# 25. Synthesis of (*R*)- and (*S*)-5-(Hydroxymethyl)-3-isopropyloxazolidin-2-one, Intermediates in the Preparation of Optically Active β-Blockers

by **Erwin G. J. C. Warmerdam, Johannes Brussee*,** and **Arne van der Gen**

Department of Chemistry, Gorlaeus Laboratories, Leiden University, P. O. Box 9502, NL–2300 RA Leiden

and **Chris G. Kruse**

*Solvay Duphar B. V.*, P. O. Box 900, NL–1380 DA Weesp

(16.IX.93)

The (*R*)- and (*S*)-5-(hydroxymethyl)-3-isopropyloxazolidin-2-ones, ((*R*)- and (*S*)-**2**, resp.), pivotal intermediates in the preparation of optically active β-blockers, were synthesized using (*R*,*E*)-2-hydroxypent-3-enenitrile (**1**) as the chiral starting material. In the synthesis of (*R*)-**2**, a known cyclization/inversion step was applied.

**Introduction.** – β-Blockers (β-adrenoceptor antagonists) are among the world's most applied pharmaceuticals. They are mainly prescribed in the treatment of hypertension, angina pectoris, and cardiac arrhythmias. Most of the *ca.* two dozen β-blockers presently marketed are 1-(alkylamino)-3-(aryloxy)propan-2-ols, having the general structure **A** in which the aryl group can be one of a large variety of aromatic substituents. The *N*-alkyl substituent is generally an i-Pr or a *t*-Bu group, although other substituents on the N-atom do occur.

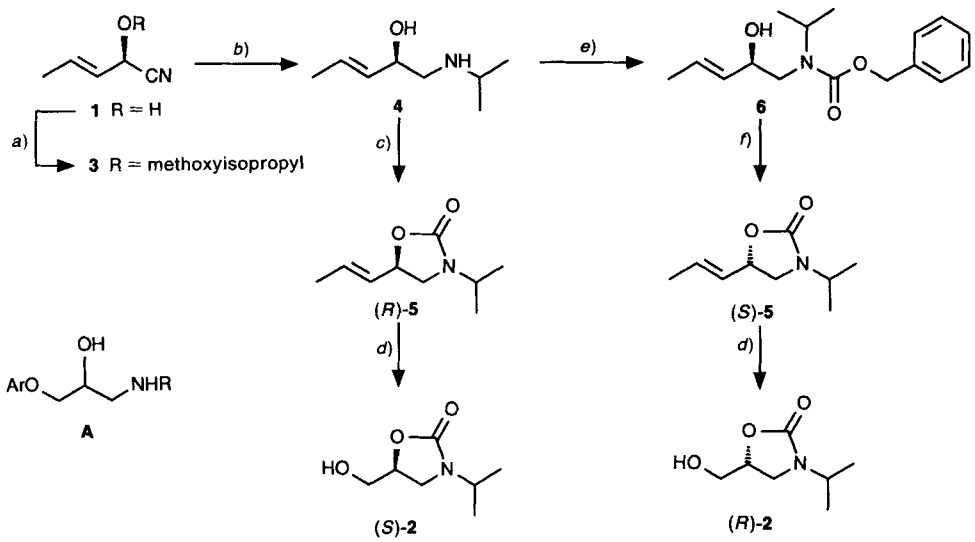
Although it is known that the (*R*)- and (*S*)-enantiomers of these compounds possess largely different β-blocking activity, most of these β-blockers are still sold as racemates. *E.g.* (*S*)-propranolol [2], (*S*)-atenolol [3], and (*S*)-carvedilol [4] display *ca.* 100 times higher β-blocking activity than their (*R*)-enantiomers. On the other hand, for some compounds, beneficial effects such as anti-glaucoma activity were claimed for the (*R*)-enantiomer. In such a case, reduction of undesired β-blocking activity can be accomplished by removal of the (*S*)-enantiomer. In recent years, the growing demand for the selective use of only the desired stereoisomer of a pharmaceutical has stimulated the search for practical methods of preparing chiral drugs in optically active form. In this context, the preparation of optically active β-blockers was studied by several groups [5] [6]. In the majority of cases, the synthetic problem can in fact be reduced to the synthesis of the corresponding optically active 1-(alkylamino)propane-2,3-diols in a suitably protected form. It is known that these can be coupled with the requisite aromatic alcohols to give the desired β-blockers [7] without loss of optical purity. Optically active β-blockers and their precursors were synthesized from D-mannitol [5], from chiral glycerol derivatives [6], by lipase-catalyzed asymmetric hydrolysis of racemic 3-alkyl-5-(hydroxymethyl)oxazolidin-2-one derivatives [7–9], and by optical resolution of racemic derivatives.

