Stereoselective synthesis of alcohols. Part LV. Domino hydroformylation-allylboration-hydroformylation reactions to give *trans*-perhydropyrano[3,2-*b*]pyridine derivatives†

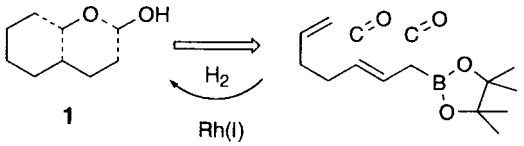
Reinhard W. Hoffmann* and David Brückner

Fachbereich Chemie, Philipps-Universität Marburg, Hans-Meerwein-Strasse, D-35032 Marburg, Germany. E-mail: rwho@chemie.uni-marburg.de; Fax: +49 6421 282 8917

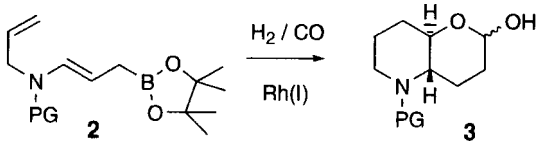
Received* (*in Freiburg, Germany*) *15th November 2000, Accepted 19th December 2000
First published as an Advance Article on the web 22nd February 2001

N-Allyl-(*E*)-γ-aminoallyl boronates **8** and **18**, when subjected to hydroformylation conditions, enter into a domino hydroformylation-allylboration-hydroformylation reaction cascade to generate the bicyclic *N*,*O*-heterocycles **12** and **20**. On reaction of the methallyl compound **8b** a stereogenic center is generated in the initial hydroformylation, which controls the relative configuration of the two new stereogenic centers resulting from the allylboration reaction.

Domino reactions,[2] that is cascades of reactions that proceed sequentially under a single set of reaction conditions, allow a rapid increase in the complexity[3] of the reaction product. This holds especially when open chain compounds are transformed into polycyclic structures in a one-pot procedure. It occurred to us that a hydroformylation-allylboration-hydroformylation sequence starting from a suitable alkadienyl boronate should allow rapid access to annellated tetrahydropyrans **1**.[4]



As initial studies showed,[5] such domino reactions proceed very well and raised the hope that the hydroformylation-allylboration-hydroformylation sequence may be generally applicable to the synthesis of annellated heterocycles. In this vein we applied this strategy in the present study to the synthesis of perhydropyrano[3,2-*b*]pyridine derivatives **3**. For a preliminary communication, see ref. 6.



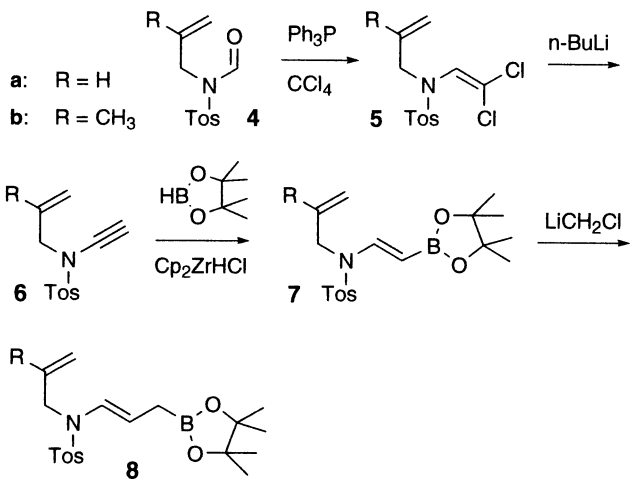
Results and discussion

Once the actual possibility of domino hydroformylation-allylboration-hydroformylation reactions was recognized, the challenge was to find good routes to precursor allylboronates of type **2**. In order to attain a *trans*-ring fusion in the product **3**, the double bond of the allylboronate moiety in **2** should have the *E*-configuration.[7] (*E*)-γ-Iminoallylboranes have been accessed by Barrett *et al.*,[8] but otherwise compounds of type **2** merited a new approach. The following method derived directly from our recent synthesis of (*E*)-γ-alkoxyallylboronates from ynolethers.[5] We therefore developed an easy route to ynamides[9] from formamides.[10] Accordingly, the synthesis of **2** originated from the formamide **4** (Scheme 1).

Compound **4a** was generated (93%) by formylation of *N*-allyl-*p*-toluenesulfonamide with *N*-formylbenzotriazole.[11] Reaction with triphenylphosphine and CCl_4 transformed **4a** into the dichlorovinylamide **5a** (97%), which was converted to the ynamide **6a** (81%). The boron moiety was introduced by zirconocene-catalyzed hydroboration[12] with pinacolborane[13] to give 82% of the vinyl boronate **7a**. The latter was homologated[14] with chloromethyllithium to furnish the desired (*E*)-γ-aminoallylboronate **8a** in 74% yield.

