Benzomorphan Synthesis

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Stereoselective Synthesis of Benzomorphan Derivatives with Perpivaloylated Galactose as the Chiral Auxiliary**

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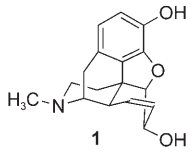
Chiral bicyclic piperidine derivatives are important pharmacophoric structural elements. Despite its undesired side effects, morphine **1**, the prototype of current opiod analgesics,



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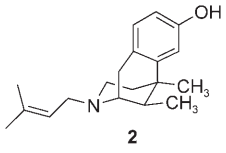

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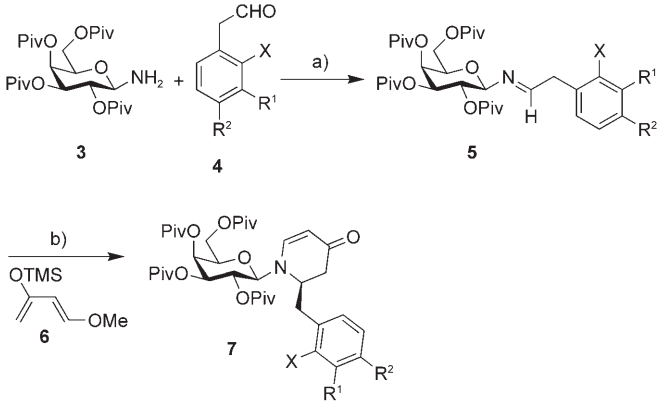
is still indispensable in pain management.[1] Starting from morphine as a lead structure, many analogues have been synthesized. These differ in the spectrum of side effects, but they most often also show lower activity on the opiod receptors. Pentazocine **2**, a representative of this structural class, has potent analgesic properties but has lower affinity to the μ receptor responsible for the addictive effect.[2]

In pentazocine **2** the polycyclic structure of morphine **1** is reduced to a tricyclic benzomorphan system. It still contains the pharmacologically essential hydroxy functionality on the aromatic ring. The substituted benzomorphan scaffold therefore has potential as a lead structure in the search for new drug candidates with selective activity on opiate receptors.

We report short stereoselective syntheses of 6,7- and 7,8-benzomorphans. To obtain the 6,7-annelated derivatives, 2-benzyl-substituted 5,6-didehydropiperidin-4-ones were applied to a domino Suzuki–Heck coupling sequence. 7,8-Benzomorphans were accessible by an acid-catalyzed cyclization of 4-benzyl-substituted 5,6-didehydropiperidin-2-ones. The employed *O*-pivaloylated D-galactose auxiliary determined the stereoselectivity of both reactions.

The synthesis of the 6,7-benzomorphan derivatives started with the condensation of halogen-substituted phenylacetic aldehydes[3] **4** and 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamine[4] (**3**). The formation of the corresponding *N*-galactosyl imines **5** proceeded smoothly at room temperature under dehydrating conditions. Higher temperatures, longer reaction times, and acid catalysis led preferentially to the formation of the undesired conjugated enamines. In a Lewis acid catalyzed tandem Mannich–Michael reaction[5] the aldimines **5** were reacted with 1-methoxy-3-trimethylsiloxybutadiene[6] (**6**) to form *N*-galactosyl 2-benzyl-didehydropiperidinones **7** (Scheme 1).



X = Cl, R^1 = H, R^2 = H, 53 %, d.r. 90:10
X = Br, R^1 = H, R^2 = H, 70 %, d.r. 94:6
X = I, R^1 = H, R^2 = H, 32 %, d.r. 95:5
X = Br, R^1 = OBn, R^2 = OMe, 38 %, d.r. 95:5

Scheme 1. Diastereoselective synthesis of 2-benzyl-5,6-dehydropiperidinones **7**: a) MS (4 Å), *i*PrOH, room temperature, 1 h; b) $ZnCl_2$, **6**, THF, −78 °C→−20 °C, 1 d, then 1 N HCl.

The efficient shielding of the *Re* face of the imine double bond by the bulky pivaloyloxy group in the 2-position of the carbohydrate moiety led to a highly stereoselective formation of the asymmetric center in the heterocycle. The diastereoselectivity of the ring formation increased with the size of the *o*-halogen substituent on the aromatic moiety. Unfortunately, the yields decreased in the same order. Upon treatment with L-Selectride, the didehydropiperidinones **7** easily underwent a chemoselective conjugate hydride addition to the enone system.[7] The corresponding enolates were *O*-sulfonated by the addition of *N*-phenylbis(trifluoromethanesulfonyl)-imide[8] to the reaction mixture which gave the enol triflates **8** (Scheme 2).

