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Hydroboration–azide alkylation as efficient tandem reactions for the synthesis of chiral non racemic substituted pyrrolidines

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Abstract

The synthesis of chiral non racemic substituted pyrrolidines from homoallylic alcohols is presented. These precursors are readily converted via the azides to the corresponding pyrrolidines using hydroboration–cycloalkylation tandem reactions as key steps.

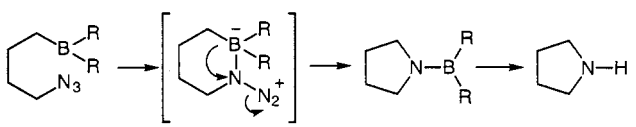
Keywords: Pyrrolidine; Azide; Organoborane; Tandem reactions; Non-racemic

1. Introduction

Pyrrolidines are an important class of five-membered heterocycles with remarkable biological properties [1]. In addition to pharmaceutical applications, the pyrrolidine moiety has also seen wide use as a chiral auxiliary for asymmetric synthesis [2]. Accordingly, development of efficient general methods for the preparation of chiral, non racemic pyrrolidines is of significant value and an increasing number of papers and reports recently appeared in the literature [3]. Besides these elegant syntheses, we sought to develop an alternative approach based on the intramolecular reaction of an azide and an organoborane (Scheme 1) [4].

We showed that the treatment of ω-azidobutylboronates (R = OEt) with boron trichloride generated the corresponding chloroboranes (R = Cl) which spontaneously cyclized to afford pyrrolidines [5]. A stereoselective synthesis of *trans*-cycloalkanopiperidines and cycloalkanopyrrolidines have been achieved similarly [6]. Another attractive route involves the application of a hydroboration-azide alkylation sequence. Such an approach can lead to several competitive reactions and its success demands that the alkene hydroboration precedes the intramolecular reaction of the borane (Scheme 2).

A very elegant preparation of a proline derivative first exploited successfullly the stereoselective bromoacetate aldol reaction and the asymmetric induction in the hydroboration step [7]. Another example using this intramolecular cycloalkylation was more recently described [8]. Previously, we examined the scope and limitations of these tandem hydroboration-azide alkylation reactions [9,10]. We here report the synthesis of chiral non-racemic 2-substituted and 2,3-disubstituted pyrrolidines from the corresponding homoallylic alcohols (Scheme 3).



Scheme 1.

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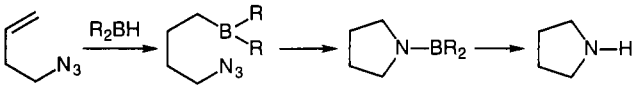


Scheme 2.

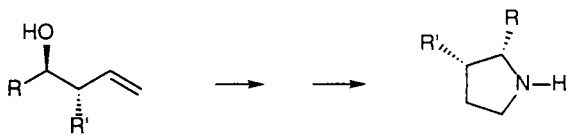
2. Results and discussion

2.1. Synthesis of 2-substituted pyrrolidines

An attractive route to optically active homoallyl alcohols is presented by the addition of chirally modified allylboranes to aldehydes [11]. We first selected B-allyldiisopinocampheylborane [12] and octanal as examples to prepare a non-racemic 2-alkylsubstituted pyrrolidine. The addition proceeded at -100°C to give after oxidation (*R*)-1-heptylbut-3-en-1-ol **1** when starting from a (+)-pinene derivative [13]. A 90% enantiomeric excess was determined by ^{1}H-NMR analysis of the corresponding Mosher ester derivative [14]. Treatment of **1** with methanesulfonyl chloride in the presence of DMAP, followed by nucleophilic substitution with azide ion led to (*S*)-1-heptyl-1-azidobut-3-ene **2**. Addition of thexylmonochloborane afforded the desired (*S*)-2-heptylpyrrolidine **3** in a 64% yield and a 90% ee determined by chiral HPLC (Scheme 4).

We then became interested in extending this preliminary result to the preparation of a 3-substituted 5-(2-pyrrolidinyl)isoxazole which have been found to have nanomolar affinities comparable to (*S*)-nicotine in a preparation of a whole rat brain. For example, ABT 418, an analogue of (*S*)-nicotine in which the pyridine ring is replaced by a 3-methyl-5-isoxazole moiety, has been shown to possess intrinsic cognitive enhancing and anxiolytic activities [15]. Our synthesis of 3-methyl-5-(2(*R*)-pyrrolidinyl)isoxazole **4** began with the preparation of the aldehyde **5** from prop-2-yn-1-ol (Scheme 5). Protection of the alcohol as its trimethylsilylether **6** [16] was followed by the 1,3-dipolar cycloaddition of the nitrile oxide generated in situ from nitroethane, phenylisocyanate and triethylamine [17]. The resulting isoxazole **7** was deprotected with citric acid in methanol [18] and oxidized by pyridine-sulfur trioxide complex in DMSO (Scheme 5) [19].

