RESEARCH ARTICLE

Asymmetric synthesis of (1R,5S)-2-methyl-6,7-benzomorphan via Aza-Prins reaction

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Abstract

(1R,5S)-2-Methyl-6,7-benzomorphan has been synthesised from (R)-(benzyloxy)(phenyl)acetaldehyde. On a 2-mmol scale Bi (OTf)$_3$ promoted Aza-Prins reaction with N-tosylhomoallylamine afforded an 88/12 mixture of 6-oxa-2-azabicyclo[3.2.1]octanes. Major diastereoisomer was converted to enantiomerically pure (2S,4S)-2-benzyl-1- methylpiperidin-4-ol via a high-yielding sequence hydrogenolysis/N-detosylation/N-methylation. Acid-catalysed intramolecular Friedel−Crafts cyclisation of the piperidinol afforded (1R,5S)-2-methyl-6,7-benzomorphan in five steps with a yield of 25%.

KEYWORDS

asymmetric synthesis, Aza-Prins reaction, benzomorphan, morphine analogues

1 | INTRODUCTION

Isolated from opium in the beginning of the 19th century,[1] morphine has been widely used to provide relief to patients that suffer from severe pain. Due to the unwanted side effects that accompany the analgesic effect of morphine, the search of strong analgesics derived from morphine skeleton simplification with attenuated or no harmful side-effects has been continuous.[2] Truncated systems containing a benzomorphan scaffold (Figure 1) have proven to be particularly useful in this regard.[3,4]

A number of synthetic routes have been developed for the synthesis of benzomorphans.[5] Among them, those using the acid-catalysed intramolecular Friedel−Crafts cyclisation—of benzyl functionalised piperidines with hydroxyl or C=C double moieties—to form ring B of the benzomorphan skeleton have been applied successfully to the synthesis of several active compounds (Figure 2).[6–13]

Because the stereochemistry of benzomorphan-based compounds plays a pivotal role in their pharmacological activity,[14–19] a convenient, straightforward and practical route to the synthesis of chiral benzomorphan analogues
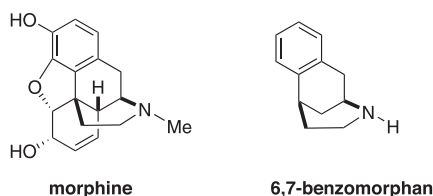
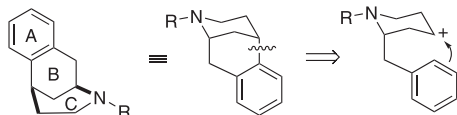**FIGURE 1** Structures of morphine and 6,7-benzomorphan

FIGURE 2 Construction of the benzomorphan scaffold by intramolecular Friedel–Crafts cyclisation

in enantiomerically pure form is highly desirable. Herein, we report the asymmetric synthesis of (1*R*,5*S*)-2-methyl-6,7-benzomorphan starting from (*R*)-(benzyloxy)(phenyl) acetaldehyde.

2 | MATERIALS AND METHODS

2.1 | General information

Unless otherwise specified, all reagents were obtained from commercial suppliers and used without purification. For anhydrous conditions, reactions were carried out under Ar in solvents dried using a solvent purification system (SPS). Heating was performed using an oil bath mounted on a hot plate magnetic stirrer. Whenever possible, the reactions were monitored by TLC. TLC analysis was performed on precoated silica gel polyester plates with an F254 indicator, and products were visualised using UV light (254 nm) and ninhydrin, anisaldehyde, potassium permanganate, or ethanolic phosphomolybdic acid solutions followed by heating. Column chromatography was performed on silica gel (Kiesegel 60, 230–400 Mesh) with air pressure. Melting points were determined in open capillaries using a Gallenkamp capillary melting point apparatus and are not corrected. The FT-IR spectra of oils were recorded as thin films on NaCl plates, the FT-IR spectra of solids were recorded on pressed KBr pellets using a Thermo Nicolet Avatar 360 FT-IR spectrophotometer, ν_{max} values expressed in cm^{-1} are given for the main absorption bands. Optical rotations were measured on a Jasco 1020 digital polarimeter at λ 589 nm and 25°C in cells with 1- or 10-cm path length, $[\alpha]_D$ values are given in 10^{-1} deg·cm^2·g^{-1} and concentrations are given in

g/100 ml. ^{1}H NMR and ^{13}C NMR spectra were acquired in deuterated solvent on a Bruker AV-400 spectrometer operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR. Spectra were acquired at room temperature unless otherwise stated using a 5-mm probe. All chemical shifts (δ) are reported in parts per million (ppm) from tetramethylsilane with the solvent resonance as the internal standard (residual solvent signals were set according to Fulmer et al[20]). Coupling constants (J) are quoted in Hertz. Splitting patterns are described as singlet (s), doublet (d), multiplet (m), broad doublet (bd), doublet of doublet (dd), doublet of doublet of doublet (ddd), and doublet of doublet of doublet of doublet (dddd). High-resolution mass spectra were recorded from methanolic solutions on a Bruker Dalton MICROTOF-Q (quadrupole time-of-flight) micro instrument using the positive electrospray ionisation mode (ESI$^+$).

