Stereoselective Synthesis of Diltiazem via Dynamic Kinetic Resolution

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Abstract: An efficient synthesis of diltiazem has been developed using dynamic kinetic resolution (DKR) as a key step. The methyl (2*S*,3*S*)-2-chloro-3-hydroxy-3-(4-methoxyphenyl)propionate was synthesized from a racemic mixture of α-chloro-β-keto ester, with high *anti* diastereoselectivity (92%) and enantioselectivity (95%), based on an asymmetric hydrogenation reaction with a chiral ruthenium(II) catalyst, simply prepared by mixing Ru(cod)(2-methylallyl)$_2$ with the atropisomeric ligand (*S*)-MeO-BIPHEP. By treatment of this α-chloro-β-hydroxy ester with a base, the corresponding *trans* methyl glycidate, a key intermediate of diltiazem, was easily obtained.

Key words: Diltiazem, drugs, kinetic resolution, asymmetric catalysis, hydrogenations, ruthenium

Diltiazem (**1**), a typical calcium channel blocker, is commonly used for the treatment of angina pectoris and hypertension.[3] Only the (+)-(2*S*,3*S*)-isomer among the four possible stereoisomers presents this potent coronary vasodilating activity, therefore diltiazem has been developed and marketed as a single stereoisomer. For its synthesis, many pathways had been investigated and the *trans* methyl (2*R*,3*S*)-3-(4-methoxyphenyl)glycidate (–)-**2** was recognized as a practical and efficient intermediate (Figure 1). A large number of formal synthesis of (–)-**2** have been reported using various strategies including asymmetric epoxidations,[4] aldol[5] or Darzens[6] reactions, asymmetric reductions,[7] preferential crystallizations[8] or enzymatic approaches.[9] At the industrial scale, (–)-**2** has been prepared by enzymatic resolution of the racemic glycidate (±)-**2** based on a lipase-catalyzed enantioselective hydrolysis;[9c] however the maximum yield cannot exceed 50%. In spite of all these studies, there is still a need for developing an efficient process for the synthesis of enantiopure (–)-**2** in terms of yield, stereoselectivity and amount of chiral material at stake in the key step.

In our continuous work on ruthenium-catalyzed asymmetric hydrogenation,[10] and its applications to the synthesis of biologically and industrially relevant molecules,[11] we report in this paper an asymmetric synthesis of diltiazem (**1**) based on the dynamic kinetic resolution of a racemic α-chloro-β-keto ester. The asymmetric hydrogenation of α-substituted β-keto ester bearing a configurationally labile stereogenic center with chiral Ru(II) catalysts is known to give preferentially one of the four possible diastereoisomers via dynamic kinetic resolution (DKR),[12] under optimized conditions. The selectivity of this DKR has already been studied by Noyori and our group and depends on the nature of the group borne at the α-position and on the reaction conditions. Whereas the hydrogenation of α-acetamido-β-keto esters[13] gave the *syn* adducts, cyclic α-alkyl-β-keto esters[14,12a,b] or γ-amino-α-methyl-β-keto esters derived from (*S*)-proline[15] were reduced to the corresponding *anti* α-substituted β-hydroxy esters. Some preliminary studies on the asymmetric hydrogenation of α-chloro-β-keto esters[16a] indicated that the *anti* diastereoisomer could also be obtained.[16b]

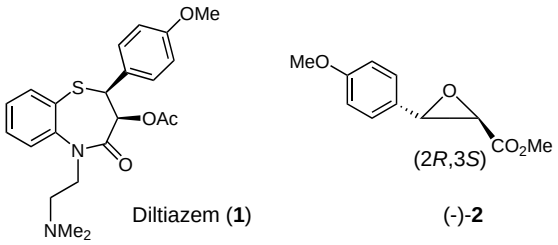
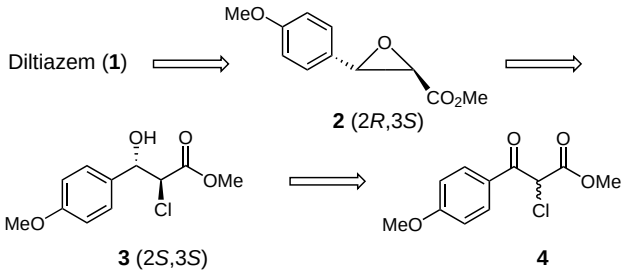


