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Tetrahedron: *Asymmetry* 17 (2006) 1074–1080

Synthesis of (+)- and (−)-dihydropinidine by diastereoselective dimethylzinc promoted allylation of 2-methyltetrahydropyridine-*N*-oxide with an allylboronic ester

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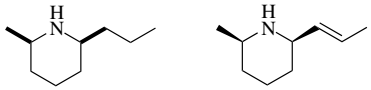
Received 3 March 2006; accepted 27 March 2006

Abstract—The enantiomers of the naturally occurring alkaloid dihydropinidine **1**, potential antifeedants against the pine weevil, *Hylobius abietis*, were prepared by diastereoselective, dimethylzinc mediated addition of pinacolyl 2-propenylboronate **14** to nitrones (*R*)- and (*S*)-2-methyl tetrahydropyridine-*N*-oxide **3**, prepared from D- and L-alanine, respectively.

1. Introduction

The piperidine alkaloid dihydropinidine **1** (Fig. 1) has been found in needles of *Picea pungens*[1] and in the bark and needles of *Picea sitchensis*[2] (absolute configuration not reported). In a preliminary study, we found that the hydrochloride salt of *rac*-**1** displayed high antifeedant activity against the pine weevil, *Hylobius abietis*, which is a major pest of newly planted conifer trees.[3] To verify this result, the synthesis and further biological testing of the compound are required. Because enantiomers can have antagonistic biological effects,[4] both the enantiomers of dihydropinidine have to be synthesised and tested individually. Another alkaloid, pinidine **2** (Fig. 1), present in various tissues of several *Pinus* and *Picea* species,[5] was also considered as a synthetic target suitable for biological testing.



1 **2**

Figure 1. Dihydropinidine **1** and pinidine **2**.

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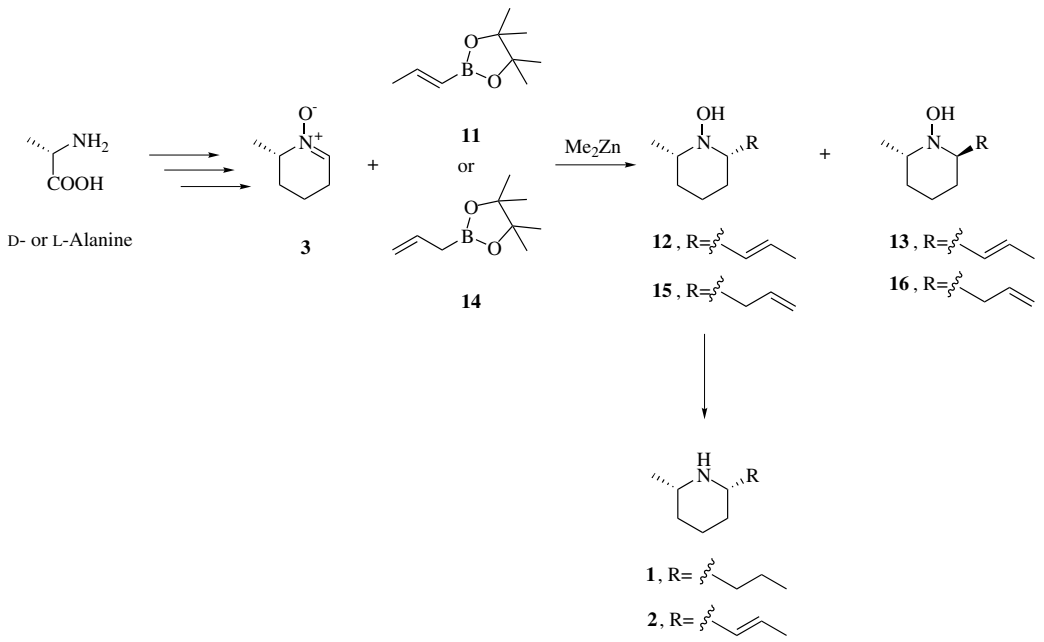
doi:10.1016/j.tetasy.2006.03.033

Numerous approaches to enantiomerically enriched asymmetric 2,6-dialkylpiperidines are described in the literature.[6] Several enantioselective approaches to dihydropinidine are also described.[7]