The formation of the pyrrolidine ring started from enantioselective allylboration of **5** with B-allyldiisopinocampheylborane (92% ee determined by examination of the ^{1}H-NMR spectrum of the (*S*)-*o*-acetyllactic derivative) [20], followed by direct conversion of the homoallylic alcohol **9** to the corresponding azide **10** using diphenyl phosphorazidate to minimize epimerization [21]. As in the synthesis of (*S*)-2-heptylpyrrolidine, but with diethylborane instead of thexylmonochloroborane [22], the hydroboration-cycloalkylation sequence afforded a 69% yield 3-methyl-5-(2(*R*)-pyrrolidinyl)isoxazole **4** which was shown to possess a 92% enantiomeric purity by chiral HPLC analysis of the *N*-benzoyl derivative (Scheme 6).



R = alkyl
R' = H, alkyl

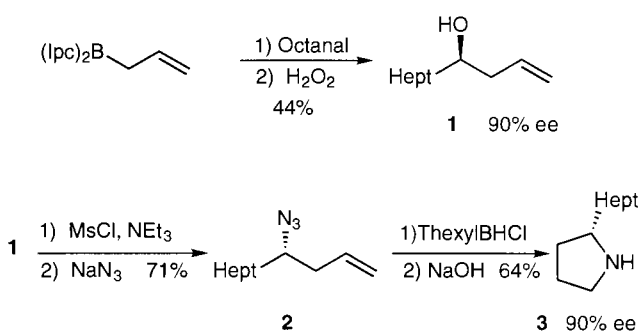
Scheme 3.

2.2. Synthesis of a 2,3-disubstituted pyrrolidine

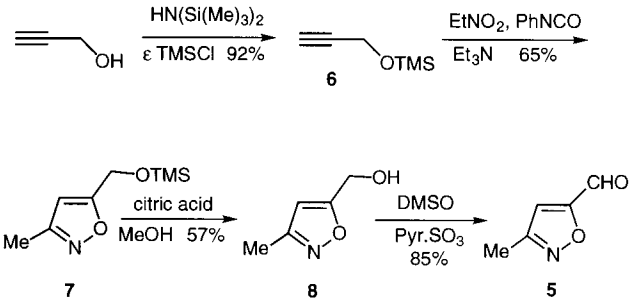
In addition, we were interested in developing a stereocontrolled approach to 2,3-disubstituted pyrrolidines. Allylboration of aldehydes with crotylboranes has been extensively studied [11]. Recently H.C. Brown and coworkers have prepared substituted allylboronates via the one-carbon homologation of stereodefined alkenylboronates using in situ generated bromomethyllithium [23]. We used this efficient route to prepare homoallylic alcohol **11** with high enantio- and diastereomeric excess (Scheme 7).

No *syn* isomer was detected by ^{1}H and ^{13}C-NMR and the enantiomeric excess was determined by analysis of the *o*-acetyllactic ester [20] on capillary gas chromatography. The alcohol so formed was converted to the corresponding azide **13** via the mesylate **12** as previously described in the synthesis of the (2*S*)-heptylpyrrolidine. **13** readily cyclized to (2*S*,3*S*)-2-pentyl-3-butylpyrrolidine **14** on treatment with diethylborane in a 68% yield (Scheme 8).

(2*S*,3*S*)-2-Pentyl-3-butylpyrrolidine **14** was shown to possess a 70% enantiomeric purity by capillary gas chromatography of the *o*-acetyllactic ester. It is worthy to note that pyrrolidines **3**, **4** and **14** have been compared with racemic samples which were prepared independently according to the same sequences using allyboronic esters derived from pinacol.



Scheme 4.

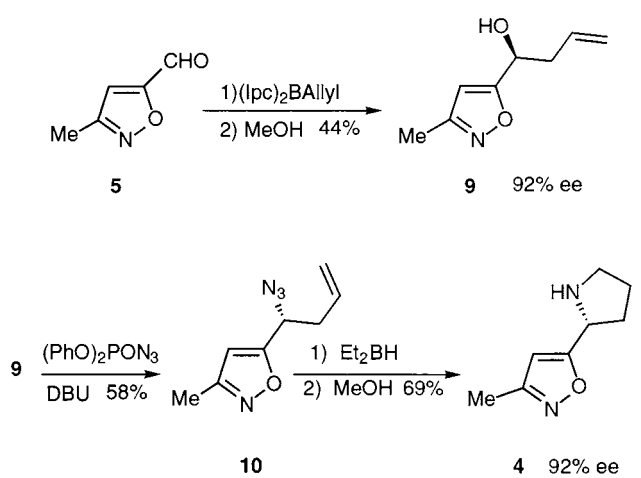


Scheme 5.

