Pergamon

Tetrahedron Letters 39 (1998) 7835–7838

TETRAHEDRON LETTERS

Auxiliary-Controlled Stereoselective Enolate Protonation: Enantioselective Synthesis of cis and trans Annulated Decahydroquinoline Alkaloids

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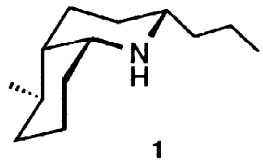
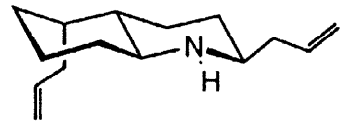
Received 29 July 1998; accepted 17 August 1998

Abstract: The diastereoselective synthesis of the octahydroquinoline enone precursor of pumiliotoxin C is achieved via tandem Mannich-Michael reaction on N-galactosyl imines. Conjugate cuprate addition to the bicyclic enone stereoselectively forms the trans annulated 4a-*epi*-pumiliotoxin C skeleton in the presence of the carbohydrate auxiliary, and the cis annulated pumiliotoxin C skeleton in its absence.

Alkaloids are important natural prototypes of pharmacologically active compounds. Their stereoselective synthesis is of general interest for drug discovery and development. More than 200 alkaloids have been isolated from glandular secretions of the South American frogs of the family *Dendrobates*.[1] Some of these compounds show strong biological effects, e. g. on the ion transport through membranes and stimulus transduction in the nervous system.[2] It is interesting to note that decahydroquinoline alkaloids isolated from *Dendrobates auratus* and *Dendrobates pumilio*, such as pumiliotoxin C **1**, have cis configuration, while frogs of the family *Dendrobates histrionicus* exclusively produce trans annulated decahydroquinolines, such as alkaloid 219 A **2**.[4]



1



2

A number of stereoselective syntheses of (-)- and (+)-pumiliotoxin C **1** have been reported.[5] An auxiliary-controlled asymmetric synthesis of **1** was achieved by Comins et al.,[5d] who subjected (-)-8-phenylmenthol-derived N-alkoxycarbonyl-3-triisopropylsilyl-4-trimethylsilyloxy-pyridinium salts to nucleophilic addition reactions.

We report here on an alternative stereoselective synthesis of either trans or cis annulated decahydroquinoline alkaloids using 2,3,4,6-tetra-O-pivaloyl-β-D-galactosylamine **3**[6] as the auxiliary in both cases. Aldimine **4** obtained from **3** and hex-5-enal was treated with 1-methoxy-3-trimethylsilyloxy-butadiene in a tandem Mannich-Michael condensation reaction[7] to give the N-galactosyl dehydropiperidone **5** in excellent diastereoselectivity. Grignard compounds and organocuprates do not react with the enaminone system of **5**. Complexes of organocuprates and boron trifluoride,[8] for example the propyl complex **6**, smoothly undergo conjugate addition to form 2,6-cis-disubstituted piperidone derivatives[9] such as **7** with high diastereoselectivity. Oxidative cleavage of the vinyl group was carried out using 3.5 mol% $K_2OsO_4 \cdot 2H_2O$ and $NaIO_4$ in aq. dioxane. The obtained aldehyde **8** was subjected to intramolecular aldol condensation using