2.2 | Experimental procedure

2.2.1 | (1*R*,5*S*,7*R*)-7-Phenyl-2-tosyl-6-oxa-2-azabicyclo[3.2.1] octane (**2A**)

To a solution of *N*-(but-3-en-1-yl)-4-methylbenzene-sulfonamide (225.3 mg, 1.0 mmol) and (*R*)-2-(benzyloxy)-2-phenylacetaldehyde **1**[21] (294.2 mg, 1.3 mmol) in acetonitrile (10 ml) at room temperature was added Bi (OTf)$_3$ (721.8 mg, 1.1 mmol). The resulting solution was stirred for 24 h at 30°C. The crude product was concentrated under reduced pressure, then diluted in CH$_2$Cl$_2$ (50 ml), and washed with a saturated aqueous solution of NaHCO$_3$ (30 ml). The aqueous layer was extracted with CH$_2$Cl$_2$ (2 × 20 ml). The combined organic layers were dried over anhydrous MgSO$_4$, filtered and evaporated under reduced pressure. The crude product was purified by column chromatography (eluent CH$_2$Cl$_2$) and recrystallised from MeOH to give 199.2 mg (58% yield) of compound **2A**. White solid; mp 158 °C; $[\alpha]_D^{25} = -5.23$ ($c = 1.02$ in CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$, δ): 7.49–7.54 (m, 2H), 7.43–7.47 (m, 2H), 7.26–7.40 (m, 3H), 7.18–7.23 (m, 2H), 5.17 (bd, $J = 3.8$ Hz, 1H), 4.92–4.96 (m, 1H), 4.65–4.71 (m, 1H), 3.41 (dd, $J = 14.0$, 7.2 Hz, 1H), 2.99 (ddd, $J = 14.0$, 11.4, 5.4 Hz, 1H), 2.41 (s, 3H), 2.13 (dddd, $J = 11.7$, 6.4, 3.4, 1.7 Hz, 1H), 1.64–1.77 (m, 2H), 1.46 (dddd, $J = 13.3$, 11.4, 7.2, 1.1 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$, δ): 142.9, 137.6, 137.4, 129.5, 128.0, 126.9, 126.8, 125.6, 82.0, 74.7, 57.0, 39.7, 37.2, 30.2, 21.4; IR (KBr): $\nu = 3079$, 3062, 3041, 1658, 1594 cm^{-1}; HRMS (ESI, *m/z*): $[M + Na]^+$ calcd. for C$_{19}$H$_{21}$NNaO$_3$S, 366.1134; found, 366.1152.

2.2.2 | (2S,4S)-2-Benzyl-1-tosylpiperidin-4-ol (3)

To a solution of compound **2A** (171.7 mg, 0.5 mmol) in CH_2Cl_2 (5 ml), methanol (10 ml), trifluoroacetic acid (15 drops) and 20% Pd $(OH)_2$/C (115 mg) were successively added, and the mixture was stirred at room temperature under an atmosphere of H_2 at atmospheric pressure for 24 h. After this period, the mixture was filtered through Celite® 545 and concentrated under reduced pressure. The crude product was purified by column chromatography (first eluent: Et_2O/hexanes 3:1, second eluent: Et_2O) to give 162.3 mg (94% yield) of compound **3**. Colourless oil; $[\alpha]_D^{25} = -28.25$ ($c = 1.12$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, δ): 7.56–7.61 (m, 2H), 7.18–7.30 (m, 7H), 4.23–4.32 (m, 1H), 4.12–4.17 (m, 1H), 3.68 (ddd, $J = 14.0, 5.3, 2.2$ Hz, 1H), 3.53 (ddd, $J = 14.0, 12.7, 2.8$ Hz, 1H), 3.22 (dd, $J = 13.2, 9.7$ Hz, 1H), 2.97 (dd, $J = 13.2, 6.4$ Hz, 1H), 2.41 (s, 3H), 1.53–1.84 (m, 5H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, δ): 142.9, 139.2, 138.1, 129.5, 129.5, 128.4, 127.0, 126.2, 64.4, 53.4, 38.7, 35.6, 32.1, 31.9, 21.4; IR (neat): $\nu = 3522$, 3062, 3027, 1598 cm^{-1}; (ESI, m/z): $[M + Na]^+$ calcd. for $C_{19}H_{23}NNaO_3S$, 368.1291; found, 368.1302.

