An Expeditious Method for the First Asymmetric Synthesis of Dexoxadrol from the Chiral Pool

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Abstract: A new, straightforward and high-yielding methodology for the asymmetric synthesis of 2-(1,3-dioxolan-4-yl)piperidines is described. This approach involves a highly stereoselective addition of vinylmagnesium bromide to *N*-(3-butenyl)imines derived from D-glyceraldehyde diphenyl ketal and a ring-closing metathesis reaction as key steps. This procedure was used for the first asymmetric synthesis of (*S*)-2-[(*S*)-2,2-diphenyl-1,3-dioxolan-4-yl]piperidine (dexoxadrol) starting from conveniently protected D-mannitol in six steps in 43% overall yield.

Key words: imines, piperidines, metathesis, ring-closure, stereoselective synthesis

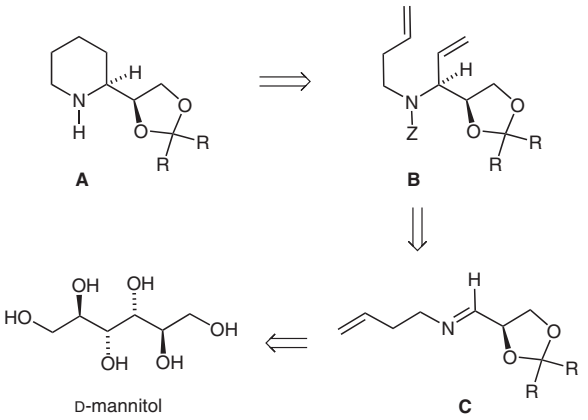
2-(1,3-Dioxolan-4-yl)piperidines were first synthesized in the mid 1960s by Hardie et al.[2] and have shown analgesic, anesthetic, spasmolytic and central nervous system activities,[3] all of which are bound up with their spatial arrangement, with the (2*S*,4′*S*) absolute configuration being the optimum stereochemistry.[4]

The high affinity of the parent compound (*S*)-2-[(*S*)-2,2-diphenyl-1,3-dioxolan-4-yl]piperidine (dexoxadrol, **1**) for the phencyclidine binding site within the NMDA-receptor has stimulated the synthesis of different analogs.[4b,5]

Even though the (2*S*,4′*S*) configuration is crucial to the activity of these compounds, we have not found any published approach for the asymmetric synthesis of these compounds. In previously described procedures to obtain these 2-substituted piperidine derivatives, the heterocycle was obtained by hydrogenation of a pyridine ring[2,4,5a] or was constructed by an aza-Diels–Alder reaction[5c,d] starting from racemic compounds. In some cases, once the piperidine ring was obtained, the diastereoisomers were separated and the racemates resolved.

As part of our continued interest in the stereoselective synthesis of biologically active piperidines from the chiral pool,[6] we propose a new approach to the asymmetric synthesis of this family of compounds starting from the cheap and readily available D-mannitol.

Retrosynthetically (Scheme 1), 2-(1,3-dioxolan-4-yl)piperidines **A** could be obtained from the corresponding bisalkene **B** by ring-closing metathesis (RCM). In turn, bisalkene **B** could be synthesized from *N*-(3-butenyl)imine **C** derived from the appropriate D-glyceraldehyde ketal by diastereoselective addition of vinylmagnesium bromide. The asymmetric synthesis of the parent compound (*S*)-2-[(*S*)-2,2-diphenyl-1,3-dioxolan-4-yl]piperidine (dexoxadrol, **1**) has been performed in order to demonstrate the viability of the proposed methodology.



Scheme 1 Retrosynthetic analysis of 2-(1,3-dioxolan-4-yl)piperidines

The synthetic route to dexoxadrol (Scheme 2) started from diol **2**, which was obtained by reaction of D-mannitol with benzophenone dimethyl ketal according to a literature procedure.[7] Oxidative cleavage of diol **2** with lead tetraacetate afforded crude aldehyde **3**. This compound was immediately treated with 3-buten-1-amine to give imine **4**, which was used in the next step without purification. Addition of vinylmagnesium bromide to **4** at –20 °C afforded an 83:17 *anti*/*syn* diastereomeric mixture of amino ketal derivatives, from which the major diastereoisomer **5** [(*S*,*S*)-configuration] was isolated as a single diastereoisomer by column chromatography in 45% overall yield from diol **2**. The absolute configuration of the major amino ketal derivative **5** was inferred later by the stereochemistry of the final product.