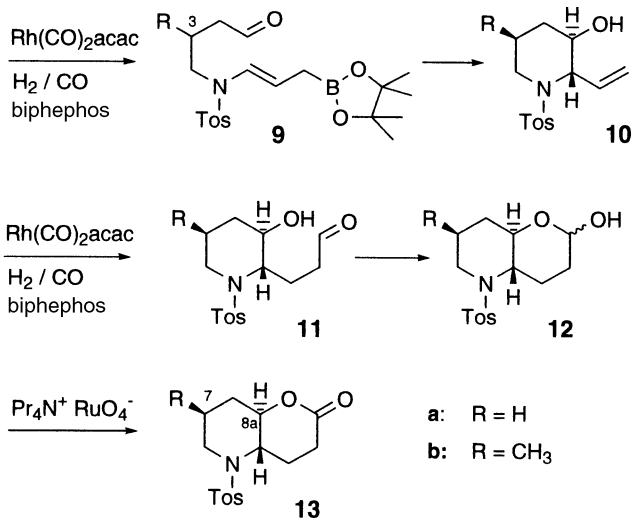
Compound **4b** was generated by reaction of *N*-formyl-*N*-tosylamide[15] with 2-methyl-2-propenyl tosylate (37%). Its subsequent elaboration into the amidoallylboronate **8b** proceeded as above.

At this stage we could study the domino hydroformylation-allylboration-hydroformylation reaction. This required regioselective introduction of the formyl group[16] at the terminal double bond in **8a** to generate the unbranched aldehyde **9a** as an intermediate (Scheme 2).



Scheme 1

† For Part LIV, see ref. 1.



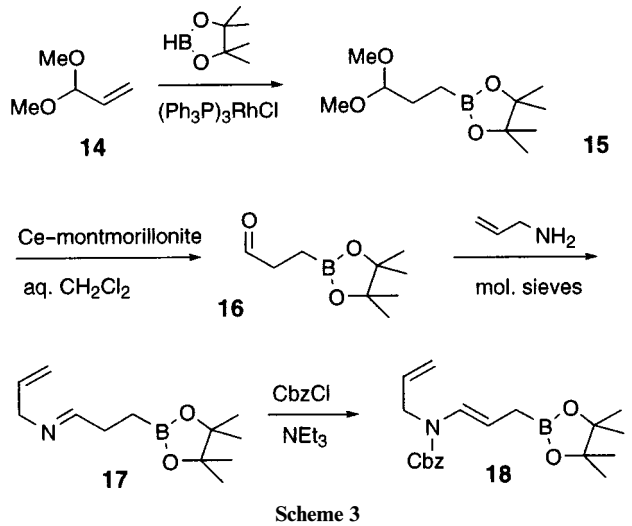
Scheme 2

High regioselectivity in favor of the "linear" aldehyde may be attained by the use of the biphephos ligand.[17] We therefore treated **8a** with 0.01 equiv. of $Rh(CO)_2acac$ and 0.02 equiv. biphephos under 5 bar of $CO–H_2$ at 60 °C. This triggered a cascade of reactions leading to the aldehyde **11a** (80%), which cyclized to the lactol **12a**. Due to the presence of two anomers the mixture was difficult to characterize. We therefore subjected the mixture to Ley oxidation[18] to give the lactone **13a** in 78% yield. The *trans* ring fusion was confirmed by the coupling constant of 9.0 Hz between H-4a and H-8a. This reaction demonstrates the facility by which the hydroformylation-allylboration-hydroformylation sequence leads to bicyclic heterocyclic compounds.

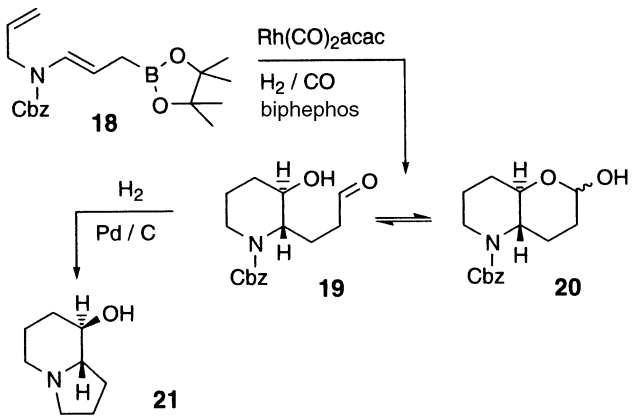
When the reaction is carried out with the methallyl starting material **8b** the initial hydroformylation generates a stereogenic center at C-3 of **9b**. This could then influence the stereochemical course of the subsequent allylboration reaction, giving **10b** with a distinct relative configuration at the three newly generated stereogenic centers.[4,19] The domino hydroformylation-allylboration-hydroformylation reaction of **9b** resulted in 83% of the lactols **12**. They were obtained with a diastereoselectivity of 97 : 3 (anomer ratio = *ca.* 1 : 1). The lactols were oxidized to the lactone **13b**, which crystallized as a single diastereomer. The *trans* ring fusion was confirmed by the coupling constant of 9.0 Hz between H-4a and H-8a. NOE experiments documented the presence of contacts between H-7 and H-8a and the absence of contacts between H-8a and C-7-CH_3.