As previously described, enol triflates of type **8** are suitable substrates for palladium-catalyzed cross-couplings. In Suzuki–Miyaura reactions with aromatic boronic acids they formed 2,4-disubstituted 4,5-didehydropiperidines.[7] In the case of the *o*-bromobenzyl derivatives **8** the reaction proceeded further after the initial coupling with the boronic acid in 4-position and led to tricyclic benzomorphan structures **9** (Scheme 2). The subsequent intramolecular Heck cyclization stereoselectively formed a new quaternary carbon center in the 4-position of the piperidine ring. The attack was controlled by the configuration of the benzyl substituent in the 2-position and thus occurred exclusively from the top face of the *endo* double bond. A Heck olefination on a similar structure has already been used in the enantioselective synthesis of (−)-morphine by Overman et al. to build the

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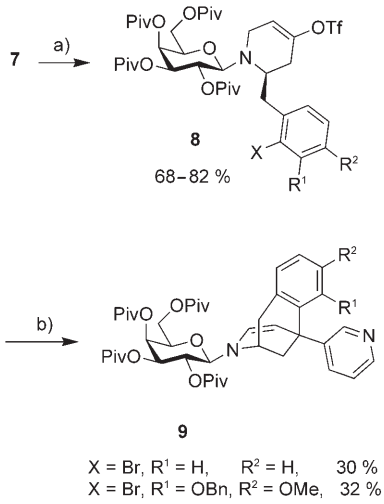
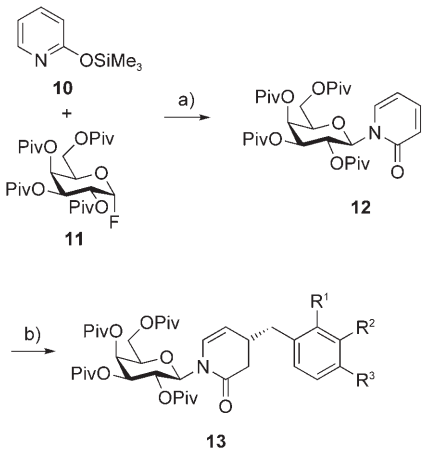


Scheme 2. Formation of the enol triflates **8** and domino Suzuki–Heck coupling to give the corresponding benzomorphans: a) L-Selectride, $PhNTf_2$, THF, −78 °C→ room temperature, 2 h; b) 3-pyridineboronic acid, $[Pd(PPh_3)_2Cl_2]$, Cs_2CO_3, DMF (trace of H_2O), *hν*, 20 min at 80 °C, then 20 min at 100 °C. Tf = trifluoromethanesulfonyl.



Scheme 3. Regio- and diastereoselective synthesis of **13**: a) 1,2-dichloroethane, 70 °C, $TiCl_4$, 2 h, 99%; b) TIPSOTf, DCM, room temperature, 1 h, then 2,6-lutidine, RMgX, 20 °C, 2 h (Table 1).

quaternary carbon in the 5-position of the benzomorphan structure as a key step.[9]

Further investigations into the domino Suzuki–Heck reaction with 3-pyrimidine boronic acid as the coupling partner showed that traces of water and the choice of the employed halogen were essential for the outcome of the reaction. In the absence of water no conversion was observed because the initial Suzuki cross-coupling did not occur. On the other hand, the presence of too much water led to side reactions in the Heck cyclization. Best results were achieved with microwave irradiation which resulted in a significant reduction of the reaction time to give the *N*-galactosyl 3,4-didehydro-6,7-benzomorphans **9** in moderate yields (Scheme 2).

The stereochemical course of the Heck coupling and the formation of the quaternary center are determined by the configuration of **8**. The orientation of the halogenated benzyl substituent in **8** allows approach of the coupling partner only from the *Si* face of the double bond and only one diastereomer results. In contrast, iodobenzyl derivatives did not undergo the Heck cyclization. Instead a (second) Suzuki cross coupling with the *ortho* position of the benzylic substituent took place. The corresponding chloro compound could be selectively converted to the 2,4-disubstituted 4,5-didehydropiperidine but further Heck olefination did not proceed even when tri-*tert*-butylphosphine ligands were used.[10]

