Construction of Dibenzazocine Skeleton by Regiocontrolled Ring-Expansion Reaction of Cyclic Oxime with DIBAL-H: Facile Synthesis of 17β-Hydroxysteroid Dehydrogenase Type 3 Inhibitor

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Abstract: Synthetic studies on a 17β-hydroxysteroid dehydrogenase type 3 (17β-HSD3) inhibitor are described. The unsymmetrical dibenzazocine skeleton was constructed by a regiocontrolled ring-expansion reaction of a cyclic oxime with DIBAL-H.

Key words: reduction, ring expansion, rearrangement, heterocycles, regioselectivity

Since 17β-hydroxysteroid dehydrogenase type 3 (17β-HSD3) is an enzyme involved in testosterone biosynthesis, inhibitors of 17β-HSD3 could be new medicines for the treatment of prostate cancer. Recently, Fink reported that several dibenzazocines inhibit 17β-HSD3 at picomolar concentrations in both cell-free enzymatic and cell-based transcriptional reporter assays (Figure 1).[1] While they synthesized a series of benzazocines by an oxidative cleavage at the 2,3-position of 2,3-fused indoles according to the known protocol,[2] the starting indanones and arylhydrazines are not always available, and a general synthetic methodology for dibenzazocines is still needed.

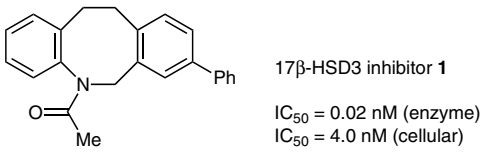
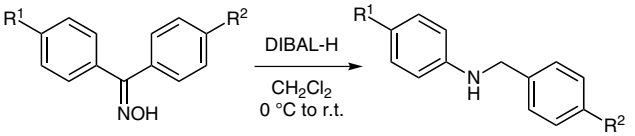


Figure 1 17β-HSD3 inhibitor for the treatment of prostate cancer

Recently, we established new synthetic methodologies for cyclic arylamines, including a tetrahydrobenzazocine, by a reductive ring-expansion reaction of cyclic oximes and hydroxylamines using aluminum hydrides such as DIBAL-H[3] and $AlHCl_2$.[4] When we applied the reaction to pseudosymmetrical benzophenone oximes, it was found that the more electron-rich aromatic ring has a stronger migratory aptitude (Scheme 1).[3c] Thus, treatment of oximes **2a** and **2b** with DIBAL-H exclusively provided the *N*-arylbenzylamines **3a** and **3b** as a single isomer.

Taking advantage of the electron-density-controlled migration, we planned a synthesis of 17β-HSD3 inhibitor **1**. A dibenzoazocine ring would be constructed by regio-

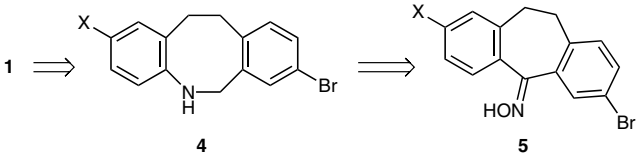


2a R^1 = OMe, R^2 = H (*E*/*Z* = ca. 1:1)
2b R^1 = H, R^2 = CF_3 (*E*/*Z* = ca. 1:1)

3a R^1 = OMe, R^2 = H; 90%
3b R^1 = H, R^2 = CF_3; 65%

Scheme 1 Regioselective rearrangement of benzophenone oxime with DIBAL-H

selective reductive ring-expansion reaction of a pseudosymmetrical dibenzosuberone oxime **5** with fine-tuned electron density of two aromatic rings by the Br group, with or without a removable substituent X. Then, N-acylation and introduction of a phenyl group by cross-coupling reaction would provide **1** (Scheme 2).



4 **5**

Scheme 2 Synthetic strategy for 17β-HSD3 inhibitor **1**, including a regiocontrolled ring expansion mediated by DIBAL-H

Herein we report a concise synthesis of 17β-HSD3 inhibitor **1** featuring a unique regiocontrolled reductive ring-expansion reaction governed by a slight difference in electron density between the two benzene rings.