An enamide subunit, as present in **2**, can also be generated from an amide and an aldehyde under dehydrating conditions.[20] Thus, when considering access to the enamide **18** we explored a combination of the easily accessible allylamine and the so far unknown γ-oxopropylboronate **16**. The known routes[21] to γ-oxoalkylboronates did not seem amenable for the preparation of the aldehyde **16**. We therefore tested a number of approaches to **16**, that shown in Scheme 3 turned out to be the most reliable.

Rhodium(I)-catalyzed hydroboration[22] of 3,3-dimethoxypropene (**14**) furnished the acetal **15** in 75% yield. Hydrolysis of the acetal could best be effected with cerium–montmorillonite[23] in dichloromethane saturated with water. The resulting aldehyde **16** (98%) was not characterized further but immediately condensed with allylamine in the presence of molecular sieves to provide the Schiff base **17**. Subsequent reaction with benzyloxycarbonyl chloride and triethylamine furnished the γ-amidoallylboronate **18** with an *E* geometry double bond (J = 14.4 Hz). This may be a consequence of thermodynamic control, as (*Z*)-enamides rapidly isomerize to their *E* isomers.[24]



Scheme 3



Scheme 4

Subjecting the crude enamide **18** to the hydroformylation conditions resulted in an equilibrium mixture of the aldehyde **19** and the lactols **20** (66% from **16**) (Scheme 4). As the mixture was difficult to characterize we removed the Cbz group by hydrogenolysis. This led in another domino hydrogenation-amination-hydrogenation cascade to the known[25] indolizidine **21** (60%).

Conclusion

After having demonstrated previously that hydroformylation-allylboration-hydroformylation domino reactions provide easy access to annellated THP derivatives, we have shown in this study that *N*-allyl-(*E*)-γ-amidoallylboronates **8** and **18**, subjected to hydroformylation conditions, likewise enter into a hydroformylation-allylboration-hydroformylation domino reaction that furnishes the perhydropyrano[3,2-*b*]pyridine derivatives **12** and **20** with good overall yields. This establishes the versatility of the hydroformylation-allylboration-hydroformylation approach to annellated bicyclic compounds.

Experimental

All temperatures quoted are uncorrected. ^1H and ^{13}C NMR spectra were acquired on Bruker ARX-200, AC-300, ARX-400 and AMX-500 spectrometers. Boiling range of petroleum ether: 40–60 °C. pH 7 buffer was prepared from 56.2 g of $NaH_2PO_4 \cdot 2H_2O$ and 213.2 g $Na_2HPO_4 \cdot 2H_2O$ in 1.0 L of water. Flash chromatography used silica gel Si60 (40–63 μm; E. Merck KGaA, Darmstadt).

Synthesis

***N*-Allyl-*N*-formyl-4-methylbenzenesulfonamide (4a).** *n*-Butyl lithium (1.64 M in hexane, 500 μL, 0.81 mmol) was added at 0 °C to a solution of *N*-allyl-4-methylbenzenesulfonamide (156 mg, 0.74 mmol) in THF (4 mL). After stirring for 5 min a solution of *N*-formylbenzotriazole[11] (130 mg, 0.89 mmol) in THF (0.5 mL) was added. After stirring for 1 h at room temperature *tert*-butyl methyl ether (15 mL) was added and the solution was extracted with saturated aqueous $NaHCO_3$ solution (15 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 15 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated. Flash chromatography of the residue with pentane–*tert*-butyl methyl ether (5 : 1) furnished compound **4a** (165 mg, 93%) as a colorless crystalline solid of m.p. 43 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.46 (s, 3 H), 4.11 (dt, J = 6.0 and 1.3, 2 H), 5.08 (dq, J = 10.2 and 1.0, 1 H), 5.15 (dq, J = 17.2 and 1.0, 1 H), 5.60 (ddt, J = 17.0, 10.3 and 6.0 Hz, 1 H), 7.36 (m, 2 H), 7.74 (m, 2 H), 9.11 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.6, 44.6, 119.0, 127.5, 130.2, 130.7, 135.2, 145.5, 160.9. $C_{11}H_{13}NO_3S$ requires: C 55.21, H 5.48, N 5.85; found: C 55.06, H 5.21, N 5.81%.