Figure 1

Therefore, the retrosynthetic plan (Scheme 1) we chose for diltiazem (**1**) was designed as follows: diltiazem (**1**) would be synthesized from the *trans* methyl glycidate (–)-**2**, which would result from the cyclization of the chlorohydroxy ester **3**. The *anti* (2*S*,3*S*)-α-chloro-β-hydroxy ester **3** would be preferentially formed by hydrogenation of the corresponding racemic α-chloro-β-keto ester **4** using Ru(II) catalyst in association with the atropisomeric (*S*)-MeO-BIPHEP as a ligand.[17]

Synthesis of the substrate **4** was achieved in two steps and 81% yield as depicted in Scheme 2. The β-keto ester **5**



Scheme 1 Retrosynthetic approach of diltiazem (1)

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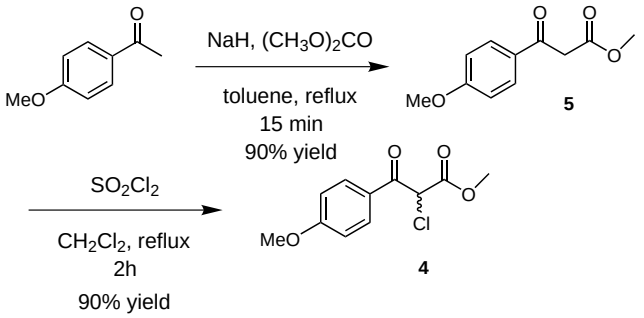
was readily prepared from commercially available 4-methoxyacetophenone in the presence of sodium hydride and dimethyl carbonate. After purification, treatment of **5** with sulfuryl chloride afforded **4** in 90% yield.

One preliminary example[16b] to hydrogenate **4**, using (*S*)-BINAP as a chiral ligand, indicated that this substrate required rather high pressures of hydrogen (80 bar) and high temperatures (80 °C) to obtain good conversions in dichloromethane. Moreover, the in situ generated chiral catalyst[18] developed in our group 'Ru[(*S*)-MeO-BIPHEP]Br_2' turned out to be inadequate for the hydrogenation of this α-chloro-β-keto ester since a large amount of degradation products was isolated, such as the β-keto ester **5**. We found that by simply mixing Ru(cod)(2-methylallyl)$_2$ and (*S*)-MeO-BIPHEP, the hydrogenation of **4** proceeded smoothly.



Scheme 2 Synthesis of the hydrogenation substrate **4**

First, we decided to investigate the effect of the solvent on the reaction. A *syn* diastereoselectivity was observed for almost all the solvents we considered, except when the hydrogenation was carried out in THF or dichloromethane (Table 1).

However the *syn* diastereoselectivity observed was poor, except in methanol; but in that case, the enantioselectivity was surprisingly below 10%. Dichloromethane turned out to be the most appropriate solvent giving access to the α-chloro-β-hydroxy ester **3** with high *anti* diastereoselectivity and enantioselectivity, since the first attempts carried out in THF gave rather moderate ee.

Table 1 Screening of Solvents for the Hydrogenation of **4**[a]

Solvent	Conv (%)[b]	de (%)[c]	ee (*syn*)[c] (2*R*,3*S*)	ee (*anti*)[c] (2*S*,3*S*)
Toluene	60	73 *syn*	98	74
t-Bu-OMe	40	42 *syn*	99	71
EtOAc	45	40 *syn*	99	79
MeOH	80	88 *syn*	9	96
THF[d]	95	85 *anti*	98	65
CH_2Cl_2	80	88 *anti*	38	95

[a] All reactions were carried out at 80 °C under 80 bar (H_2) and for 16 h with 1 mol% of catalyst.
[b] Conversion (Conv) was determined by ^{1}H NMR.
[c] De and ee were determined by HPLC analysis.
[d] Reaction carried out for 60 h.