Preparation of dibenzosuberone oximes **5a** and **5b** for the key reaction was performed as shown in Scheme 3. Sonogashira coupling of methyl 5-bromo-2-iodobenzoate and trimethylsilylacetylene followed by basic removal of the TMS group gave arylacetylene **6**. The second Sonogashira coupling, with the corresponding iodobenzene or 3-iodo-1-methylthiobenzene,[5,6] provided 1,2-diarylacetylenes **7**. While hydrogenation of **7a** smoothly gave ester **8a** with catalytic platinum oxide under atmospheric pressure; in the case of **7b** high pressure (68.95 bar) was necessary for the high-yielding process. Hydrolysis of **8** and subsequent Friedel–Crafts acylation gave dibenzosuberones **10** using P_2O_5–MsOH,[7] which were converted into the corresponding oximes **5** by treatment with $NH_2OH{\cdot}HCl$ in pyridine.

We next focused on the reductive ring-expansion reaction for the regiocontrolled construction of the dibenzazocine

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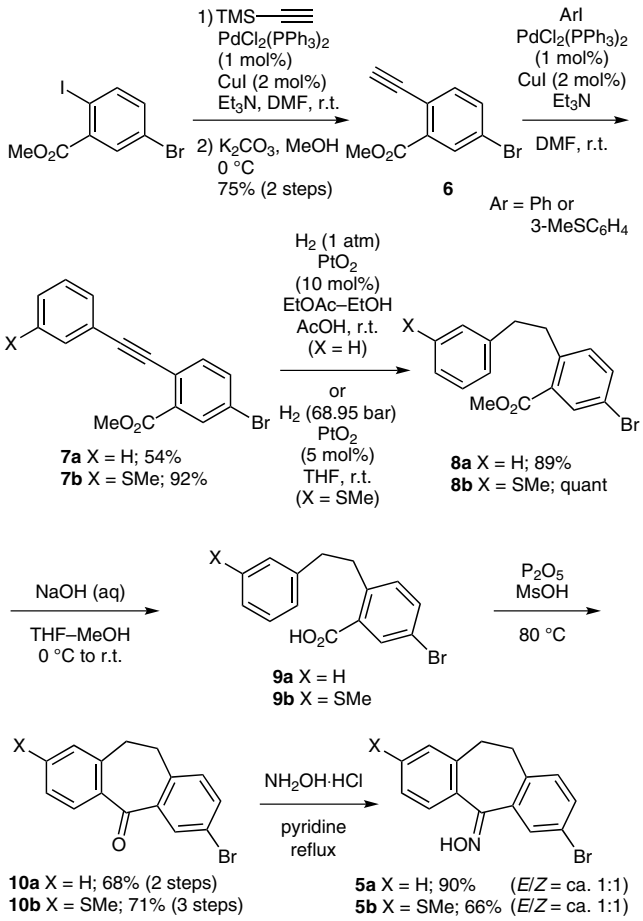
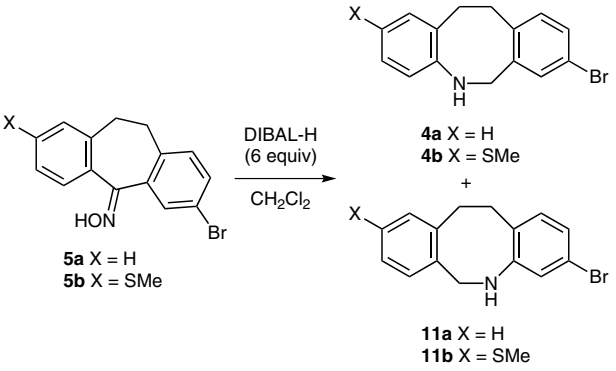


Scheme 3 Preparation of oxime **5**

ring (Table 1). First, we treated oxime **5a** with six equivalents of DIBAL-H at 0 °C,[3] which resulted in incompletion of the reaction even at room temperature, and a mixture of azocines **4a** and **11a** (**4a**/**11a** = 3.3:1.0) was obtained in 46% yield with recovery of the starting oxime **5a** (28%) (Table 1, entry 1). At 80 °C in 1,2-dichloroethane, oxime **5a** was completely consumed to provide a mixture of azocines (**4a**/**11a** = 2.0:1.0) in 73% yield (Table 1, entry 2). These results suggested that we should add a removable electron-donating group (X) on the other benzene ring. We selected a methylthio group as substituent X and examined the ring-expansion reaction. Thus, treatment of **5b** with DIBAL-H at 0 °C also gave a mixture of azocines with better regioselectivity (**4b**/**11b** = 8.5:1.0), although in lower yield (42%, Table 1, entry 3). Finally, we found that the use of six equivalents of DIBAL-H at room temperature gave azocines in satisfactory yield and selectivity (67% yield, **4b**/**11b** = 6.0:1.0, Table 1, entry 4).[8]