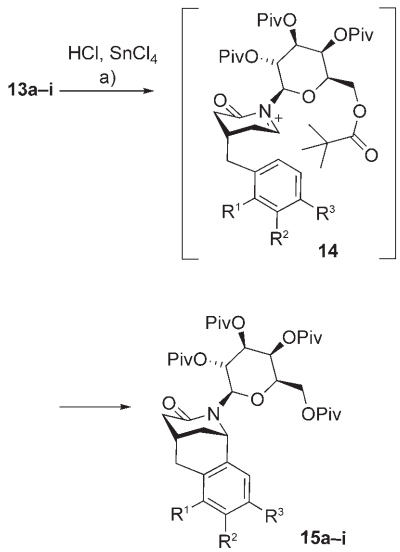
An alternative strategy led to the stereoselective formation of 7,8-benzomorphans. β-Selective *N*-glycosylation of 2-(trimethylsilyloxy)pyridine **10** with *O*-pivaloylated galactosyl fluoride **11** gave the *N*-galactosyl 2-pyridone **12** in excellent yield (Scheme 3).[11] This unsaturated heterocyclic structure was transformed regio- and stereoselectively by reaction with benzyl Grignard reagents. After activating *O*-silylation using triisopropylsilyltrifluoromethanesulfonate (TIPSOTf), the Grignard addition gave 4-benzylated 5,6-didehydropiperidin-2-ones **13** in moderate to excellent yields (Table 1). The regioselectivity and the high diastereomeric ratio of this process was determined by the facial differentiation of the carbohydrate auxiliary.[12] Previously published syntheses using the same benzylpiperidine moiety to form 7,8-benzomorphans required highly activated aromatic systems and proceeded in a nonregioselective manner.[13,14]

Table 1: Stereoselective synthesis of 4-substituted *N*-galactosyl 4-benzyldidehydropiperidinones (Scheme 3).

Cmpd.	RMgX	Yield [%]	d.r. (*R*/*S*)[a]
13a	BnMgCl	73	>99:1
13b	*m*-$MeC_6H_4CH_2MgCl$	83	92:8
13c	*m*-$MeOC_6H_4CH_2MgCl$	41	86:14
13d	*m*-$ClC_6H_4CH_2MgCl$	66	>99:1
13e	*m*-$BrC_6H_4CH_2MgBr$	30	>99:1
13f	*p*-$MeC_6H_4CH_2MgCl$	88	85:15
13g	*p*-$MeOC_6H_4CH_2MgCl$	98	92:8
13h	*p*-$ClC_6H_4CH_2MgCl$	61	94:6
13i	*o*-$MeC_6H_4CH_2MgCl$	98	91:9
13j	*o*-$BrC_6H_4CH_2MgBr$	52	>99:1
13k	2,5-$Me_2C_6H_3CH_2MgCl$	63	92:8
13l	2,4-$Me_2C_6H_3CH_2MgCl$	34	89:11
13m	3,5-$(MeO)_2C_6H_3CH_2MgCl$	54	82:18
13n	1-NaphtCH_2MgCl[b]	68	>99:1

[a] 400 MHz ^1H NMR spectrum and analytical HPLC. [b] Napht = naphthyl; the C-6 regioisomer is formed in < 5% yield.

In the case of the 4-benzyldidehydropiperidinones **13**, the intramolecular aminoalkylations took place at low temperatures in the presence of a mixture of $HCl/SnCl_4$. The intermediate *N*-acyl iminium ion **14** underwent cyclization to yield the tricyclic benzazocinones **15** (Scheme 4). Thus, this synthesis provided 7,8-benzomorphans **15** in high yields and is a significant improvement over previous syntheses of the tricyclic core via *N*-acyl iminium species.[13c,d,14] The electrophilic attack at the phenyl ring occurred exclusively from the *cis* side. The X-ray structure analysis of **15a** shows the diaxial



Scheme 4. Acid-catalyzed intramolecular aminoalkylation: a) HCl (4 equiv), $SnCl_4$ (2 equiv), CH_2Cl_2, −78 °C→20 °C.

configuration on the piperidine ring of the 7,8-benzomorphan (Figure 1).[15]

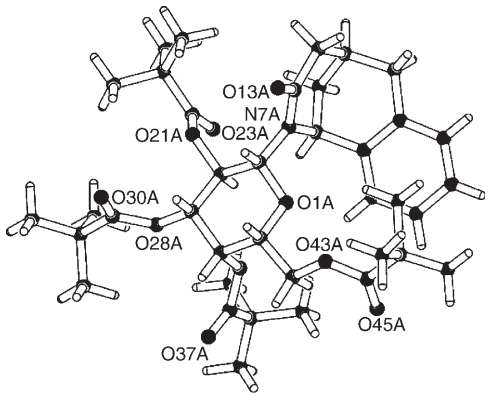


Figure 1. X-ray structure analysis of **15a**.