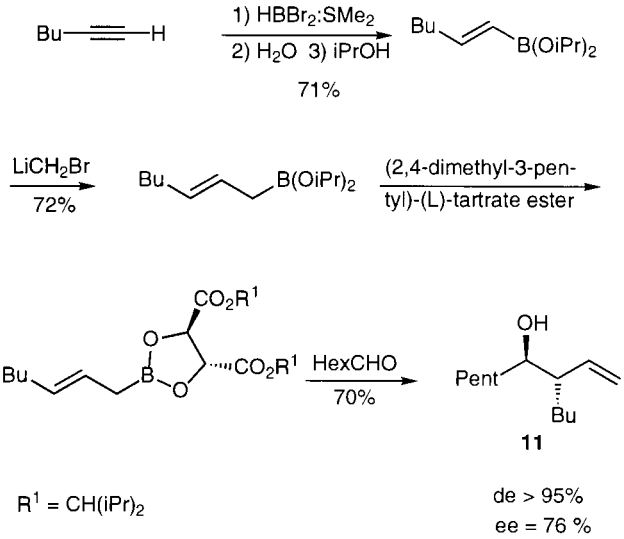
In conclusion, we have developed an efficient preparation of enantiomerically enriched substituted pyrrolidines. This approach utilizes the hydroboration-azide alkylation tandem reactions as key sequence and takes advantage of the efficient stereocontrolled routes available to prepare the starting homoallylic alcohols. Application of this method to the synthesis of other natural and non-natural pyrrolidines is currently in progress.

3. Experimental

Reactions involving boranes require an atmosphere of dry nitrogen and were performed in flame-dried glassware. Anhydrous CH_2Cl_2 was obtained by distillation over P_2O_5 and anhydrous THF over sodium benzophenone. Melting points were measured on a Kofler apparatus (uncorrected). NMR spectra were recorded in $CDCl_3$ solutions (except when another solvent is precised) on a Bruker ARX 200 (200.131 MHz for ^1H, 50.329 MHz for ^{13}C-NMR) or a Bruker ACP 300 (300.13 MHz for ^1H, 75.47 MHz for ^{13}C-NMR). Chemical shifts, δ, are expressed in ppm downfield from internal tetramethylsilane. Optical rotations were measured using a Perkin-Elmer 241 spectrophotometer.



Scheme 6.



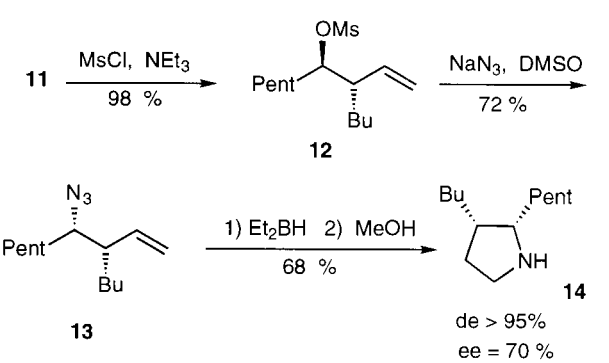
Scheme 7.

High resolution mass spectra were obtained on a Varian MAT 311 (Centre Régional de Mesures Physiques, Université de Rennes I). Microanalysis were performed at the Central Laboratory for Analysis, CNRS, Lyon, France.

3.1. Synthesis of (S)-2-heptylpyrrolidine *3*

3.1.1. Allylboration of octanal

Anhydrous diethylether (60 ml) was added to 30 mmol of Ipc_2BAll, [12] and the resulting solution was cooled to $-100°C$. A solution of octanal (3.84 g, 30 mmol) in diethylether (30 ml), maintained at $-78°C$, was slowly added along the side of the flask to the solution of allylborane keeping the temperature at $-100°C$. After 1 h at this temperature, methanol (5 ml) was added to quench the reaction. The volatile components were pumped off the reaction mixture and 12 ml of a 3N NaOH, followed by 24 ml of 30% aqueous H_2O_2, were added. The solution was heated for 3 h at reflux. After cooling, the product was extracted into diethylether (3×25 ml). The combined organic layers



Scheme 8.

