Synthesis of (+)-Febrifugine and a Formal Synthesis of (+)-Halofuginone Employing an Organocatalytic Direct Vinylogous Aldol Reaction

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Received: 19.02.2013; Accepted after revision: 14.04.2013

Dedicated to Professor Scott E. Denmark on the occasion of his 60th birthday

Abstract: The enantioselective organocatalytic direct vinylogous aldol reaction of γ-crotonolactone and a suitable aldehyde was utilized in the synthesis of a functionalized γ-butenolide. The γ-butenolide (aldol product) was stereoselectively converted into a 5-aminoalkyl butyrolactone, which isomerized to the key 2,3-disubstituted piperidinone, a common intermediate to (+)-febrifugine and (+)-halofuginone.

Key words: asymmetric catalysis, aldol reaction, stereoselective synthesis, piperidines, total synthesis

The prevalence of malaria in tropical regions and the need for new medicines to combat malaria have resulted in a persistent, and often challenging, search for new antimalarial agents.[1] In this context, febrifugine (**1**, Figure 1) and halofuginone (**2**) have attracted considerable interest due to their pronounced antimalarial activity.[2] In solution, febrifugine (**1**) is gradually converted to isofebrifugine (**3**) which is less potent, but exhibits antimalarial activity similar to febrifugine.[2d] The asymmetric synthesis of febrifugine[3] continues to be actively investigated and the reported syntheses often showcase new methodology for stereoselective construction of the 2,3-disubstituted piperidine ring in the targets. Only two asymmetric syntheses of halofuginone[3a,4] are reported. Febrifugine and halofuginone also have numerous other applications, which have contributed to a continued interest in these alkaloids. Notably, in addition to its antimalarial properties, halofuginone is used as an antiprotozoal agent in poultry[5] and also as an antiangiogenic agent.[6] It has been approved for the treatment of scleroderma and is active against estrogen-deficient osteoporosis in mice.[7] Recently, the molecular mechanism of action of febrifugine and halofuginone in mice has been determined.[8] These studies have highlighted the importance of structural analogues of febrifugine in the treatment of multiple sclerosis, scleroderma, and rheumatoid arthritis. Hence, an important consideration in devising a synthesis of the title compounds is the flexibility of the approach for making analogues of febrifugine.

Accordingly, we decided to develop a synthesis of febrifugine (**1**) that would proceed through a precursor that could also be converted into halofuginone and, potentially, other heteroaryl-linked piperidines by simple coupling

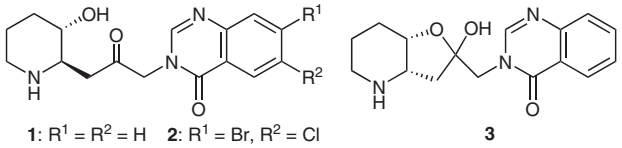
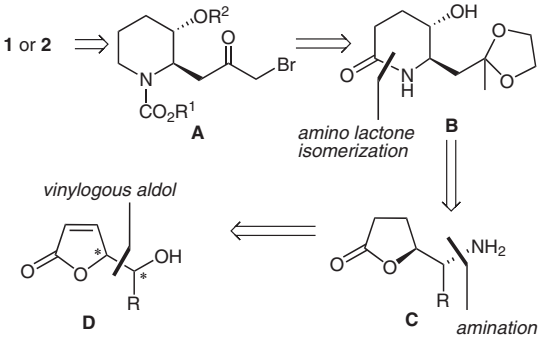


Figure 1 (+)-Febrifugine (**1**), (+)-halofuginone (**2**) and isofebrifugine (**3**)

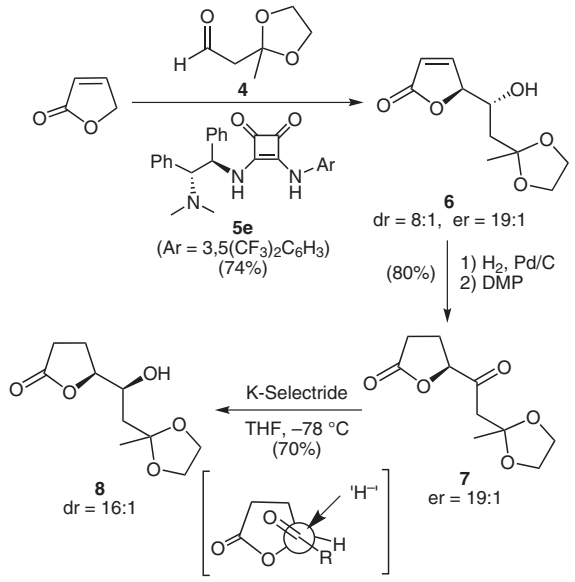
with a suitable heterocycle. Retrosynthetically, the common precursor to **1** or **2** is a suitably protected piperidinyl bromoketone[3j] such as **A** (Scheme 1), which derives from the functionalized piperidinone **B**. The piperidinone **B** can be obtained by isomerization[9] of an aminoalkyl lactone such as **C**. Ultimately, **C** derives from the functionalized butenolide **D**, which leads us to the organocatalytic direct vinylogous aldol reaction[10] of crotonolactone and an appropriate aldehyde. The vinylogous aldol reaction[11] directly sets the absolute stereochemistry at C-3 in the piperidine ring of the target. The stereochemistry at C-2 is indirectly controlled by the aldol reaction and is achieved by manipulation of the secondary alcohol stereocenter in the aldol adduct (Scheme 1).