It was observed[8] that pre-complexation of the imine with $BF_3{\cdot}OEt_2$ led to a significant increase in the *anti* diastereoselectivity of the addition of some organometallic reagents to *N*-benzylimines derived from (*R*)-2,3-*O*-isopropylideneglyceraldehyde. Unfortunately, this strategy was unsuccessful with imine **4**, and addition of vinylmagnesium bromide to $BF_3{\cdot}OEt_2$ pre-complexed with imine **4** afforded amino ketal derivative **5** as an 85:15 *anti*/

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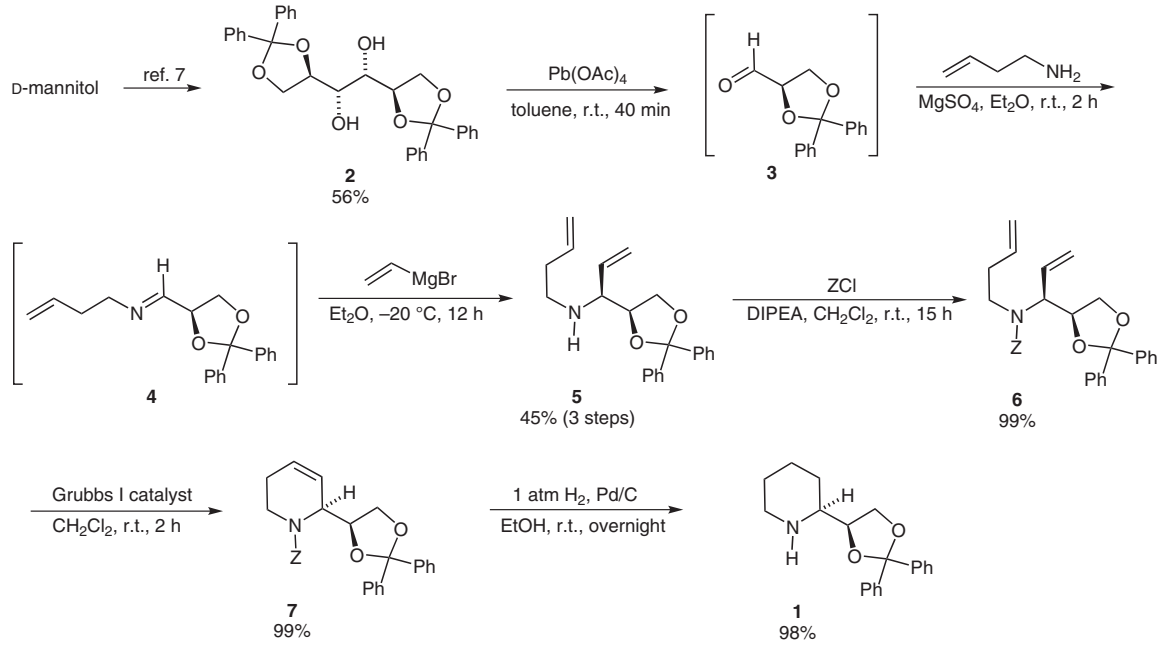

Scheme 2 Synthesis of dexoxadrol **1**

syn diastereomeric mixture from which the major *anti* diastereoisomer was isolated in a reduced 28% yield.

At this stage, ring-closing metathesis was used as a synthetic tool to construct the piperidine ring.[9,10] The presence of an unhindered basic amino group may have an adverse effect in RCM reactions and one efficient strategy to increase the amino group compatibility with RCM catalysts is to transform the amino group into a carbamate moiety.[10b]

N-Benzylcarbamate **6** was cleanly obtained in nearly quantitative yield by treatment of amino ketal **5** with benzyl chloroformate in the presence of DIPEA as base. Performing the RCM reaction of **6** with 10 mol% of Grubb's first generation catalyst[11] in methylene chloride at room temperature for two hours, *N*-benzyloxycarbonyltetrahydropyridine **7** was obtained in nearly quantitative yield. Finally, the desired compound **1** was obtained, also in nearly quantitative yield, by hydrogenation of the C=C double bond with concomitant N-deprotection of compound **7** by catalytic hydrogenation in ethanol using Pd/C as catalyst under atmospheric pressure of molecular hydrogen.

The absolute configuration of the final product **1** was established as (2*S*,4′*S*) by X-ray diffraction analysis of a single crystal obtained from compound **1**[12] as the hydrochloride salt. In addition, the physical data for compound **1** as a hydrochloride salt are fully consistent with those previously reported in the literature[2] for (*S*)-2-[(*S*)-2,2-diphenyl-1,3-dioxolan-4-yl]piperidine hydrochloride.

