Natural Product Synthesis

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Stereoselective Synthesis of Enantiomerically Pure Nupharamine Alkaloids from Castoreum**

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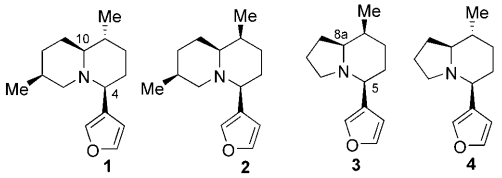
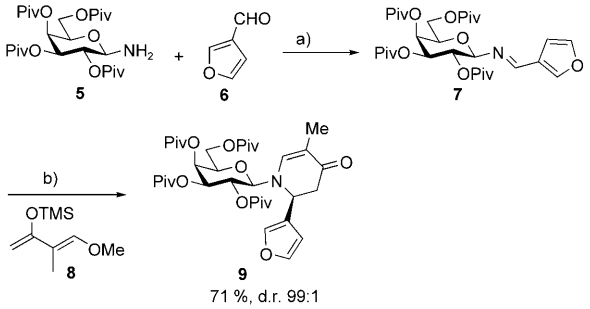
Castoreum, the extract of the dried scent glands of the Canadian beaver (*Castor fiber* L.), was once considered one of the most valuable animal-based components in the perfume industry;[1,2] today it is approved only for homeopathic applications. Castoreum contains a number of nitrogen bases[3] that are properly classified as furan sequiterpenes but are traditionally considered alkaloids.[4] They have a quinolizidine or indolizidine structure and make up the group of nuphar alkaloids. A minor component accounting for $< 0.0002\,\%$ of castoreum is a 5-(3′-furyl)-8-methylindolizidine. Its constitution was elucidated with the aid of mass spectrometric analysis,[1] but its relative and absolute configuration are unknown to date.

All known quinolizidines from castoreum have *S* configuration at C4 and C10. Both (−)-deoxynupharidine (**1**) and its epimer, (−)-1-*epi*-deoxynupharidine (**2**), are found in the scent glands of the beaver. Based on this fact, the diastereomeric structures **3** and **4** can be assumed for the natural 5-(3′-furyl)-8-methylindolizidine. Two enantioselective total syntheses of compound **4** have already been reported.[5,6] Nupharamine **3**, however, has not been synthesized enantioselectively to date.

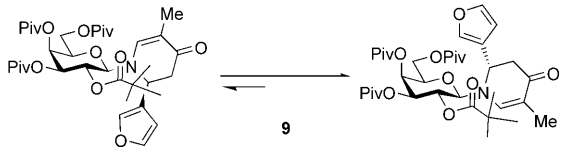


We describe herein the enantioselective total syntheses of **3** and **4**. To control the relative and absolute stereochemistry, galactosylamine **5**[7] was applied as the chiral auxiliary. To obtain the key intermediate *N*-galactosyldidehydropiperidinone, furan-3-carboxaldehyde (**6**) was condensed with **5** in boiling 2-propanol to afford *N*-galactosylimine **7**. In a highly diastereoselective domino Mannich–Michael reaction[8] catalyzed by zinc chloride, aldimine **7** reacted with the methyl-substituted Danishefsky diene **8**[9] to give piperidinone **9** after acidic workup (Scheme 1). Since the *Re* face of the imine is shielded by the bulky 2-pivaloyloxy group of the auxiliary, the stereogenic center of the heterocycle was formed with high selectivity.[8,10,11]



Scheme 1. Diastereoselective synthesis of **9**: a) HOAc (cat.), *i*PrOH, 80 °C, 45 min; b) $ZnCl_2$, **8**, THF, −78 to −30 °C, 72 h, then 1 N HCl. Piv = pivaloyl (2,2,2-trimethylacetyl), TMS = trimethylsilyl.

The *O*-protected alkyl side chain[12] was introduced through conjugate addition of an organocopper compound. The best results were achieved using the "complex reagent" $RCu{\cdot}BF_3$ ($R = (CH_3)_2OTIPS$),[13] which was prepared from the corresponding Grignard compound by transmetalation with $CuBr{\cdot}SMe_2$. As a result of the shielding of the 2-pivaloyloxy group, the addition of the organocuprate proceeded *cis* to the furyl substituent with high diastereoselectivity and yield (Scheme 2). The formed enolate was protonated at low temperature with astonishingly high stereoselectivity to form the all-*cis* isomer **11a** as the major product (Scheme 3). This protonation also is controlled by the carbohydrate, which, as a result of the *exo*-anomeric effect and the steric repulsion between the introduced side chain and the 2-pivaloyloxy substituent, forces the heterocycle to adopt the chair conformation **11**. Diastereomer **11b** logically is the stronger C*H* acid as its C–H σ bond is located parallel to the π*-orbital lobes of the C=O bond. In the formed



Scheme 2. Rotamers of *N*-galactosyldidehydropiperidinone **9**.