were washed with water, dried over $MgSO_4$ and the solvent removed under reduced pressure. The crude product was chromatographied on silica gel (heptane/ethyl acetate: 8:2, $R_f = 0.15$) to give 2.09 g of (*R*)-1-heptylbut-3-en-1-ol **1**. Yield 41%. B.p. (0.1 mm Hg) = 60–65°C. $[\alpha]_D^{20} = +6.25$ ($c = 0.7$, $CHCl_3$) (lit. [24] $[\alpha]_D^{20} = +6.51$°C (c = 1.4, $CHCl_3$). A 90% enantiomeric purity was determined from the ^{1}H-NMR spectrum of the corresponding Mosher ester derivative [14]. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.88 (t, $J = 6.7$ Hz, CH_3, 3H); 1.28–1.46 (m, CH_2, 12H); 1.91 (s, OH, 1H); 2.09–2.34 (m, $C\underline{H}_2CH{=}CH_2$, 2H); 3.60–3.68 (m, CHOH, 1H); 5.07–5.16 (m, $CH_2{=}CH$, 2H); 5.76–5.90 (m, $CH_2{=}C\underline{H}$, 1H). RMN ^{13}C ($CDCl_3$, 75 MHz) δ: 14.1 (CH_3); 22.7 (CH_2); 25.7 (CH_2); 29.3 (CH_2); 29.7 (CH_2); 31.9 (CH_2); 36.8 (CH_2); 41.9 (CH_2); 70.7 (CHOH); 118.0 ($\underline{C}H_2{=}CH$); 135.0 ($CH_2{=}\underline{C}H$). HRMS *m*/*z* calc. for $C_8H_{17}O$ $[M-C_3H_5^{\cdot}-N_2]^+$: 129.1279; found: 129.1280.

3.1.2. Synthesis of (S)-1-heptyl-1-azidobut-3-ene **2**

In a 50 ml round-bottom flask fitted with a magnetic stirring bar and rubber septa, 20 ml of dichloromethane, 840 mg (4.94 mmol) of **1**, 600 mg (5.93 mmol) of triethylamine and 5 mg of DMAP are mixed. The solution was cooled at 0°C and 590 mg (5.2 mmol) of methanesulfonylchloride was added dropwise. After 5 h at room temperature (r.t.), the solid was eliminated by filtration and the filtrate was diluted with diethylether (20 ml), washed with 0.1 N aqueous HCl (2 × 10 ml), dried over $MgSO_4$ and evaporated to give 1.03 g of the mesylate as a a colorless oil. Yield = 84%. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.88 (t, $J = 6.7$ Hz, CH_3, 3H); 1.20-1.73 (m, CH_2, 12H); 2.45–2.50 (m, $C\underline{H}_2CH{=}CH_2$, 2H); 3.00 (s, CH_3SO_3, 3H); 4,72 (quint, $C\underline{H}OMs$, 1H); 5.13–5.19 (m, $C\underline{H}_2{=}CH$, 2H); 5.73–5.87 (m, $CH_2{=}C\underline{H}$, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 14.1 (CH_3); 22.6 (CH_2); 25.0 (CH_2); 29.1 (CH_2); 29.3 (CH_2); 31.6 (CH_2); 34.2 (CH_2); 38.7 (CH_3SO_3); 52.6 (CH_2); 83.0 ($\underline{C}HOMs$); 118.9 ($\underline{C}H_2{=}CH$); 132.6 ($CH_2{=}\underline{C}H$).

To a stirred solution of 1.02 g (4.11 mmol) of the mesylate in 10 ml of DMSO, 401 mg (6.17 mmol) of NaN_3 was added. The reaction mixture was heated for 12 h at 60°C. The resulting slurry was partitioned between diethylether (25 ml) and water (10 ml). The organic phase was washed with brine (2 × 10 ml), dried over $MgSO_4$, evaporated and purified by Kugelrohr distillation to afford 674 mg (Yield = 84%) of **2**. B.p. (0.1 mm Hg) = 50–55°C. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.88 (t, $J = 6.7$ Hz, CH_3, 3H); 1.18–1.56 (m, CH_2, 12H); 2.27–2.32 (m, $C\underline{H}_2CH{=}CH_2$, 2H); 3.28–3.36 (m, CHN_3, 1H); 5.10–5.18 (m, $C\underline{H}_2{=}CH$, 2H); 5.75–5.88 (m, $CH_2{=}C\underline{H}$, 1H). RMN ^{13}C ($CDCl_3$, 75 MHz) δ: 14.1 (CH_3); 22.7 (CH_2); 26.1 (CH_2); 29.2 (CH_2); 29.4 (CH_2); 31.8 (CH_2); 33.9 (CH_2); 38.8 (CH_2); 62.3 (CHN_3); 118.0 ($\underline{C}H_2{=}CH$); 134.1 ($CH_2{=}\underline{C}H$). HRMS *m*/*z* calc. for $C_8H_{16}N$ $[M-C_3H_5^{\cdot}-N_2]^+$: 126.1283; found: 126.1284.