***N*-Allyl-*N*-(2,2-dichlorovinyl)-4-methylbenzenesulfonamide (5a).** Compound **4a** (940 mg, 3.93 mmol) and triphenylphosphine (3.09 g, 11.8 mmol) were heated in THF (40 mL) to 55 °C. CCl_4 (3.8 mL, 39 mmol) was added dropwise over 4 h. After cooling to room temperature *tert*-butyl methyl ether (40 mL) was added and the solution was extracted with saturated aqueous $NaHCO_3$ solution (40 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 30 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. Flash chromatography of the residue with pentane–*tert*-butyl methyl ether (10 : 1) furnished **5a** (1.17 g, 97%) as a colorless crystalline solid of m.p. 90 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.43 (s, 3 H), 4.00 (d, J = 6.3, 2 H), 5.15 (dq, J = 10.0 and 1.0, 1 H), 5.18 (dq, J = 17.1 and 1.2, 1 H), 5.68 (ddt, J = 17.0, 10.2 and 6.3 Hz, 1 H), 6.31 (s, 1 H), 7.32 (m, 2 H), 7.69 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.6, 51.7, 119.4, 124.3, 124.8, 127.4, 129.9, 131.9, 135.7, 144.2. $C_{12}H_{13}Cl_2NO_2S$ requires: C 47.07, H 4.28, N 4.57; found: C 47.01, H 4.27, N 4.45%.

***N*-Allyl-*N*-ethynyl-4-methylbenzenesulfonamide (6a).** *n*-Butyl lithium (1.53 M in hexane, 5.4 mL, 8.3 mmol) was added dropwise at −78 °C to a solution of compound **5a** (1.16 g, 3.78 mmol) in THF (19 mL). After stirring for 30 min the mixture was allowed to reach −20 °C over 2 h. Methanol (0.77 mL, 19 mmol) and *tert*-butyl methyl ether (30 mL) were added. The mixture was extracted with saturated aqueous $NaHCO_3$ solution (30 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 20 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. Flash chromatography of the residue over alumina (basic) with pentane–*tert*-butyl methyl ether (5 : 1) furnished compound **6a** (721 mg, 81%) as a slightly yellowish solid of m.p. 70 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.37 (s, 3 H), 2.65 (s, 1 H), 3.88 (dt, J = 6.2 and 1.2, 2 H), 5.11–5.24 (m, 2 H), 5.66 (ddt, J = 17.1, 10.1 and 6.3 Hz, 1 H), 7.29 (m, 2 H), 7.74 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.5, 53.9, 59.2, 75.8, 120.0, 127.7, 129.7, 130.5, 134.6, 144.8. $C_{12}H_{13}NO_2S$ requires: C 61.25, H 5.57, N 5.95; found: C 61.35, H 5.41, N 5.89%.

***N*-Allyl-4-methyl-*N*-[(*E*)-2-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)-vinyl]benzenesulfonamide (7a).** Pinacolborane[13] (269 mg, 2.1 mmol) and zirconocene hydridochloride (51 mg, 0.2 mmol) were added to a solution of compound **6a** (471 mg, 2 mmol) in dichloromethane (1 mL). After 8 h at room temperature *tert*-butyl methyl ether (20 mL) was added and the mixture was extracted with saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 15 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was filtered over a 2 cm layer of silica gel (previously deactivated with triethylamine) using pentane–*tert*-butyl methyl ether (10 : 1) containing 1% triethylamine. This furnished compound **7a** as a slightly yellowish solid that was used as obtained in the next step. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (s, 12 H), 2.42 (s, 3 H), 4.03 (m, 2 H), 4.46 (d, J = 16.2, 1 H), 5.00–5.19 (m, 2 H), 5.58 (ddt, J = 17.3, 10.4 and 5.2, 1 H), 7.30 (m, 2 H), 7.61 (d, J = 16.1 Hz, 1 H), 7.70 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.5, 24.7, 47.4, 83.0, 118.1, 127.1, 129.8, 131.0, 136.3, 142.7, 144.0.

***N*-Allyl-4-methyl-*N*-[(*E*)-3-(4,4,5,5-tetramethyl[1,3,2]dioxaborolan-2-yl)-propenyl]-4-benzenesulfonamide (8a).** A solution of compound **7a** (540 mg, 1.48 mmol) and chloroiodomethane (140 μL, 1.92 mmol) in THF (7.5 mL) was cooled to −100 °C. *n*-Butyllithium (1.54 M in hexane, 1.25 mL, 1.92 mmol) was added dropwise and the mixture was allowed to reach room temperature over 12 h. *tert*-Butyl methyl ether (20 mL) was added and the mixture was extracted with pH 7 buffer solution (15 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 15 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was filtered over a 2 cm layer of silica gel (previously deactivated with triethylamine) using pentane–*tert*-butyl methyl ether (6 : 1) containing 1% triethylamine. This furnished compound **8a** (450 mg, 74%) as a slightly yellowish oil that was used as obtained in the next step. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (s, 12 H), 1.62 (m, 2 H), 2.41 (s, 3 H), 3.95 (m, 2 H), 4.90 (dt, J = 14.2 and 7.4, 1 H), 5.08–5.22 (m, 2 H), 5.65 (ddt, J = 17.2, 10.3 and 5.4, 1 H), 6.52 (dt, J = 14.2 and 1.3 Hz, 1 H), 7.28 (m, 2 H), 7.68 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.5, 24.8, 48.4, 83.3, 109.3, 117.6, 125.7, 127.1, 29.5, 132.1, 136.5, 143.3.