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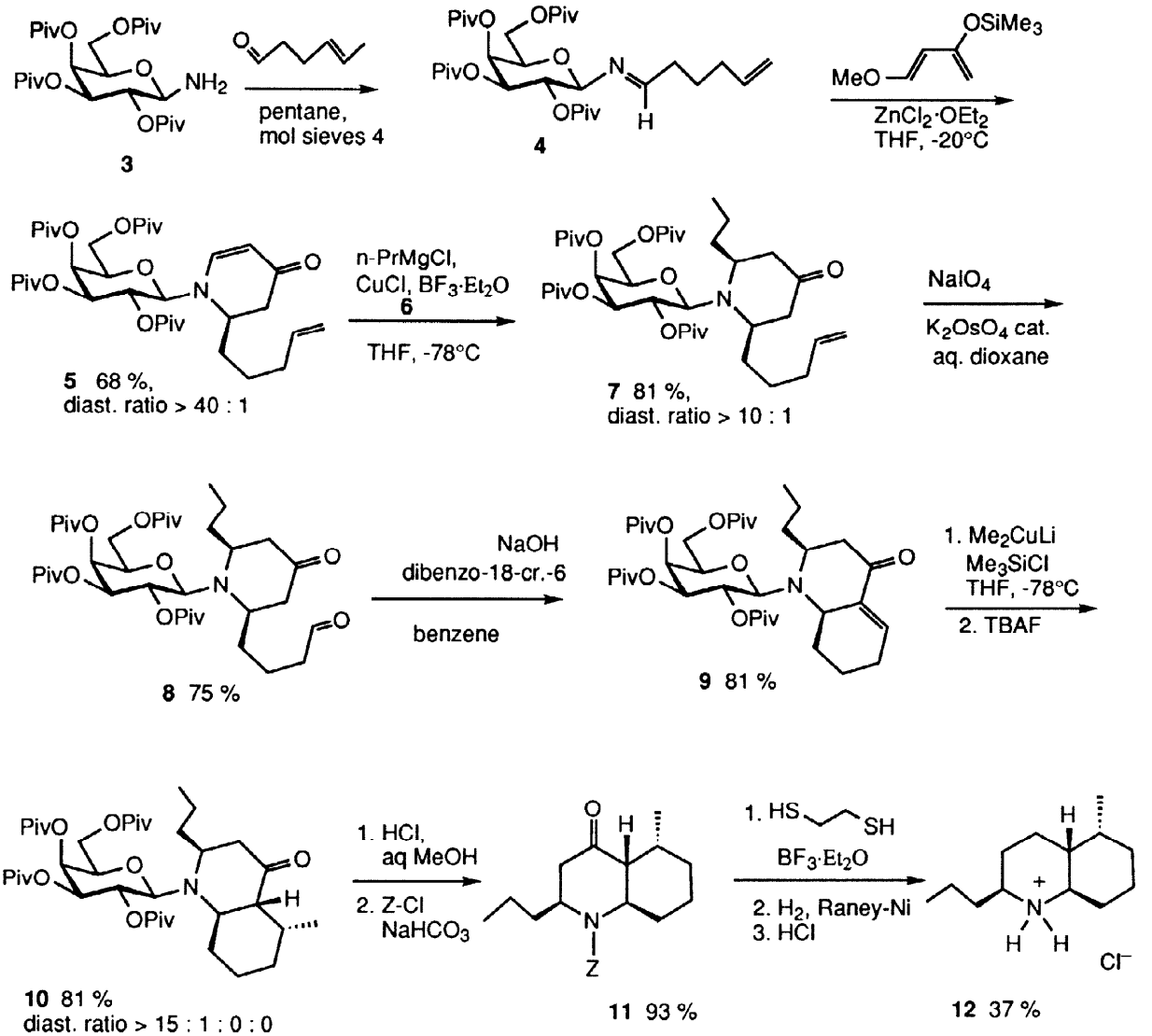
PII: S0040-4039(98)01745-6

sodium hydroxide/dibenzo-18-crown-6 in benzene to give **9**. Acid catalysis of the aldol reaction[5d] results in cleavage of the N-glycosidic bond, whereas application of alkali hydroxide in aqueous methanol causes partial saponification of the pivaloyl esters.



Scheme 1: Piv = Me_3C-CO; Z = Ph-CH_2-O-CO; TBAF = Bu_4NF

The reaction of enone **9** with $Me_2CuLi/BF_3{\cdot}OEt_2$[5d] did not give the 1,4 adduct, since the intermediate enolate was degraded by immediate β-elimination of the amino substituent. Successful 1,4 methyl addition to **9** was accomplished by treatment with Me_2CuLi in combination with trimethylsilyl chloride. The adduct obtained after cleavage of the silyl enolether in high yield and excellent diastereoselectivity (ratio of diastereomers >15:1:0:0) showed the expected configuration at the methyl-substituted carbon (*5R*). However, the ^1H NMR signal of H-8a (dt, $J_{8a,4a}=J_{8a,8'}=3.5$ Hz) as well as the X-ray analysis[10] of compound **10** (Figure 1) unequivocally confirmed, that the product has the trans decahydroquinoline configuration.

This result is very surprising, because enones analogous to **9** but carrying a simple N-phenoxycarbonyl group preferentially give the cis annulated decahydroquinoline skeleton after 1,4 cuprate addition and subsequent hydrolysis,[5d] and, therefore, the synthesis of the corresponding trans annulated compounds normally requires a multistep conversion.[11] Acidolytic cleavage of the N-glycosidic bond (1M aq. HCl/methanol 1:5) and introduction of the benzyloxycarbonyl (Z)-group gave **11**. Conversion of **11** into the dithiolane and subsequent simultaneous desulfurization and removal of the Z-group yielded 4a-trans *epi*-pumiliotoxin C **12**.[12]