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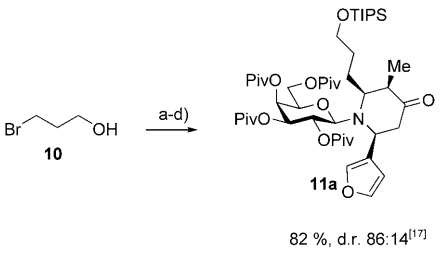
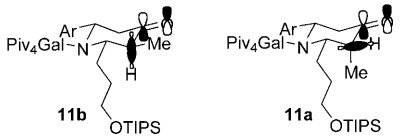


82 %, d.r. 86:14[17]

Scheme 3. Diastereoselective 1,4-addition and protonation. a) TIPS-Cl, imidazole, CH_2Cl_2, 20 h, quant.; b) Mg, THF, RT, 2 h; c) CuBr·SMe_2, THF, −65 to −50 °C, 1 h; d) BF_3·OEt_2, THF, −78 °C, **9**, 15 h, 82 %. TIPS = triisopropylsilyl.

diastereomer **11a**, however, the C–H bond is located within the σ plane of the carbonyl group (Scheme 4). In an optimized experimental procedure the proton source was added dropwise to the enolate. Thus, the enolate is always present in excess, and proton exchange between enolate and protonated product is certainly possible.

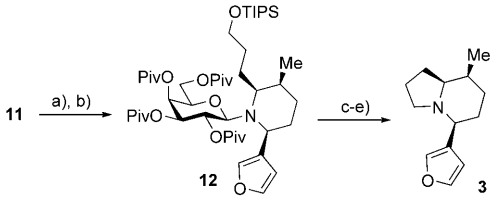


Scheme 4. Orbital overlap of the possible protonation products. Piv_4Gal = 2,3,4,6-tetra-*O*-pivaloylgalactosylamine, Ar = 3-furyl.

Once formed, the diastereomer **11a** can no longer be deprotonated to give the enolate because of its low C*H* acidity. In this way, the carbohydrate auxiliary controls the relative and absolute configuration of the three formed stereogenic centers. Subsequently **11a** was deprotonated regioselectively with lithium diisopropylamide (LDA), and the resulting enolate was trapped using 5-chloro-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]pyridine (5ClPyrN-Tf_2)[14] to give the enol triflate. Catalytic hydrogenation of the enol triflate over palladium/charcoal afforded the deoxygenated heterocycle **12** (Scheme 5).

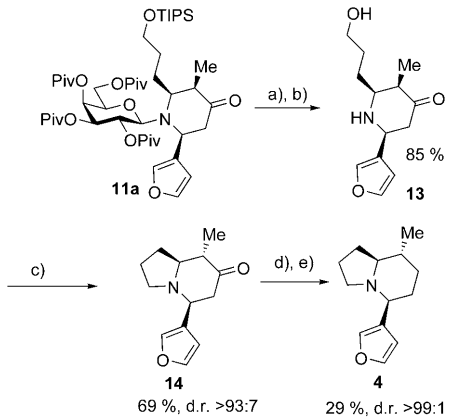
The enantioselective synthesis of the alkaloid was completed by removal of the protecting silyl group, conversion of the alcohol to the corresponding chloride using triphenylphosphine/*N*-chlorosuccinimide,[15] acidolytic detachment of the auxiliary, and subsequent cyclization to give indolizidine **3**.[16] Separation of the diastereomers (d.r. 86:14[17]) was achieved by column chromatography on basic alumina. The specific optical rotation of the free base **3** is $[\alpha]_D^{23} = -57.9$ (c = 1.0, $CHCl_3$), that of its hydrochloride is $[\alpha]_D^{23} = -21.1$ (c = 0.5, $CHCl_3$).