(4a*R,8a*S**)-5-(Toluene-4-sulfonyl)octahydropyrano[3,2-*b*]-pyridin-2-one (13a).** Biphephos[17] (17.3 mg, 0.022 mmol) was added to a solution of dicarbonyl rhodium acetylacetonate (2.8 mg, 0.011 mmol) in THF (2 mL). After stirring for 10 min a solution of compound **8a** (415 mg, 1.10 mmol) in THF (4 mL) was added. This mixture was transferred to an autoclave, adding THF (4 mL) in the transfer. The autoclave was heated to 60 °C for 4 days under 5 bar of CO–H_2 (1 : 1). The contents were diluted with *tert*-butyl methyl ether (20 mL) and the mixture was extracted with saturated aqueous $NaHCO_3$ solution (15 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 15 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. Flash chromatography of the residue over silica gel using CH_2Cl_2–*tert*-butyl methyl ether (3 : 1) furnished a 1 : 1 anomeric mixture of compound **12a** (274 mg, 80%) as a colorless oil.

An aliquot of this mixture (100 mg, 1.32 mmol) was taken up in dichloromethane (1 mL). *N*-Methylmorpholine *N*-oxide (56 mg, 0.48 mmol), powdered molecular sieves (4 Å, 116 mg) and tetrapropylammonium perruthenate (5.6 mg, 0.016 mmol) were added. After stirring for 1 h at room temperature the mixture was filtered over a 2 cm layer of silica gel using CH_2Cl_2–*tert*-butyl methyl ether (4 : 1) and the solution was concentrated. Flash chromatography of the residue over silica gel with pentane–ethyl acetate (1 : 1) furnished compound **13a** (77 mg, 78%) as a colorless crystalline solid of m.p. 152 °C. ^{1}H NMR (500 MHz, C_6D_6): δ 0.85 (tdd, J = 13.1, 11.5 and 4.5, 1 H). 1.06–1.13 (m, 1 H), 1.21 (ttd, J = 13.6, 12.3 and 4.0, 1 H), 1.66 (m, 1 H), 1.90–2.11 (m, 4 H), 1.97 (s, 3 H), 2.17–2.25 (m, 2 H), 3.47 (ddd, J = 11.4, 9.0 and 4.7, 1 H), 3.93 (ddd, J = 12.1, 4.0 and 2.9 Hz, 1 H), 6.84 (m, 2 H), 7.52 (m, 2 H). ^{13}C NMR (125 MHz, C_6D_6): δ 21.1, 22.8, 25.1, 28.5, 30.6, 49.2, 58.5, 78.0, 127.6, 129.7, 136.2, 143.3, 167.9. $C_{15}H_{19}NO_4S$ requires: C 58.23, H 6.19, N 4.53; found: C 58.10, H 6.11, N 4.66%.

***N*-Formyl-4-methylbenzenesulfonamide.** A solution of sodium methoxide was prepared from sodium (1.73 g, 75 mmol) and methanol (100 mL). *p*-Toluenesulfonamide (8.56 g, 50 mmol) was added and after stirring for 30 min at 40 °C ethyl formate (20.2 mL, 250 mmol) was added dropwise. Stirring was continued for 6 h at 50 °C. After cooling the mixture was neutralized by addition of aqueous hydrochloric acid (2 M). The mixture was concentrated *in vacuo* and the residue was taken up in *tert*-butyl methyl ether (100 mL). Water was added dropwise until the precipitate was completely dissolved. The mixture was acidified by addition of aqueous hydrochloric acid (2 M) and the aqueous phase was extracted with *tert*-butyl methyl ether (5 × 50 mL). The combined extracts were concentrated to leave 9.7 g of a colorless solid that still contained *p*-toluenesulfonamide. For this reason the crude product was again dissolved in *tert*-butyl methyl ether (50 mL) and was washed with saturated aqueous $NaHCO_3$ solution (100 mL). The aqueous phase was acidified with concentrated hydrochloric acid and extracted with *tert*-butyl methyl ether (4 × 50 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was recrystallized from *tert*-butyl methyl ether to furnish 8.3 g (83%) of the product as colorless crystals of m.p. 103 °C. Melting point and spectroscopic data agreed with those given in ref. 27.

