–C, MeOH, r.t. (99%); (e) PCC, CH_2Cl_2, r.t. (74%); (f) KOH, MeOH, 0 °C (74% or 85% based on starting material recovered); (g) $KHSO_4$, MeOH, r.t. (50% or 72% based on starting material recovered); (h) H_2, 10% Pd–C, 1 N HCl, r.t. (71%).



With these considerations in mind, our attention next focused on epimeric transformation of **22** with the benzyl group as a nitrogen protecting group. Thus, the benzamide **21** was converted by reduction with $LiAlH_4$ to the *N*-benzyl derivative **25** as a mixture of the alcohol epimers (87%). This mixture was oxidized under Swern conditions to afford a 1.2:1 (by ^1H NMR) epimeric mixture of the 5α- and 5β-methyl isomers **22** and **24**, respectively. The formation of the 5β isomer **24** in this reaction is consistent with concomitant epimerization of the initially formed **22** under the reaction conditions. After prolonged heating (4 days) of this epimeric mixture of **22** and **24** with $Zn(OTf)_2$ in CH_2Cl_2, the reaction mixture was treated with 1,2-ethanedithiol (reflux, 4 days). Upon this one-pot procedure, epimerization at C-5 as expected followed by dithioketalization proceeded to produce the thermodynamically more stable 5β-methyl epimer **26** as a single

isomer (based on 400-MHz ^1H NMR) in 66% yield. Finally, **26** with the correctly oriented side chains at C-2 and C-5 underwent desulfurization with Raney Ni followed by hydrogenolytic removal of the benzyl protecting group to yield (–)-pumiliotoxin C (**1**). Treatment with methanolic HCl and subsequent recrystallization from *i*-PrOH–Et_2O gave the HCl salt of **1** as colorless needles, mp 284–288 °C (sealed capillary) [lit.[3c] mp 286–288 °C (sealed capillary under Ar)]; $[\alpha]^{24}_D$ –15.2° (*c* 0.46, MeOH) [lit.[3c] $[\alpha]^{21}_D$ –16.2° (*c* 1.00, MeOH)]. The synthetic sample of **1** exhibited ^1H and ^{13}C NMR spectra identical with those reported[5b] for natural pumiliotoxin C.

Scheme 3



(a) $LiAlH_4$, THF, reflux (87%); (b) $(COCl)_2$, DMSO, CH_2Cl_2, –90 °C, then Et_3N, r.t. (84%); (c) $Zn(OTf)_2$, CH_2Cl_2, reflux, 4 days, then $(CH_2SH)_2$, reflux, 4 days (66%); (d) Raney Ni, dioxane, reflux (68%); (e) H_2, 10% Pd–C, MeOH (92%).

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