In the approach described here, (*R*,*E*)-2-hydroxypent-3-enenitrile (**1**), easily accessible by enzyme-catalyzed addition of HCN to but-2-enal [10] [11], is used as a potential $C_3$ chiral building block, in which the double bond can be selectively converted into an O-functionality by ozonolysis followed by reductive workup. The usefulness of this approach is demonstrated by the transformation of **1** into the pure (*R*)- and (*S*)-enantiomers of 5-(hydroxymethyl)-3-isopropyloxazolidin-2-one, (*R*)-**2** and (*S*)-**2**, respectively. The *N*-isopropyl substituent was selected, because it is the one mostly encountered in commercial *β*-blockers. The synthetic route, however, is amenable to the introduction of any other desired alkyl substituent at the N-atom.

**Results and Discussion.** – In (*R*,*E*)-2-hydroxypent-3-enenitrile (**1**; e.e. 96%), conveniently prepared from but-2-enal and HCN, with the aid of the enzyme oxynitrilase as present in almond meal [11], the alcohol moiety was protected as a methoxyisopropyl ( = 1-methoxy-1-methylethyl) ether (*Scheme*). This protecting group was introduced by reaction with 2-methoxypropene in the presence of a catalytic amount of $POCl_3$ (→ **3**; quant.) and proceeded without loss of optical purity[1]). Other advantages of this protecting group are that it is not affected by diisobutylaluminium hydride (DIBAL) reduction conditions and that it can be easily removed by acidic workup.

The protected cyanohydrin **3** was then subjected to a one-pot DIBAL reduction/transimination/hydride reduction sequence as described earlier [13]. In this conversion, the initially formed metalloimine is protonated *in situ* and subsequently transiminated with a

Scheme. *Reaction Route to (*R*)- and (*S*)-5-(Hydroxymethyl)-3-isopropyloxazolidin-2-one*




*a*) 2-Methoxypropene. *b*) 1. DIBAL; 2. MeOH, $NH_4Br$, i-$PrNH_2$; 3. $NaBH_4$; 4. $H_3O^+$. *c*) 1,1′-Carbonylbis(1*H*-imidazole). *d*) 1. $O_3$; 2. $NaBH_4$. *e*) Benzyl chloroformate. *f*) $SOCl_2$.

[1]) For the introduction of an analogous protecting group under similar conditions without racemization, see [12].

primary amine, in this case i-$PrNH_2$, to give a secondary imine which is then reduced with $NaBH_4$. Thus, the CN function was converted into a i-$PrNHCH_2$ group, and after workup, (*R*,*E*)-1-(isopropylamino)pent-3-en-2-ol (**4**) was obtained in 81% yield.

Prior to ozonolysis, the OH and NH functions had to be protected against oxidation. This was accomplished in one step by formation of the oxazolidinone (*R*)-**5** (75%) on reaction of **4** with 1,1′-carbonylbis(1*H*-imidazole). Ozonolysis of (*R*)-**5** at low temperature in the presence of excess MeOH, followed by reductive workup with $NaBH_4$ gave (*S*)-**2** in 80% yield after crystallization and an enantiomeric excess of $\geq 99\%$. To prepare the enantiomeric oxazolidinone (*R*)-**2**, a procedure first described by *Kano et al.* [1] was followed. First compound **4** was treated with benzyl chloroformate to introduce a benzyloxycarbonyl group at the N-atom ($\rightarrow$ **6**; 96%). Subsequent ring closure using thionyl chloride as the activator yielded (*S*)-**5** in fair yield. The ring closure had proceeded with complete inversion of the configuration as indicated by the optical rotation ($[\alpha]_D^{20} = +28$ ($c = 1$, $CH_2Cl_2$) for (*R*)-**5** and $[\alpha]_D^{20} = -28$ ($c = 1$, $CH_2Cl_2$) for (*S*)-**5**). Ozonolysis of (*S*)-**5** and reduction as described before gave (*R*)-**2** with an e.e. $\geq 99\%$. Alternatively, (*R*)-**2** can be obtained by the procedure followed for (*S*)-**2**, using the (*S*)-enantiomer of **1** as starting material. We recently described the conversion of **1** into its (*S*)-enantiomer by a *Mitsunobu* esterification, followed by acid-catalyzed hydrolysis [14].