Scheme 1

Our investigations began with the synthesis of **6** (Scheme 2). Initially, the direct vinylogous aldol reaction of commercially available γ-crotonolactone and the aldehyde **4**[12] was examined in the presence of selected cyclohexanediamine, stilbenediamine, and cinchonidine derived thioureas[13] (**5a**, **5b**, **5c**) and cyclohexanediamine and stilbenediamine derived squaramides[14] (**5d** and **5e**, Figure 2).

SYNTHESIS 2013, 45, 1863–1869
Advanced online publication: 08.05.2013
DOI: 10.1055/s-0033-1338706; Art ID: SS-2013-C0140-OP



Scheme 2

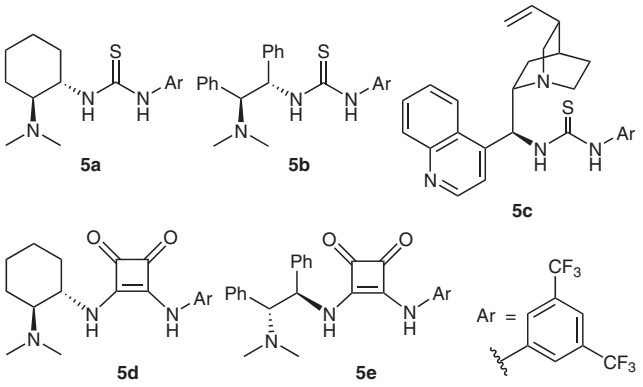
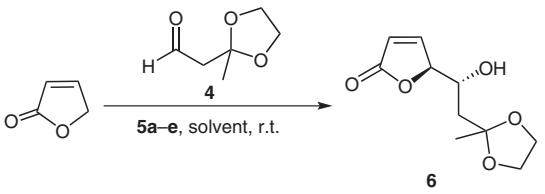


Figure 2 Selected aminothiourea and aminosquaramide catalysts

Orienting experiments with the catalyst **5a** suggested dichloromethane as a solvent for further studies based on the yield and enantiomeric excess of **6** (Table 1, entries 1–4). Although lowering the temperature (0 °C), increased the diastereoselectivity and enantiomeric excess for **6**, the reaction was prohibitively slow (Table 1, entry 5, 8% yield of **6**). The stilbenediamine-derived aminothiourea **5b** was ineffective as a catalyst and provided only a trace of **6** in dichloromethane (entries 6–8). Catalyst **5c** provided **6** in low yield and moderate enantiomeric excess (entry 9). Reactions with the aminosquaramide catalysts **5d** and **5e** were slower, but provided **6** with higher enantiomeric excess (entries 10–16) than the aminothiourea catalysts **5a**–**c**. For catalyst **5d**, the use of dichloromethane as the solvent provided the highest enantiomeric excess (entries 10–12), but the yield and diastereostelectivity for **6** remained low. Further studies with the aminosquaramide catalyst **5e**[14a] in ethyl acetate provided **6** with good enantiomeric excess (entry 14, 95%) but low diastereoselectivity and yield. In comparison, the reaction with **5e** was synthetically more useful when dichloromethane was

Table 1 Optimization of the Vinylogous Aldol Reaction of Crotonolactone and Aldehyde **4**



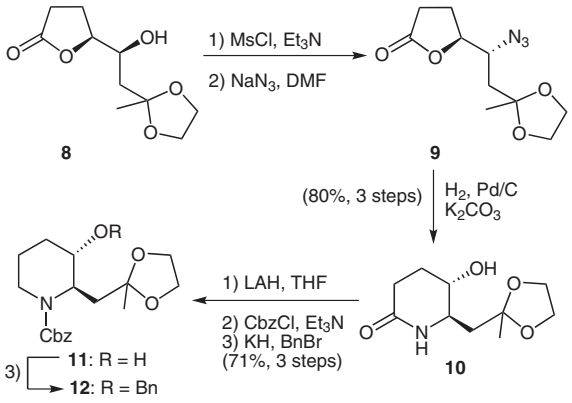
Entry[a]	Cat.[b]	Solvent	Time (h)	Yield (%)	dr[c] (*anti*/*syn*)	ee[d] (%) *anti*
1	**5a**	CH_2Cl_2	24	59	1.1:1	–55
2	**5a**	toluene	24	68	1:1	–18
3	**5a**	EtOAc	24	31	1.1:1	–58
4	**5a**	DMF	24	12	1:1	–30
5	**5a**	CH_2Cl_2	144[e]	8	4.2:1	–62
6	**5b**	CH_2Cl_2	144	2	–	–61
7	**5b**	EtOAc	144	0	–	–
8	**5b**	toluene	144	0	–	–
9	**5c**	CH_2Cl_2	48	13	1.5:1	–74
10	**5d**	CH_2Cl_2	48	31	1.9:1	–90
11	**5d**	CH_2Cl_2	144[e]	16	2.2:1	–93
12	**5d**	EtOAc	48	20	1.6:1	–88
13	**5d**	toluene	48	39	1.5:1	–88
14	**5e**	EtOAc	120	18	2.4:1	95
15	**5e**	CH_2Cl_2	192	74	8:1	91
16	**5e**	toluene	120	27	2.9:1	90

[a] Crotonolactone used: 2 equiv.
[b] Catalyst: 20 mol%.
[c] Based on ^{1}H NMR of crude products.
[d] Based on chiral HPLC analysis; negative ee values indicate formation of the enantiomer of **6**.
[e] Reaction at 0 °C.