***N*-Formyl-4-methyl-*N*-(2-methylallyl)benzenesulfonamide (4b).** *n*-Butyllithium (1.54 M in hexane, 3.6 mL, 5.5 mmol) was added at −78 °C to a solution of methallyl alcohol (463 μL, 5.5 mmol) in THF (10 mL). The mixture was allowed to reach 0 °C over 1 h. *p*-Toluenesulfonyl chloride (953 mg, 5.0 mmol) was added and stirring was continued for 30 min at 0 °C. *tert*-Butyl methyl ether (20 mL) was added and the solution was extracted with saturated aqueous $NaHCO_3$ solution (20 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (2 × 15 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated. The residual colorless oil (1.06 g, 94%) of methallyl tosylate was added into a solution of *N*-formyl-*p*-toluenesulfonamide (1.86 g, 9.32 mmol) and triethylamine (3.90 mL, 28.0 mmol) in THF (10 mL). The mixture was stirred for 1 day at room temperature. *tert*-Butyl methyl ether (20 mL) was added and the mixture was extracted with saturated aqueous NH_4Cl solution (20 mL). The aqueous phase was extracted with *tert*-butyl methyl ether (3 × 15 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated. Flash chromatography of the residue over silica gel with pentane–*tert*-butyl methyl ether (6 : 1) furnished compound **4b** (431 mg, 37%) as a colorless oil that solidified. The analytical data for compound **4b** have been reported in ref. 10.

***N*-(2,2-Dichlorovinyl)-4-methyl-*N*-(2-methylallyl)benzenesulfonamide (5b).** Compound **4b** (285 mg, 1.12 mmol) was converted into compound **5b** as described for **5a**. This resulted in isolation of **5b** (350 mg, 97%) as a colorless crystalline solid of m.p. 84 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.76 (s, 3 H), 2.44 (s, 3 H), 3.88 (s 2 H), 4.85 (m, 1 H), 4.91 (m, 1 H), 6.20 (s, 1 H), 7.34 (m, 2 H), 7.69 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.8, 21.5, 55.2, 115.1, 124.7, 125.2, 127.2, 129.8, 135.4, 139.4, 144.2. $C_{13}H_{15}Cl_2NO_2S$ requires: C 48.76, H 4.72, N 4.37; found: C 48.95, H 4.89, N 4.23%.

***N*-Ethynyl-4-methyl-*N*-(2-methylallyl)benzenesulfonamide (6b).** Compound **5b** was converted into compound **6b** as described for **6a**. This resulted in isolation of **6b** (95%) as a slightly yellowish solid of m.p. 69 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.72 (s, 3 H), 2.46 (s, 3 H), 2.71 (s, 1 H), 3.86 (s, 2 H), 4.93 (m, 1 H), 4.96 (m, 1 H), 7.35 (m, 2 H), 7.81 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.5, 21.6, 57.5, 59.0, 75.8, 115.8, 127.7, 129.7, 134.5, 138.4, 144.7. $C_{13}H_{15}NO_2S$ requires: C 62.62, H 6.06, N 5.62; found: C 62.32, H 5.90, N 5.77%.

4-Methyl-*N*-(2-methylallyl)-*N*-[(*E*)-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolane-2-yl)vinyl]benzenesulfonamide (7b). Compound **6b** was converted into compound **7b** as described for **7a**. This resulted in 89% of **7b** as a slightly yellowish solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.25 (s, 12 H), 1.67 (m, 3 H), 2.42 (s, 3 H), 3.89 (m, 2 H), 4.43 (d, J = 16.0, 1 H), 4.80 (m, 1 H), 4.86 (m, 1 H), 7.31 (m, 2 H), 7.61 (d, J = 16.0 Hz, 1 H), 7.70 (m, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.7, 21.5, 24.7, 50.7, 83.0, 112.6, 127.0, 129.8, 136.1, 137.8, 143.0, 144.0. The material was used as obtained in the next steps.

4-Methyl-*N*-(2-methylallyl)-*N*-[(*E*)-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolane-2-yl)propenyl]benzenesulfonamide (8b). Compound **7b** was converted into compound **8b** as described for **8a**. This resulted in 74% of the allylboronate as a slightly yellowish oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.23 (s, 12 H), 1.59 (dd, J = 7.5 and 1.0, 2 H), 1.70 (m, 3 H), 2.42 (s, 3 H), 3.80 (m, 2 H), 4.82–4.98 (m, 3 H), 6.47 (dt, J = 14.2 and 1.4 Hz, 1 H), 7.28 (m, 2H), 7.67 (m, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.7, 21.5, 24.7, 51.8, 83.2, 110.1, 112.8, 125.6, 127.0, 129.5, 136.1, 139.2, 143.3. The material was used in the next step as obtained.

