J. prakt. Chem. 336 (1994) 628–631

Journal für praktische Chemie
Chemiker-Zeitung

Studies of the Resolution of Racemates in the Synthesis of Diltiazem

Tibor Gizur and Kálmán Harsányi

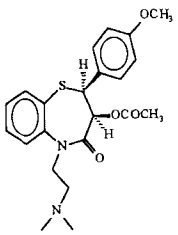
Budapest, Gedeon Richter Chemical Works, Ltd.

Elemér Fogassy

Budapest, Technical University, Department of Organic Chemical Technology

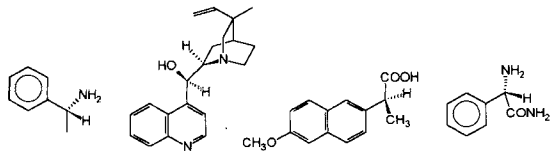
Received September 27th, 1993 respectively January 24th, 1994

Diltiazem (2S,3S)-3-acetoxy-5-(2-dimethylaminoethyl)-2,3-dihydro-2-(4-methoxyphenyl)-5H-1,5-benzothiazepin-4-one (**1**) has been developed by Tanabe Seiyaku as a cardia drug of calcium antagonist action [1]. Numerous research groups have

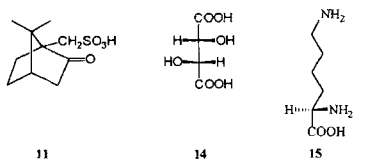


(2S,3S)-1

been working on its synthesis for years. As there are four possible stereoisomers, the needed isomer can be synthesized either by stereoselective synthesis or can be separated by chiral resolution. The aim of the present work is to explore the most economical ways of the manufacturing of **1** starting from the key intermediate (2RS,3SR)-**2** taking into consideration the elaborate resolution methods for racemic intermediates. Five synthetic routes starting from the (2RS,3SR)-**2** intermediate have been compared using the seven resolving agents **3**, **6**, **9–11** and **14–15** (Scheme 2). Among them there are widely used chiral bases and acids or novel resolving agents (e.g., **9** and **10**).



3 6 9 10



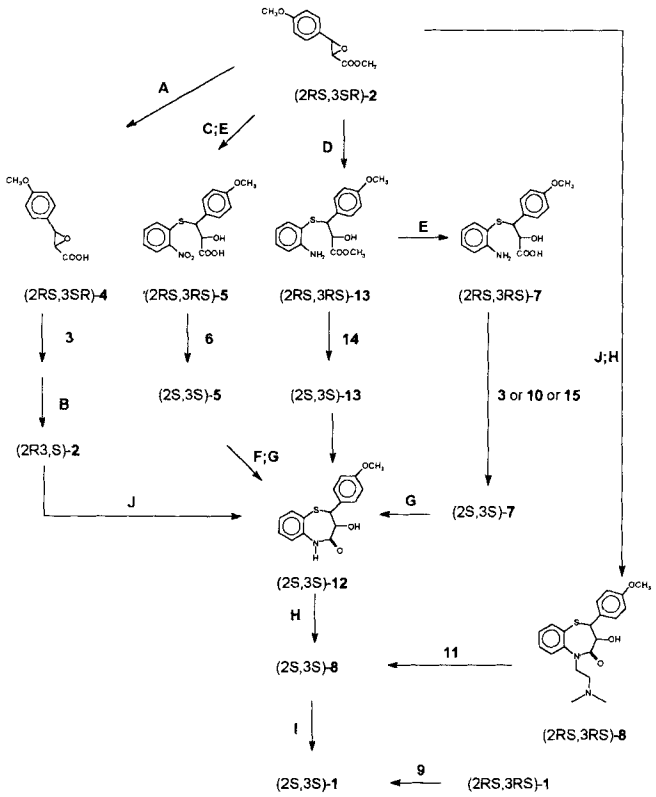
11 14 15

The chiral resolution of the free acid (2RS,3SR)-**4** prepared from (2RS,3SR)-**2** is carried out with the base S-α-methylbenzylamine S-**3** then after re-esterification it was cyclised with 2-aminothiophenol to compound (2S,3S)-**12** [2, 3, 5, 7]. The compound (2RS,3RS)-**5** obtained in the reaction of (2RS,3SR)-**2** with 2-nitrothiophenol and subsequent ester hydrolysis was resolved with cinchonidine (**6**), then cyclisation was accomplished after the reduction of the nitro group to the compound (2RS,3RS)-**12** [1]. If the compound (2RS,3SR)-**2** is reacted with 2-aminothiophenol, the obtained (2RS,3RS)-**13** was resolved with R,R-tartaric acid (**14**), then cyclised also to (2S,3S)-**12** [6]. If the ester obtained in the former reaction is hydrolysed to (2RS,3RS)-**7** the resolvation can be performed by L-lysine (**15**) [13] or with R-α-methylbenzylamine (R-**3**) in a 1:1 molar ratio [8] or in 1:0.5 molar ratio when the sodium salt of (2R,3R)-**7** remains in the solution. Instead of the above resolving agents, (–)-α-phenylglycinamide (**10**) can be also employed. The compound (2R,3R)-**7** obtained in this reaction is very appropriate for the resolution of racemic **10** [10, 11]. In the former resolution procedures the enantiomeric mixture remained in the mother liquor can be separated into excess enantiomeric and racemic mixtures by selective purification methods as, e.g., recrystallization [9] or partial precipitation [12].