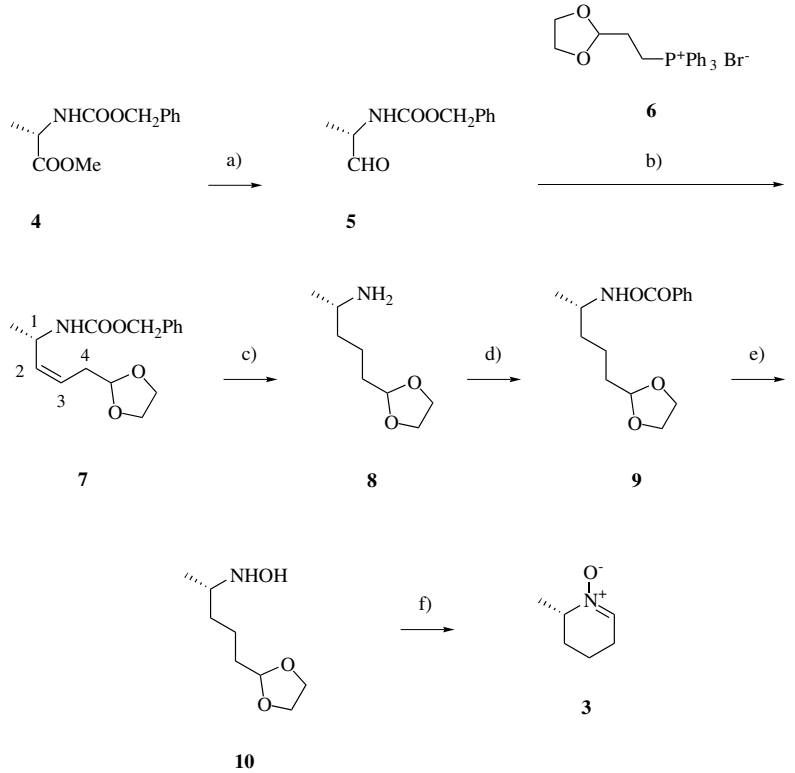
Vinylboronic esters of pinacol can, according to Pandya et al., readily be added to nitrones in the presence of dimethylzinc, forming *N*-allylic hydroxylamines.[8] Although the nitrones prepared in that work are quite different from those required for making pinidines, these results inspired us to explore the potential of using this method for the preparation of the enantiomers of dihydropinidine **1** and pinidine **2** (Scheme 1). Thus, both enantiomers of nitrone **3** were required as the substrate for a similar addition reaction. Both enantiomers of **3** can be prepared starting from either D- or L-alanine.[9]

2. Results and discussion

The nitrones, (*S*)- and (*R*)-2-methyl tetrahydropyridine-*N*-oxide **3** and *ent*-**3**, were prepared as described by Chackalamannil and Wang[9] with some modifications (Scheme 2). The synthetic sequence started with either (*S*)- or (*R*)-*N*-carbobenzyloxyalanine methyl ester (**4** or *ent*-**4**), which was prepared in two steps from L- and D-alanine, respectively.[10] Diisobutylaluminium hydride reduction of carbamate ester **4** gave the corresponding aldehyde **5** (Scheme 2). A Wittig reaction of **5** with the commercially available

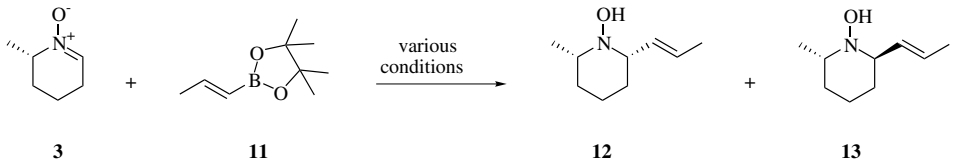


Scheme 1. Planned synthesis of dihydropinidine **1** and pinidine **2**.



Scheme 2. Synthesis of nitrone **3**. Reagents and conditions: (a) DIBAL-H (2.0 equiv), CH_2Cl_2, −78 °C, 96%. (b) (1) **6** (1.38 equiv), THF, KO-*t*-Bu (1.38 equiv); (2) addition of **5**, rt, 51%. (c) H_2, Pd/C, EtOH/EtOAc, 99%. (d) $(PhCO)_2O_2$ (2.0 equiv), CH_2Cl_2, $NaHCO_3$/NaOH buffer (pH 10.5), 56%. (e) LiOH (2 M, aq), THF/MeOH, 95%. (f) HCl (2 M aq), 15 min.

