*Chimia 45 (1991) 86–88*


# Radical Cyclization *vs.* Elimination in the Vitamin-$B_{12}$-Catalyzed Reduction of Unsaturated Bromo Acetals and Bromo Orthoesters***

**Kazumasa Yamamoto**, Stefan Abrecht,** and **Rolf Scheffold***

*Abstract.* Reduction of the 2-bromoacetaldehyde acetals of cinnamyl alcohol or propargyl alcohol with $Zn/NH_4$ in presence of catalytic amounts of $B_{12}$ in DMF affords oxolanes by free radical 5-*exo*-cyclization and the corresponding alcohols by reductive elimination. 2-(Bromoethyl) dimethyl orthopropiolate mainly decomposes by reductive elimination and by hydrogenolysis of the bromide.

The free-radical cyclization of 2-bromo- or 2-iodoacetaldehyde acetals of allylic or propargylic alcohols to oxolanes is a well known reaction [1]. It is usually achieved by reagents like organotin hydrides [2] or cobaloximes on the $Co^I$ oxidation state [3] or – in the catalytic version – by reducing agents in presence of $B_{12}$ [4] or $B_{12}$-related Co complexes as catalysts [5].

A practical and very mild procedure is the $B_{12}$-catalyzed reduction by $Zn/NH_4Cl$. Under these reaction conditions and depending on the structure of the bromo derivative, radical cyclization to oxolanes [6a], reductive $\beta$-elimination to olefins and alcohols [6b] and hydrogenolysis of the halide may take place as shown by three representative examples.

## Synthesis of 2-Bromo Derivatives

1-Bromo-2,2-di(cinnamyloxy)ethane **1** (space group $C_s$) has been chosen as starting material, since this molecule contains two enantiotopic olefinic groups, each having diastereotopic faces. It serves as a test substrate for potential asymmetric catalysis by the enantiomerically pure catalyst $B_{12}$ in the cyclization to the oxolane **2**. For the preparation of the acetal **1**, neither acid-catalyzed acetalization of 2-bromoacetaldehyde [7] nor transacetalization of its diethyl acetal proved to be valuable. Cinnamyl alcohol **3** was, therefore, first transformed into its vinyl ether **4** [8]. Bromination with *N*-bromosuccinimide (NBS) in presence of **3** in $CH_2Cl_2$ at –40° [9] afforded the acetal **1** in 88% yield. Benzyl vinyl ether **5** was first brominated with $Br_2$ in $Et_2O$ at –78° and then converted to the acetal **6** in 68% yield by the addition of prop-2-ynol in the presence of $Li_2CO_3$. (Trimethylsilyl)acetylene **8** was first deprotonated with EtMgBr and reacted with tetramethyl orthocarbonate to afford **9** in 64% yield; acid catalyzed solvolysis with 1 equiv. of 2-bromoethanol gave the mixed orthoester **10** in 58% yield from which the $Me_3Si$ group was removed with $KF \cdot H_2O$ in DMF [10] to afford the bromoalkyne **11**.

## $B_{12}$-Catalyzed Reduction of Bromo Derivatives

All experiments for the reductive cyclization of **1**, **6**, and **11** were carried out with $Zn/NH_4Cl$ as reducing agent and hydroxocobalamin hydrochloride (2 mol-% $B_{12a}$ with respect to substrate = 100 mol-%) as catalyst in DMF under Ar. $B_{12a}$ was first reduced until the green colour of the catalytically active $Co^I$ complex ($B_{12s}$) appeared. On addition of the bromoalkene the red colour of alkylcob(III)alamins appeared immediately and remained, until all starting material was consumed. The end of the reaction is marked by the colour change from red to green (recycled $B_{12s}$). Results are presented in the *Table*.