In the case when the ring closure is performed with the compound (2RS,3RS)-**7** the resolution of the compound (2RS,3RS)-**8** obtained by alkylation of the lactam nitrogen can be resolved with R-camphorsulfonic acid (**11**) [1], but in very poor yield. If in the course of the synthetic route (2RS,3RS)-**1** is prepared then **11** or S-naproxene (**9**) can be advantageously employed for resolution. As naproxene can be readily reused its usage is more advantageous [14]. The side product (2R,3R)-**1** is suitable for the resolution of R,S-**9** (Scheme 3).

It is a generally employed principle that if in a synthesis racemic intermediates are formed possibly the earliest racemic product is to be resolved. This principle, of course, can be a function of the ease of resolution of the intermediates, and the success of the resolution procedures. In our case none of the intermediates can be resolved in one simple step, it requires several steps [15, 16, 17].

Among the procedures the yield of (2S,3S)-**1** related to the glycidic ester (2RS,3SR)-**2** may be the true indicator of the



A hydrolysis of glycidic ester [2, 3, 5, 7]
B esterification of glycidic acid [2, 3, 5, 7]
C reaction of glycidic ester with 2-nitrothiophenol [4]
D, J reaction of glycidic ester with 2-aminothiophenol [19]
E ester hydrolysis [1]
F reduction of nitro group [1]
G ring closure [6, 17]
H alkylation [18]
I acylation [18]

differences. The overall yields of the various synthetic paths are compiled in Table 1. If more procedures are known for the resolution of a certain compound, the best result is always taken into account.

The comparison clearly shows that the best route is when (2S,3S)-**1** is prepared by resolution of (2RS,3RS)-**1** with S-naproxene (**9**). In the data the racemisation is not taken into account. As the resolving agent in this case can be regenerated in the simplest way, we demonstrate such a case when the optimum resolution can be performed at the final stage of the synthetic route.

In the experimental part we describe our own results. The results of others are given in the references.

Experimental

*(2S,3S)-3-(2-Aminophenylthio)-2-hydroxy-3-(4-methoxyphenyl)-propionic acid (2S,3S)-***7**

Resolution with R-α-methyl-benzylamine (R-**3**)

31.9 g (0.1 mol) (2RS,3RS)-**7** was dissolved in a mixture of 100 ml of 1N sodium hydroxide solution and 190 ml of water. A solution of 7.25 g (0.06 mol) R-**3** in 60 ml of 1N HCl was added to this mixture during a period of 3 hours. Then the reaction mixture was stirred for 4 hours at 10 °C. The crystalline product was filtered off and recrystallized from boiling water. The recrystallized product was suspended in 260 ml of water and 40 ml of 1N HCl was added during 1 hour and stirred for 1 hour. The crystalline product was filtered off and dried. Yield: 11.95 g (75 %) (2S,3S)-**7** m.p.: 137–138 °C, $[\alpha]_D^{20}$ = +346° (c = 0.3, ethanol).

The filtrate of the diastereomer salt and the mother liquor of the recrystallisation were combined and acidified with 1:1 HCl to pH 3. The crystalline product was filtered off. After then it was stirred in 50 ml boiling ethanol for 5 minutes. The unsolved material was filtered off from the boiling suspension

Table 1 The yields and overall yields of the various synthetic paths

							overall yields
(2RS,3SR)-**2**	32 % → A; **3**; B	(2R,3S)-**2**	80 % → J	(2S,3S)-**12**	67 % → H; I	(2S,3S)-**1**	≈17 %
(2RS,3SR)-**2**	74 % → C; E	(2RS,3RS)-**5**	30 % → **6**	(2S,3S)-**5**	47 % → F; G; H; I	(2S,3S)-**1**	≈10 %
(2RS,3SR)-**2**	100 % → D	(2RS,3RS)-**13**	39 % → **14**	(2S,3S)-**13**	55 % → E; G; H; I	(2S,3S)-**1**	≈21 %
(2RS,3SR)-**2**	87 % → D; E	(2RS,3RS)-**7**	36 % → **3** or **10**	(2S,3S)-**7**	63 % → G; H; I	(2S,3S)-**1**	≈19 %
(2RS,3SR)-**2**	75 % → J; H	(2RS,3RS)-**8**	15 % → **11**	(2S,3S)-**8**	71 % → I	(2S,3S)-**1**	≈8 %
(2RS,3SR)-**2**	53 % → J; H; I	(2RS,3RS)-**1**	45 % → **9**	(2S,3S)-**1**			≈24 %

and was dried. This product 10.8 g [yield of (2RS,3RS)-**7** 7.9 g $[\alpha]_D^{20}$ = –60° (c = 0.2, DMF)] was resolved according to a previous experiment.