[2-(1,3-dioxolan-2-yl)ethyl]triphenylphosphonium bromide **6** gave *Z*-alkene **7** as a single isomer. The *Z*-configuration of the alkene moiety was confirmed by an observed NOE between H^4 and H^1, which would not have been observed for the *E*-isomer; also, the coupling constant of H^2–H^3 (~9–10 Hz) was in the range for a *Z*-alkene. Compound **7** was subjected to palladium catalysed hydrogenation resulting in α-methyl-1,3-dioxolan-2-butanamine **8** which in turn was transformed to the corresponding hydroxylamine benzoate **9** by oxidation with benzoyl peroxide.[11]



3 11 12 13

Scheme 3. Addition of 1-propenyl pinacolyl boronate **11** to nitrone **3**.

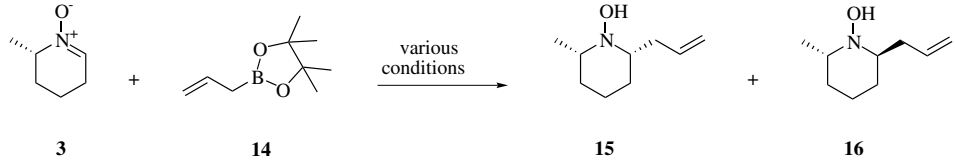
Hydrolysis of the resulting benzoate **9** using LiOH[9] gave the corresponding hydroxylamine **10**. Acetal removal using aqueous HCl[12] yielded nitrone **3**, which was used immediately in the addition reaction (Scheme 3).

In our first attempt to prepare pinidine **2**, 1-propenyl pinacolyl boronate **11**[13] was added to nitrone **3** following the procedure developed by Pandya et al.,[8] for the addition of boronic esters to other nitrones (2.5 equiv dimethylzinc, DMF, 60 °C) (Scheme 3). Due to the low conversion of the nitrone, only trace amounts of hydroxylamine products **12** and **13** were detected. Thus, in order to increase the yield of the hydroxylamine products, the reaction conditions were modified: choice of solvent, replacement of dimethylzinc with diethylzinc, and variation of the reaction temperature. Moreover, if an alkyl/vinyl exchange on zinc was a prerequisite for the reaction to proceed, the addition order of the reagents was altered, that is, dialkylzinc and boronic ester were mixed before the addition of nitrone. Despite these efforts, no appreciable conversion of nitrone could be achieved.

When, however, the latter was reacted with either di-1-propenylzinc (prepared in situ) or 1-propenylmagnesium bromide, full conversion of nitrone was obtained. Unfortunately, the hydroxylamine products were, in both cases, obtained as virtually equimolar mixtures of **12** and **13**, which in turn were equimolar mixtures of the *E*- and *Z*-1-propenyl isomers. Attempts to separate the four isomers by chromatography were unsuccessful. Thus, the synthesis of pinidine was not accomplished via any of these methods.

Pinacolyl allylboronate **14** (Table 1) was prepared in a similar way to that used for vinylboronate **11**.[13] The ^{1}H NMR spectrum of **14** was in good agreement with that reported earlier.[14] When dimethylzinc mediated addition of boronate **14** to nitrone **3** was attempted using the general reaction conditions developed by Pandya et al.,[8] complete conversion of nitrone was observed (Table 1, entry 1). However, a major part (47% of the addition products) consisted of diastereomeric products resulting from methyl addition. In order to increase the yields of the desired allyl adducts, **15** and **16**, and to investigate if the diastereoselectivity could be directed in favour of **15**, the reaction conditions were varied (Table 1). When CH_2Cl_2 was used as a solvent and the addition of dimethylzinc (2 equiv) was performed at −78 °C, the lowest yield of alkyl adduct and the highest yield of the desired **15** (dr: 71/29) was obtained (Table 1, entry 8). Chromatographic separation of diastereomeric hydroxylamines **15** and **16** gave the desired *cis*-isomer **15** in 31% isolated yield, based on hydroxylamine **10**.