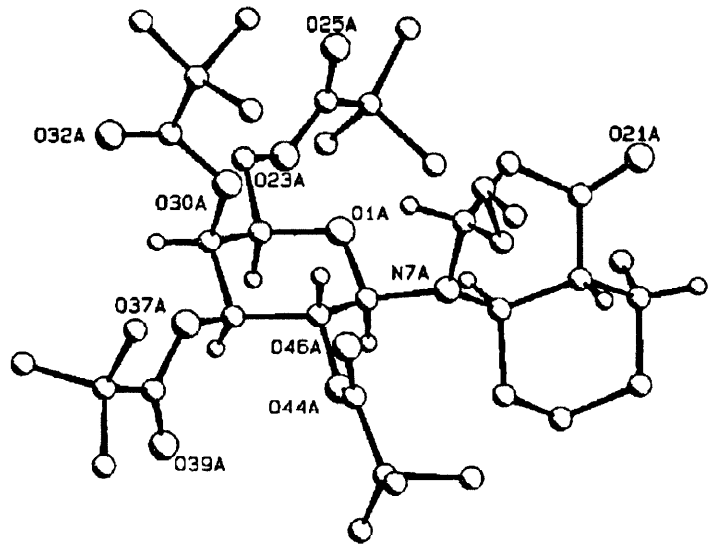
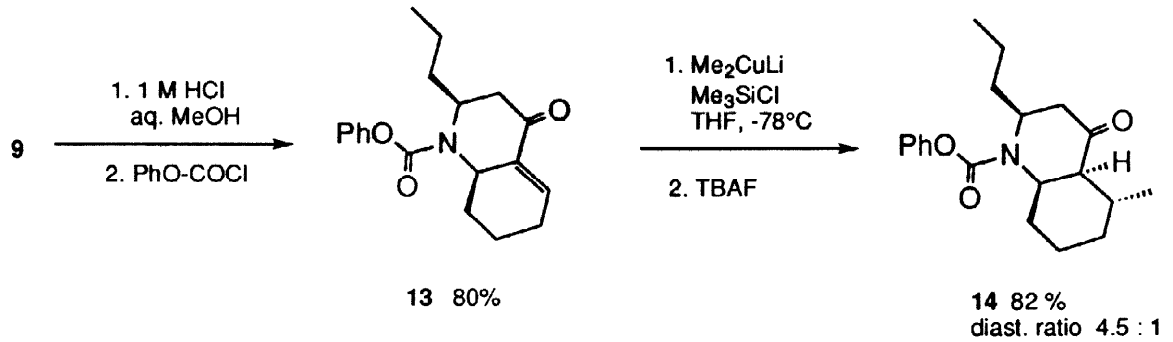


Figure 1: X-Ray Structure of **10**

In order to prove the conclusion that the carbohydrate auxiliary steers the stereoselective protonation of the enolate of **10**, educt **9** was subjected to acidolytic removal of the galactose moiety and reaction with phenyl chloroformate to yield **13**.[5d] Reaction of **13** with $Me_2CuLi/BF_3{\cdot}OEt_2$ preferentially gave the cis annulated precursor **14** of pumiliotoxin C (Scheme 2) in a diastereomeric ratio (crude product) of cis:trans = 9 : 2 (lit.[5d] 97 : 3).

It can be concluded from these results, that the cis annulated decahydroquinolinone **14** is thermodynamically favored compared to the trans epimer. To prove this conclusion, the phenoxycarbonyl analog of **11** (trans annulated) was treated with triethylamine/tetrahydrofuran (1:200 v/v). After 2 minutes, epimerization to form the preferred cis annulated epimer **14** (cis:trans 3 : 1, analytical HPLC) had occurred.



13 80%

14 82 %
diast. ratio 4.5 : 1

Scheme 2

Acknowledgement: This work was supported by the *Deutsche Forschungsgemeinschaft* and by the *Fonds der Chemischen Industrie.*

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(10) $C_{39}H_{65}NO_{10}$, $P2_12_12_1$ (orthorhombic), a=17.229 (4) Å, b=20239 (7) Å, c=24.396 (8) Å, V = 85609 $Å^3$, z = 8, F(000) = 3088; Turbo CAD 4, Mo-Kα, SIR 92, SHELXL - 93. We thank Dr. D. Schollmeyer, Institut für Organische Chemie, Universität Mainz, for the X-ray analysis and for the calculations. Further details of the crystal structure analysis are available on request from the Fachinformationszentrum Karlsruhe GmbH, D-76344 Eggenstein-Leopoldshafen (Germany), on quoting the deposit number CSD-380168, the names of the authors and journal citation.
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(12) Loss in product is caused, because nickel retains the epi-pumilio toxin C. For isolation of **12**, the nickel is dissolved in aq. HCl. After addition of conc. NH_3, the solution is extracted with $CHCl_3$. After addition of conc. HCl to the organic layer, the solvents are evaporated, the hydrochloride **12** is extracted from the residue using chloroform and the crude product purified by preparative t.l.c.: m. p. 256-258°C; $[\alpha]_D^{22}$ = -11.3 (c 0.5, $CHCl_3$); 400 MHz-^{1}H-NMR ($CDCl_3$): δ = 2.89 (dt, $J_{8a,4a} = J_{8a,8'}$ = 11.5 Hz, $J_{8a,8}$ = 4.1 Hz, 1H, H-8a); FD-MS: m/z (cation) = 195.8 (calc. 196.2).