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A HIGHLY EFFICIENT SYNTHESIS OF (–)-PINIDINOL

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Abstract – A short step synthesis of the bioactive piperidine alkaloid (–)-pinidinol was achieved using a cross metathesis and a reductive amination as the key steps.

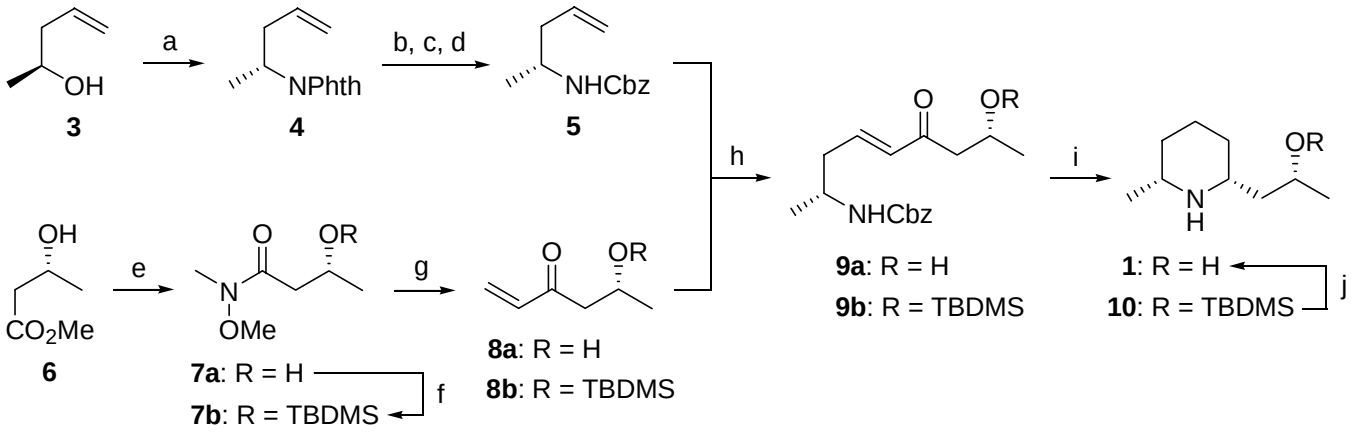
North American conifers of the *Pinaceae* family have shown to contain several biologically active 2,6-disubstituted piperidine alkaloids of particular ecological importance.[1] Although (–)-pinidinol (**1**)[2] exhibits interesting antifeedant activity against Eastern spruce budworms,[3] only three enantioselective syntheses have been described,[4] two of which suffer from lengthy procedures and low overall yields.[4a,c]

(–)-pinidinol (**1**) (+)-6-epi-9-epipinidinol (**2**)

Figure 1. Pinidinols from *Picea* and *Pinus*.

Using our well-established cross metathesis (CM) – reductive amination strategy[5] which has already been applied to the stereoselective synthesis of several other natural piperidines,[6] we envisaged that (–)-pinidinol (**1**) would be readily accessible in just a few steps starting from the commercially available substrates (**3**) and (**6**) (Scheme 1).

Thus, our intended total synthesis started with a *Mitsunobu* transformation of (*S*)-4-penten-2-ol (**3**) into the homochiral phthalimide (**4**). The following one-pot exchange of the protecting group[7] then furnished the desired benzyl carbamate (**5**) in high overall yield, whose optical rotation {$[\alpha]_D^{20}$ = +13.5 (*c* 1.0, $CHCl_3$)} corresponded with that reported for the (*S*)-enantiomer {$[\alpha]_D^{24}$ = –13.0 (*c* 1.02, $CHCl_3$)}.[8] Concerning the preparation of the enantiopure CM partner (**8**) the *β*-hydroxy butyrate (**6**) was first converted to its *Weinreb* amide according to the published procedure.[9] Subsequent treatment of **7a** with vinyl magnesium bromide at 0 °C in THF produced the required enone (**8a**) in rather low yield (52%) which could be significantly improved by previous introduction of a TBDMS protecting group (85%).



Scheme 1. *Reagents and conditions*: (a) phthalimide, PPh_3, DEAD, THF, 0 °C, 2 h (82%); (b) $NaBH_4$, *i*-PrOH/H_2O, 16 h; (c) HCl, 80 °C, 2 h; (d) CbzCl, K_2CO_3, 16 h (81% for 3 steps); (e) MeONHMe · HCl, *i*-PrMgCl, THF, -30 °C (80%); (f) TBDMSCl, imidazole, DMF, 16 h (92%); (g) C_2H_3MgBr, THF, 0 °C, 2 h (52% for **8a**, 85% for **8b**); (h) 5 mol% [1,3-Bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro (2-isopropoxyphenylmethylene)ruthenium, CH_2Cl_2, 40 °C, 16 h (86% for **9a**, 80% for **9b**); (i) H_2, 5 mol% Pd/C, MeOH, 3 h (97% for **1**, 100% for **10**); (j) HCl, THF, 0 °C, 15 min (89%).