Table 1. Optimisation of reaction conditions for addition of boronic ester **14** to nitrone **3**

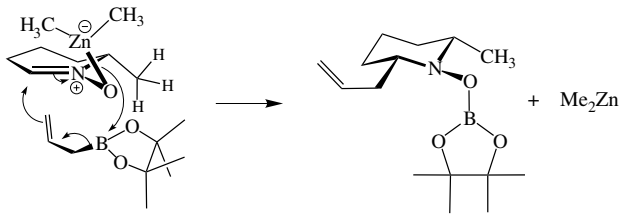


3 14 15 16

Entry	Boronic ester **14**[a]	Time (h)	Solvent	Temperature (°C)	Organo-metal reagent	**15**[g] (%)	**16**[g] (%)	Alkyl adduct[g] (%)
1	1.2	4	DMF	rt→60	Me_2Zn[c], 2.5[a]	8.8	44.3	46.9
2	1.2	6	DMF	−78	Me_2Zn[c], 2.5[a]	11.8	57.9	30.3
3	1.2	12	CH_2Cl_2	−78	Me_2Zn[c], 2.5[a]	57.7	31.4	10.8
4	1.2	12	CH_2Cl_2	−78	Me_2Zn[d], 2.5[a]	50.9	21.7	27.4
5	1.2	12	CH_2Cl_2	−78	Me_2Zn[d], 1.2[a]	38.3	20.8	40.9
6	1.2[b]	12	CH_2Cl_2	−78	Me_2Zn[d], 2.5[a]	37.3	19.5	43.2
7	1.2	12	Et_2O	−78	Me_2Zn[c], 2.5[a]	15.1	22.3	62.5
8	1.2	12	CH_2Cl_2	−78	Me_2Zn[c], 2.0[a]	67.8	28.0	4.2
9	1.2	12	CH_2Cl_2	−78	Et_2Zn[e], 2.5[a]	45.9	33.6	20.5
10	—	12	CH_2Cl_2	−78	*n*-PrMgBr[f], 1.1[a]	58.4	41.6	—

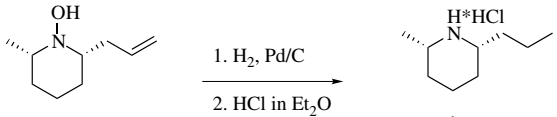
[a] mol/mol nitrone.
[b] Boronic ester and zinc reagent mixed before addition of nitrone.
[c] 2.0 M in toluene.
[d] 1.0 M in heptane.
[e] 1.0 M in hexane.
[f] 2.0 M in Et_2O.
[g] Relative area% (GC), rt = room temperature.

A mechanistic suggestion explaining the observed preferential formation of *cis*-hydroxylamine **15** is given in Scheme 4. In polar noncoordinating solvents, dimethylzinc coordinates as a Lewis acid to the nitrone oxygen on the face opposite to the methyl group. The allyl nucleophile (allylboronate (shown), allylmethylborate or allylmethylzinc formed via transmetallation)[8] approaches from the face opposite to that blocked by the O-coordinated dimethylzinc yielding the *cis*-adduct. In polar aprotic solvents, dimethylzinc is probably coordinated to the solvent rather than to the nitrone leading to more *trans*-allylation in such solvents.



Scheme 4. Suggested mechanism for addition of the allyl moiety of **14** to cyclic nitrone **3**.

Palladium catalysed hydrogenation of *cis*-isomer **15** produced dihydropinidine without epimerisation (Scheme 5). Dihydropinidine was isolated as its HCl salt: (2*S*,6*R*)-dihydropinidine hydrochloride **1**·HCl: $[\alpha]_D^{20} = -12.6$ (*c* 0.1, EtOH) {lit.[7t] $[\alpha]_D^{20} = -13$ (*c* 0.075, EtOH)}. In a similar way but starting from *ent*-**4**, (2*R*,6*S*)-dihydropinidine hydrochloride *ent*-**1**·HCl was obtained (Schemes 2, 3 and 5): $[\alpha]_D^{20} = +12.4$ (*c* 0.1, EtOH) {lit. [7t] $[\alpha]_D^{20} = +13$ (*c* 1.12, EtOH)}. The enantiomeric purity of each enantiomer was >97% ee, as determined by GC-analysis of the trifluoroacetamides on a capillary column covered with a chiral liquid phase (see Sections 3.1 and 3.2.11).



Scheme 5. Hydrogenation of hydroxylamine **15**.