(4a*R,7*R**,8a*S**)-7-Methyl-5-(toluene-4-sulfonyl)octahydropyrano[3,2-*b*]pyridine-2-one (13b).** Compound **8b** was subjected to hydroformylation as described for compound **13a**. This resulted in 83% of the lactols **12b** and after subsequent oxidation in 86% of **13b** as a colorless crystalline solid of m.p. 180 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.98 (d, J = 6.4, 3 H), 1.13 (q, J = 12.2, 1 H), 1.93 (m, 1 H), 2.13 (t, J = 11.3, 1 H), 2.19 (m, 1 H), 2.32–2.41 (m, 1 H), 2.46 (s, 3 H), 2.49–2.54 (m, 3 H), 2.72–2.81 (m, 1 H), 4.06 (ddd, J = 11.8, 3.6 and 1.6, 1 H), 4.19 (ddd, J = 11.3, 9.0 and 4.6, 1 H), 7.36 (m, 2 H), 7.64 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.4, 21.5, 24.5, 28.5, 29.1, 39.0, 55.9, 58.0, 78.7, 127.2, 130.0, 134.8, 144.1, 169.9. $C_{16}H_{21}NO_4S$ requires: C 59.42, H 6.54, N 4.33; found: C 59.26, H 6.24, N 4.47%.

2-(3,3-Dimethoxypropyl)-4,4,5,5,-tetramethyl[1,3,2]dioxaborolane (15). Tris(triphenylphosphine)chlororhodium (370 mg, 0.4 mmol) was added into a solution of 3,3-dimethoxypropene (4.7 mL, 50 mmol) and pinacolborane[13] (6.40 g, 50 mmol) in dichloromethane (50 mL). After stirring for 1 day the mixture was fractionated to give compound **15** (8.65 g, 85%) as a colorless liquid of b.p. 105 °C (7 mbar). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.76 (t, J = 7.8, 2 H), 1.21 (s, 12 H), 1.68 (td, J = 7.8 and 5.8, 2 H), 3.28 (s, 6 H), 4.28 (t, J = 5.8 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.8, 26.9, 52.8, 83.0, 105.9. $C_{11}H_{23}BO_4$ requires: C 57.42, H 10.07; found: C 57.41, H 10.29%.

3-(4,4,5,5-Tetramethyl[1,3,2]dioxaborolane-2-yl)propanal (16). Dichloromethane (100 mL) was saturated at room temperature with water. Compound **15** (1.56 g, 6.78 mmol) was dissolved followed by addition of cerium(III)–montmorillonite[23] (135 mg). The mixture was held for 1 h under reflux. As the reaction stopped after 70% conversion, the solvents were removed *in vacuo* and the residue was refluxed anew in dichloromethane (water-saturated, 100 mL). This resulted in complete conversion (TLC) after 30 min. The mixture was filtered and the filtrate was concentrated to give the aldehyde **16** as a colorless liquid (1.22 g, 98%) that was characterized by spectroscopic data only. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (t, J = 7.2, 2 H), 1.21 (s, 12 H), 2.57 (td, J = 7.2 and 0.7, 2 H), 9.75 (t, J = 0.9 Hz, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.7, 38.8, 83.3, 202.8.

(8*R,8a*S**)-Octahydroindolizidine-8-ol (21).** The conversion of the aldehyde **16** *via* the encarbamate **18** and the lactols **20** to product **21** has been described in detail in our preliminary communication.[6]

Acknowledgements

This study has been supported by the Deutsche Forschungsgemeinschaft (SFB 260) and the Fonds der Chemischen Industrie as well as by the European Community, HCM Network Nr. ERB-CHRX-CT94-0620. We would like to thank these organizations for their support.