The bromoacetal **1** afforded the products of reductive $\beta$-elimination (**3** and **4**) *vs.* cyclization in a molar ratio of *ca.* 3:2. The oxolane **2** was obtained as a mixture of the racemic *syn*- and *anti*-isomers (ratio 2:1) indicating a 5-*exo*-*trig*-cyclization *via* a 'free' carbon radical. 5-*exo*-*dig*-cyclization is the main process in the reduction of the propargylic bromoacetal **6** [5d,e]. An easy access to oxolanes of type **7** is of interest, since such substructures are part of certain biologically active compounds as *e.g.* sesbanimide [11]. On the other hand, the 2-(bromoethyl) ester of orthopropiolic acid **11** afforded only a small amount of the corresponding oxolane **12** by a 5-*exo*-*dig*-cyclization; it mainly decomposed to methyl propiolate (**13**) *via* reductive $\beta$-elimination and to 1-ethoxy-1,1-dimethoxyprop-2-yne (**14**) *via* hydrogenolysis of the halide. The corresponding silylated orthoester **10** afforded under the same reaction conditions only products resulting from $\beta$-elimination and hydrogenolysis.

## Experimental

*General*

Vitamin $B_{12a}$ (hydroxocobalamine hydrochloride-pyrogen free *Fr.Ph.BP*, 10.7% loss on drying, <2% cyanocobalamine) from *Roussel Uclaf*. IR-Spectra: *Perkin Elmer* 782. $^1$H-NMR Spectra: 60-MHz Spectrometer *Varian EM 360L*. MS Spectra: *Varian MAT CH-7a*.

***Preparation of Bromides***

*Cinnamyl Vinyl Ether* (**4**)

A soln. containing cinnamyl alcohol (**3**) (27.0 g, 0.202 mol), ethyl vinyl ether (158 g, 2.2 mol), and mercuric acetate (3.0 g, 9.4 mmol) was heated at rf. for 9 h. To the mixture was added at 0° a soln. of 10% aq. $Na_2CO_3$ (100 ml) and stirred for 30 min. The org. layer was separated, dried ($K_2CO_3$), concentrated *i.v.* to *ca.* 40 ml and chromatographed at silica gel (300 g, *Merck 60*) with hexane/AcOEt 8:1: 34.18 g of **4** (70.9%) as colourless oil. IR (neat): 3120*m*, 3080*m*, 3060*m*, 3020*m*, 1635*s*, 1615*s*, 1495*m*, 1450*m*, 1370*m*, 1320*m*, 1190*s*, 965*s*, 820*m*, 740*m*, 690*m*. $^1$H-NMR ($CDCl_3$): 4.05 (*dd*, *J* = 7, 2 Hz, 1 H); 4.27 (*dd*, *J* = 14, 2 Hz, 1 H); 4.38 (*d*, *J* = 5 Hz, 2 H); 6.20 (*dt*, *J* = 16, 5 Hz, 1 H); 6.50 (*dd*, *J* = 14, 7, 1 H); 6.70 (*d*, *J* = 16 Hz, 1 H); 7.35 (*m*, 5 H).

*1-Bromo-2,2-di(cinnamyloxy)ethane* (**1**)

To a stirred soln. of *N*-bromosuccinimide (7.46 g, 41.9 mmol) and **3** (6.73 g, 50.3 mmol) in $CH_2Cl_2$ (30 ml) was added at –35 to –40° for 2 h a soln. of **4** (6.70 g, 41.9 mmol) in $CH_2Cl_2$ (10 ml) and allowed to stir for 1 h at –35° and 6 h at r.t. The precipitated succinimide

Table. *Reduction of Bromides* **1**, **6**, *and* **11** *with* $Zn/NH_4Cl$, *2 mol-%* $B_{12a}$ *in DMF*