Resolution with S-α-phenylglycinamide (S-**10**)

3.19 g (0.01 mol) of (2RS,3RS)-**7** was dissolved in a mixture of 5 ml of 2N sodium hydroxide and 30 ml of water by heating. To the solution were added 40 ml of methanol and a mixture of 1.0 g (5.4 mmol) of S-**10** HCl in 10 ml of water. The solution was stirred at 10 °C for one hour. The crystalline product was filtered off and recrystallized from 85 ml of water. The (S)-**10**-(2R,3R)-**7** salt was suspended in 50 ml of water and acidified with 1N HCl to a pH 3. Then the crystalline product was stirred at 10 °C for 2 hours and filtered off. Yield: 1.1 g (68.8 %) of (2R,3R)-**7**, m.p.: 137–139 °C, $[\alpha]_D^{20}$ = –330° (c = 0.3, ethanol).

The filtrate of the diastereomer salt was acidified with 1N HCl to a pH 3. The suspension was stirred at 10 °C for one hour. After then the product was filtered off. Yield: 1.5 g (93.8 %) of (2S,3S)-**7**, $[\alpha]_D^{20}$ = +261° (c = 0.3, ethanol).

Resolution with R-α-phenylglycinamide (R-**10**)

3.7 g (0.0198 mol) of R,S-α-phenylglycinamide HCl was dissolved in 40 ml water and a solution of 3.6 g (0.0113 mol) of (2R,3R)-**7** in 22 ml of 0.5 N sodium hydroxide and 22 ml of water was added at 80–90 °C. After cooling the product was filtered off.

Yield: 5 g (94.3 %) of (S)-**10**-(2R,3R)-**7** salt, $[\alpha]_D^{20}$ = –215° (c = 0.3, water).

6.4 g (0.02 mol) of (2RS,3RS)-**7** was dissolved in a mixture of 43 ml of 0.5 N sodium hydroxide and 17 ml of water at 90 °C. Then the filtrate of the (S)-**10**-(2R,3R)-**7** salt was added. After cooling the precipitated crystalline product was filtered off. The (R)-**10**-(2S,3S)-**7** salt was dissolved in 70 ml of boiling water and was acidified with 1N HCl to pH 3. The mixture was cooled under 10 °C. The white crystalline product was filtered off. Yield: 2.1 g (65.6 %) of (2S,3S)-**7**, m.p.: 138–139 °C, $[\alpha]_D^{20}$ = +346° (c = 0.3, ethanol).

Purification of (2S,3S)-**7** ($[\alpha]_D^{20}$ > 300°)

7.8 g (0.024 mol) of (2S,3S)-**7** {$[\alpha]_D^{20}$ +314° (c = 0.3, ethanol)} was dissolved in a mixture of 70 ml of water and 24 ml of 1N sodium hydroxide at 80 °C. To a this mixture 5.6 ml of 1N HCl was added at the same temperature. After stirred for 1 hour it was cooled under 10 °C. The crystalline product was filtered off. Yield: 2.7 g (34.6 %), $[\alpha]_D^{20}$ = +259° (c = 0.3, ethanol).

The filtrate was warmed to 80 °C and 1N HCl was added to pH 3. After cooling under 10 °C it was stirred for 1 hour. The product was filtered off. Yield: 4.8 g (61.5 %) of (2S,3S)-**7**, m.p.: 138–139 °C, $[\alpha]_D^{20}$ = +347° (c = 0.3, ethanol).

(2S,3S)-3-Acetoxy-5-(2-dimethylaminoethyl)-2,3-dihydro-2-(4-methoxyphenyl)-5H-1,5-benzothiazepin-4-one [(2S,3S)-**1**]

9 g (0.02 mol) of (2RS,3RS)-**1** was dissolved in 100 ml of water and a solution of 2.4 g (0.01 mol) of (S)-**9** in 10 ml of 1N sodium hydroxide and 80 ml of methanol were added. Then the mixture was stirred for 8 hours and cooled under 10 °C. The product was filtered off and washed with 5 ml of water. Yield: 6.8 g (98.6 %) of (S-**9**)-(2R,3R)-**1** salt, m.p.: 121–122 °C, $[\alpha]_D^{20}$ = –67.8° (c = 0.3, methanol).