When tested in micro-feeding assays,[15] high antifeedant activity against *H. abietis* was found for both (2*S*,6*R*)- and (2*R*,6*S*)-dihydropinidine hydrochlorides (**1**·HCl and *ent*-**1**·HCl, respectively), as well as for the hydrochloride salts of some other naturally occurring piperidine alkaloids.[16]

3. Experimental

3.1. Chemicals and instruments

Unless otherwise stated, commercially available chemicals were used as received from the suppliers without further purification. Diethyl ether (Et_2O) was distilled from $LiAlH_4$, dimethylformamide (DMF) was dried over 4 Å molecular sieves and distilled under reduced pressure, tetrahydrofuran (THF) was distilled from potassium–benzophenone under argon, and dichloromethane (CH_2Cl_2) was distilled from calcium hydride. Medium pressure liquid chromatography (MPLC) was performed on straight phase silica gel (Merck 60, 230–400 mesh, 0.040–0.063 mm) employing a gradient with increasing concentrations of ethyl acetate in cyclohexane as the eluent. The GC-analyses were performed using a Varian 3400 instrument, equipped with an EC-1 column (30 m × 0.32 mm i.d., $d_f = 0.25$ μm, carrier gas N_2) or using a Varian 3300 instrument, equipped with a capillary column, chiral phase: Gamma-Dex™ 225 [Supelco, 25% 2,3-di-*O*-acetyl-6-*O*-TBDMS-γ-cyclodextrin in SPB-20 poly(205 phenyl/80% dimethylsiloxane) 30 m × 0.25 mm i.d., $d_f = 0.25$ μm, carrier gas He]. The NMR analyses were carried out using a Bruker Avance 500 MHz spectrometer (500 MHz ^{1}H and 125.7 MHz ^{13}C) at 25 °C with $CDCl_3$ as the solvent and TMS as the internal standard. Optical rotations were measured in a 1 dm cell using a Perkin–Elmer polarimeter (model 341). The elemental analyses were performed by Mikrokemi AB, Uppsala, Sweden.

3.2. Experimental procedures

3.2.1. (*S*)-Benzyl-(1-methyl-2-oxoethyl)carbamate 5. To a solution of *N*-(benzyloxycarbonyl)-L-alanine methyl ester **4** (5.82 g, 24.5 mmol) in CH_2Cl_2 (230 ml) at −78 °C, diisobutylaluminium hydride in CH_2Cl_2 (1.0 M, 49.0 mmol) was added dropwise over a 2 h period. The solution was stirred at −78 °C for 5 h, after which any further reaction was stopped by the addition of HCl (1 M, aq, 50 ml). The mixture was allowed to reach room temperature. The organic layer was separated and washed with HCl (1 M, aq, 50 ml) and water (2 × 50 ml), dried over $MgSO_4$, filtered and concentrated to give crude aldehyde **5** (4.88 g, 96.0%), which was used in the next step without further purification. ^{1}H NMR δ 1.35 (3H, d, $J = 7.3$ Hz), 4.29 (1H, m), 5.11 (2H, s), 5.50 (1H, br s), 7.35 (5H, m), 9.53 (1H, s).

The (*R*)-enantiomer *ent*-**5** was prepared by the same procedure starting from *N*-(benzyloxycarbonyl)-D-alanine methyl ester *ent*-**4**, ^{1}H NMR spectral data were identical to those of **5**.

3.2.2. (*S*)-Benzyl-[(2*Z*)-4-(1,3-dioxolan-2-yl)-1-methylbut-2-en-1-yl]carbamate 7. Phosphonium bromide **6** (Aldrich) (3.81 g, 8.6 mmol) was dissolved in dry THF (38 ml). Potassium *tert*-butoxide (0.96 g, 8.6 mmol) was added and the resulting orange mixture was stirred at room temperature for ~1 h. A solution of aldehyde **5** (1.29 g, 6.23 mmol) from the previous step dissolved in dry THF (13 ml) was added slowly. The mixture was stirred for 1 h and saturated ammonium chloride (aq, 40 ml) added. The mixture was extracted with ether (3 × 50 ml) and the resulting organic phase was dried over $MgSO_4$, filtered and concentrated. The crude product was purified by MPLC (EtOAc in cyclohexane, 1.25%→20%), yielding **7** as a single isomer (0.93 g, 51.3%, 93.1% purity according to GC). IR [ν_{max}(neat)/cm^{-1}]: 3334, 3031, 2967, 2886, 1709, 1525,

1454, 1376, 1234, 1051, 699 (this peak and the absence of a strong one at 970–960 cm^{-1} indicate a *cis*-double bond). $[\alpha]_D^{20} = +50.3$ (*c* 0.61, $CHCl_3$). ^1H NMR δ 1.22 (3H, d, $J = 6.6$ Hz), 2.54 (2H, m), 3.82 (2H, m), 3.94 (2H, m), 4.50 (1H, m), 4.91 (2H, m), 5.08 (2H, s), 5.41 (1H, dd (app t), $J = 9.0$, 10.4 Hz), 5.51 (1H, m), 7.30 (5H, m). ^{13}C NMR δ 21.7, 32.5, 44.6, 64.9, 65.0, 66.5, 103.5, 124.5, 128.02, 128.04 (2C), 128.5 (2C), 134.5, 136.6, 155.5.