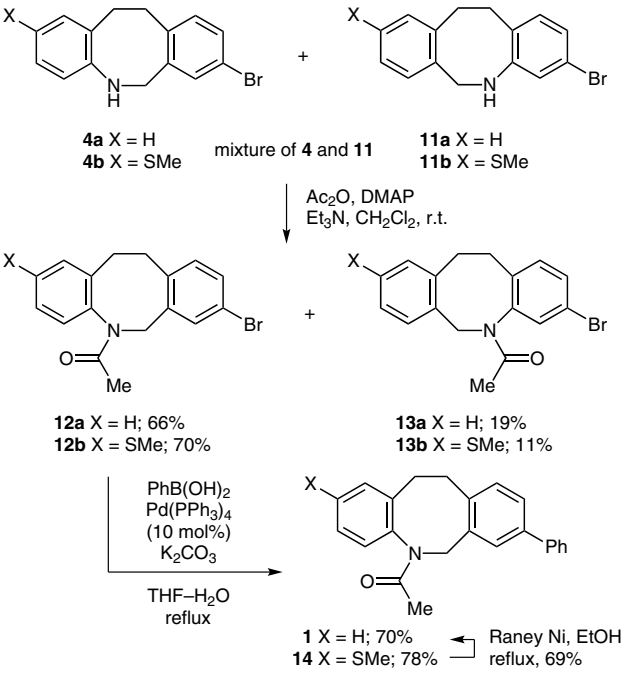
With the desired azocines **4** in hand as a mixture of regioisomers, we then converted them into 17β-HSD3 inhibitor **1** (Scheme 4). After acetylation of azocines **4** and **11**, we separated each regioisomer. The structure of compound **12a**[9] was confirmed by X-ray crystallographic analysis (Figure 2).[10] Subjection of **12a** under the Suzuki–Miyaura coupling conditions provided 5-acetyl-5,6,11,12-tetra-

Table 1 DIBAL-H-Mediated Ring-Expansion Reaction[a]



Entry	X	Temp	Time (h)	Yield (%)[b]	**4**/**11**[c]
1	H	0 °C to r.t.	12	46[d]	3.3:1.0
2[e]	H	80 °C	16	73	2.0:1.0
3	SMe	0 °C to r.t.	12	42[f]	8.5:1.0
4	SMe	r.t.	12	67	6.0:1.0

[a] Reaction conditions: DIBAL-H (6 equiv) was added to the mixture of **5** in CH_2Cl_2 (0.1 M).
[b] Isolated yields as a mixture of **4** and **11**.
[c] Determined by ^{1}H NMR analysis.
[d] Starting material **5a** (28%) was recovered.
[e] Instead of CH_2Cl_2, DCE was used as a solvent.
[f] Starting material **5b** (36%) was recovered.



Scheme 4 Synthesis of 17β-HSD3 inhibitor **1**

hydro-8-phenyldibenz[*b*,*f*]azocine (**1**) in 70% yield. Desulfurization of **14**, which was prepared from **12b**[11] in the same route with Raney Ni, gave **1** in good yield.[12]

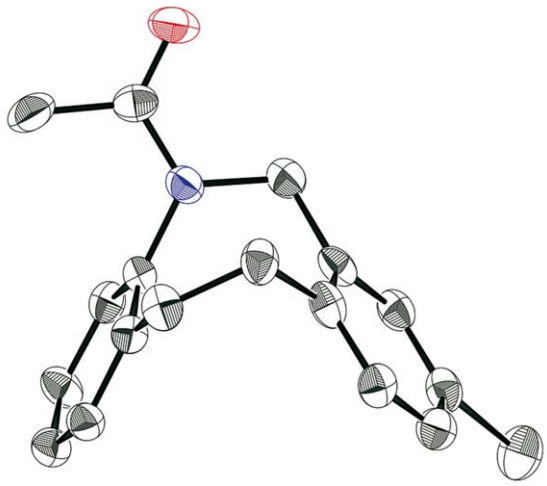


Figure 2 ORTEP drawing of the molecular structure of compound **12a** with thermal ellipsoids at 50% probability levels

In conclusion, we achieved a concise synthesis of 17β-HSD3 inhibitor **1** with a dibenzazocine skeleton. The synthesis features the regiocontrolled reductive ring-expansion reaction of cyclic ketoxime.