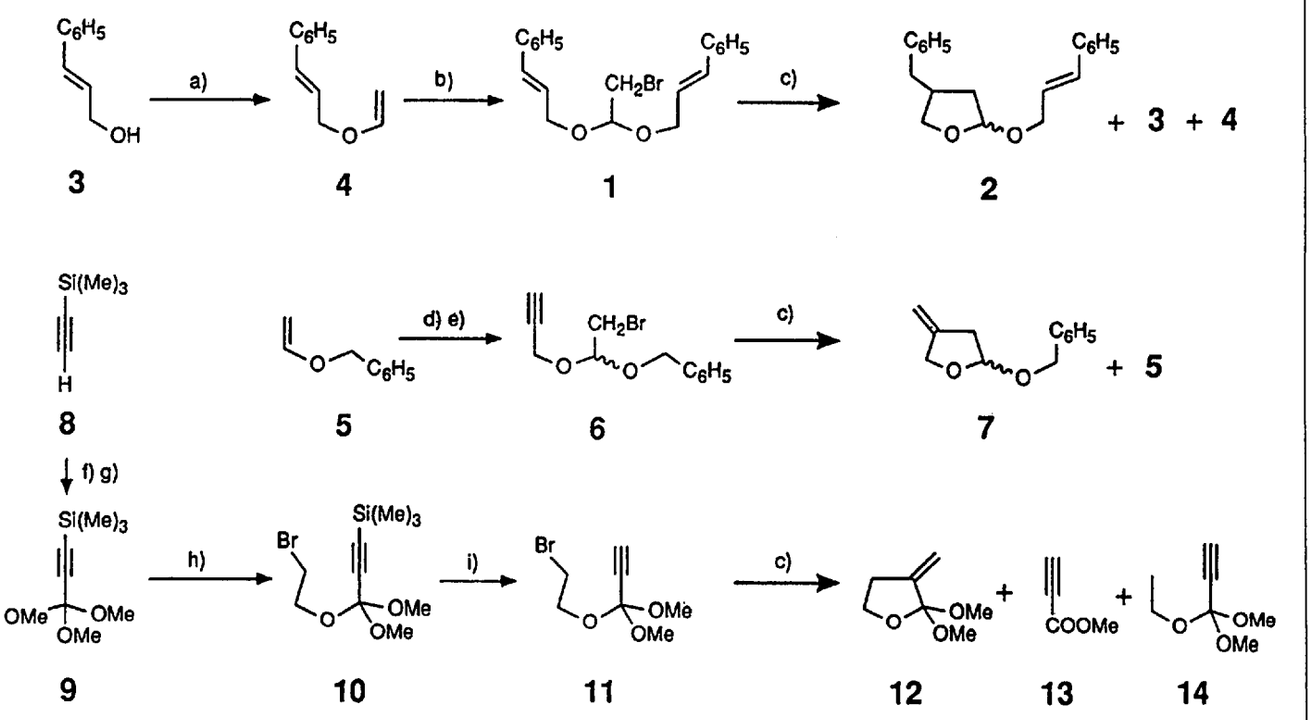
| Starting material | Reaction Conditions | | Products (% isol. Yield) | | | |
|---|---|---|---|---|---|---|
| | Temp. [°C] | Time [h] | | | | |
| **1** | 0 | 40 | **2**[a]) (26) | **3** (*ca.* 40) | **4** (28) | |
| **1** | 20 | 3 | **2**[a]) (14) | **3** (*ca.* 40) | **4** (40) | |
| **6** | 20 | 18 | **7**[b]) (77) | **5**[c]) benzylalcohol[c]) | | |
| **11** | 20 | 5 | **12** (7) | **13**[c]) | **14**[c]) | |

[a]) Mixture of *syn*- and *anti*-diastereoisomers (ratio *ca.* 2:1), $[\alpha]_D^{20}$ pract. 0°.
[b]) Reaction with $Bu_3SnH$ (1.1 equiv.), AIBN (cat.) in boiling benzene for 18 h afforded **7** (75%).
[c]) Qualitatively determined by MS.