3.1.3. Hydroboration-cyclisation. Synthesis of (S)-2-heptylpyrrolidine **3**

To a stirred solution of 1.8 mmol of thexylmonochloroborane [25] in 5 ml of dichloromethane at 0°C, 351 mg (1.1 mmol) of (*S*)-1-heptyl-1-azidobut-3-ene **2** was added dropwise. The mixture was allowed to warm at r.t. and stirred overnight. After methanolysis (0.5 ml), the reaction mixture was extracted with 1 N aqueous HCl (6 × 10 ml). The acidic aqueous phases were combined and most of water was removed using a water aspirator. After adding diethylether (20 ml), the residual material was made strongly alkaline by adding solid sodium hydroxide. The organic phase was separated and the aqueous layer extracted with diethylether (2 × 20 ml). The combined organic phases were dried over potassium carbonate and filtered. The pyrrolidine was purified by bulb to bulb distillation to afford 122 mg (Yield = 40%) of **3**. B.p. (0.05 mm Hg) = 50–55°C. $[\alpha]_D^{20} = +20$ (c = 2, $CHCl_3$). (lit [26]: $[\alpha]_D^{20} = +14°$ (c = 1.1, $CHCl_3$))^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 0.88 (t, $J = 6.4$ Hz, CH_3, 3H); 1.20–1.43 (m, 13H); 1.67–1.86 (m, 4H); 2.80–3.01 (m, $C\underline{H}_2{-}NH{-}C\underline{H}$, 3H). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 14.1 (CH_3); 22.7 (CH_2); 25.4 (CH_2); 29.3 (CH_2); 29.9 (CH_2); 31.9 (CH_2); 32.0 (CH_2); 36.6 (CH_2); 46.6 (CH_2N); 59.4 (CHN).

3.1.4. Preparation of the N-benzoyl derivative of **3**

A sample of 40 mg (0.24 mmol) of **3**, 480 μl (0.48 mmol) of a 1 M aqueous NaOH, 34 mg (0.48 mmol) of benzoyl chloride and 5 ml de CH_2Cl_2 were mixed and stirred overnight at r.t. The organic phase was separated and the aqueous layer was extracted with diethylether (2 × 20 ml). The combined organic phases were dried over anhydrous magnesium sulfate. Solvents were evaporated and the residual material was analyzed by HPLC using a Pirkle (*S*,*S*) WHELK-0 1 column (25 cm × 4.6 mm i.d.). Eluent: hexane/isopropanol = 9:1.

3.2. Synthesis of 3-methyl-5-(2(R)-pyrrolidinyl)isoxazole

3.2.1. Synthesis of 1-trimethylsilyloxy-prop-2-yne **6**

To a mixture of 5.60 g (100 mmol) of propargyl alcohol and 8.07 g (50 mmol) of hexamethyldilazane 543 mg (5 mmol) of trimethylsilyl chloride was added and the solution was gradually heated to 50°C overnight. The reaction mixture was cooled and distilled to afford 11.8 g (Yield = 92%) of **6**. B.p. (15 mm Hg) = 27°C. ^{1}H-NMR($CDCl_3$, 300 MHz) δ: 0.01(s, $Si(CH_3)_3$, 9H); 2.24 (t, $J = 2.3$ Hz, H–C≡, 1H); 4.10 (d, $J = 2.3$ Hz, $CH_2{-}C{\equiv}$, 2H).

3.2.2. Synthesis of 3-methyl-5-(trimethylsilyloxymethyl)isoxazole **7**

To a solution of 6 g (46.8 mmol) of the trimethylsilylether **6**, 4.2 g (56.12 mmol) of nitroethane and 10.03

g (84.2 mmol) of phenylisocanate in 70 ml of anhydrous toluene 0.1 ml of triethylamine was added dropwise. After stirring at r.t. overnight, diphenylurea was separated by filtration and the resulting solution concentrated. The residual material was purified by bulb to bulb distillation to afford 5.26 g (Yield = 65%) of **7**. bp 0.01 mm Hg = 35–40°C. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 0.17 (s, $(CH_3)_3Si$, 9H); 2.28 (s, CH_3, 3H); 4.69 (s, CH_2, 2H); 6.04 (s, CH=C, 1H). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 0.6 (CH_3Si); 12.5 (CH_3); 57.7 (CH_2); 103.6 (CH=C); 160.8 (C); 172.5 (C=N).