Next, we tried to optimize this hydrogenation reaction in dichloromethane, at the scale of several grams. To prevent the formation of degradation products and slow down the reaction rate in order to favor a better discrimination of the catalyst, we chose to drop the hydrogen pressure to 60 bar. The diastereoselectivity rose then from moderate levels (72%) to very good ones (> 90%). It appeared also important to conduct the reaction at low concentration (*c* 0.5 mol/L) to keep a good *anti* diastereoselectivity. Eventually, with 0.5 mol% of catalyst (in order to decrease the reaction rate) and a controlled reaction time, we found a compromise between stereoselectivity, conversion and yield (Table 2). Several grams of *anti* (2*S*,3*S*)-α-chloro-β-hydroxy ester **3** were then prepared by ruthenium-catalyzed hydrogenation of racemic **4** via DKR with excellent diastereoselectivity (92% which could be raised up to 98% by purification with MPLC, cyclohexane–EtOAc, 9:1) and enantioselectivity (95%).

Table 2 Optimization of the Asymmetric Hydrogenation of **4** in Dichloromethane

S/C	P (H_2)	Temp (°C)	Time (h)	Conv (%)[b] (Yield, %)	de (%)[c] *anti*	ee (%)[c] (2*S*,3*S*)
100[a]	80	80	25	90 (63)	71	93
100	60	80	21	75 (43)	95	94
200	60	80	21	55 (51)	92	95
200	60	80	26	68 (55)[e]	92	95

[a] *c* 0.7 mol/L, otherwise *c* 0.5 mol/L.
[b] Conversion was determined by ^{1}H NMR.
[c] De and ee were determined by HPLC analysis.
[d] Reactions were all conducted on multigram-scale (1 to 5 grams).
[e] 32% of the racemic starting material was recovered and reloaded in the Ru-promoted hydrogenation reaction.

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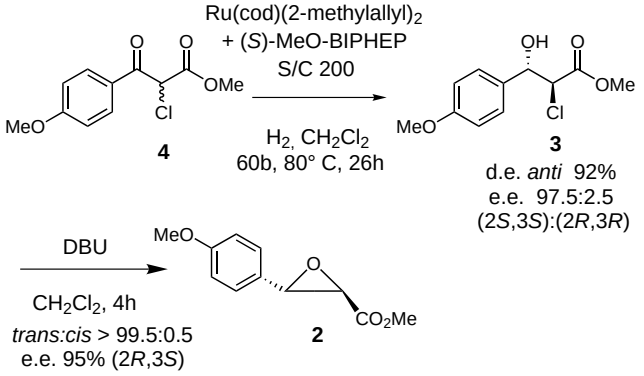
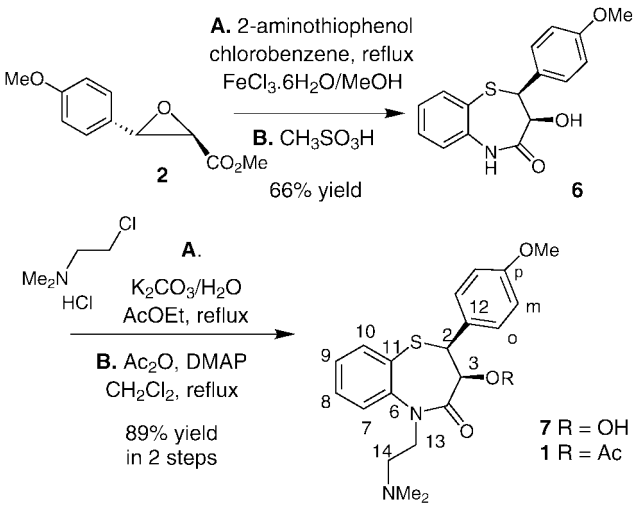
The *trans* methyl glycidate (–)-**2** was easily obtained by treatment of **3** with DBU (1,8-diazabicyclo[5,4,0]undec-7-ene) in 98% yield. The *trans–cis* ratio of (–)-**2** was determined by HPLC analysis (Chiralcel OD-H; hexane–2-propanol, 98:2, 0.5 mL/min; *trans–cis* >99.5:0.5, ee 2*R*,3*S* 95%) (Scheme 3).