The diastereomeric nupharamine **4** was also accessible from ketone **11a**. To this end, the silyl group was removed with TBAF. Subsequently, the auxiliary was cleaved off using HCl/MeOH. The resulting amino alcohol **13** was transformed into the bromide,[15] which cyclized under basic conditions to give indolizidinone **14** (Scheme 6). In the course of this



d.r. >99:1

Scheme 5. Deoxygenation of piperidinone **11a**. a) 1.1 equiv LDA, THF, −78 °C, 2 h, then 5ClPyrNTf_2, 3.5 h, 65 %; b) 20 mol % Pd/C, H_2, MeOH, RT, 4.5 h, 70 %; c) TBAF, THF, RT, 4 h, 91 %; d) PPh_3, NCS, CH_2Cl_2, −40 °C to 25 °C, 4 h, RT, 69 %; e) 1 N HCl, MeOH, RT, 18 h, then Na_2CO_3, EtOH, reflux, 1.5 h, 60 %. NCS = *N*-chlorosuccinimide, TBAF = tetrabutylammonium fluoride.



Scheme 6. a) TBAF, THF, RT, 1.5 h, 85 %; b) 1 N HCl, MeOH, RT, 18 h, quant.; c) PPh_3, NBS, CH_2Cl_2, RT, 1.5 h, then NEt_3, 20 h, RT, 69 %; d) LDA, THF, −78 °C, 1 h, then 5ClPyrNTf_2, 2 h; e) Pd/C, H_2, 2 h, MeOH, RT, 29 % over 2 steps. NBS = *N*-bromosuccinimide

reaction, now without the effect of carbohydrate auxiliary, inversion of configuration occurred at C8 to afford the thermodynamically more stable *cis–trans* isomer (ratio of diastereomers > 93:7). For the concluding deoxygenation, the enol triflate was formed by regio- and diastereoselective deprotonation using LDA and trapping of the enolate.[14] Catalytic hydrogenation of the enol triflate over palladium/charcoal gave the nuphar alkaloid **4** (Scheme 6).

Its optical rotation $[\alpha]_D^{25} = -94.5$ (c = 0.35, $CHCl_3$) is in the range of that reported by Barluenga et al. ($[\alpha]_D^{20} = -99.0$ (c = 1.3, CH_2Cl_2)).[5] The structure of the all-*cis* nupharamine enantiomer **3**, which has been synthesized for the first time, is confirmed, in particular, by the ^1H–^1H NOESY NMR signals between the axial 8-methyl group (δ = 1.05 ppm) and the axial protons in the 1- (δ = 1.65 ppm) and 6-positions (δ = 1.80 ppm). In the case of *cis–trans* nupharamine **4**, the equatorial 8-methyl group (δ = 0.90 ppm) showed ^1H–^1H-'NOESY contacts only to the two protons at position 7 (δ = 1.79 and 1.09 ppm). The EI mass spectrum (70 eV) of the all-*cis* nupharamine **3** is identical with that of the natural product,[1] while in the EI mass spectrum of the epimer **4** signals for fragments with *m*/*z* 191.1, 176.9, 162.7, and 149.9 are missing.

The methodology described here has resulted in the enantioselective total synthesis of two diastereomers of 5-(3′-

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furyl)-8-methylindolizidine using the same galactose auxiliary. The *N*-galactosyl auxiliary induces high stereo- and regioselectivity in the key reactions. The all-*cis* furylindolizidine **3** is odorless, whereas the 8-epimer **4** has a slightly stale, amine-like odor. The scope of the strategy of this enantioselective total synthesis is extended by the fact that the both optical antipodes of the indolizidine alkaloids can be synthesized analogously using the quasi-enantiomeric D-arabinosyl auxiliary.[19]