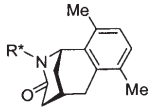
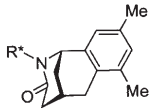
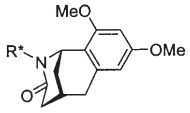
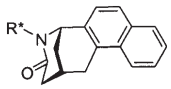
The diversity of the stereoselective ring formation was demonstrated by applying a large variety of differently substituted 4-benzyldidehydropiperidinones **13b–13n** (Scheme 4, Table 2). Benzyl derivatives with electron-donating groups (+I and +M) as well as halogen-substituted compounds were easily transformed into the corresponding 7,8-benzomorphans **15** (Table 2). The conversions of the deactivated aromatics (**13d**, **13e**, **13h**, **13j**) were incomplete.[16] The regioselectivity of the cyclization of the *meta*-substituted derivatives **13b–e** ($R^1 = H$) is supported by the favored reaction in *para* position, and, in addition, by the 6-pivaloyloxy group of the galactose auxiliary (Scheme 4). The aminoalkylation of the disubstituted benzylic compounds **13k–m** as well as the naphthylmethyl derivative **13n** proceeded regio- and stereoselectively in high yields (Table 3).

Table 2: Cyclization of monosubstituted compounds **13a–j** (Scheme 4).

Cmpd.	R^1	R^2	R^3	Yield [%]	*t* [h]
15a	H	H	H	85	18
15b	H	Me	H	83	8
15c	H	OMe	H	85	10
15d	H	Cl	H	48[a]	20
15e	H	Br	H	58[a]	15
15f	H	H	Me	84	8
15g	H	H	OMe	67	12
15h	H	H	Cl	52[a]	22
15i	Me	H	H	71	8
15j	Br	H	H	69[a]	48

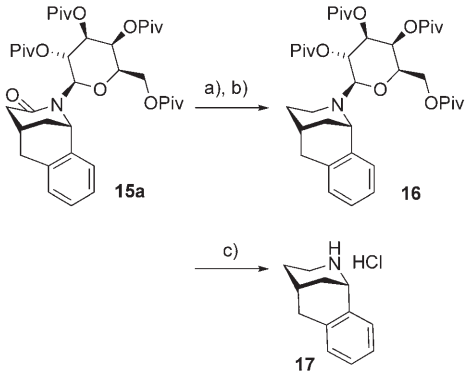
[a] Incomplete conversion.

Table 3: Intramolecular reaction of disubstituted compounds **13k–13n**.

Starting cmpd.	Product[a]		Yield [%]	*t* [h]
13k		**15k**	83	8
13l		**15l**	88	8
13m		**15m**	87	8
13n		**15n**	72	8

[a] R* = 2,3,4,6-Tetra-*O*-pivaloyl-galactose.

To release the 7,8-benzomorphan moiety from the carbohydrate auxiliary the diastereomerically pure benzazocine **15a** was treated with Lawesson's reagent[17] to give the corresponding thioamide, which was subsequently desulfurated on Raney nickel to give **16** (Scheme 5). Acidic cleavage of the *N*-glycosidic bond using aqueous HCl in methanol gave the 7,8-benzomorphan hydrochloride **17** in almost quantitative yield.



Scheme 5. Synthesis of 7,8-benzomorphan: a) Lawesson's reagent (0.5 equiv), toluene, 110 °C, 1.5 h, 83%; b) Raney Ni, H_2, *i*PrOH, 70 °C, 2 h, 74%; c) 2 N HCl in methanol, 20 °C, 24 h, 96%.

Herein we have described a stereoselective approach to the regioisomeric series of 6,7- and 7,8-benzomorphans employing benzyl-substituted *N*-galactosyl didehydropiperidinones. In both processes the galactosyl auxiliary exhibits excellent stereo- and regiocontrol in the key steps. The corresponding enantiomeric products are accessible by use of the quasi-enantiomerc D-arabinosyl auxiliary.[18]

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[15] X-ray structure analysis of **15a** (MeOH): triclinic, space group $P1$, $a = 10.951(2)$, $b = 13.406(2)$, $c = 15.086(3)$ Å, $\alpha = 105.61\ (2)$, $\beta = 106.08(1)$, $\gamma = 104.65\ (1)°$. At a cell volume of $V = 1917.0(7)$ Å^3, two independent molecules and $M_r = 685.83$ results in a density of $d = 1.188\ \mathrm{g\,cm^{-3}}$. Total number of electrons per elemental cell $F(000) = 740$. Diffractometer CAD4, $Cu_{K\alpha}$ graphite monochromator. Scan type $\omega/2\theta$, scan width $0.9 + 0.15\tan(\theta)$. Measuring range $2° \le \theta < 70°$, $-13 \le h \le 13$, $-16 \le k \le 16$, $-18 \le l \le 18$. Measured reflex number: 14163, independent: 13426 ($R_{int} = 0.0130$), observed: 13229 ($|F|/\sigma(F) > 4.0$). Corrections: Lorentz and polarization correction. Intensity decline of ca. 5% corrected with cubic spline; solution: program: SIR-92 (direct method), refinement: program: SHELXL-97. CCDC 283243 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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