3.2.3. Synthesis of 3-methyl-5-formylisoxazole **8**

To a stirred solution of the ether **7** (7.47 g, 43.11 mmol) in 25 ml of methanol 83 mg (0.43 mmol) of citric acid was added. The resultant mixture was kept at r.t. for 4 h. The solution was concentrated and the residual material was partitioned between diethylether and water. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by bulb to bulb distillation to afford 2.8 g (Yield = 57%) of **8**. bp 0.1 mm Hg = 60–65°C. Lit [27]: M.p. = 47–48°C. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 2.27 (s, CH_3, 3H); 3.0 (broad s, OH, 1H); 4.66 (s, CH_2OH, 2H); 6.08 (s, CH=C, 1H). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 11.3 (CH_3); 55.9 (CH_2); 102.6 (CH=C); 160.0 (C=); 171.7 (C=N).

To a solution of 1.22 g of the alcohol **8** (10.8 mmol), 11.4 g (146 mmol) of dry DMSO and 5.45 g (54 mmol) of dry triethylamine in dry dichloromethane (40 ml), 477 mg (30 mmol) of sulfur trioxide-pyridine complex was added in small portions. After stirring for 1 h at 0°C, the resultant mixture was washed with 1 N aqueous HCl (3 × 15 ml), dried over $MgSO_4$ and concentrated. The product was used in the next step without supplementary purification. m = 1.02 g. Yield = 85%. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 2.42 (s, CH_3, 3H); 6.84 (s, CH=C, 1H); 9.96 (s, CHO, 1H).

3.2.4. Allylboration of the aldehyde **5**

To a solution of 2.97 g (9.12 mmol) of Ipc_2BAll [12] in 18 ml of diethylether at −100°C, 1.01 g (9.12 mmol) of **5** in 10 ml of diethylether maintained at −78°C was added . The temperature was kept at −100°C for 1 h and then was allowed to warm at r.t. and stirred overnight. Methanol (5 ml) was added to quench the reaction. The volatile components were pumped off from the reaction mixture and the residual material was partitioned between water and dichloromethane. The organic layer was separated, dried over $MgSO_4$ and concentrated. The crude product was chromatographied on silica gel (heptane/ethyl acetate: 85:15, R_f = 0.1) to give 612 mg of **9**. Yield = 44%. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.25 (s, CH_3, 3H); 2.44–2.62 (m, CH_2, 2H); 3.88 (d, J = 4.8 Hz, OH, 1H); 4.74–4.80 (m, CHOH, 1H); 5.04–5.13 (m, CH_2=CH, 2H); 5.72–5.86 (m, CH_2=CH, 1H); 6.05 (s, CH=C, 1H). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 11.3 (CH_3); 40.2 (CH_2); 66.1 (CHOH); 101.7 (CH=C); 119.0 (CH_2=CH); 132.8 (CH_2=CH); 159.7 (C); 174.0 (C=N). HRMS m/z calc. for $C_5H_6NO_2$ $[M-C_3H_5^{\cdot}]^+$: 112.0398. Found 112.0399. $[\alpha]_D^{20}$ = −14 (c = 1.02, MeOH). A 92% ee was determined by examination of the ^{1}H-NMR spectrum of the (*S*)-*o*-acetyllactic derivative [20]. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.48 (1.50 minor diastereoisomer) (d, J = 7.1 Hz, CH_3–CH, 3H); 2.13 (s, CH_3CO_2, 3H); 2.29 (s, CH_3–CH = N, 3H); 2.71–2.78 (m, CH_2–CH=CH_2, 2H); 5.02–5.21 (m, CH=CH_2 and $CHCO_2$, 3H); 5.61–5.80 (m, CH=CH_2, 1H); 5.92–6.00 (m, O–CH–CH_2, 1H); 6.06 (s, H_4, 1H); 6.11 (minor diastereoisomer).