References

1 A. Schlapbach and R. W. Hoffmann, *Eur. J. Org. Chem.*, 2001, 323.
2 (*a*) L. F. Tietze and U. Beifuss, *Angew. Chem.*, 1993, **105**, 137; *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 131; (*b*) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115.
3 S. H. Bertz, *J. Am. Chem. Soc.*, 1982, **104**, 5801.
4 R. W. Hoffmann, A. Hense, I. Münster, J. Krüger, D. Brückner and V. J. Gerusz, in *Organoboranes for Synthesis*, ed. P. V. Ramachandran and H. C. Brown, ACS Symp. Ser., American Chemical Society, Washington, DC, 2001, vol. 783, pp. 160–175.
5 R. W. Hoffmann, J. Krüger and D. Brückner, *New J. Chem.*, 2001, **25**, 102.
6 R. W. Hoffmann, D. Brückner and V. J. Gerusz, *Heterocycles*, 2000, **52**, 121.
7 R. W. Hoffmann, T. Sander and A. Hense, *Liebigs Ann. Chem.*, 1993, 771.
8 (*a*) A. G. M. Barrett and M. A. Seefeld, *Tetrahedron*, 1993, **49**, 7857; (*b*) A. G. M. Barrett, M. A. Seefeld, A. J. P. White and D. J. Williams, *J. Org. Chem.*, 1996, **61**, 2677.
9 (*a*) Z. Janousek, J. Collard and H. G. Viehe, *Angew. Chem.*, 1972, **84**, 993; Z. Janousek, J. Collard and H. G. Viehe, *Angew. Chem., Int. Ed. Engl.*, 1972, **11**, 917; (*b*) A. Balsamo, B. Macchia, F. Macchia and A. Rossello, *Tetrahedron Lett.*, 1985, **26**, 4141; (*c*) B. Witulski and T. Stengel, *Angew. Chem.*, 1998, **110**, 495; B. Witulski and T. Stengel, *Angew. Chem., Int. Ed.*, 1998, **37**, 489.
10 D. Brückner, *Synlett.*, 2000, 1402.
11 A. R. Katritzky, H.-X. Chang and B. Yang, *Synthesis*, 1995, 503.
12 S. Pereira and M. Srebnik, *Organometallics*, 1995, **14**, 3127.
13 C. E. Tucker, J. Davidson and P. Knochel, *J. Org. Chem.*, 1992, **57**, 3482.
14 (*a*) K. M. Sadhu and D. S. Matteson, *Organometallics*, 1985, **4**, 1687; (*b*) H. C. Brown, S. M. Singh and M. V. Rangaishenvi, *J. Org. Chem.*, 1986, **51**, 3150.
15 S. I. Burmistrov and G. E. Krakovtseva, *Ukr. Khim. Zh.*, 1958, **24**, 348; S. I. Burmistrov and G. E. Krakovtseva, *Chem. Abstr.*, 1959, **53**, 1219c.
16 (*a*) I. Ojima, C.-Y. Tsai, M. Tzamarioudaki and D. Bonafoux, *Org. React.*, 2000, **56**, 1; (*b*) B. Breit and W. Seiche, *Synthesis*, 2001, 1.
17 (*a*) G. D. Cuny and S. L. Buchwald, *J. Am. Chem. Soc.*, 1993, **115**, 2066; (*b*) L. A. van der Veen, P. C. J. Kramer and P. W. N. M. van Leeuwen, *Angew. Chem.*, 1999, **111**, 349; L. A. van der Veen, P. C. J. Kramer and P. W. N. M. van Leeuwen, *Angew. Chem., Int. Ed.*, 1999, **38**, 336.
18 (*a*) W. P. Griffith, S. V. Ley, G. P. Whitcombe and A. D. White, *J. Chem. Soc., Chem. Commun.*, 1987, 1625; (*b*) W. P. Griffith and S. V. Ley, *Aldrichim. Acta*, 1990, **23**, 13.
19 (*a*) R. W. Hoffmann and T. Sander, *Liebigs Ann. Chem.*, 1993, 1185; (*b*) T. Sander and R. W. Hoffmann, *Liebigs Ann. Chem.*, 1993, 1193.
20 (*a*) H. Breederveld, *Recl. Trav. Chim. Pays-Bas*, 1960, **79**, 1197; (*b*) H. Böhme and K. Hartke, *Chem. Ber.*, 1963, **96**, 600; (*c*) O. Meth-Cohn and K. T. Westwood, *J. Chem. Soc., Perkin Trans. 1*, 1984, 1173; (*d*) G. J. Meuzelaar, M. C. A. van Vliet, E. Neeleman, L. Maat and R. A. Sheldon, *Liebigs Ann./Recueil*, 1997, 1159; (*e*) A. P. Johnson, R. W. A. Luke and A. N. Boa, *J. Chem. Soc., Perkin Trans. 1*, 1996, 895.
21 (*a*) J. J. Mears and A. Whiting, *Tetrahedron*, 1993, **49**, 177; (*b*) R. J. Mears, H. E. Sailes, J. P. Watts and A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3250.
22 S. Pereira and M. Srebnik, *Tetrahedron Lett.*, 1996, **37**, 3283.
23 J.-I. Tateiwa, H. Horiuchi and S. Uemura, *J. Org. Chem.*, 1995, **60**, 4039.
24 G. A. Weisenburger and P. Beak, *J. Am. Chem. Soc.*, 1996, **118**, 12218.
25 M. J. Martin-López and F. Bermejo-González, *Tetrahedron Lett.*, 1994, **35**, 8843.
26 G. H. Baker, P. J. Brown, R. J. J. Dorgan, J. R. Everett, S. V. Ley, A. M. Z. Slawin and D. J. Williams, *Tetrahedron Lett.*, 1987, **28**, 5565.
27 F. Babudri, L. Di Nunno, S. Florio and S. Valzano, *Tetrahedron*, 1984, **40**, 1731.