**Conclusion.** – A new method was developed for the preparation of both enantiomers (*R*)- and (*S*)-**2** of 5-(hydroxymethyl)-3-isopropyloxazolidin-2-one in optically pure form. These compounds are known to be excellent chiral building blocks for the preparation of optically active $\beta$-blockers without racemization [7]. The present approach allows the introduction of a large variety of substituents at the N-atom, since the transimination step proceeds well with most primary amines, even bulky ones[2]). In the case of *t*-$BuNH_2$, slightly prolonged reaction times (2 h) were needed to complete the transimination. Thus, (*R*,*E*)-2-hydroxypent-3-enenitrile (**1**), readily available in optically active form, was shown to be a versatile starting material for the synthesis of both (*S*)- and (*R*)-oxazolidinones, important intermediates in the synthesis of optically active $\beta$-blockers of the 1-(alkylamino)-3-(aryloxy)propan-2-ol type **A**.

## Experimental Part

*General.* Enantiomeric purities of starting materials were determined by HPLC using a *Chiralcel-OD* column and hexane/i-PrOH mixtures. The enantiomeric purity of **1** was determined after conversion into its (*tert*-butyl)diphenylsilyl ether [14] (hexane/i-PrOH 99.75:0.25) and that of (*R*)- and (*S*)-**2** by $^{19}$F-NMR ($C_6D_6$, $CF_3COOH$ as external ref.) on a *Bruker-WM-300* instrument after conversion into diastereoisomeric esters with (+)-(*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (e.e. 98%; *Aldrich*; (*S*,*S*)- and (*R*,*S*)-isomer at 4.27 and 4.15 ppm, resp.). Optical rotations: *Perkin-Elmer-141* polarimeter. $^1$H- and $^{13}$C-NMR Spectra: *Jeol-FX-200* instrument; $CDCl_3$ solns.; $Me_4Si$ as internal reference for $^1$H and $CDCl_3$ as an internal reference for $^{13}$C; $\delta$ in ppm, *J* in Hz; **6** was measured at 60° (interconversion of rotamers).

*(R,E)-2-Hydroxypent-3-enenitrile* (**1**) was prepared as described [11] on a 200-mmol scale in 85% yield. Anal. data: in agreement with those published; e.e. 96% by anal. HPLC (see above).

---

[2]) A variety of primary amines, including $MeNH_2$, $EtNH_2$, i-$PrNH_2$, benzylamine, 2-phenylethylamine, and various aminoethanols were successfully used in transimination procedures, see *e.g.* [13] [15]. Transimination with *t*-$BuNH_2$ was not reported earlier.

*(+)-(R,E)-2-(1-Methoxy-1-methylethoxy)pent-3-enenitrile* (**3**). To a soln. of **1** (9.7 g, 100 mmol) in 2-methoxypropene (30 ml), a cat. amount of $POCl_3$ (13 mg) was added and the mixture stirred at r.t. for 15 min. $Et_3N$ (29 mg) was then added, the mixture taken up in $Et_2O$ (100 ml), and the soln. washed with brine (2 × 10 ml), dried ($MgSO_4$), and evaporated: 16.4 g (97%) of **3**. Slightly yellow oil. $[\alpha]_D^{20} = +32$ (*c* = 1, $CHCl_3$); e.e. 96% [12]. $^1$H-NMR: 1.38, 1.48 (2*s*, $Me_2C$); 1.78 (*d*, 3 H–C(5)); 3.24 (*s*, MeO); 4.91 (*d*, H–C(2)); 5.53 (*dd*, H–C(3)); 6.05 (*m*, H–C(4)). $^{13}$C-NMR: 131.55 (C(4)); 124.30 (C(3)); 118.46 (CN); 102.11 ($Me_2C$); 59.39 (C(2)); 49.35 (MeO); 24.67, 24.00 ($Me_2C$); 17.32 (C(5)).