used as the solvent (entries 14–16). Thus the direct vinylogous aldol reaction of γ-crotonolactone with the aldehyde **4** using **5e** as the catalyst provided the butenolide **6** in good yield and diastereoselectivity (entry 15, 74%, *anti*/*syn* = 8:1) and excellent enantiomeric excess (er = 19:1 for the *anti*-diastereomer) when the reaction was conducted in dichloromethane[15] (Scheme 2). Following the planned synthetic strategy (Scheme 1), it may be noted that the 2,3-*trans* substitution in the target piperidine can be obtained only from the *anti*-diastereomer of the corresponding amino butyrolactone (Scheme 1, **C**). Since our approach to this amino lactone would involve an invertive amination of the precursor alcohol, a switch of the aldol product stereochemistry from the *anti*- to the *syn*-isomer is required. For this, **6** was first hydrogenated and then Mitsunobu inversion of the secondary alcohol was exam-

ined under a variety of conditions. These attempts invariably lead to complex mixtures and hence an alternate strategy for alcohol inversion became necessary. Accordingly, the alcohol was first oxidized to provide the ketolactone **7**. Reduction of **7** with K-Selectride® gave *syn*-**8** (70%) with good diastereoselectivity (*syn*/*anti* = 16:1, presumably via the Felkin–Anh mode,[16] Scheme 2).[17]

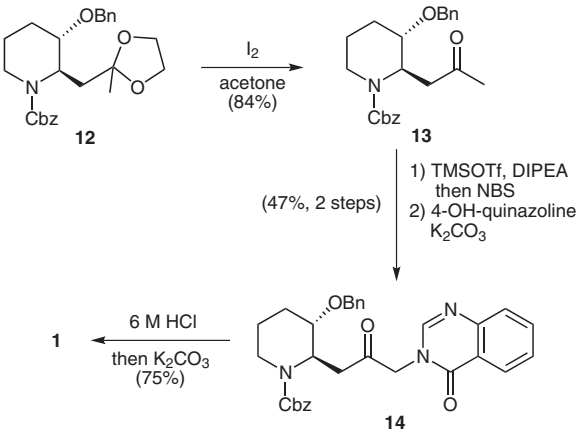
The lactone **8** was readily converted into the azido lactone **9** (mesylation and azidation with inversion) with the required *anti* stereochemistry (*anti*/*syn* = 16:1). Reduction of the azide (H_2, Pd/C) generated a mixture of the corresponding amino butyrolactone and the required piperidone **10**, obtained from the intramolecular N-acylation of the amino lactone. Notably, hydrogenation of **9** in the presence K_2CO_3 significantly facilitated this rearrangement to directly provide **10** (80% from **8**) without any residual amino lactone. Reduction of the lactam in **10** provided the corresponding piperidine, which was isolated as a single diastereomer, presumably due to enrichment of the *trans*-isomer during the reduction and isolation. N-Protection of the piperidine provided **11**, which was benzylated to provide the key intermediate **12** (71% from **10**, Scheme 3).



Scheme 3

With the piperidine **12** in hand, the final steps of the synthesis were initiated (Scheme 4). The ketone in **12** was unmasked by treatment of the ketal with iodine in acetone to provide **13**. Comparison of the spectral data of **13** with reported values[3a,i] confirmed the *trans* orientation of the substituents on the piperidine ring. This also confirms the initial stereochemical assignments for **6**. Bromination of the ketone in **13** was achieved by the procedure reported by Honda (TMSOTf, DBU then NBS)[3i] and the crude bromoketone was reacted with 4-hydrazoquinazoline to provide the protected febrifugine derivative **14**. Deprotection of **14** (aq 6 M HCl) and subsequent neutralization provided (+)-febrifugine (**1**) ($[\alpha]_D^{23}$ +17.7 (*c* 0.6, EtOH) {Lit.[3a] $[\alpha]_D^{25}$ +14.6 (*c* 1.0, EtOH), 86% ee}.

In conclusion, a stereoselective synthesis of (+)-febrifugine (**1**, 14 steps, 6.8% overall yield) was achieved by employing an organocatalytic asymmetric direct vinylogous aldol reaction of γ-crotonolactone and the isomerization of a 2-aminoalkyl furanone to the 2,3-disubstituted piperidine core of the target as the key steps. Since the bromoketone obtained from **13** can be converted into (+)-halofuginone by coupling with 7-bromo-6-chloro-4-hydroxyquinazoline,[3a] the present study also constitutes a formal synthesis of (+)-halofuginone.



Scheme 4

All commercially available reagents were used without purification. All reactions requiring anhyd conditions were performed under an atmosphere of dry N_2 using oven-dried glassware. CH_2Cl_2 and THF were distilled from CaH_2 and sodium/benzophenone, respectively. Commercial precoated silica gel plates were used for TLC. Silica gel for column chromatography was 230–400 mesh. All melting points are uncorrected. Optical rotations were measured at the sodium D line on a digital polarimeter at r.t.

(*S*)-5-[(*R*)-1-Hydroxy-2-(2-methyl-1,3-dioxolan-2-yl)ethyl]furan-2(5*H*)-one (6)

A mixture of the catalyst **5e** (20 mol%, 1.17 g), the aldehyde **4** (1.4 g, 10.75 mmol), and 2-(5*H*)-furanone (1.5 mL, 21.5 mmol) in CH_2Cl_2 (10 mL) was stirred for 192 h at r.t. The mixture was diluted with EtOAc (100 mL), filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (CH_2Cl_2–EtOAc, 10:1) to provide 1.73 g (74%) of **6** as a pale yellow solid (*anti*/*syn* = 8:1 as determined by ^{1}H NMR analysis of the crude product); R_f = 0.30 (EtOAc–hexanes, 4:1); ee: 90% (*anti*).