2.2.3 | (2S,4S)-2-Benzyl-1-methylpiperidin-4-ol (4)

Sodium naphthalenide (1 M in THF) was prepared by stirring naphthalene (512.7 mg, 4.0 mmol) and small pieces of sodium (101.2 mg, 4.4 mmol) in dry THF (4 ml) at room temperature for 1 h under an argon atmosphere. To a solution of compound **3** (155.5 mg, 0.45 mmol) in dry THF (4 ml) at −78°C under an argon atmosphere, the above freshly prepared solution of sodium naphthalenide (1 ml) was added dropwise until the green colour persisted. The reaction was stirred for 10 min at −78°C and then quenched with MeOH (0.5 ml). The solution was neutralised with 3-M aqueous HCl, and the organic solvents were evaporated under reduced pressure. The residue was dissolved in water (10 ml), and the aqueous solution was brought to pH 1 by addition of 3-M aqueous HCl and washed with diethyl ether (3 × 10 ml). The aqueous solution was basified until pH 13 with 5-M aqueous NaOH solution and extracted with CH_2Cl_2 (3 × 20 ml). Drying over anhydrous $MgSO_4$, filtration and evaporation of the solvent under reduced pressure yielded 75 mg of crude (2S,4S)-2-benzyl-1-methylpiperidin-4-ol that was used without further purification. To a solution of crude (2S,4S)-2-benzyl-1-methylpiperidin-4-ol dissolved in methanol (5 ml), formalin (37% CH_2O, 365.2 mg, 4.5 mmol) was added.

After stirring for 10 min at room temperature, $NaBH_3CN$ (84.8 mg, 1.35 mmol) was added and the resulting mixture was stirred for 1 h at room temperature. Solvent was removed in vacuo, and the residue was dissolved in water (5 ml) and was extracted with CH_2Cl_2 (3 × 20 ml). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by column chromatography (AcOEt/MeOH/Et_3N 8.5:1:0.5) to give 65.6 mg (71% yield) of compound **4**. White solid; mp 143°C [lit.[13] mp 118–120°C]; $[\alpha]_D^{25} = 93.20$ ($c = 1.08$ in $CHCl_3$) [lit.[13] $[\alpha]_D^{23} = 55.2$ ($c = 1.28$ in $CHCl_3$)]; ^1H NMR (400 MHz, $CDCl_3$, δ): 7.18–7.24 (m, 2H), 7.06–7.16 (m, 3H), 3.43 (dddd, $J = 10.9, 10.9, 4.5, 4.5$ Hz, 1H), 3.15 (dd, $J = 13.1, 4.0$ Hz, 1H), 2.92 (ddd, $J = 12.2, 4.0, 3.3$ Hz, 1H), 2.41 (dd, $J = 13.1, 9.9$ Hz, 1H), 2.39 (s, 3H), 2.16–2.26 (m, 2H), 1.85 (dddd, $J = 4.5, 2.7, 2.7, 2.7$ Hz, 1H), 1.69 (dddd, $J = 12.7, 4.8, 2.5, 2.5$ Hz, 1H), 1.58 (dddd, $J = 12.6, 12.6, 11.0, 4.2$ Hz, 1H), 1.18 (ddd, $J = 12.4, 11.1, 11.1$ Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, δ): 138.4, 129.4, 128.4, 126.3, 68.5, 63.6, 55.0, 41.8, 39.8, 39.0, 34.1; IR (nujol): $\nu = 3137$, 3023 cm^{-1}; HRMS (ESI, m/z): $[M + H]^+$ calcd. for $C_{13}H_{20}NO$, 206.1539; found, 206.1529.