*(−)-(R,E)-1-(Isopropylamino)pent-3-en-2-ol* (**4**). To a cooled soln. (−70°) of **3** (3.34 g, 20 mmol) in dry $Et_2O$ (160 ml) was added 1M DIBAL in cyclohexanes (40 ml, 40 mmol). After stirring at −70° for 3 h, $NH_4Br$ (4.0 g, 40 mmol) in dry MeOH (60 ml) was added. The cooling bath was removed and i-$PrNH_2$ (5.9 g, 100 mmol) added. Stirring was continued for 45 min during which time the temp. was allowed to rise to r.t. The mixture was then cooled with an ice-bath, $NaBH_4$ (1.5 g, 40 mmol) added in 3 portions, the mixture stirred for another 2 h, and 1N HCl (250 ml) added. The org. layer was extracted with an additional 1N HCl (50 ml). The aq. layer was made alkaline with 5N NaOH (→clear soln.) and then extracted with $CH_2Cl_2$ (5 × 50 ml). The combined org. layers were dried ($K_2CO_3$) and evaporated: 2.31 g (81%) of yellowish oil. $[\alpha]_D^{20} = -35$ (*c* = 1, $CH_2Cl_2$); e.e. 96%[3]. $^1$H-NMR: 1.06 (*d*, $Me_2CH$); 1.70 (*d*, 3 H–C(5)); 2.24 (br., OH, NH); 2.49 ('*dd*', *ABX*, $J_{AB} = 11.99$, $J_{AX} = 8.56$, 1 H–C(1)); 2.74 ('*dd*', *ABX*, $J_{AB} = 11.99$, $J_{BX} = 3.85$, 1 H–C(1)); 2.80 (*m*, $Me_2CH$); 4.04 (*m*, H–C(2)); 5.46 (*m*, H–C(3)); 5.73 (*m*, H–C(4)). $^{13}$C-NMR: 132.16 (C(4)); 126.82 (C(3)); 70.43 (C(2)); 52.68 (C(1)); 48.39 ($Me_2CH$); 22.60 ($Me_2CH$); 17.49 (C(5)).

*(+)-(R)-3-Isopropyl-5-(prop-1-enyl)oxazolidin-2-one* ((*R*)-**5**). To a soln. of **3** (1.43 g, 10 mmol) in dry $CH_2Cl_2$ (30 ml) under $N_2$ at 0°, 1,1′-carbonylbis(1*H*-imidazole) (3.2 g, 20 mmol) was added and the mixture stirred overnight. The mixture was then acidified (pH *ca.* 3) with 0.5N HCl, the aq. layer extracted with $CH_2Cl_2$ (4 × 25 ml), and the combined org. phase dried ($MgSO_4$) and evaporated: 1.26 g (75%) of (*R*)-**5**. $[\alpha]_D^{20} = +28$ (*c* = 1, $CH_2Cl_2$); e.e. 96%. $^1$H-NMR: 1.16 (*dd*, $Me_2CH$); 1.75 (*dd*, *Me*CH=CH); 3.16 (*dd*, *ABX*, $J_{AB} = 8.56$, $J_{AX} = 7.49$, 1 H–C(4)); 3.57 ('*t*', '*ABX*', $J_{AB} = J_{BX} = 8.56$, 1 H–C(4)); 4.11 (*m*, $Me_2CH$); 4.85 (*q*, H–C(5)); 5.54 (*m*, MeCH=C*H*); 5.84 (*m*, MeC*H*=CH). $^{13}$C-NMR: 156.75 (C(2)); 130.96 (Me*C*H=CH); 127.49 (MeCH=*C*H); 73.85 (C(5)); 44.85 (C(4)); 44.24 ($Me_2CH$); 19.51, 19.04 ($Me_2CH$); 17.23 (*Me*CH=CH).