*Correspondence: Prof. Dr. R. Scheffold
Institut für Organische Chemie
Universität Bern
Freiestrasse 3, CH-3012 Bern

**Prof. Dr. Kazumasa Yamamoto, on leave from
Konan Women's University
Higashinada-ku, Kobe 658, Japan

***This work was supported by the Swiss National Science Foundation




was filtered off, the soln. concentrated *i.v.* to *ca.* 20 ml, and chromatographed at silica gel (200 g, *Merck 60*) with hexane/AcOEt 8:1: 13.75 g of **1** (88.1%) as colourless oil. IR (neat): 3080*m*, 3060*m*, 3020*m*, 1600*w*, 1575*w*, 1490*s*, 1450*s*, 1120*s*, 1030*s*, 965*s*, 740*s*, 690*s*. $^1$H-NMR ($CDCl_3$): 3.49 (*d*, *J* = 5 Hz, 2 H); 4.31 (*d*, *J* = 5 Hz, 4 H); 4.91 (*t*, *J* = 5 Hz, 1 H); 6.30 (*dt*, *J* = 16, 5 Hz, 2 H); 6.72 (*d*, *J* = 16 Hz, 2 H); 7.36 (*m*, 10 H). $^{13}$C-NMR ($CDCl_3$): $\delta$ = 137.0 (*s*), 133.3 (*d*), 129.1 (*d*), 128.3 (*d*), 127.0 (*d*), 125.7 (*d*), 100.8 (*d*), 67.4 (*t*), 31.7 (*t*). MS (*m/e*): 374 (0.2%, $M^+$), 372 (0.2%, $M^+$), 142 (3%), 140 (3%, [$M-C_9H_8O$]$^+$), *117* (100).

*2-Bromo-1-(benzyloxy)-1-(prop-2-yn-1-oxy)ethane* (**6**)

To a soln. of benzyl vinyl ether (**5**) (1.00 g, 7.46 mmol) in abs. $Et_2O$ (10 ml) was added under $N_2$ at –78° drop by drop $Br_2$ (1.2 g, 7.5 mmol), until the colour remained slightly yellow. After the addition of dry $LiCO_3$ (1.20 g, 16.2 mmol) prop-2-yn-1-ol (460 mg, 8.2 mmol) in abs. $Et_2O$ (0.5 ml) was added dropwise at –78° and stirred for 18 h at r.t. The LiBr was filtered off, $Et_2O$ removed *i.v.* and the remaining oil distilled at 95–110°/0.04 Torr (bulb-to-bulb): 1.362 g of **6** (68%) as colourless oil. IR (neat): 3300*s*, 3070*w*, 3040*w*, 2930*s*, 2880*w*, 2120*w*, 1500*m*, 1455*m*, 1425*m*, 1350*m*, 1270*w*, 1185*m*, 1120*s*, 1040*s*, 1020(sh), 740*s*, 700*s*, 640*m*. $^1$H-NMR ($CDCl_3$): 2.45 (*t*, *J* = 2 Hz, 1 H); 3.42 (*d*, *J* = 5.8 Hz, 2 H); 4.22 (*m*, 2 H); 4.60 (*d*, 11 Hz, 1 H); 4.68 (*d*, 1 H); 4.93 (*d*, 1 H); 7.30 (*m*, 5 H). MS (*m/e*): 270 (<1, $M^+$), 268 (>1, $M^+$), 175 (1), 163 (2), 161 (2), 133 (6), 129 (5), 107 (17), 92 (19), *91* (100), 77 (6), 69 (6), 65 (12). Anal. calc. for $C_{12}H_{13}BrO_2$: C 53.55, H 4.87; found: C 53.61, H 4.84.

*1,1,1-Trimethoxy-3-(trimethylsilyl)prop-2-yne* (**9**)