Starting from (*R*)-benzyl-(1-methyl-2-oxoethyl)carbamate *ent*-**5**, the (*R*)-enantiomer *ent*-**7** was prepared using the same procedure. The purity was 87% according to GC. $[\alpha]_D^{20} = -45.1$ (*c* 0.73, $CHCl_3$). The NMR spectral data were identical to those of **7**.

3.2.3. (*S*)-5-(1,3-Dioxolan-2-yl)pentan-2-amine 8. Compound **7** (2.32 g, 7.97 mmol) was dissolved in EtOH/EtOAc (1:2, v/v, 41 ml), 10% palladium on charcoal (0.3 g) was added and the mixture was hydrogenated at room temperature and ambient pressure overnight. Filtration through a pad of Celite and concentration in vacuo yielded free amine **8** (1.26 g, 99.3%, 98.5% purity according to GC) as a pale yellow oil. IR [ν_{max}(neat)/cm^{-1}]: 3286, 2953, 2873, 1617, 1461, 1378, 1142. $[\alpha]_D^{20} = +1.9$ (*c* 0.78, $CHCl_3$). ^1H NMR δ 1.09 (3H, d, $J = 6.3$ Hz), 1.37–1.54 (4H, m), 1.64–1.71 (2H, m), 1.97 (2H, m), 2.92 (1H, m), 3.82–3.98 (4H, m), 4.86 (1H, t, $J = 4.8$ Hz). ^{13}C NMR δ 20.8, 23.4, 33.8, 39.5, 46.9, 64.9 (2C), 104.4.

Starting from (*R*)-benzyl-[(2*Z*)-4-(1,3-dioxolan-2-yl)-1-methylbut-2-en-1- yl]carbamate (*ent*-**7**), the (*R*)-enantiomer *ent*-**8** was prepared by the same procedure. The purity was 97.9% according to GC. $[\alpha]_D^{20} = -1.3$ (*c* 0.79, $CHCl_3$). The NMR spectral data were identical to those of **8**.

3.2.4. (*S*)-*N*-(Benzoyloxy)-5-(1,3-dioxolan-2-yl)pentan-2-amine 9. Amine **8** (0.58 g, 3.64 mmol) was dissolved in an aqueous buffer [pH 10.5, 18.2 ml, prepared from $NaHCO_3$ (0.75 M, aq) and NaOH (1.5 M, aq)].[11] Benzoyl peroxide (25% w/w in H_2O, 2.35 g, 7.28 mmol) dissolved in CH_2Cl_2 (18.2 ml) was added dropwise at ambient temperature and the resulting mixture stirred vigorously for 24 h. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 ml). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated off. The crude product was purified by chromatography on silica gel (EtOAc in cyclohexane, 1%→25%) yielding product **9** (0.57 g, 56.1%). IR [ν_{max}(neat)/cm^{-1}]: 3236, 3063, 2950, 2878, 1718, 1451, 1271, 733, 710. $[\alpha]_D^{20} = -1.5$ (*c* 0.4, CH_2Cl_2). ^1H NMR δ 1.20 (3H, d, $J = 6.4$ Hz), 1.44–1.61 (3H, m), 1.70 (3H, m), 3.23 (1H, m), 3.84 (2H, m), 3.95 (2H, m), 4.85 (1H, m), 7.46 (2H, m), 7.58 (1H, m), 8.02 (2H, m). ^{13}C NMR δ 17.9, 20.4, 24.0, 33.82, 33.84, 56.7, 64.8, 64.9, 104.3, 104.5, 128.46, 128.51, 129.3, 133.3, 166.8. Calcd for $C_{15}H_{21}NO_4$: C, 64.5; H, 7.6; N, 5.0. Found: C, 64.2; H, 7.9; N, 4.6.