*(+)-(S)-5-(Hydroxymethyl)-3-isopropyloxazolidin-2-one* ((*S*)-**2**). Through a soln. of (*R*)-**5** (0.85 g, 5 mmol) in $CH_2Cl_2$ (30 ml) and MeOH (2 ml, 50 mmol, 10 equiv.) cooled to −70°, ozone was passed until a blue color persisted. Stirring was continued for 1 h allowing the temp. to rise to −30° after which $NaBH_4$ (0.18 g, 5 mmol) was added. After stirring for 2 h at −30°, 6N HCl (3 ml) was introduced. $H_2O$ was removed by azeotropic distillation with toluene and the remaining residue passed over a short silica-gel column with $CH_2Cl_2$. Evaporation and subsequent crystallization from $Et_2O$ yielded 0.64 g (80%) of (*S*)-**2**. M.p. 53–55° ([5] [7]: m.p. 56.5–57.5°). $[\alpha]_D^{20} = +53$ (*c* = 1, $CHCl_3$); e.e. ≥ 99% (by $^{19}$F-NMR; corrected for e.e. 98% of (+)-(*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride; [5]: $[\alpha]_D^{20} = +57.12$ (*c* = 1.17, $CHCl_3$) for product with e.e. ≥ 99%; [7]: $[\alpha]_D^{20} = +53.5$ (*c* = 1, $CHCl_3$) for product with e.e. ≥ 99%). $^1$H-NMR: 1.18 (*dd*, $Me_2CH$); 2.38 (br., OH); 3.41 ('*dd*', *ABX*, $J_{AB} = 8.57$, $J_{AX} = 6.64$, 1 H–C(4)); 3.53 ('*dd*', *ABX*, $J_{AB} = 8.57$, $J_{BX} = 8.78$, 1 H–C(4)); 3.65 ('*dd*', *ABX*, $J_{AB} = 12.42$, $J_{AX} = 4.29$, 1 H, $CH_2OH$); 3.88 ('*dd*', *ABX*, $J_{AB} = 12.42$, $J_{BX} = 3.42$, 1 H, $CH_2OH$); 4.11 (*m*, $Me_2CH$); 4.59 (*m*, H–C(5)). $^{13}$C-NMR: 157.75 (C(2)); 73.41 (C(5)); 62.34 ($CH_2OH$); 44.36 ($Me_2CH$); 40.62 (C(4)); 19.30, 19.07 ($Me_2CH$).

*(+)-(R,E)-N-(Benzyloxycarbonyl)-1-(isopropylamino)pent-3-en-2-ol* (**6**). To a soln. of **4** (1.44 g, 10 mmol) in $H_2O$ (8 ml) at 5°, benzyl chloroformate (1.58 g, 11 mmol) was added followed by $K_2CO_3$ (1.66 g, 12 mmol). After stirring for 4 h, the mixture was acidified and extracted with $CH_2Cl_2$ (3 × 20 ml). The combined org. layers were washed with saturated brine (10 ml), dried ($MgSO_4$), and evaporated. The crude product was chromatographed (silica gel, $Et_2O$/light petroleum ether 1:1): 2.68 g (96%). $[\alpha]_D^{20} = +13$ (*c* = 1, $CH_2Cl_2$); e.e. 96%. $^1$H-NMR (60°): 1.17 (*dd*, $Me_2CH$); 1.68 (*d*, 3 H–C(5)); 3.16 ('*dd*', *ABX*, $J_{AB} = 14.65$, $J_{AX} = 3.60$, 1 H–C(1)); 3.32 ('*dd*', *ABX*, 1 H, $J_{AB} = 14.65$, $J_{BX} = 8.22$, 1 H–C(1)); 4.18 (*m*, $Me_2CH$); 4.23 (*m*, H–C(2)); 5.15 (*s*, $PhCH_2$); 5.49 (*m*, H–C(3)); 5.71 (*m*, H–C(4)); 7.34 (*m*, Ph). $^{13}$C-NMR (60°): 157.30 (CO); 136.66 ($C_{ipso}$); 131.84 (C(4)); 128.36 (arom. C); 127.87 (arom. C); 127.75 (C(3)); 127.17 (arom. C); 72.88 (C(2)); 67.19 ($PhCH_2$); 50.17 (C(1)); 48.88 ($Me_2CH$); 20.76, 20.56 ($Me_2CH$); 17.41 (C(5)).