In course of the upcoming CM reaction, the carbamate (**5**) was initially reacted with stoichiometrical amounts of each coupling partner in the presence of 5 mol% of the *Hoveyda-Blechert* catalyst.[10] Under these conditions, the amino enone (**9b**) was formed predominantly (80%, *E*/*Z* > 20:1) whereas the cross product (**9a**) was obtained in only moderate yield (65%, *E*/*Z* > 20:1) due to partial dimerisation of the amino component. Consequently, a complete conversion was achieved using a slight excess (1.5 equiv) of enone (**8a**) allowing the hydroxy enone (**9a**) to be isolated with an improved yield of 86%. The final reductive aminations proceeded smoothly to give (–)-pinidinol (**1**), after acidic TBDMS deprotection of the crude product (**10**), in both cases as a single diastereoisomer whose spectroscopical and physical data {$[\alpha]_D^{20}$ = –14.0 ° (*c* 0.83, $CHCl_3$)} was consistent with the literature {$[\alpha]_D^{26}$ = –15.0 ° (*c* 0.55, $CHCl_3$)}.[4c]

In summary, we have described an exceptionally short and efficient approach to (–)-pinidinol affording the natural product in only 6 steps with an overall yield of 55% starting from commercial (*S*)-4-penten-2-ol.

EXPERIMENTAL

Melting points were measured with a Leica Galen III melting point apparatus and are uncorrected. Optical rotations were determined for solutions in $CHCl_3$ using a Perkin-Elmer 341 polarimeter. Infrared spectra (Attenuated Total Reflectance) were obtained on a Perkin-Elmer 881 spectrophotometer and are reported in wave numbers (cm^{-1}). ^1H and ^{13}C NMR spectra were recorded at 500 and 125 MHz on a Bruker DRX 500 in $CDCl_3$ and chemical shifts are given in ppm relative to the internal solvent peak. The samples for high resolution mass spectra (HRMS) were ionized at an ionization potential of 70 eV using a Finnigan MAT 95 SQ or Varian MAT 711. Elemental analyses were performed on an Elementar Vario EI analyser.

2-[(*R*)-1-Methyl-but-3-enyl]-isoindole-1,3-dione (4): To a stirred solution of **3** (430 mg, 5.0 mmol), PPh_3 (1.45 g, 5.5 mmol) and phthalimide (810 mg, 5.5 mmol) in dry THF (20 mL) under nitrogen was added DEAD (960 mg, 5.5 mmol) dropwise at 0 °C. After 2 h at rt the reaction mixture was diluted with Et_2O and filtered. Evaporation of the solvent and purification by flash chromatography (SiO_2; Et_2O/hexane 1:10) afforded **4** (880 mg, 82%) as a colorless oil: $[\alpha]_D^{20}$ –19.5 ° (*c* 1.0, $CHCl_3$); IR *v* 2978, 2938, 1773, 1706, 1468, 1394, 1365, 1333, 1060, 920, 873, 720; ^{1}H NMR δ 7.80 (m, 2H), 7.69 (m, 2H), 5.71 (m, 1H), 5.06-4.95 (m, 2H), 4.44 (m, 1H), 2.80 (m, 1H), 2.51 (m, 1H), 1.50 (d, *J* = 7 Hz, 3H); ^{13}C NMR δ 168.5, 134.8, 133.8, 132.0, 123.1, 117.8, 47.1, 38.3, 18.4; HRMS *m/z* calcd for $C_{13}H_{13}NO_2$ (M^+) 215.0946, found 215.0943. *Anal.* Calcd for $C_{13}H_{13}NO_2$: C 72.54, H 6.09, N 6.51. Found: C 72.28, H 5.85, N 6.43.