Starting from (*R*)-5-(1,3-dioxolan-2-yl)pentan-2-amine *ent*-**8**, the (*R*)-enantiomer *ent*-**9** was prepared by the same procedure. $[\alpha]_D^{20} = +1.5$ (*c* 0.4, CH_2Cl_2). The NMR spectral data were identical to those of **9**.

3.2.5. (*S*)-5-(1,3-Dioxolan-2-yl)-*N*-hydroxypentan-2-amine 10. Hydroxylamine benzoate **9** (0.57 g, 2.04 mmol) was dissolved in THF–MeOH (6.2 ml, 1:1 v/v) and LiOH (2 M, aq, 6.2 ml) was added dropwise. The mixture was stirred for 2 h at room temperature. Et_2O (25 ml) was added and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 25 ml) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo to yield hydroxylamine **10** (0.34 g, 95%). IR [ν_{max}(neat)/cm^{-1}]: 3281, 3056, 2917, 2849, 1662, 1368, 1140, 736. $[\alpha]_D^{20} = -5.0$ (*c* 0.12, $CHCl_3$). ^1H NMR δ 1.10 (3H, d, $J = 6.4$ Hz), 1.30–1.55 (3H, m), 1.59–1.71 (3H, m), 3.00 (1H, m), 3.800–4.01 (4H, m), 4.86 (1H, t, $J = 4.7$ Hz), 5.84 (2H, br). ^{13}C NMR δ 17.5, 20.4, 33.4, 33.9, 57.2, 64.9 (2C), 104.4. Anal. Calcd for $C_9H_{17}NO$: C, 54.8; H, 9.8; N, 8.0. Found: C, 54.9; H, 9.8; N, 7.8.

Starting from (*R*)-*N*-(benzoyloxy)-5-(1,3-dioxolan-2-yl)-pentan-2-amine *ent*-**9**, the (*R*)-enantiomer *ent*-**10** was prepared using the same procedure. $[\alpha]_D^{20} = +5.0$ (*c* 0.12, $CHCl_3$). The NMR spectral data were identical to those of **10**.

3.2.6. (*S*)-2-Methyl-2,3,4,5-tetrahydropyridine 1-oxide 3. To hydroxylamine **10** (1 g, 5.71 mmol) was added 2 M HCl (aq, 10 ml). The solution was stirred at room temperature for 25 min after which water (30 ml) was added and the pH adjusted to ~11 with Na_2CO_3. The reaction mixture was extracted with Et_2O (2 × 50 ml) and $CHCl_3$ (5 × 50 ml). The combined $CHCl_3$ phases were filtered through $MgSO_4$ and the filtrate evaporated to give nitrone **3** (yellow oil), which was used immediately in the next step.

In the same way, enantiomer *ent*-**3** was prepared, starting from hydroxylamine *ent*-**10**, and used immediately in the next step.

3.2.7. (2*S*,6*S*)-2-Allyl-6-methylpiperidin-1-ol 15. To allyl boronic ester **14** (1.15 g, 6.85 mmol) at −78 °C, nitrone **3** (5.71 mmol) in CH_2Cl_2 (20 ml) was added. Dimethylzinc (2.0 M in toluene, 5.71 ml, 11.4 mmol) was added slowly after which the mixture was allowed to reach room temperature and stirred overnight. The mixture was cooled in an ice bath and water (5 ml) was added slowly. The mixture was filtered through a pad of Celite and the filtrate evaporated. The crude product was purified by MPLC on silica gel (EtOAc–*c*-hexane, 0%→100%) yielding 2-(*S*)-allyl-6-(*S*)-methylpiperidin-1-ol **15** (0.3 g, 33.8%). IR [ν_{max}-(neat)/cm^{-1}]: 3375, 3077, 2935, 2862, 996, 919. $[\alpha]_D^{20} = -7.8$ (*c* 0.32, $CHCl_3$). ^1H NMR δ 1.10 (3H, d, $J = 6.4$ Hz), 1.21–1.35 (3H, m), 1.55–1.85 (3H, m), 2.17 (1H, m), 2.47 (2H, m), 2.69 (1H, m), 4.95–5.10 (3H, m), 5.84 (1H, m). ^{13}C NMR δ 20.5, 23.7, 31.2, 34.2, 38.6, 63.3, 67.0, 116.4, 136.1. Anal. Calcd For $C_9H_{17}NO$: C, 69.6; H, 11.0; N, 9.0. Found: C, 69.4; H, 10.9; N, 8.8.

trans-Isomer **16** (0.15 g, 17.0%): ^1H NMR δ 5.78 (1H, m), 5.05 (2H, m), 3.30 (1H, m), 2.98 (1H, m), 2.68 (1H, m), 2.20 (1H, m), 1.30–1.95 (5H, m), 1.20 (1H, m), 1.15 (3H, d, $J = 5.7$ Hz).