HPLC: Chiralpak AS-H, hexanes–propan-2-ol (92:8), 210 nm, *anti*-**6**: t_R = 42.4 min (minor), 76.7 min (major); *syn*-**6**: t_R = 57.9 min (major), 83.1 min (minor). In repeated runs *anti*-**6** was obtained in 89–93% ee.

IR (neat): 3467, 2988, 2889, 1795, 1748, 1378, 1163, 1104, 1034, 826 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ (*anti*) = 7.67–7.66 (dd, *J* = 5.8, 1.5 Hz, 1 H), 6.18–6.17 (dd, *J* = 5.8, 1.9 Hz, 1 H), 4.86–4.84 (dt, *J* = 7.0, 1.7 Hz, 1 H), 4.04–3.99 (m, 4 H), 3.90–3.86 (ddd, *J* = 10.1, 7.0, 2.0 Hz, 1 H), 3.83 (s, 1 H), 2.19–2.16 (dd, *J* = 14.6, 1.9 Hz, 1 H), 1.95–1.89 (m, 1 H), 1.37 (s, 3 H); δ (*syn*) = 7.53–7.51 (dd, *J* = 5.7, 1.5 Hz, 1 H), 6.19 (part of dd, 1 H), 5.04–5.02 (m, 1 H), 4.28–4.25 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (*anti*) = 172.8, 154.9, 122.1, 110.0, 85.2, 69.6, 64.7, 64.3, 41.4, 24.1; δ (*syn*) = 172.9, 153.8, 122.7, 109.8, 84.9, 67.4, 64.8, 64.3, 40.1, 24.0.

MS (APCI, +): *m*/*z* = 215.1 (M + 1).

HRMS (CI): *m*/*z* (M + H) calcd for $C_{10}H_{15}O_5$: 215.0919; found: 215.0915.

(*S*)-5-[(*S*)-1-Hydroxy-2-(2-methyl-1,3-dioxolan-2-yl)ethyl]dihydrofuran-2(3*H*)-one (7)

Pd/C (10%, 340 mg) was added to a stirred solution of **6** (1.7 g, 7.93 mmol) in MeOH (80 mL). The mixture was stirred for 16 h at r.t. under a balloon filled with H_2 and then filtered through a pad of Celite. The filter cake was washed with MeOH (2 × 30 mL) and the combined filtrates were concentrated under reduced pressure to provide 1.7 g (99%) of (*S*)-dihydro-5-[(*R*)-1-hydroxy-2-(2-methyl-1,3-dioxolan-2-yl)ethyl]furan-2(3*H*)-one as a white solid (*anti*/*syn* = 8:1); R_f = 0.30 (EtOAc–hexanes, 3:2).This was pure (^{1}H NMR) and was directly used in the next step.

(*S*)-Dihydro-5-[(*R*)-1-hydroxy-2-(2-methyl-1,3-dioxolan-2-yl)ethyl]furan-2(3*H*)-one

IR (neat): 3500, 2985, 2892, 1770, 1658, 1567, 1549, 1459, 1377, 1278, 1190, 1171, 1119, 1027, 996 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ (*anti*) = 4.37–4.32 (m, 1 H), 4.06–3.99 (m, 5 H), 3.58 (br s, 1 H), 2.62–2.57 (ddd, *J* = 17.8, 9.4, 6.4 Hz, 1 H), 2.53–2.48 (m, 1 H), 2.28–2.23 (m, 1 H), 2.04–1.98 (dd, *J* = 14.6, 2.0 Hz, 1 H), 1.83–1.78 (dd, *J* = 14.6, 10.0 Hz, 1 H), 1.38 (s, 3 H); δ (*syn*) = 4.43–4.40 (m, 1 H), 2.68–2.64 (m, 1 H), 2.46–2.45 (m, 1 H), 2.11–2.04 (dd, *J* = 14.9, 10.5 Hz, 1 H), 1.88–1.85 (dd, *J* = 14.8, 1.8 Hz, 1 H), 1.37 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (*anti*) = 177.2, 110.0, 82.3, 69.1, 64.8, 64.3, 40.9, 28.3, 24.2, 22.8; δ (*syn*) = 177.9, 109.9, 82.4, 69.8, 68.5, 64.8, 40.8, 28.3, 24.0, 23.9.

MS (APCI, +): *m*/*z* = 217.1 (M + 1).

HRMS (CI): *m*/*z* (M + H) calcd for $C_{10}H_{17}O_5$: 217.1076; found: 217.1072.

To a solution of the above alcohol (900 mg, 4.16 mmol) in CH_2Cl_2 (30 mL) was added Dess–Martin periodinane (3.53 g, 8.32 mmol) and the mixture was stirred at r.t. for 16 h. Sat. aq $NaHCO_3$ (30 mL) was added, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (hexanes–EtOAc, 1:1) to provide 714 mg (80%) of **7** as a pale yellow liquid; R_f = 0.30 (EtOAc–hexanes, 1:1); $[\alpha]_D^{23}$ +18.8 (*c* 0.92, $CHCl_3$).

7

IR (neat): 2996, 2893, 1769, 1718, 1373, 1252, 1153, 1043, 995, 947, 874 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.91–4.88 (m, 1 H), 3.99–3.95 (m, 4 H), 3.09 (d, *J* = 13.4 Hz, 1 H), 2.88 (d, *J* = 13.4 Hz, 1 H), 2.55–2.45 (m, 3 H), 2.38–2.33 (m, 1 H), 1.44 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.0, 176.3, 108.0, 82.2, 64.8, 64.7, 47.5, 27.3, 24.7, 24.2.