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(5) (a) Mongin, O.; Papamicaël, C.; Hoyler, N.; Gossauer, A. *J. Org. Chem.* **1998**, *63*, 5568. (b) We prepared 3-iodo-1-methylthiobenzene from 3-(methylthio)aniline by Sandmeyer reaction. This procedure is described in ref. 6.

(6) **Procedure for the Sandmeyer Reaction for the Synthesis of 3-Iodo-1-methylthiobenzene**
A 300 mL round-bottomed flask equipped with a magnetic stirring bar was charged with 3-(methylthio)aniline (4.00 mL, 32.5 mmol), crushed ice (24 g), and MeCN (24 mL). To the stirred solution was added concd H_2SO_4 (24 mL) at 0 °C over 30 min. To the slurry was added aq $NaNO_2$ (4.04 g, 58.6 mmol) in cold H_2O (8 mL) at 0 °C dropwise over 30 min to maintain an internal temperature below 5 °C. After the mixture was stirred at 0 °C for 30 min, the mixture was poured into a solution of KI (18.9 g, 114 mmol) in H_2O (24 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 5 min, and then the mixture was allowed to warm to r.t. and the solution was stirred for 1 h, after which time TLC (hexanes–EtOAc, 3:1) indicated complete consumption of the starting aniline. The reaction was quenched with H_2O, and the mixture was extracted with $CHCl_3$ three times. The combined organic extracts were washed with sat. aq $NaHCO_3$, sat. aq $Na_2S_2O_3$, and brine, dried over anhyd Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes) to afford 3-iodo-1-methylthiobenzene (7.71 g, 30.8 mmol, 95%) as a pale yellow oil. The spectral data of 3-iodo-1-methylthiobenzene was identical with those reported in ref. 5a.

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(8) **Procedure for the DIBAL-H-Mediated Reductive Ring-Expansion Reaction of 5b**
A two-necked 30 mL round-bottomed flask equipped with a magnetic stirring bar was charged with oxime **5b** (175 mg, 0.503 mmol) and dry CH_2Cl_2 (5.0 mL). To the solution was added DIBAL-H (1.03 M in hexane, 3.0 mL, 3.09 mmol) dropwise at r.t. in a water bath for 10 min. The solution was stirred for 12 h, after which time TLC (hexanes–EtOAc, 3:1) indicated complete consumption of **5b**. The reaction mixture was cooled to 0 °C, and diluted with Et_2O. The reaction was then quenched with MeOH and 2 M aq NaOH, and the mixture was extracted with Et_2O three times. The combined organic extracts were washed with brine, dried over anhyd Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes–EtOAc, 9:1) to afford an inseparable mixture of **4b** and **11b** (113 mg, 0.337 mmol, 67%) as a yellow solid.
Analytical Data
IR (neat): 3376 (br), 2919, 2891, 1592, 1484, 1258, 813, 756 cm^{-1}. ^1H NMR [400 MHz, $CDCl_3$, isomeric mixture (6:1)]: δ (major isomer) = 7.22–7.15 (m, 2 H), 6.96 (d, 1 H, *J* = 2.0 Hz), 6.90 (dd, 1 H, *J* = 8.0, 2.0 Hz), 6.89 (d, 1 H, *J* = 7.6 Hz), 6.46 (d, 1 H, *J* = 8.0 Hz), 4.35 (s, 2 H), 3.27–3.18 (m, 2 H), 3.16–3.08 (m, 2 H), 2.37 (s, 3 H); δ (minor isomer) = 7.02–7.15 (m, 3 H), 6.81 (d, 1 H, *J* = 8.0 Hz), 6.77 (dd, 1 H, *J* = 7.6, 2.0 Hz), 6.61 (d, 1 H, *J* = 2.0 Hz), 4.37 (s, 2 H), 3.27–3.18 (m, 2 H), 3.16–3.08 (m, 2 H), 2.41 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.5, 145.3, 140.7, 139.3, 137.3, 133.7, 132.5, 132.2, 132.1, 131.9, 131.8, 131.2, 130.22, 130.19, 129.7, 128.3, 127.7, 127.6, 125.8, 124.6, 122.5, 121.2, 119.9, 119.8, 51.1, 50.8, 35.4, 34.8, 32.1, 31.6, 17.9, 15.6. HRMS (ESI^+): *m/z* calcd for $C_{16}H_{17}BrNS$ [M + H^+]: 334.0260; found: 334.0249.