*(−)-(S)-3-Isopropyl-5-(prop-1-enyl)oxazolidin-2-one* ((*S*)-**5**). Compound **6** (2.68 g, 9.6 mmol) was dissolved in thionyl chloride (12 ml) at 0° and stirred for 17 h at r.t. The mixture was then poored on ice and extracted with $CH_2Cl_2$ (4 × 25 ml). The combined org. layer was dried ($MgSO_4$) and evaporated and the crude product (2.7 g)

---

[3]) DIBAL Reduction/transimination/hydride reduction was shown to proceed without racemization, see [12] [13].

chromatographed (silica gel, $Et_2O$/light petroleum ether 1:1): 0.82 g (50%) of (*S*)-**5**. Colorless oil. $[\alpha]_D^{20} = -28$ ($c = 1$, $CH_2Cl_2$); e.e. 96%. Anal. data: in complete agreement with those of (*R*)-**5**.

*(+)-(R)-5-(Hydroxymethyl)-3-isopropyloxazolidin-2-one* ((*R*)-**2**) was prepared from (*S*)-**5** by a procedure identical to the one followed for (*S*)-**2**. Anal. data: identical to those of (*S*)-**2**, with $[\alpha]_D^{20} = -53$ ($c = 1$, $CHCl_3$) for (*R*)-**2**; e.e. $\geq 99\%$ (by $^{19}F$-NMR; corrected for e.e. 98% of (+)-(*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride).

## REFERENCES

[1] S. Kano, T. Yokomatsu, H. Iwasawa, S. Shibuya, *Tetrahedron Lett.* **1987,** *28,* 6331.
[2] See, *i.a.*, K. Stoschitzky, W. Lindner, M. Rath, C. Leitner, G. Uray, G. Zernig, T. Moshammer, W. Klein, *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1989,** *339,* 474.
[3] K. Stoschitzky, G. Egginger, G. Zernig, W. Klein, W. Linder, *Chirality* **1993,** *5,* 15.
[4] R. R. Ruffolo, M. Gellai, J. P. Hieble, R. N. Willette, A. J. Nichols, *Eur. J. Clin. Pharmacol.* **1990,** *38,* S82.
[5] Y. Tsuda, K. Yoshimoto, T. Nishikawa, *Chem. Pharm. Bull.* **1981,** *29,* 3593.
[6] Y. Terao, M. Murata, K. Achiwa, T. Nishio, M. Akamtsu, M. Kamimura, *Tetrahedron Lett.* **1988,** *29,* 5173.
[7] K. Kan, A. Miyama, S. Hamaguchi, T. Ohashi, K. Watanabe, *Agric. Biol. Chem.* **1985,** *49,* 207.
[8] S. Hamaguchi, M. Asada, J. Hasegawa, K. Watanabe, *Agric. Biol. Chem.* **1984,** *48,* 2331.
[9] D. Bianchi, P. Cesti, E. Battistel, *J. Org. Chem.* **1988,** *53,* 5531.
[10] J. Brussee, W. Loos, C. G. Kruse, A. Van der Gen, *Tetrahedron* **1990,** *46,* 979.
[11] P. Zandbergen, J. Van der Linden, J. Brussee, A. Van der Gen, *Synth. Commun.* **1991,** *21,* 1387.
[12] P. Zandbergen, H. M. G. Willems, G. A. Van der Marel, J. Brussee, A. Van der Gen, *Synth. Commun.* **1992,** *22,* 2781.
[13] P. Zandbergen, A. M. C. H. Van den Nieuwendijk, J. Brussee, A. Van der Gen, C. G. Kruse, *Tetrahedron* **1992,** *48,* 3977.
[14] E. G. J. C. Warmerdam, J. Brussee, C. G. Kruse, A. Van der Gen, *Tetrahedron* **1993,** *49,* 1063.
[15] J. Brussee, A. Van der Gen, *Recl. Trav. Chim. Pays-Bas* **1991,** *110,* 25; E. F. J. De Vries, P. Steenwinkel, J. Brussee, C. G. Kruse, A. Van der Gen, *J. Org. Chem.* **1993,** *58,* 4315.