MS (APCI, +): *m*/*z* = 215.1 (M + 1).

HRMS (CI): *m*/*z* calcd for $C_{10}H_{14}O_5$: 214.0841; found: 214.0808.

(*S*)-5-[(*S*)-1-Hydroxy-2-(2-methyl-1,3-dioxolan-2-yl)ethyl)furan-2(5*H*)-one (8)

K-Selectride® (1.0 M soln in THF, 2.8 mL, 2.8 mmol) was added to a stirred solution of the ketone **7** (400 mg, 1.86 mmol) in THF (2 mL) at –78 °C and the mixture was stirred at –78 °C for 1 h. Sat. aq NH_4Cl (15 mL) was added followed by EtOAc (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (hexanes–EtOAc, 1:1) to provide 283 mg (70%) of **8** as a colorless liquid (*syn*/*anti* = 16:1); R_f = 0.30 (EtOAc–hexanes, 3:2).

IR (neat): 3498, 2986, 2960, 2933, 2890, 1765, 1378, 1260, 1167, 1110, 1038, 913, 845 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ (*syn*) = 4.44–4.39 (m, 1 H), 4.02–4.01 (m, 4 H), 4.00–3.95 (m, 1 H), 3.57 (br s, 1 H), 2.74–2.63 (m, 1 H), 2.50–2.39 (m, 1 H), 2.31–2.25 (m, 2 H), 2.15–2.02 (m, 1 H), 1.89–1.84 (dd, *J* = 14.8, 1.8 Hz, 1 H), 1.38 (s, 3 H); δ (*anti*) = 4.43–4.40 (m, 1 H), 2.68–2.64 (m, 1 H), 1.88–1.85 (dd, *J* = 14.6, 2.0 Hz, 1 H), 1.37 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (*syn*) = 177.9, 109.9, 82.4, 69.8, 64.8, 64.3, 40.8, 28.3, 24.1, 23.9; δ (*anti*) = 177.2, 110.0, 82.2, 69.1, 64.8, 40.9, 28.3, 24.2, 22.8.

MS (APCI, +): *m*/*z* = 217.1 (M + 1).

HRMS (CI): *m*/*z* (M + H) calcd for $C_{10}H_{17}O_5$: 217.1076; found: 217.1072.

(*S*)-5-[(*R*)-1-Azido-2-(2-methyl-1,3-dioxolan-2-yl)ethyl]-dihydrofuran-2(3*H*)-one (9)

To a solution of **8** (600 mg, 2.77 mmol) in CH_2Cl_2 (10 mL) at 0 °C under N_2 was added Et_3N (463 μL, 3.32 mmol) followed by MsCl (259 μL, 3.32 mmol). The mixture was stirred for 1 h at 0 °C and H_2O (20 mL) was added at 0 °C. The mixture was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to provide 810 mg (99%) of the mesylate as a yellow oil. This was used immediately in the next step without purification. NaN_3 (822 mg, 12.6 mmol) was added to a solution of the crude mesylate (744 mg, 2.53 mmol) in DMF (8 mL) and the mixture was stirred at 80 °C for 96 h under N_2. The mixture was cooled to r.t. and EtOAc (30 mL) was added followed by H_2O (30 mL). The resulting biphase was separated and the aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to provide 610 mg (quant) of **9** as a yellow oil (*anti*/*syn* = 16:1). This was pure (^{1}H NMR) and was directly used in the next step. An analytical sample (*anti*/*syn* = 25:1) was obtained by flash column chromatography on silica gel (hexanes–EtOAc, 7:3); R_f = 0.50 (EtOAc–hexanes, 3:2).

IR (neat): 2987, 2959, 2923, 2852, 2108, 1772, 1462, 1378, 1255, 1186, 1144, 1029, 948 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ (*anti*) = 4.56–4.52 (m, 1 H), 4.04–3.96 (m, 4 H), 3.94–3.91 (m, 1 H), 2.66–2.60 (ddd, *J* = 17.9, 10.2, 5.5 Hz, 1 H), 2.55–2.48 (m, 1 H), 2.27–2.19 (m, 1 H), 2.15–2.07 (m, 1 H), 1.96–1.91 (dd, *J* = 14.9, 7.3 Hz, 1 H), 1.90–1.86 (dd, *J* = 14.9, 4.5 Hz, 1 H), 1.37 (s, 3 H); δ (*syn*) = 4.60–4.57 (m, 1 H), 3.58–3.54 (m, 1 H), 1.39 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (*anti*) = 176.5, 108.1, 80.9, 64.7, 64.5, 60.5, 39.3, 28.2, 24.3, 22.2; δ (*syn*) = 176.4, 108.2, 81.8, 64.64, 64.61, 60.5, 39.2, 28.1, 24.5, 22.4.

MS (CI, +): *m*/*z* = 242.1 (M + 1).

HRMS (APCI, +): *m*/*z* calcd (M + H) for $C_{10}H_{16}N_3O_4$: 242.1141; found: 242.1145.