(9) **5-Acetyl-5,6,11,12-tetrahydro-8-bromo-dibenz[*b*,*f*]-azocine (12a)**
Colorless plates. IR (neat): 2944, 1651, 1496, 1386, 1282, 724 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.12 (m, 4 H), 7.10–7.00 (m, 2 H), 6.96–6.88 (m, 1 H), 5.75 (d, 1 H, *J* = 14.8 Hz), 4.02 (d, 1 H, *J* = 14.8 Hz), 3.26–3.12 (m, 2 H), 2.94–2.72 (m, 2 H), 1.80 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2, 140.5, 139.3, 139.0, 137.3, 132.7, 131.2, 131.1, 130.8, 128.7, 128.5, 128.0, 119.7, 52.0, 34.6, 30.9, 22.7. HRMS (ESI^+): *m/z* calcd for $C_{17}H_{17}BrNO$ [M + H^+]: 330.0488; found: 330.0489.

(10) **Crystal Data for 12a**
$C_{17}H_{16}BrNO$; *MW* = 330.22, triclinic, *a* = 8.647(4) Å, *b* = 8.985(4) Å, *c* = 9.396(5) Å, α = 90.802(5)°, β = 96.809(6)°, γ = 102.040(6)°, *V* = 708.4(6) Å^3, *T* = 173(2) K, space group *P*1, *Z* = 2. The final residuals were *R* = 0.0663 and *wR*2 = 0.1682. Crystallographic data of **12a** have been deposited with the Cambridge Crystallographic Data Centre (CCDC) as supplementary publication no. CCDC 903314. Copies of the data can be obtained free of charge from the CCDC via http://beta-www.ccdc.cam.ac.uk/pages/Home.aspx.

(11) **5-Acetyl-5,6,11,12-tetrahydro-8-bromo-2-methylthio-dibenz[*b*,*f*]azocine (12b)**
Colorless oil. IR (neat): 3002, 2921, 1657, 1491, 1386, 1286, 754 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.20 (m, 2 H), 7.03 (dd, 1 H, *J* = 8.0, 2.0 Hz), 6.97 (dd, 1 H, *J* = 8.0 Hz), 6.91 (d, 1 H, *J* = 8.0 Hz), 6.89 (d, 1 H, *J* = 2.0 Hz), 5.73 (d, 1 H, *J* = 14.8 Hz), 3.99 (d, 1 H, *J* = 14.8 Hz), 3.24–3.10 (m, 2 H), 2.88–2.70 (m, 2 H), 2.42 (s, 3 H), 1.80 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.3, 139.4, 139.3, 139.1, 137.3, 137.2, 132.7, 131.1, 130.8, 128.8, 128.4, 125.1, 119.8, 52.0, 34.7, 30.7, 22.7, 15.3. HRMS (ESI$^+$): *m/z* calcd for $C_{18}H_{19}BrNOS$ [M + H$^+$]: 376.0365; found: 376.0381.

(12) **5-Acetyl-5,6,11,12-tetrahydro-8-phenyldibenz[*b*,*f*]azocine (1)**
Colorless oil. IR (neat): 3027, 2930, 1658, 1494, 1389, 765 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49 (d, 2 H, *J* = 7.2 Hz), 7.45–7.27 (m, 5 H), 7.21–7.00 (m, 5 H), 5.83 (d, 1 H, *J* = 14.8 Hz), 4.16 (d, 1 H, *J* = 14.8 Hz), 3.38–3.15 (m, 2 H), 3.00–2.81 (m, 2 H), 1.82 (s, 3 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 170.3, 140.5, 139.43, 139.37, 139.1, 135.4, 131.2, 129.9, 128.8, 128.7, 128.6, 128.54, 128.46, 127.8, 127.1, 126.9, 126.3, 52.8, 34.8, 31.2, 22.8. HRMS (ESI$^+$): *m/z* calcd for $C_{23}H_{22}NO$ [M + H$^+$]: 328.1696; found: 328.1699.