To the *Grignard* reagent prepared from Mg (930 mg, 38.3 mmol) and EtBr (4.20 g, 38.5 mmol) in $Et_2O$ (10 ml) was added a soln. of *(trimethylsilyl)acetylene* (**8**) (3.40 g, 34.7 mmol) in $Et_2O$ (7 ml) and stirred for 1 h at r.t. and 15 min at reflux. At r.t. a soln. of tetramethoxymethane (5.74 g, 42.2 mol) in $Et_2O$ (5 ml) was added dropwise and then heated at reflux for 8 h. The suspension was cooled to r.t., poured on sat. aq. $NH_4Cl$ (70 ml) and extracted with $Et_2O$ (2 × 50 ml). The org. layer was washed with brine (2×40 ml), dried ($Na_2SO_4$), the solvent evaporated *i.v.* and the residual oil dist. at 70–75°/0.15 Torr (bulb-to-bulb): 4.49 g (64%) of **9** (containing *ca.* 10% tetramethoxymethane). IR (neat): 2960*s*, 2900(sh), 2840*m*, 1470*w*, 1440*w*, 1250*s*, 1225*s*, 1145*s*, 1105*s*, 1075*s*, 1040*s*, 1000*s*, 860*s*, 840*s*, 760*s*, 700*w*, 630*w*. $^1$H-NMR ($CDCl_3$): 0.23 (*s*, 9 H); 3.38 (*s*, 9 H). MS (*m/e*): 187 (3), 172 (13), *171* (100), 141 (3), 125 (6), 113 (5), 105 (5), 99 (5), 97 (14), 89 (25), 73 (9).

*1-(2-Bromoethoxy)-1,1-dimethoxy-3-(trimethylsilyl)-prop-2-yne* (**10**)

In a round-bottom flask with condenser, a mixture of **9** (3.43 g, 17.0 mmol), 2-bromoethanol (2.12 g, 17.0 mmol) and TsOH (50 mg, 0.26 mmol) was stirred for 19 h at 45° at reduced pressure (150 Torr). The mixture was then diluted with $Et_2O$ (100 ml), washed with sat. aq. $NH_4Cl$ (50 ml), brine (50 ml), dried ($Na_2SO_4$), and the solvent evaporated *i.v.* and dist. at 80–85°/0.08 Torr (bulb-to-bulb): 1.82 g of **10**. Repeated dist. of the mixture of the first fraction and the residue in presence of traces of TsOH afforded additional **10** (850 and 540 mg) totally 3.21 g (64%). IR (neat): 2960*s*, 2900(sh), 2840*s*, 1720*w*, 1440*w*, 1250*s*, 1220*s*, 1150*s*, 1105*s*, 1040(sh), 1000(sh), 950(sh), 865*s*, 845*s*, 760*s*, 700*m*, 630*s*. $^1$H-NMR ($CDCl_3$): 0.25 (*s*, 9 H); 3.43 (*s*, 6 H); 3.50 (*t*, *J* = 6 Hz, 2 H); 3.95 (*t*, *J* = 6 Hz, 2 H). MS (*m/e*): 265 (15), 263 (17), *171* (100), 161 (36), 159 (37), 125 (15), 113 (5), 109 (25), 107 (26), 97 (17), 89 (45), 73 (47), 59 (25).

*1-(2-Bromoethoxy)-1,1-dimethoxyprop-2-yne* (**11**)

A soln. of **10** (1.13 g, 3.84 mmol), KF (670 mg, 11.6 mmol), and $H_2O$ (416 mg, 23.1 mmol) in DMF (25 ml) was stirred under Ar for 75 min. The soln. was diluted with pentane/$Et_2O$ 1:1 (60 ml), poured on sat. aq. $NH_4Cl$/ice (50 ml) and extracted with pentane/$Et_2O$ (2 × 50 ml). The org. phase was washed with $H_2O$ (2 × 50 ml) dried ($Na_2SO_4$), the solvent evaporated *i.v.* and the residual oil dist. 55°/0.08 Torr (bulb-to-bulb): 844 mg of **11** as colourless oil. IR (neat): 3290*m*, 2980(sh), 2950*m*, 2840*m*, 2120*m*, 1460*m*, 1440*m*, 1280*m*, 1220*s*, 1150(sh), 1110*s*, 1040(sh), 1000(sh), 950(sh), 670*s*. $^1$H-NMR ($CDCl_3$): 2.65 (*s*, 1 H); 3.43 (*s*, 6 H); 3.50 (*t*, *J* = 6 Hz, 2 H); 3.98 (*t*, *J* = 6 Hz, 2 H). MS (*m/e*): 193 (12), 191 (12), 109 (36), 107 (38), *99* (100), 53 (57).