(5*S*,6*R*)-5-Hydroxy-6-[(2-methyl-1,3-dioxolan-2-yl)methyl]piperidin-2-one (10)

To a stirred solution of the azide **9** (281 mg, 1.16 mmol) in MeOH (5 mL) at r.t. was added K_2CO_3 (56 mg, 20%) followed by 10% Pd/C (56 mg). The mixture was stirred for 16 h at r.t. under a balloon filled with H_2 and then filtered through a pad of Celite. The filter cake was washed with MeOH (2 × 20 mL) and the combined filtrates were concentrated under reduced pressure to provide a yellow gum. This was purified by flash chromatography on silica gel (CH_2Cl_2–MeOH, 19:1) to provide 200 mg (80%) of **10** as a white solid (*trans*/*cis* = 17:1). The overall yield of **10** (from **8**) is 80%; R_f = 0.25 (CH_2Cl_2–MeOH, 4:1).

IR (neat): 3352, 3229, 1633, 1464, 1420, 1384, 1255, 1215, 1173, 1129, 1064, 1029, 988, 947, 902, 855 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ (*trans*) = 6.63 (br s, 1 H), 4.01–3.97 (m, 4 H), 3.56 (br t, *J* = 9.5 Hz, 1 H), 3.43–3.39 (m, 1 H), 2.86 (br s, 1 H), 2.52–2.46 (ddd, *J* = 18.0, 6.2, 3.4 Hz, 1 H), 2.41–2.34 (ddd, *J* = 17.9, 11.4, 6.4 Hz, 1 H), 2.33–2.30 (dd, *J* = 14.5, 2.1 Hz, 1 H), 2.08–2.03 (m, 1 H), 1.89–1.83 (m, 1 H), 1.75–1.70 (dd, *J* = 14.5, 9.8 Hz, 1 H), 1.35 (s, 3 H); δ (*cis*) = 6.47 (s, 1 H), 3.67–3.64 (m, 1 H), 2.01–1.99 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (*trans*) = 170.9, 109.7, 68.9, 64.7, 64.3, 55.5, 41.8, 29.1, 29.0, 24.0; δ (*cis*) = 171.5, 109.4, 65.7, 64.6, 53.1, 40.5, 27.6, 25.8, 24.2.

MS (APCI, +): *m*/*z* = 216.1 (M + 1).

HRMS (CI): *m*/*z* (M + H) calcd for $C_{10}H_{18}NO_4$: 216.1236; found: 216.1235.

Benzyl (2*R*,3*S*)-3-Hydroxy-2-[(2-methyl-1,3-dioxolan-2-yl)methyl]piperidine-1-carboxylate (11)

To a stirred suspension of $LiAlH_4$ (101 mg, 2.66 mmol) in THF (5 mL) was added **10** (190 mg, 0.88 mmol) dissolved in THF (5 mL) and the mixture was heated to reflux for 24 h. The mixture was cooled to 0 °C, H_2O (0.5 mL) was added slowly, and the mixture was stirred for 20 min at r.t. Na_2SO_4 (1 g) was added to the mixture and it was stirred for 10 min. The mixture was then filtered through a pad of Celite. The filter cake was washed with EtOAc (3 × 20 mL) and the combined filtrates were concentrated under reduced pressure to provide 160 mg (90%) of (2*R*,3*S*)-2-[(2-methyl-1,3-dioxolan-2-yl)methyl]piperidin-3-ol as a white solid; mp 108–111 °C; R_f = 0.30 (CH_2Cl_2–MeOH, 4:1). This was exclusively the *trans*-diastereomer (500 MHz ^{1}H NMR) and was used in the next step without purification.

(2*R*,3*S*)-2-[(2-Methyl-1,3-dioxolan-2-yl)methyl]piperidin-3-ol

IR (neat): 3316, 3122, 2928, 2862, 2824, 1439, 1374, 1252, 1117, 1086, 1036, 958 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.01–3.96 (m, 4 H), 3.22–3.18 (ddd, *J* = 13.1, 8.7, 4.4 Hz, 1 H), 2.96–2.92 (m, 1 H), 2.56–2.53 (td, *J* = 11.8, 2.7 Hz, 1 H), 2.52–2.46 (ddd, *J* = 11.0, 7.3, 3.7 Hz, 1 H), 2.24–2.21 (dd, *J* = 14.8, 3.7 Hz, 1 H), 2.09–2.04 (m, 1 H), 1.74–1.69 (dd, *J* = 14.8, 7.2 Hz, 1 H), 1.68–1.66 (m, 1 H), 1.54–1.50 (m, 1 H), 1.38 (s, 3 H), 1.35–1.27 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 110.1, 72.2, 64.6, 64.4, 59.9, 46.1, 42.2, 34.2, 25.4, 24.1.

MS (APCI, +): *m*/*z* = 202.1 (M + 1).

HRMS (CI): *m*/*z* (M – H) calcd for $C_{10}H_{18}NO_3$: 200.1287; found: 200.1287. *m*/*z* (M + H) calcd for $C_{10}H_{20}NO_3$: 202.1443; found: 202.1444.

To a solution of the above amino alcohol (160 mg, 0.79 mmol) in CH_2Cl_2 (10 mL) were added benzyl chloroformate (113 μL, 0.79 mmol), and Et_3N (133 μL, 0.95 mmol) at 0 °C. The solution was stirred at r.t. for 16 h, H_2O (10 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the residue by flash chromatography on silica gel (hexanes–EtOAc, 2:3) provided 243 mg (91%) of **11** as a colorless oil; R_f = 0.30 (EtOAc–hexanes, 3:2); $[\alpha]_D^{23}$ –20.9 (*c* 0.38, $CHCl_3$).