3.2.5. Synthesis of azide **10**

To a solution of 100 mg (0.653 mmol) of the alcohol **5** and 216 mg (0.783 mmol) of $(PhO)_2PON_3$ in 5 ml of dry toluene, 119 mg (0.783 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene was added. The solution was stirred at r.t. overnight, then heated at 60°C for 1 h. After cooling, the reaction mixture was washed with water (2 × 5 ml), 1 N aqueous HCl and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel to afford 68 mg (Yield = 58%) of **10**. R_f = 0.2 (heptane/ethyl acetate = 92:8). ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 2.31 (s, CH_3, 3H); 2.62 (m, CH_2, 2H); 4.59 (t, J = 7 Hz, CHN_3, 1H); 5.14–5.26 (m, CH_2=CH, 2H); 5.75–5.87 (m, CH_2=CH, 1H); 6.10 (s, CH=C, 1H). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 11.4 (CH_3); 37.3 (CH_2); 57.0 (CHN_3); 102.9 (CH=C); 119.4 (CH_2=CH); 132.0 (CH_2=CH); 160.0 (C); 169.2 (C=N). HRMS m/z calc. for $C_5H_5NO_4$ $[M-C_3H_5^{\cdot}]^+$: 137.0463. Found 137.0464.

3.2.6. Synthesis of 3-methyl-5-(2(R)-pyrrolidinyl)isoxazole **4**

To a solution of diethylborane prepared from 54 mg (0.549 mmol) of triethylborane and 25 μl (0.254 mmol) of borane dimethylsulfide complex [22] in 5 ml of diethylether, 68 mg (0.381 mmol) of azide **10** was added dropwise at −15°C . The mixture was allowed to warm at r.t., stirred overnight, methanolyzed (0.5 ml) and extracted with 1 N aqueous HCl (6 × 10 ml). The acidic aqueous phases were combined and most of water was removed using a water aspirator. After adding diethylether (20 ml), the residual material was made strongly alkaline by adding solid sodium hydroxide. The organic phase was separated and the aqueous layer extracted with diethylether (2 × 20 ml). The combined organic phase was dried over potassium carbonate and filtered. The pyrrolidine was purified by bulb to bulb distillation to afford 40 mg (Yield = 69%) of **4**. B.p. (0.01 mm Hg) = 65–70°C. ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.76–1.86 (m, 3H); 2.07–2.24 (m, 2H); 2.19 (s,

CH_3, 3H); 2.92–3.06 (m, 2H); 4.23 (dd, $J = 5.4$ and 7.4 Hz, 1H); 5.88 (s, CH=C, 1H). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 10.4 (CH_3); 24.2 (CH_2); 45.6 (CH_2); 53.6 (CH); 61.4 (CH); 99.8 (CH=C); 158.6 (C=); 174.5 (C=N). HRMS calc. for $C_{15}H_{16}O_2N_2$ $[M]^+$ 256.1211. Found. 256.1203. $[\alpha]_D^{20} = +11$ (c = 0.2, $CHCl_3$). Lit [[15]a]: $[\alpha]_D^{20} = +11.6°C$ (c = 1.0, MeOH). The ratio of enantiomeric products (96:4) was determined by HPLC of the *N*-benzoyl derivative (Pirkle column, (*S*,*S*) WHELK-0 1 (25 cm × 4.6 mm i.d.). Eluent: hexane/isopropanol = 85:15).

3.3. Synthesis of (2S)-pentyl-(3S)-butylpyrrolidine **14**

3.3.1. Synthesis of (1R)-pentyl-(2S)-butylbut-3-en-1-ol **11**

To a solution of 670 mg (6.69 mmol) of hexanal in 4 ml of dry THF, 6.69 mmol of the bis(2,4-dimethyl-3-pentyl)-tartrate ester of hept-2-ene boronic acid was added [23]. The reaction mixture was stirred overnight at r.t. and partitioned between diethylether and water. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel to afford 923 mg (Yield = 70%) of **11**. R_f = 0.06 (heptane/ethyl acetate = 98:2). ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 0.89 (t, CH_3CH_2, 6H); 1.14–1.65 (m, CH_2 and OH, 15H); 1.92–2.02 (m, CH, 1H); 3.41–3.48 (m, CHOH); 5.03–5.20 (m, CH_2=CH, 2H); 5.55 (m, CH_2=CH, 1H). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 14.1 (2 CH_3); 22.7 (CH_2); 22.8 (CH_2); 25.5 (CH_2); 29.6 (CH_2); 30.5 (CH_2); 32.0 (CH_2); 34.7 (CH_2); 50.3 (CH); 73.7 (CHOH); 117.7 (CH_2=CH); 139.1 (CH_2=CH). HRMS calc. for $C_7H_{14}^{+\bullet}$ 98.1095. Found 98.1099. $[\alpha]_D^{20} = +15$ (c = 1.15, $CHCl_3$).