Scheme 3 Synthesis of *trans* methyl (2*R*,3*S*)-3-(4-methoxyphenyl)glycidate (**2**) via DKR of racemic **4**

The synthesis of diltiazem (**1**) was achieved in three subsequent steps according to known procedures (Scheme 4).[8b,6a] First, ring-opening of **2** with 2-aminothiophenol and in situ condensation on the methyl ester afforded the benzothiazepinone **6** in 66% yield, whose characteristics were consistent with literature data {^{1}H NMR, $[\alpha]_D^{20}$ +100 (*c* 0.5 DMF) compared to $[\alpha]_D^{20}$ +109 (*c* 0.5 DMF)[8b]}. Then, alkylation of the amine function with 2-(dimethylamino)ethyl chloride hydrochloride led to the *N*-alkylbenzothiazepinone **7** in 89% isolated yield. Finally, diltiazem (**1**) was isolated as a white solid after acetylation of the alcohol function in 90% yield. The spectroscopic properties of (**1**) were similar to those described earlier.[6a]



Scheme 4 Synthesis of diltiazem (**1**) from pure *trans* methyl glycidate (–)-**2**

In summary, we have reported a practical total synthesis of diltiazem in 7 steps with an overall yield of 25% from commercially 4-methoxyacetophenone. This convenient synthetic procedure involved the ruthenium-promoted hydrogenation reaction of a α-chloro-β-keto ester into an *anti* α-chloro-β-hydroxy ester via dynamic kinetic resolution. High levels of enantio- and diastereoselectivity were obtained due to the excellent discrimination of the catalytic ruthenium(II) system, simply formed by mixing Ru(cod)(2-methylallyl)$_2$ and (*S*)-MeO-BIPHEP. This reaction is easy to perform on large scale with high substrate/catalyst ratio and represents thus a highly convenient synthesis of diltiazem.

CH_2Cl_2 and toluene were distilled from calcium hydride. Other solvents were used without any purification. Chemical shifts (δ) are reported in ppm downfield relative to internal TMS. Coupling constants (*J*) are reported in Hz and refer to apparent peak multiplicities (recorded as s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; and br, broad). All reactions were carried out under an atmosphere of argon unless otherwise noted.

Methyl 3-(4-Methoxyphenyl)-3-oxopropionate (5)

In a three-necked flask equipped with an argon inlet and a condenser were placed sodium hydride (165 mmol, 2.5 equiv, 6.41 g) (60% in oil, washed twice with anhyd hexane before use), dimethyl carbonate (165 mmol, 2.5 equiv, 13.8 mL) and anhyd toluene (20 mL). The mixture was stirred at reflux and a solution of 4-methoxyacetophenone (66 mmol, 9.9 g) in anhyd toluene (30 mL) was added dropwise. After 15 min at reflux, the reaction was cooled down and a solution of HOAc (5 mL) in H_2O (20 mL) was added. The organic layer was separated and the aq layer was extracted with Et_2O (2 ×). The combined organic layers were washed with sat. aq K_2CO_3, dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow oil. The residue was purified by silica gel column chromatography (cyclohexane–EtOAc, 8:2) to give the β-keto ester **5** (12.3 g, 90% yield).

Pale yellow oil; mp <50 °C.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.93 (d, 2 H, *J* = 8.9 Hz, H_o), 6.94 (d, 2 H, *J* = 8.9 Hz, H_m), 3.95 (s, 2 H, CH_2), 3.86 (s, 3 H, $PhOCH_3$), 3.74 (s, 3 H, CO_2CH_3).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 190.7 (CO ketone), 168.1 (CO_2CH_3), 163.9 (C_p-OMe), 130.8 (C_o), 128.9 ($C_{Ar}CO$), 113.9 (C_m), 55.4 ($PhOCH_3$), 52.3 (CO_2CH_3), 45.4 (CH_2).

MS (DCI, NH_3): *m*/*z* = 226 (6%, $[M + NH_4]^+$), 209 (100%, $[M + H]^+$).

HRMS (DCI^+): *m*/*z* calcd for $C_{11}H_{13}O_4$: 209.0814; found: 209.0816.