[(*R*)-1-Methyl-but-3-enyl]-carbamic acid benzyl ester (5): A solution of **4** (500 mg, 2.32 mmol) in *i*-PrOH (17 mL) and H_2O (3 mL) was treated with $NaBH_4$ (440 mg, 11.6 mmol), stirred for 16 h at rt and acidified with concd HCl (1.5 mL). The mixture was heated to 80 °C for 2 h, cooled to rt and neutralised with K_2CO_3 (pH ~ 8) before CbzCl (475 mg, 2.78 mmol) was added dropwise. After another 2 h at rt the mixture was diluted with brine (30 mL) and extracted with Et_2O (3 x 30 mL). Drying of the organic phase, evaporation of the solvent and purification by flash chromatography (SiO_2; Et_2O/hexane 1:5) afforded **5** (410 mg, 81%) as a colorless oil: $[\alpha]_D^{20}$ +13.5 ° (*c* 1.0, $CHCl_3$); IR *v* 3327, 3034, 2973, 2933, 1695, 1533, 1454, 1335, 1255, 1223, 1061, 916, 783, 697; ^{1}H NMR δ 7.35 (m, 5H), 5.77 (m, 1H), 5.08 (m, 4H), 4.62 (br s, 1H), 3.80 (m, 1H), 2.22 (m, 2H), 1.16 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR δ 155.7, 136.7, 134.3, 128.6, 128.1, 118.0, 66.6, 46.6, 41.2, 20.6; HRMS *m/z* calcd for $C_{10}H_{12}NO_2$ ($M^+ - C_3H_5$) 178.0868, found 178.0861. *Anal.* Calcd for $C_{13}H_{17}NO_2$: C 71.26, H 7.82, N 6.39. Found: C 70.96, H 7.54, N 6.50.

[(*E*)-(1*R*,7*R*)-7-Hydroxy-1-methyl-5-oxo-oct-3-enyl]-carbamic acid benzyl ester (9a): To a solution of **5** (70 mg, 320 μmol) and **8a** (55 mg, 480 μmol) in dry CH_2Cl_2 (6 mL) under nitrogen was added the *Hoveyda-Blechert* catalyst (10 mg, 5 mol%) and the mixture was stirred at 40 °C for 16 h. Evaporation of the solvent and purification by flash chromatography (SiO_2; Et_2O/hexane 3:1) afforded **9a** (84 mg, 86%) as a light brown viscous oil: $[\alpha]_D^{20}$ –9.8 ° (*c* 1.4, $CHCl_3$); IR *v* 3324, 3033, 2969, 2931, 1693, 1659, 1627, 1530, 1454, 1334, 1248, 1103, 1056, 980, 944, 738, 697; ^{1}H NMR δ 7.33 (m, 5H), 6.80 (dt, *J* = 16, 7.5 Hz, 1H), 6.10 (d, *J* = 16 Hz, 1H), 5.08 (m, 2H), 4.65 (br s, 1H), 4.23 (m, 1H), 3.92 (m, 1H), 3.19 (br s, 1H), 2.70 (d, *J* = 17 Hz, 1H), 2.60 (dd, *J* = 17, 9 Hz, 1H), 2.41 (m, 2H), 1.21 (d, *J* = 6.5 Hz, 3H), 1.19 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR δ 200.7, 155.7, 144.0, 136.5, 133.0, 128.6, 128.3, 128.2, 66.8, 64.1, 47.7, 46.3, 40.0, 22.5, 20.8; HRMS *m/z* calcd for $C_{17}H_{24}NO_4$ (MH^+) 306.1705, found 306.1716. *Anal.* Calcd for $C_{17}H_{23}NO_4$: C 66.90, H 7.60, N 4.59. Found: C 66.82, H 7.34, N 4.53.

(–)-Pinidinol (1): To a degassed solution of **9a** (28 mg, 92 μmol) in MeOH (1.8 ml) was added 10% Pd/C (5 mg, 5 mol%) and the mixture was stirred under an atmosphere of hydrogen for 3 h. Filtration and evaporation of the solvent afforded **1** (14 mg, 97%) as a white solid: mp 74-75 °C; $[\alpha]_D^{20}$ –14.0 ° (*c* 0.83, $CHCl_3$); IR *v* 3272, 2962, 2927, 2856, 2722, 1455, 1442, 1374, 1320, 1115, 1058, 1013, 932, 819; ^{1}H NMR δ 4.12 (m, 1H), 2.93 (m, 1H), 2.60 (m, 1H), 1.80 (m, 1H), 1.58 (m, 2H), 1.52 (m, 1H), 1.46 (m, 1H), 1.35 (m, 2H), 1.16 (d, *J* = 6 Hz, 3H), 1.03 (d, *J* = 6 Hz, 3H), 1.00 (m, 1H); ^{13}C NMR δ 65.1, 55.1, 52.6, 43.8, 33.9, 30.4, 24.8, 23.7, 23.2; HRMS *m/z* calcd for $C_9H_{19}NO$ (M^+) 157.1467, found 157.1472.

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