3.3.2. Synthesis of (1R)-pentyl-(1R)-azido-(2S)-butylbut-3-ene **13**

In a 50 ml round-bottom flask fitted with a magnetic stirring bar and rubber septa, 20 ml of dichloromethane, 700 mg (3.53 mmol) of **11**, 428 mg (4.24 mmol) of triethylamine and 5 mg of DMAP are mixed. The solution was cooled at 0°C and 422 mg (3.7 mmol) of methanesulfonyl chloride was added dropwise. After 5 h at r.t., the solid was eliminated by filtration and the filtrate was diluted with diethylether (20 ml), washed with 0.1 N aqueous HCl (2 × 10 ml), dried over $MgSO_4$ and evaporated to give 901 mg of the mesylate **12** as a a colorless oil. Yield = 98%. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.89 (t, CH_3CH_2, 6H); 1.20–1.69 (m, CH_2, 14H); 2.30 (m, CH–CH=, 1H); 3.00 (s, CH_3S, 3H); 4.63–4.72 (m, CHOMs, 1H); 5.04–5.20 (m, CH_2=CH, 2H); 5.50–5.69 (m, CH_2=CH, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 12.9 (CH_3); 13.0 (CH_3); 21.4 (CH_2); 21.5 (CH_2); 23.9 (CH_2); 29.1 (CH_2); 30.5 (CH_2); 31.1 (CH_2); 37.8 (CH_3S); 46.5 (CH); 85.5 (CHOMs); 117.2 (CH_2=CH); 136.0 (CH_2=CH). HRMS calc. for $C_{13}H_{24}$ $[M-CH_3SO_3H]^+$ 180.1877. Tr. 180.1887.

To a stirred solution of 804 mg (3.09 mmol) of the mesylate **12** in 10 ml of DMSO 301 mg (4.63 mmol) of NaN_3 was added. The reaction mixture was heated for 12 h at 60°C. The resulting slurry was partitioned between diethylether (25 ml) and water (10 ml). The organic phase was washed with brine (2 × 10 ml), dried over $MgSO_4$, evaporated and purified by column chromatography to afford 495 mg (Yield = 72%) of **13**. $R_f = 0.7$ (heptane). ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 0.89 (t, CH_3CH_2, 6H); 1.18–1.57 (m, CH_2, 14H); 2.13 (m, CH–CH=, 1H); 3.09–3.22 (m, CHN_3, 1H); 5.01–5.13 (m, CH_2=CH, 2H); 5.47–5.65 (m, CH_2=CH, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 14.0 (2CH_3); 22.6 (CH_2); 22.7 (CH_2); 26.1 (CH_2); 29.4 (CH_2); 30.4 (CH_2); 31.7 (2CH_2); 48.9 (CH); 66.8 (CHN_3); 117.1 (CH_2=CH); 138.9 (CH_2=CH). $C_{13}H_{25}N_3$: Calc.: C 69.91; H 11.28; N 18.81. Found: C 70.0; H 11.2; N 19.1.

3.4. Synthesis of (2S)-pentyl-(3S)-butylpyrrolidine **14**

To a solution of diethylborane prepared from 126 mg (1.29 mmol) of triethylborane and 60 μl (0.597 mmol) of borane dimethylsulfide complex in 5 ml of diethylether [22], 200 mg (0.895 mmol) of azide **13** was added dropwise at −15°C. The mixture was allowed to warm at r.t., stirred overnight and then extracted with 1 N aqueous HCl (6 × 10 ml). The acidic aqueous phases were combined and most of water was removed using a water aspirator. After adding diethylether (20 ml), the residual material was made strongly alkaline by adding solid sodium hydroxide with stirring. The organic phase was separated and the aqueous layer extracted with diethylether (2 × 20 ml). The combined organic phase was dried over potassium carbonate and filtered. The pyrrolidine was purified by bulb to bulb distillation to afford 120 mg (Yield = 68%) of **14**. B.p. (0.01 mm Hg) = 65–70°C. ^{1}H-NMR ($CDCl_3$, 200 MHz) 0.87 (t, CH_3CH_2, 6H); 1.06–1.55 (m, CH_2, 12H); 1.77–2.01 (m, 2H); 2.19 (1H); 2.60–3.06 (m, 3H). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 14.1 (CH_3); 14.2 (CH_3); 22.7 (CH_2); 23.0 (CH_2); 27.3 (CH_2); 28.8 (CH_2); 30.4 (CH_2); 30.7 (CH_2); 31.0 (CH_2); 41.7 (CH); 44.7 (CH_2N); 61.5 (CHN). $C_{14}H_{25}N$, $C_6H_3N_3O_6$ (picrate): Calc.: C 53.51; H 7.09; N 13.13. Tr: C 53.5; H 7.3; N 13.3. The ratio of enantiomeric products (85:15) was determined by capillary gas chromatography using a 30 m DB Wax column and the (*S*)-*o*-acetyllactic ester [20].

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