2.2.4 | (1R,5S)-2-methyl-6,7-benzomorphan (5)

Compound **4** (61.6 mg, 0.3 mmol) was heated in polyphosphoric acid (1.20 g) with stirring at 140°C for 72 hours. Cooling to room temperature and water addition (5 ml) gave a brown solution which was made basic with 5-M aqueous NaOH and extracted with CH_2Cl_2 (3 × 20 ml). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2, the solution was brought to pH 1 using 2 M ethereal HCl and the organic solvents were evaporated under reduced pressure. A suspension of crude hydrochloride in a mixture of diethyl ether (8 ml) and acetone (1 ml) was stirred at room temperature for 24 h and filtered. The solid was dissolved in 5-M aqueous NaOH (5 ml) and was extracted with CH_2Cl_2 (2 × 20 ml). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to give 36.0 mg (64% yield) of compound **5**. Brownish oil; $[\alpha]_D^{25} = 64.21$ ($c = 1.19$, $CHCl_3$) [lit. [13] $[\alpha]_D^{23} = 116$ ($c = 0.1$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, δ): 7.08–7.15 (m, 3H), 7.02–7.07 (m, 1H), 3.20–3.26 (m, 1H), 3.13 (d, $J = 18.5$ Hz, 1H), 3.00–3.05 (m, 1H), 2.72 (dd, $J = 18.5, 5.9$ Hz, 1H), 2.47–2.56 (m, 1H), 2.44 (s, 3H), 2.08–2.23 (m, 3H), 1.91 (ddd, $J = 12.5, 5.7, 2.8$ Hz, 1H), 1.52 (ddd, $J = 9.2, 4.6, 2.3$ Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, δ): 140.3,

136.9, 128.1, 127.7, 125.9, 125.7, 53.4, 45.9, 43.0, 32.9, 31.9, 31.4, 26.3; HRMS (ESI, *m/z*): $[M + Na]^+$ calcd. for $C_{13}H_{17}NNa$, 210.1253; found, 210.1243.

3 | RESULTS AND DISCUSSION

We have reported[22] a diastereoselective approach the construction of the 6-oxa-2-azabicyclo[3.2.1]octane scaffold from chiral α-hydroxyaldehyde derivatives through Aza-Prins reaction. Hydrogenolysis of chiral adduct obtained by reaction of (*R*)-(benzyloxy)(phenyl)acetaldehyde with *N*-tosylhomoallylamine would offer a straightforward approach to chiral (2*S*,4*S*)-2-benzyl-1-methylpiperidin-4-ol required for intramolecular Friedel−Crafts cyclisation as outlined in our retrosynthetic analysis (Scheme 1).

The synthesis of the tricyclic core of (1*R*,5*S*)-2-methyl-6,7-benzomorphan was started from (*R*)-(benzyloxy)(phenyl)acetaldehyde **1** (Scheme 2). Reaction of **1** with *N*-tosylhomoallylamine according to Mahía et al[22] afforded the 6-oxa-2-azabicyclo[3.2.1]octane **2** as an 87/13 mixture of diastereoisomers in 69% yield from which major diastereoisomer could be isolated in 40% yield. In order to improve these results, we investigated the key Aza-Prins cyclisation under different reaction conditions (Table 1).

Reaction of **1** with *N*-tosylhomoallylamine promoted by $BF_3 \cdot OEt_2$, In $(OTf)_3$ or $TsOH \cdot H_2O$ at 30°C* and using toluene, dichloromethane or acetonitrile as solvent was first investigated (entries 1–9). The induced diastereoselectivity was clearly better when acetonitrile was used as reaction medium and the yield depended on the catalyst (entries 7–9). Indium triflate provided the higher yield of major compound (entry 8). With acetonitrile as solvent, we also tested bismuth triflate, scandium triflate or trifuoromethane sulphonic acid as catalysts. With bismuth triflate or scandium triflate, the reaction efficiency was maintained or even improved and can be used as alternative Lewis acids (entries 10 and 11), whereas when
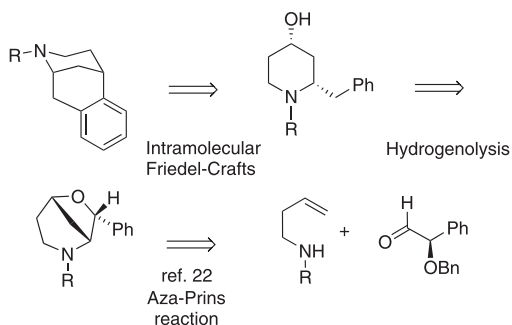
SCHEME 1 Retrosynthetic analysis of 6,7-benzomorphans
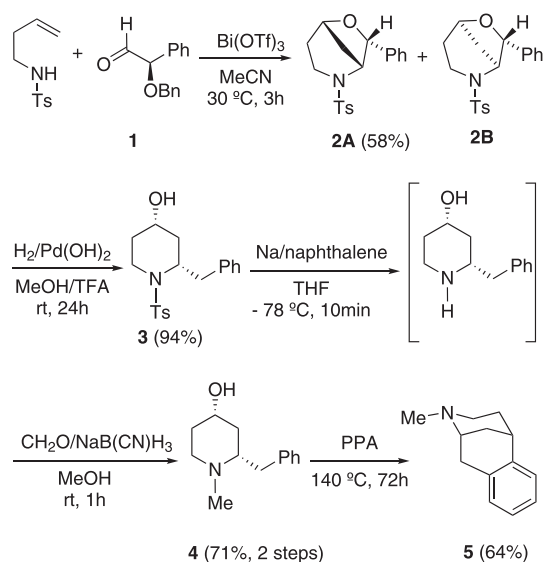
SCHEME 2 Synthesis of (1*R*,5*S*)-2-methyl-6,7-benzomorphan **5**