6.8 g previous salt was dissolved in 30 ml of chloroform and 20 ml of 1N sodium hydroxide was added. The organic layer was separated and extracted with 2×30 ml of chloroform. The combined organic layer was dried and acidified with 8 ml of ethanolic HCl. Then the solution was evaporated under reduced pressure. The residue was (2R,3R)-**1**. Yield: 4.0 g (88.9 %), m.p.: 207–209 °C, $[\alpha]_D^{20}$ = –94.7° (c = 3, methanol). The filtrate of (S)-**9**-(2R,3R)-**1** salt was evaporated and 20 ml of 1N NaOH and 30 ml of chloroform were added to the residue. Then the organic layer separated and the inorganic layer was extracted with 2×30 ml of chloroform. The combined organic layers were dried and acidified with 8 ml of ethanolic HCl. The solution was evaporated under reduced pressure. The residue product was recrystallized from ethanol (15 ml). Yield: 3.4 g (75.6 %) o (2S,3S)-**1**, m.p.: 207–209 °C, $[\alpha]_D^{20}$ = +100.9° (c = 3, methanol).

The filtrate was evaporated and 1.4 g (2RS,3RS)-**1** was obtained as residue. To the combined inorganic layers 10 ml of concentrated HCl was added. The precipitated product was filtered off and washed with 2×5 ml of water. Yield: 2.2 g (91.7 %) of (S)-**9**, m.p. 133–135 °C, $[\alpha]_D^{20}$ = +66.8° (c = 1, chloroform).

References

[1] H. Ionue, S. Takao, M. Kawazu, H. Kugita, Yakugaku Zasshi **93** (1973) 729

[2] Sawai Seiyaku Co. JP 60-13, 775; Chem. Abstr. **103** (1985) 71180q

[3] H. Masatoshi, Y. Masao, JP 61-145, 160; Chem. Abstr. **106** (1987) 32600u

[4] H. Ionue, T. Hashiyama, EP 59335; Chem. Abstr. **98** (1983) 34388w

[5] G. Rossey, I. Chekroun, A. Ugolini, A. Wick, B. Gerin, A. Bourbon, J. B. Graux, EP 378455; Chem. Abstr. **114** (1991) 81901s

[6] D. Tentorio, EP 392543; Chem. Abstr. **14** (1991) 122436q

[7] H. Wynberg, W. Ten Hoere, EP 342903; Chem. Abstr. **113** (1990) 131978z

[8] S. Nagao, JP 57-136, 581; Chem. Abstr. **98** (1983) 89404

[9] T. Gizur, I. Szabadkai, J. Felméri, B. Benke, P. Horváth, J. Aracs, K. Harsányi, K. Berki, Zs. Bertha Somodi, HU 193230; Chem. Abstr. **107** (1987) 58653j

[10] E. Fogassy, M. Ács, T. Gizur, K. Harsányi, J. Aracs, K. Berki, L. Töke, Zs. Jászay, HU 205896; Chem. Abstr. **115** (1991) 28893k

[11] E. Fogassy, M. Ács, T. Gizur, K. Harsányi, J. Aracs, K. Berki, L. Töke, Zs. Jászay, HU 204774; Chem. Abstr. **115** (1991) 28893k

[12] E. Fogassy, M. Ács, T. Gizur, K. Harsányi, J. Aracs, K. Berki, L. Töke, Zs. Jászay, HU 204782; Chem. Abstr. **115** (1991) 182840x

[13] E. Manghisi, G. Cascio, DE 3,337,176; Chem. Abstr. **101** (1984) 110549x

[14] E. Fogassy, M. Ács, T. Gizur, K. Harsányi, J. Aracs, K. Berki, L. Töke, Zs. Jászay, HU 208684

[15] C. Ionue, JP 60-25,982; Chem. Abstr. **103** (1985) 87918x C. Ionue, JP 60-25,983; Chem. Abstr. **103** (1985) 142030d

[16] C. Giordano, R. Casagrande, DE 4,038,676; Chem. Abstr. **115** (1991) 159190b
[17] H. Hironori, N. Shigeru, O. Tamotsu, K. Masashi, M. Sadao, EP 395323; Chem. Abstr. **114** (1991) 122432k
[18] G. Mitsunori, I. Ikou, N. Shigeru, I. Kuichiro, F. Tokuo, EP 81234; Chem. Abstr. **99** (1983) 175819v
[19] A. Bousquet, B. Charpiot, A. Heymes, EP 381570; Chem. Abstr. **114** (1991) 102070u

Address for correspondence:
Dr. T. Gizur
Gedeon Richter Chemical Works, Ltd.
H-1475, Budapest, Hungary
P.O.B. 27