It is worth mentioning that acidic hydrolysis of compound **1** provides (*S*)-2-[(*S*)-1,2-dihydroxyethyl]piperidine,[4b] which has been used as an intermediate in the synthesis of etoxadrol[4b] and other analogs of dexoxadrol.[5a,13]

In conclusion, enantiomerically pure (*S*)-2-[(*S*)-2,2-diphenyl-1,3-dioxolan-4-yl]piperidine (dexoxadrol) has been obtained in six steps and 43% overall yield from conveniently protected D-mannitol. This straightforward and high-yielding synthesis involves the highly diastereoselective addition of vinylmagnesium bromide to a chiral *N*-(3-butenyl)imine and ring-closing metathesis as key steps. This approach represents the first asymmetric synthesis of dexoxadrol, a potent phencyclidine-like antagonist that has shown tremendous potential as a synthetic intermediate to obtain even more potent analogs.

Synthesis of 5. Lead tetraacetate (887 mg, 2.0 mmol) was added to a solution of diol **2** (510 mg, 1.0 mmol) in toluene (20 mL) at r.t. and the resulting suspension was stirred at r.t. for 40 min. The reaction mixture was filtered and the residue was washed with diethyl ether (30 mL). The filtrate was washed with saturated aqueous $NaHCO_3$ (2·30 mL) and the combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated to give aldehyde **3**, which was immediately dissolved in anhydrous diethyl ether (20 mL) and used in the next step without purification. The solution was stirred at r.t. and anhydrous $MgSO_4$ (361 mg, 3.0 mmol) and 3-buten-1-amine (142 mg, 2.0 mmol) were added successively. The reaction mixture was stirred for 2 h at r.t., filtered and evaporated. The resultant oil was dissolved in anhydrous diethyl ether (20 mL) and cooled to –20 °C. A solution of vinylmagnesium bromide (1.0 M in THF, 4.0 mL, 4.0 mmol) was added dropwise under an argon atmosphere at –20 °C and the reaction mixture was stirred for 12 h at the same temperature. The stirred reaction mixture was cooled (ice bath), quenched with water (20 mL) and extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated in vacuo to give the corresponding amino ketal as an 83:17 *anti*/*syn* mixture of diastereoisomers. Purification of the crude product by silica gel column chromatography (Et_2O–hexanes, 1:2), afforded diastereomerically pure compound **5** (302 mg, 45%) with *anti* configuration as a colorless oil; $[\alpha]_D^{25}$ +43.4 (*c* 1.00, $CHCl_3$). IR (neat): 3325, 1640 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.40 (br s, 1 H), 2.10 (ddddd,

J = 7.0, 6.8, 6.8, 1.2, 1.2 Hz, 2 H), 2.41 (ddd, *J* = 11.4, 6.8, 6.8 Hz, 1 H), 2.63 (ddd, *J* = 11.4, 7.0, 7.0 Hz, 1 H), 3.20 (dd, *J* = 8.1, 4.6 Hz, 1 H), 3.89 (dd, *J* = 7.7, 7.2 Hz, 1 H), 4.04 (dd, *J* = 7.7, 6.3 Hz, 1 H), 4.10 (ddd, *J* = 7.2, 6.3, 4.6 Hz, 1 H), 4.89 (br d, *J* = 10.2 Hz, 1 H), 4.96 (dddd, *J* = 17.1, 1.4, 1.4, 1.4 Hz, 1 H), 5.10–5.19 (m, 2 H), 5.56 (ddd, *J* = 17.8, 9.8, 8.1 Hz, 1 H), 5.65 (dddd, *J* = 17.1, 10.2, 6.8, 6.8 Hz, 1 H), 7.15–7.31 (m, 6 H), 7.38–7.49 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.2, 46.3, 63.0, 66.4, 78.8, 109.8, 116.2, 118.1, 126.1, 126.2, 127.9, 128.0, 128.1, 128.1, 136.3, 136.7, 141.9, 142.1. HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{26}NO_2$: 336.1958; found: 336.1961.