Methyl 2-Chloro-3-(4-methoxyphenyl)-3-oxopropionate (4)

A mixture of **5** (59 mmol, 12.3 g), anhyd CH_2Cl_2 (120 mL) and sulfuryl chloride (59 mmol, 1 equiv, 4.8 mL) was stirred for 15 min at r.t. then heated at reflux until the formation of gas stopped. The reaction was then cooled down and the solvent evaporated. The residual oil was purified by silica gel column chromatography (cyclohexane–EtOAc, 8:2) give the α-chloro-β-keto ester **4**.

Yield: 12.9 g (90% yield); white solid; mp < 50 °C.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.99 (dd, 2 H, *J* = 2.0, 8.9 Hz, H_o), 6.95 (dd, 2 H, *J* = 2.0, 8.9 Hz, H_m), 5.60 (s, 1 H, CHCl), 3.89 (s, 3 H, $PhOCH_3$), 3.82 (s, 3 H, CO_2CH_3).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 186.5 (CO ketone), 165.9 (CO_2CH_3), 164.5 (C_p-OMe), 131.7 (C_o), 126.0 ($C_{Ar}CO$), 114.1 (C_m), 57.5 (CHCl), 55.5 ($PhOCH_3$), 53.6 (CO_2CH_3).

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MS (DCI, NH_3): *m*/*z* = 260 (100%, $[M + NH_4]^+$), 243 (17%, $[M + H]^+$).

HRMS (DCI^+): *m*/*z* calcd for $C_{11}H_{12}O_4Cl$: 243.0424; found: 243.0427.

Methyl (2*S*,3*S*)-2-Chloro-3-hydroxy-3-(4-methoxyphenyl)propionate (3)

In a 100-mL flask were placed $Ru(cod)[\eta^3\text{-}(CH_2)_2CHCH_3]_2$ (0.1 mmol, 31.9 mg, 0.5 mol%), (*S*)-MeO-BIPHEP (0.11 mmol, 64.1 mg, 0.55 mol%) and methyl 2-chloro-3-(4-methoxyphenyl)-3-oxopropionate (**4**) (20 mmol, 4.85 g) and the vessel was purged by one vacuum-argon cycle. Anhyd CH_2Cl_2 (40 mL) previously degassed by three vacuum-argon cycles was added at r.t. The flask was then placed under argon in a 250-mL stainless steel autoclave. The argon atmosphere was replaced with hydrogen by three cycles of pressurizing and the pressure was adjusted to 60 bar. The autoclave was heated at 80 °C and stirring was maintained for 26 h. After cooling, the reaction mixture was concentrated under reduced pressure. ^1H NMR analysis revealed a conversion of 68%. The residue was purified by silica gel column chromatography (cyclohexane–EtOAc, 8:2) to afford the α-chloro-β-hydroxy ester **3**.

Yield: 2.69 g (55% yield); white solid; 92% de and 95% ee; the diastereoisomeric and enantiomeric excess were determined by HPLC analysis (Chiralcel OJ, hexane–2-propanol, 70:30, 1 mL/min; detector 254 nm, 30 °C; t_R 12.4 and 13.4 min for 2*R*,3*R* and 2*S*,3*S*, respectively, and t_R 16.5 and 20.5 min for 2*R*,3*S* and 2*S*,3*R*, respectively); $[\alpha]_D^{20}$ +36 (*c* 0.94, $CHCl_3$); mp 83–85 °C.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.31 (dd, 2 H, *J* = 2.1, 6.7 Hz, H_o), 6.90 (dd, 2 H, *J* = 2.1, 6.7 Hz, H_m), 4.99 (dd, 1 H, *J* = 4.7, 8.0 Hz, C*H*OH), 4.36 (d, 1 H, *J* = 8.0 Hz, CHCl), 3.81 (s, 6 H, PhOCH_3, CO_2CH_3), 2.87 (d, 1 H, *J* = 4.7 Hz, OH).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 169.3 (*C*O_2CH_3), 159.8 (C_p-OMe), 130.7 (C_{Ar}-CHOH), 128.0 (C_o), 113.8 (C_m), 74.8 (CHOH), 59.0 (CHCl), 55.2 (PhO*C*H_3), 52.9 (CO_2*C*H_3).