(2*R*,6*R*)-Enantiomer *ent*-**15** was prepared following the same procedure starting from nitrone *ent*-**3**. $[\alpha]_D^{20} = +7.5$ (*c* 0.32, $CHCl_3$). The NMR spectral data were identical to those of **15**.

3.2.8. (2*S*,6*R*)-Dihydropinidine hydrochloride 1–HCl. Hydroxylamine **15** (0.096 g, 0.62 mmol) was dissolved in EtOAc (1 ml) and EtOH (2 ml). Palladium on charcoal (10%, 0.013 g) was added and the mixture was hydrogenated at ambient pressure for 10 days, after which time the palladium was filtered off and HCl (0.62 ml, 1.0 M in Et_2O) was added to the filtrate. The solvents were evaporated and the residue purified by crystallisation (MeOH–Et_2O), yielding (2*S*,6*R*)-dihydropinidine hydrochloride (**1**·HCl) (0.07 g, 60%). $[\alpha]_D^{20} = -12.6$ (*c* 0.1, EtOH), lit.[7t] $[\alpha]_D^{20} = -13$ (*c* 0.075, EtOH). The NMR spectral data were in agreement with those reported earlier.[7l]

Starting from *ent*-**15**, the (2*R*,6*S*)-enantiomer *ent*-**1**·HCl was prepared following the same procedure. $[\alpha]_D^{20} = +12.4$ (*c* 0.1, EtOH), lit.[7t] $[\alpha]_D^{20} = +13$ (*c* 1.12, EtOH). The NMR spectral data were identical to those of **1**–HCl.

3.2.9. Reaction of nitrone 3 with di-1-propenylzinc. To $ZnCl_2$ (1.5 equiv with regard to nitrone, 1.0 M in Et_2O) was added 1-propenylmagnesiumbromide (2.0 equiv with regard to $ZnCl_2$, 2.57 ml, 0.5 M in THF) dropwise. The resulting slurry was left to stir at room temperature for 1.5 h and thereafter cooled to −78 °C, after which nitrone **3** in THF was added. The solution was left to reach room temperature and stirred overnight after which the conversion was determined by GC.

3.2.10. Experimental procedures for experiments in Table 1. *Entries 1–9*: Nitrone **3**, in the appropriate solvent (3.5 ml/mmol nitrone), was added to the boronic ester. Unless otherwise stated, the organozinc reagent was added dropwise to the solution at the given temperature and stirred thereafter. The conversion was monitored by GC after the time listed in the table.

Entry 10: The Grignard reagent was added dropwise to nitrone **3** in CH_2Cl_2 at −78 °C. The resulting slurry was allowed to reach room temperature and was then stirred overnight, after which the conversion was determined by GC.

3.2.11. (2*S*,6*R*)-2-Methyl-6-propyl-1-(trifluoroacetyl)piperidine. For GC analysis, (2*S*,6*R*)-dihydropinidine **1** was converted to its trifluoroacetyl derivative. Trifluoroacetic anhydride (0.1 ml) was added dropwise to a solution of the free amine ~2–4 mg in Et_2O. The resulting mixture was stirred for ~10 h after which $NaHCO_3$ (aq satd) was added slowly. The organic layer was separated, dried over $MgSO_4$ and filtered resulting in (2*S*,6*R*)-2-methyl-6-propyl-1-(trifluoroacetyl)piperidine of >97% ee according to GC (GammaDex™ 225 column, see Section 3.1).

The same procedure was repeated for (2*R*,6*S*)-dihydropinidine *ent*-**1** resulting in (2*R*,6*S*)-2-methyl-6-propyl-1-(trifluoroacetyl)piperidine of >97% ee according to GC.

Acknowledgements

The authors would like to thank Ms. Rebecka From, for technical assistance and Dr. Tessa Pocock, for valuable comments on the manuscript. Financial support from MISTRA (The Foundation for Strategic Environmental Research, 'Pheromones and kairomones for control of pest insects', http://biosignal.org.) and EU, Objective 1 the Region of South Forest Counties, is also warmly acknowledged.

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