*Reductive Cyclisation with $B_{12}$/Zn/$NH_4Cl$. syn- and anti-4-Benzyl-2-(cinnamyloxy)oxolane* (**2**)

Under Ar, a mixture of $NH_4Cl$ (400 mg, 7.5 mmol), Zn wool (activated [12], 2.5 g, 38 mmol), and hydroxycobalamin hydrochloride (70 mg, 0.05 mmol) in DMF (35 ml) was stirred at r.t. for 1 h. The initially red colour turned to dark green. The mixture was cooled to 0° and a soln. of **1** (1.00 g, 2.68 mmol) in DMF (4 ml) was added; the colour changed immediately to red. After stirring for 40 h under Ar at 0°, the colour turned to dark green. To the soln. was added at 0° brine (35 ml) and 25% aq. $NH_4OH$ (5 ml), then it was extracted with pentane (5 × 35 ml). The org. phase was dried ($Na_2SO_4$) and the solvent evaporated *i.v.* The liquid residue was chromatographed at silica gel (*Merck 60*, 20 with hexane/AcOEt 8:1 to give 3 fractions: *Fr. 1*, $R_f$ 0.77, 205 mg (28%) of **4**; *Fr. 2*, $R_f$ 0.45, 202 mg (26%) of a 1:2 mixture of *syn*- and *anti*-oxolane **2**; *Fr. 3*, $R_f$ 0.1, 253 mg (*ca.* 40%) of **3**. Analytical data of *Fr. 2*: IR (neat): 3090*m*, 3060*m*, 3030*m*, 2940*m*, 2860*m*, 1600*w*, 1495*s*, 1450*s*, 1350*m*, 1090*s*, 1015*s*, 965*s*, 740*s*, 690*s*. $^1$H-NMR ($CDCl_3$): 1.6–2.6 (*m*, 5 H); 3.5–4.2 (*m*, 2 H); 4.30–4.37 (2*d*, *J* = 5 Hz, 2 H); 5.28–5.30 (2*m*, 1 H); 6.29–6.34 (2 × *dt*, *J* = 16, 5 Hz, 1 H); 6.70–6.73 (2*d*, *J* = 16 Hz, 1 H); 7.25 and 7.35 (2*m*, totally 10 H, rel. intensity of the two *m ca.* 2:1). MS (*m/e*): 294 (1, $M^+$), 161 (47, [$M-C_3H_5O$]$^+$), *143* (100), 117 (70), 91 (53).

*2-(Benzyloxy)-4-methylideneoxolane* (**7**)

As described above, **6** (1.00 g, 3.72 mmol) was reduced in presence of Zn (3.5 g), $NH_4Cl$ (600 mg) and hydroxycobalamin hydrochloride (100 mg, 0.072 mmol) in DMF (50 ml) at r.t. for 18 h. Product after dist. 50°/

0.01 Torr (bulb-to-bulb) 543 mg of **7** (77%) as colourless oil. IR (neat): 3060*w*, 3030*w*, 2920*m*, 2860*m*, 1670*w*, 1500*m*, 1455*m*, 1430*m*, 1340*s*, 1250*m*, 1170*s*, 1090*s*, 1035(sh), 1020*s*, 920*s*, 880*s*, 730*s*, 690*s*. $^1$H-NMR ($CDCl_3$): 2.65 (*m*, 2 H); 4.45 (*m*, 2 H); 4.50 (*d*, *J* = 11 Hz, 1 H); 4.75 (*d*, 1 H); 5.00 (*m*, 2 H); 5.30 (*m*, 1 H); 7.38 (*m*, 5 H). MS (*m/e*): 190 (1, $M^+$), 144 (1), 129 (5), 99 (17), 92 (34), 91 (100), 83 (22), 65 (11), 55 (17). Anal. calc. for $C_{12}H_{14}O_2$: C 75.76, H 7.42; found: C 75.55, H 7.60.