TABLE 1 Aza-Prins cyclisation[a]

Entry	Solvent	Catalyst	Yield 2A (%)[b]	d.r.[c]
1[d]	Toluene	$BF_3 \cdot OEt_2$	59	68/32
2	Toluene	In $(OTf)_3$	53	60/40
3	Toluene	$TsOH \cdot H_2O$	0	—
4[d]	DCM	$BF_3 \cdot OEt_2$	27	63/37
5	DCM	In $(OTf)_3$	63	66/34
6	DCM	$TsOH \cdot H_2O$	53	78/22
7[d]	Acetonitrile	$BF_3 \cdot OEt_2$	59	88/12
8	Acetonitrile	In $(OTf)_3$	80	88/12
9	Acetonitrile	TsOH·H2O	52	90/10
10	Acetonitrile	Bi $(OTf)_3$	82	89/11
11	Acetonitrile	Sc $(OTf)_3$	88	87/13
12	Acetonitrile	CF_3SO_3H	0	—
13[e]	Acetonitrile	In $(OTf)_3$	48 (37)	88/12
14[e]	Acetonitrile	Bi $(OTf)_3$	78 (58)	89/11

[a]Reaction conditions: aldehyde (0.26 mmol), tosylamine (0.2 mmol), catalyst (0.22 mmol), solvent (2 ml), 30°C, 24 h.
[b]Determined from the crude reaction mixture by ^1H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard.
[c]Determined from the crude reaction mixture by ^{13}C NMR.
[d]Anhydrous solvent.
[e]Reaction conditions: Aldehyde (2.6 mmol), tosylamine (2 mmol), catalyst (2.2 mmol), solvent (20 ml), 30°C, 24 h. The yield of the major isolated compound is in brackets.

trifuoromethane sulphonic acid was used as an alternative Brønsted acid, the formation adducts was not detected (entry 12). When the reaction was performed increasing the amount of reagents (entries 13 and 14), isolated yields were optimal with the use of bismuth triflate as catalyst.

The complete synthetic route to (1*R*,5*S*)-2-methyl-6,7-benzomorphan is represented in Scheme 2. Reaction of (*R*)-(benzyloxy)(phenyl)acetaldehyde **1** (2.6 mmol) with *N*-tosylhomoallylamine (2 mmol) in acetonitrile at 30°C using Bi (OTf)$_3$ (2.2 mmol) as the Lewis acid afforded the 6-oxa-2-azabicyclo [3.2.1]octane **2** as an 89/11 mixture of diastereoisomers. Diastereomerically pure **2A** was isolated in 58% yield after column chromatography on silica gel and recrystallisation. Catalytic hydrogenolysis of benzyl ether in intermediate **2A** over palladium hydroxide gave tosylpiperidinol **3** in 94% yield. Removal of the tosyl group of **3** with sodium naphthalenide generated in situ prepared from sodium and naphthalene in dry THF under argon and subsequent reductive methylation with formaldehyde and sodium cyanoborohydride in methanol at room temperature afforded (2*S*,4*S*)-2-benzyl-1-methylpiperidin-4-ol **4** in 71% yield over two steps. Friedel–Crafts cyclisation of piperidinol **4** in hot polyphosphoric acid[13,23,24] led to the desired benzomorphan **5** in 64% yield.

4 | CONCLUSION

In summary, we have shown that diastereoselective Aza-Prins reaction of (*R*)-(benzyloxy)(phenyl)acetaldehyde **1** with *N*-tosylhomoallylamine can be an efficient key step to the synthesis of enantiomerically pure (1*R*,5*S*)-2-methyl-6,7-benzomorphan **5**. Hydrogenolysis of Aza-Prins adduct **2A** and subsequent detosylation/methylation provides enantiopure (2*S*,4*S*)-2-benzyl-1-methylpiperidin-4-ol **4** from which benzomorphan **5** is obtained by a known intramolecular Friedel–Crafts cyclisation.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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ENDNOTE
* With some Lewis acids, we have observed variations in the reaction yield depending on which is the room temperature. These variations are minimised with optimal reaction yields if temperature is fixed at 30°C.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.