11

IR (neat): 3467, 2940, 2880, 1672, 1428, 1352, 1257, 1153, 1117, 1077, 1033, 983 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.28 (m, 5 H), 5.15 (s, 2 H), 4.49 (br s, 1 H), 4.07 (br s, 1 H), 3.90–3.88 (br m, 5 H), 2.89 (br m, 1 H), 1.98–1.83 (m, 2 H), 1.82–1.77 (dd, *J* = 14.6, 6.1 Hz, 1 H), 1.74–1.68 (m, 3 H), 1.45–1.35 (br m, 1 H), 1.32 (br s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.3, 136.9, 128.4, 127.9, 127.8, 109.0, 68.2, 67.2, 64.54, 64.50, 54.0, 39.1, 38.2, 25.7, 23.9, 19.1.

MS (APCI, +): *m*/*z* = 336.2 (M + 1).

HRMS (CI): *m*/*z* (M + H) calcd for $C_{18}H_{26}NO_5$: 336.1811; found: 336.1813.

Benzyl (2*R*,3*S*)-3-(Benzyloxy)-2-[(2-methyl-1,3-dioxolan-2-yl)methyl]piperidine-1-carboxylate (12)

To a solution of the carbamate **11** (80 mg, 0.24 mmol) in THF (3 mL) under N_2 at r.t. was added KH (30% dispersion in mineral oil, 32 mg, 0.24 mmol) followed by benzyl bromide (29 μL, 0.24 mmol) at r.t. The mixture was stirred at r.t. for 2 h, cooled to 0 °C, and H_2O (5 mL) was added. The resulting mixture was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel (hexanes–EtOAc, 1:1) to give 87 mg (86%) of **12** as a colorless oil; R_f = 0.60 (EtOAc–hexanes, 1:1); $[\alpha]_D^{23}$ –12.4 (*c* 0.48, $CHCl_3$).

IR (neat): 2930, 2881, 1692, 1423, 1351, 1255, 1200, 1157, 1090, 1045, 1025, 946 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ (major rotamer) = 7.34–7.24 (m, 10 H), 5.11–5.07 (AB system, *J* = 12.4 Hz, 2 H), 4.69 (t, *J* = 5.6 Hz, 1 H), 4.54 (d, *J* = 12.2 Hz, 1 H), 4.43 (d, *J* = 12.2 Hz, 1 H), 4.18–4.15 (dd, *J* = 13.5, 3.5 Hz, 1 H), 3.91–3.82 (m, 3 H), 3.74–3.72 (m, 1 H), 3.50–3.46 (m, 1 H), 2.88–2.82 (td, *J* = 13.5, 2.9 Hz, 1 H), 2.04–1.82 (m, 3 H), 1.78–1.73 (m, 1 H), 1.70–1.62 (m, 2 H), 1.25 (s, 3 H); δ (minor rotamer) = 5.19–5.14 (AB system, *J* = 12.6 Hz, 2 H), 4.88 (t, *J* = 5.8 Hz, 1 H), 4.73 (d, *J* = 12.0 Hz, 1 H), 4.47 (d, *J* = 12.0 Hz, 1 H), 4.07–4.04 (dd, *J* = 13.4, 3.4 Hz, 1 H), 3.54–3.52 (m, 1 H), 2.92–2.89 (td, *J* = 13.6, 2.8 Hz, 1 H), 1.36 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (major rotamer) = 155.9, 138.9, 137.0, 128.3, 128.2 (2 C), 127.9, 127.7, 127.1, 109.1, 74.5, 69.8, 67.1, 64.5, 64.4, 49.8, 39.1, 38.4, 24.1, 24.0, 19.6; δ (minor rotamer) = 155.7, 137.3, 128.4, 127.7, 127.6, 127.3, 109.2, 75.7, 70.1, 66.8, 64.6, 64.4, 48.9, 39.2, 38.0, 24.6, 24.0, 19.9.

MS (APCI, +): *m*/*z* = 426.2 (M + 1).

HRMS (CI): *m*/*z* (M + H) calcd for $C_{25}H_{32}NO_5$: 426.2280; found: 426.2284.

Benzyl (2*R*,3*S*)-3-(Benzyloxy)-2-(2-oxopropyl)piperidine-1-carboxylate (13)

To a solution of **12** (64 mg, 0.15 mmol) in acetone (2 mL) was added a solution of I_2 (1.0 mg, 7.8×10^{-2} mmol, 5 mol%) in acetone (1 mL) at r.t. The solution was stirred at r.t. for 30 min and then concentrated. The residue was dissolved in CH_2Cl_2 (10 mL) and aq 5% $Na_2S_2O_3$ (5 mL) was added. The biphase was stirred vigorously for a few minutes and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (hexanes–EtOAc, 7:3) to provide 48 mg (84%) of **13** as a colorless oil; R_f = 0.25 (hexanes–EtOAc, 7:3); $[\alpha]_D^{23}$ –29.2 (*c* 1.0, $CHCl_3$) {Lit.[3a] $[\alpha]_D^{25}$ –26.8 (*c* 1.0, $CHCl_3$) with 86% ee[3a]}.

IR (neat): 2943, 2866, 1689, 1422, 1355, 1254, 1200, 1132, 1050, 959, 737, 697 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32–7.25 (m, 10 H), 5.15–5.09 (AB system, *J* = 12.5 Hz, 2 H), 5.01 (br s, 1 H), 4.65 (br s, 1 H), 4.51 (d, *J* = 12.0 Hz, 1 H), 4.13 (br s, 1 H), 3.44 (br s, 1 H), 2.84 (br s, 1 H), 2.69–2.58 (m, 2 H), 2.11 (br s, 3 H), 1.94–1.85 (m, 2 H), 1.65–1.59 (m, 1 H), 1.40 (br d, *J* = 11.8 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 205.9, 155.9, 138.6, 136.8, 128.4, 128.3, 127.9, 127.8, 127.5, 127.4, 73.3, 70.2, 67.2, 49.7, 43.7, 39.5, 30.0, 24.4, 19.5.