Synthesis of 6. Benzyl chloroformate (256 mg, 1.5 mmol) was added dropwise to a solution of pure *anti* diastereoisomer **5** (335 mg, 1.0 mmol) and DIPEA (387 mg, 3.0 mmol) in CH_2Cl_2 (20 mL) at r.t. and the resulting mixture was stirred at r.t. for 15 h. The reaction mixture was washed with water (10 mL) and the organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated in vacuo. Purification of the crude product by silica gel column chromatography (CH_2Cl_2) afforded compound **6** (464 mg, 99%) as a colorless oil; $[\alpha]_D^{25}$ +1.5 (*c* 1.00, $CHCl_3$). IR (neat): 1699, 1641 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 333 K): δ = 2.14–2.30 (m, 2 H), 3.17–3.31 (m, 2 H), 3.84 (dd, *J* = 8.1, 6.1 Hz, 1 H), 3.95 (dd, *J* = 8.1, 7.4 Hz, 1 H), 4.19–4.34 (m, 1 H), 4.38–4.52 (m, 1 H), 4.91 (br d, *J* = 10.2 Hz, 1 H), 4.93 (br d, *J* = 17.1 Hz, 1 H), 5.03 (d, *J* = 12.5 Hz, 1 H), 5.07 (d, *J* = 12.5 Hz, 1 H), 5.16 (br d, *J* = 17.1 Hz, 1 H), 5.19 (br d, *J* = 10.5 Hz, 1 H), 5.63 (dddd, *J* = 17.1, 10.2, 6.8, 6.8 Hz, 1 H), 5.97 (ddd, *J* = 17.1, 10.5, 6.4 Hz, 1 H), 7.14–7.31 (m, 11 H), 7.39–7.45 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$, 333 K): δ = 33.8, 46.0, 61.7, 67.3, 67.8, 77.6, 110.6, 116.5, 118.8, 126.1, 126.1 (×2), 127.8, 128.0, 128.0, 128.0, 128.1, 128.4, 133.4, 135.2, 136.6, 142.4, 142.5, 156.0. HRMS (ESI+): *m*/*z* $[M + Na]^+$ calcd for $C_{30}H_{31}NO_4Na$: 492.2145; found: 492.2156.

Synthesis of 7. A solution of compound **6** (469 mg, 1.0 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a solution of Grubb's first generation catalyst (82 mg, 0.10 mmol) in CH_2Cl_2 (20 mL) at r.t. and the resulting solution was stirred at r.t. for 2 h. The solvent was evaporated in vacuo and the residue was purified by silica gel column chromatography (Et_2O–hexanes, 1:2), to afford compound **7** (436 mg, 99%) as a colorless oil; $[\alpha]_D^{25}$ –140.9 (*c* 1.00, $CHCl_3$). IR (neat): 1702, 1655 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 333 K): δ = 1.91 (br d, *J* = 17.2 Hz, 1 H), 2.04–2.28 (m, 1 H), 2.85–3.13 (m, 1 H), 3.83–4.04 (m, 1 H), 3.96–4.24 (m, 2 H), 4.22 (ddd, *J* = 6.6, 6.6, 6.6 Hz, 1 H), 4.37–4.63 (m, 1 H), 5.08 (d, *J* = 12.3 Hz, 1 H), 5.13 (d, *J* = 12.3 Hz, 1 H), 5.82–5.95 (m, 2 H), 7.17–7.38 (m, 11 H), 7.40–7.56 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$, 333 K): δ = 24.6, 38.4, 54.0, 67.3, 67.8, 78.6, 110.3, 125.2, 126.2 (×2), 127.0, 127.0, 127.8, 127.9, 127.9, 128.0, 128.1, 128.5, 136.6, 142.4, 142.4, 155.4. HRMS (ESI+): *m*/*z* $[M + Na]^+$ calcd for $C_{28}H_{27}NO_4Na$: 464.1832; found: 464.1850.

Synthesis of 1. 10% Pd/C (15 mg) was added to a solution of compound **7** (221 mg, 0.50 mmol) in EtOH (10 mL) and the mixture was vigorously stirred overnight at r.t. under an atmospheric pressure of H_2. After completion of the reaction, the catalyst was removed by filtration on Celite and the filtrate was evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (20 mL) and washed with 2.0 N aqueous NaOH (10 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and evaporated in vacuo to afford compound **1** (152 mg, 99%) as a colorless oil; $[\alpha]_D^{25}$ +36.6 (*c* 1.00, $CHCl_3$). IR (neat): 3334 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (dddd, *J* = 12.4, 12.4, 12.4, 3.9 Hz, 1 H), 1.22–1.52 (m, 3 H), 1.52–1.67 (m, 1 H), 1.62–1.81 (m, 2 H), 1.77–1.90 (m, 1 H), 2.62 (ddd, *J* = 11.8, 11.3, 2.7 Hz, 1 H), 2.86 (ddd, *J* = 11.3, 4.4, 2.5 Hz, 1 H), 3.08 (br d, *J* = 11.8 Hz, 1 H), 3.98 (dd, *J* = 7.2, 7.2 Hz, 1 H), 4.06 (ddd, *J* = 7.2, 6.6, 4.5 Hz, 1 H), 4.18 (dd, *J* = 7.2, 6.6 Hz, 1 H), 7.26–7.41 (m, 6 H), 7.48–7.55 (m, 2 H), 7.54–7.61 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.5, 26.4, 28.6, 46.7, 57.9, 65.9, 79.6, 109.3, 126.1, 126.2, 127.9, 128.0, 128.0, 128.1, 142.1, 142.2. HRMS (ESI+): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{24}NO_2$: 310.1802; found: 310.1801.

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