Experimental Section

Synthesis of **11**: All manipulations were carried out under argon atmosphere: 1,2-Dibromethane (0.44 mL, 5.0 mmol) was added to magnesium turnings (1.28 g, 52.7 mmol) in anhydrous oxygen-free tetrahydrofuran (20 mL), and the mixture was stirred at RT for 1 h. In order to remove the formed $MgBr_2$, the THF was removed with a syringe, and the remaining magnesium was washed with THF (2 × 15 mL). After addition of fresh THF (30 mL) and the *O*-TIPS-protected bromo alcohol **10**, the mixture was stirred at RT for 2 h. The resulting grayish-brown clear Grignard solution was poured into a suspension of $CuBr{\cdot}SMe_2$ (6.37 g, 31.0 mmole) in THF (70 mL) at −65 °C within 1 h. During the addition the color of the turbid solution changed from almost colorless to yellow to orange. The mixture was warmed up to −54 to −50 °C within 1 h, and the color changed to gray and then brown, indicating the formation of the organocuprate. The mixture was then cooled to −78 °C and stirred for 15 min. After the addition of $BF_3{\cdot}OEt_2$ (4.2 mL, 38.0 mmol) the reaction mixture was stirred for 15 min at this temperature before a solution of furylpiperidinone **9** (3.0 g, 4.44 mmol) in THF (90 mL) was added dropwise by syringe over 1.5 h with vigorous stirring. After 30 min, more $BF_3{\cdot}OEt_2$ (4.2 mL, 38.0 mmol) was added, and the stirring continued for 15 h at −78 °C. The grayish-brown reaction mixture was stirred at this temperature, and a mixture of conc. ammonia and sat. NH_4Cl solution (1:1) was added within 1 h. After the reaction mixture had warmed up to RT, diethyl ether (400 mL) was added. The organic layer was washed with a mixture of conc. NH_4OH/sat. NH_4Cl solution (1:1, 80 mL) until the blue color disappeared. The combined aqueous solutions were extracted with Et_2O (2 × 100 mL). The combined organic phases were washed with brine (250 mL) and dried over $MgSO_4$, and the solvents were evaporated in vacuo. The crude product was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 17:1). Yield: 3.26 g (82 %); colorless oil, d.r. 86:14[17] (^{1}H NMR); $R_f = 0.34$ (cyclohexane/ethyl acetate 5:1); $[\alpha]_D^{25} = -22.6$ ($c = 1.0$, $CHCl_3$).

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Keywords: asymmetric synthesis · chiral auxiliaries · domino reactions · indolizidines · terpenoids

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[16] Spectroscopic data of **3**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.35$–7.31 (m, 2H, furyl-5, furyl-2), 6.43 (s_{br}, 1H, furyl-4), 2.91–2.82 (m, 2H, H-5_{ax}, H-$3_{a,ax}$), 2.15–2.06 (m, 1H, H-$8a_{,ax}$), 1.97–1.89 (m, 1H, H-8_{eq}), 1.88–1.75 (m, 2H, H-$3_{b,eq}$, H-$6_{a,ax}$), 1.71–1.53 (m, 6H, H-$7_{a,b}$, H-$1_{a,b}$ H-$2_{a,b}$), 1.52–1.45 (m, 1H, H-$6_{b,eq}$), 1.04 ppm (d, $^3J = 7.0$, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 142.58$ (furyl-5), 139.06 (furyl-2), 128.70 (furyl-3), 109.71 (furyl-4), 67.54 (C-8a), 60.91 (C-5), 53.40 (C-3), 32.14 (C-1), 29.42 (C-8), 28.92 (C-6), 26.84 (C-7), 20.06 (C-2), 12.19 ppm (CH_3); ESI-MS (pos.): 206.16 ($[M+H]^+$, calcd. 206.15); HR ESI-MS (pos.): 206.1552 ($[M+H]^+$, calcd. 206.1545).
[17] Addition of the protonating reagent at −95 °C increased the diastereomeric ratio to 93:7.
[18] Spectroscopic data of **4**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.35$ (m, 2H, furyl-5, furyl-2), 6.47 (s_{br}, 1H, furyl-4), 2.99–2.78 (m, 2H, H-3_a, H-5), 2.01–1.90 (m, 2H, H-1_a, H-3_b), 1.84–1.70 (m, 3H, H-7_a, H-$6_{a,b}$), 1.68–1.55 (m, 3H, H-$2_{a,b}$, H-8a), 1.54–1.36 (m, 2H, H-1_b, H-8), 1.14–1.01 (m, 1H, H-7_b), 0.91 (d, $^3J = 6.5$, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): 142.75 (furyl-5), 139.38 (furyl-2), 128.01 (furyl-3), 109.73 (furyl-4), 71.50 (C-8a), 59.81 (C-5), 53.09 (C-3), 36.25 (C-8), 33.99 (C-6), 33.83 (C-7), 28.97 (C-1), 20.03 (C-2), 18.82 ppm (CH_3); ESI-MS (pos.): 206.16 ($[M+H]^+$, calcd. 206.15); HR ESI-MS (pos.): 206.1539 ($[M+H]^+$, calcd. 206.1545).
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