HRMS (CI): *m*/*z* (M + H) calcd for $C_{23}H_{28}NO_4$: 382.2018; found: 382.2021.

The ^{1}H NMR and ^{13}C NMR data are in agreement with reported data.[3a,i] See the Supporting Information for a detailed comparison.

(2*R*,3*S*)-3-Benzyloxy-2-[2-oxoquinazolin-3(4*H*)-yl)propyl]piperidine-1-carbamic Acid Benzyl Ester (14)

Bromination[3i] of **13** and coupling of the bromide with 4-hydroxyquinazoline according to the literature procedure[3g] provided **14** (47%) as a colorless liquid; R_f = 0.30 (EtOAc); $[\alpha]_D^{23}$ –24.8 (*c* 1.7, $CHCl_3$) {Lit.[3m] $[\alpha]_D^{25}$ –22.0 (*c* 1.0, $CHCl_3$)}.

IR (neat): 1726, 1674, 1610, 1424, 1358, 1257, 1085, 1049, 910 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.28–8.26 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.92 (br s, 1 H), 7.79–7.73 (m, 2 H), 7.52–7.49 (m, 1 H), 7.32–7.26 (m, 10 H), 5.18–5.15 (d, *J* = 12.4 Hz, 1 H), 5.11–5.09 (d, *J* = 12.4 Hz, 1 H), 5.01–4.98 (m, 1 H), 4.94 (br s, 1 H), 4.65–4.63 (m, 1 H), 4.54–4.52 (br d, *J* = 11.9 Hz, 1 H), 4.06 (br s, 1 H), 3.52 (br s, 1 H), 2.97 (br s, 1 H), 2.88–2.83 (dd, *J* = 14.7, 8.7 Hz, 1 H), 2.80–2.76 (br dd, *J* = 14.7, 6.1 Hz, 1 H), 1.94–1.88 (br m, 2 H), 1.75 (br s, 1 H), 1.70–1.63 (m, 1 H), 1.45–1.43 (app br d, *J* = 12.5 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.0, 160.9, 156.2, 148.2, 146.5, 138.3, 136.5, 134.5, 128.5, 128.4, 128.0, 127.8, 127.7, 127.6, 127.5, 127.3, 126.7, 121.8, 73.7, 70.4, 67.4, 53.9, 50.6, 41.0, 39.6, 24.3, 19.4.

MS (APCI, +): *m*/*z* = 526.2 (M + 1).

HRMS (EI+): *m*/*z* (M + H) calcd for $C_{31}H_{31}N_3O_5$: 525.2264; found: 525.2285.

Spectroscopic data (IR, ^{1}H NMR, ^{13}C NMR) and optical rotation for **14** are in agreement with the reported data.[3a,m]

3-{3-[(2*R*,3*S*)-3-Hydroxypiperidin-2-yl]-2-oxopropyl}quinazolin-4(3*H*)-one [(+)-Febrifugine, 1]

Acid hydrolysis of **14** and purification of the crude product according to the literature procedure[3a] provided (+)-**1** (75%); amorphous white solid; mp 133–136 °C; (Lit.[3a] mp 135–138 °C); R_f = 0.20 (CH_2Cl_2–MeOH–Et_3N, 9.00:0.95:0.05); $[\alpha]_D^{23}$ +17.7 (*c* 0.6, EtOH) {Lit.[3a] $[\alpha]_D^{25}$ +14.6 (*c* 1.0, EtOH)}.

IR (neat): 3306, 3052, 2926, 2851, 2687, 1726, 1669, 1607, 1468, 1361, 1325, 1078, 997 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.27 (d, *J* = 7.9 Hz, 1 H), 7.91 (s, 1 H), 7.78–7.71 (m, 2 H), 7.54–7.48 (m, 1 H), 4.93–4.80 (AB system, *J* = 17.5 Hz, 2 H), 3.30–3.26 (m, 1 H), 3.11 (dd, *J* = 16.0, 4.5 Hz, 1 H), 2.96 (d, *J* = 11.9 Hz, 1 H), 2.88–2.87 (m, 1 H), 2.64 (dd, *J* = 16.1, 7.5 Hz, 1 H), 2.58 (dt, *J* = 12.2, 3.0 Hz, 1 H), 2.22 (br s, 2 H), 2.10–2.06 (m, 1 H), 1.74–1.70 (m, 1 H), 1.53–1.47 (m, 1 H), 1.38–1.30 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.7, 161.0, 148.2, 146.4, 134.5, 127.6, 127.4, 126.8, 121.8, 72.2, 60.2, 54.9, 46.0, 44.0, 34.5, 25.6.

The ^{1}H NMR and ^{13}C NMR data are in agreement with the reported data.[3a,i] See the Supporting Information for a detailed comparison.

Acknowledgment

Financial support from the Natural Sciences and Engineering Research Council of Canada and the Canada Foundation for Innovation is gratefully acknowledged.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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(15) The stereochemical assignments for **6** were based on our earlier studies of the organocatalytic vinylogous aldol reaction of γ-crotonolactone in which aromatic aldehydes provided the *anti*-aldol as the major product. For the *anti* and *syn* assignments in the present study, the trend in chemical shifts of the methine protons (CHO) in these aldol products were compared with those observed for **6**; see ref. 10d. The formation of (+)-febrifugine (**1**) in the present study confirms the absolute configuration of **6**.

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