*2,2-Dimethoxy-3-methylideneoxolane* (**12**)

As described above, **11** (374 mg, 1.68 mmol) was reduced in presence of Zn (1.75 g), $NH_4Cl$ (300 mg) and hydroxycobalamin hydrochloride (70 mg, 0.05 mmol) in DMF (25 ml) at r.t. for 5 h. Product after dist. at 60°/20 Torr (bulb-to-bulb) 25 mg of **12** (13%, purity according GC/GC-MS 54%). $^1$H-NMR ($CDCl_3$): 2.72 (*dt*, *J* = 7, 2 Hz, 2 H); 3.33 (*s*, 6 H); 3.97 (*t*, 2 H); 5.24 (*m*, 2 H). GC-MS (sample with ret. time of **12**): (*m/e*): 143 (1, $M^+$), 129 (*s*), 113 (100), 91 (9), 81 (55), 69 (11), 59 (55), 55 (22). Compounds **13** and **14** have been detected qualitatively by MS.

Received: December 11, 1990

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[12] Activated by 1N HCl (5 min r.t.) then washed with EtOH, $Et_2O$ and dried at 20°/0.1 Torr.



# Herbstversammlung Bern 19. Oktober 1990 Sektion für Medizinische Chemie

*Chimia 45 (1991) 88–89*


## Structure-Activity Studies for Potassium-Channel Opening in Pinacidil-Type Cyanoguanidines and Nitroethenediamines

**Paul W. Manley*** and **Ulrich Quast**

Pinacidil (*rac*-**1**; *N*-cyano-*N'*-(4-pyridinyl)-*N''*-(1,2,2-trimethylpropyl)guanidine) is a vasorelaxant drug [1] which acts primarily through the opening of membrane K channels in vascular smooth-muscle cells [2]. As part of a structure-activity study aimed towards the elucidation of the pharmacophore responsible for K-channel opening, the enantiomers of pinacidil and the bioisosteric nitroethenediamines [3] were prepared and evaluated pharmacologically.

The enantioselective syntheses of the compounds were achieved as follows: pinacolone was reacted with the individual (+)-(*R*)- and (–)-(*S*)-1-phenylethylamines to afford the corresponding chiral (*E*)-imines (*Scheme 1*). Reduction of the imines with $BH_3 \cdot THF$ resulted in addition of $H_2$ to the less hindered face of the azomethine to give the individual (*R,R*)- and (*S,S*)-benzylamines, which, on hydrogenolysis (10% Pd/C, $H_2$), afforded the (*R*)- and (*S*)-1,2,2-trimethylpropylamines having high enantiomeric purity. These, on addition to 4-pyridyl isothiocyanate, followed by elimination of $H_2S$ from the resulting thioureas using dicyclohexylcarbodiimide and $EtN(i\text{-}Pr)_2$ gave the diimides, which were reacted *in situ* with cyanamide to give the (*R*)- and (*S*)-enantiomers of pinacidil in high overall yield, having $[\alpha]_D^{20} = -148$ and $[\alpha]_D^{20} = +144$ (*c* = 1.00; EtOH) and ee > 99.5% by NMR. (These values compare favourably with those of $[\alpha]_D^{20} = -135$ and +135 in the literature[4]).

The corresponding nitroethenediamine analogues (**3** and **4**; *Scheme 2*) were prepared *via* the consecutive addition of the required pyridineamine followed by the (*R*)- or (*S*)-1,2,2-trimethylpropylamines to $(Me_2S)_2CHNO_2$ [5], having high enantiomeric purity and existing exclusively in the *E*-configuration as shown by NOE studies.

Biological activity was quantified *in vitro* by simultaneous measurements of inhi-

*Correspondence*: Dr. P.W. Manley
Cardiovascular Department, Preclinical Research
*Sandoz Pharma Ltd.*
CH-4002 Basel