MS (DCI, NH_3): *m*/*z* 262 (100%, $[M + NH_4]^+$), 244 (37%, $[M + NH_4 - H_2O]^+$), 227 (16%, $[M + H - H_2O]^+$).

HRMS (DCI^+): *m*/*z* calcd for $C_{11}H_{17}O_4NCl$ ($[M + NH_4]^+$): 262.0846; found: 262.0838.

HRMS (DCI^+): *m*/*z* calcd for $C_{11}H_{15}O_3NCl$ ($[M + NH_4 - H_2O]^+$): 244.0740; found: 244.0748.

Methyl *trans*-(2*R*,3*S*)-3-(4-methoxyphenyl)glycidate (2)

DBU (13 mmol, 1.3 equiv, 1.96 mL) was added to a stirred solution of α-chloro-β-hydroxy ester **3** (10 mmol, 2.45 g) in anhyd CH_2Cl_2 (40 mL). After being stirred for 4 hours at r.t., the reaction was quenched with a buffer solution (pH 7). The organic layer was separated and the aq layer was extracted with CH_2Cl_2 (2 ×). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give the crude glycidate **2**. The residue was purified by silica gel column chromatography (cyclohexane–EtOAc, 6:4) to afford (2*R*,3*S*)-**2**.

Yield: 1.98 g (95%); colorless amorphous crystals; 95% ee as determined by HPLC analysis (Chiralcel OD-H, hexane–2-propanol, 98:02, 0.5 mL/min; detector 254 nm, 30 °C, t_R 27.3 min and 37.2 min for 2*R*,3*S* and 2*S*,3*R*, respectively); $[\alpha]_D^{26}$ –196 (*c* 1.0, MeOH); mp 86–88 °C.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.21 (d, 2 H, *J* = 8.7 Hz, H_o), 6.89 (d, 2 H, *J* = 8.7 Hz, H_m), 4.05 (d, 1 H, *J* = 1.5 Hz, ArC*H*O), 3.82 (s, 3 H, PhOCH_3), 3.81 (s, 3 H, CO_2CH_3), 3.51 (d, 1 H, *J* = 1.5 Hz, C*H*CO_2Me).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 168.6 (*C*O_2CH_3), 160.1 (C_p-OMe), 127.1 (C_o), 126.6 (C_{Ar}-CHO), 113.9 (C_m), 57.7 and 56.3 (CHO), 55.1 (PhO*C*H_3), 52.3 (CO_2*C*H_3).

MS (DCI, NH_3): *m*/*z* = 226 (100%, $[M + NH_4]^+$), 209 (65%, $[M + H]^+$).

HRMS (DCI^+): *m*/*z* calcd for $C_{11}H_{13}O_4$: 209.0814; found: 209.0817.

***cis*-(+)-2,3-Dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one (6)**

A solution of *trans* methyl glycidate **2** (9 mmol, 1.87 g) in chlorobenzene (45 mL) was heated at reflux. 2-Aminothiophenol (9.9 mmol, 1.1 equiv, 1.07 mL) and a solution of $FeCl_3 \cdot 6\ H_2O$ (9.10^{-4} mmol, 10^{-4} equiv, 0.24 mg) in MeOH (90 μL) were added and the resulting mixture stirred at reflux for 30 min. Methanesulfonic acid (0.18 mmol, 0.02 equiv, 11.7 μL) was then added and the reflux maintained for an additional 2 h. After cooling down the reaction, the solvent was concentrated under reduced pressure to give the crude benzothiazepinone **6** as a yellow powder. The residue was purified by silica gel column chromatography (cyclohexane–EtOAc, 8:2) to afford *cis*-(+)-**6**.

Yield: 1.79 g (66%); white powder; $[\alpha]_D^{20}$ +100 (*c* 0.53, DMF); mp 204–206 °C.

^1H NMR (DMSO, 400 MHz): δ = 10.29 (s, 1 H, N*H*), 7.59 (dd, 1 H, *J* = 1.3, 7.4 Hz, H10), 7.43 (dd, 1 H, *J* = 1.3, 7.4 Hz, H8), 7.38 (d, 2 H, *J* = 8.6 Hz, H_o), 7.16 (m, 2 H, H9, H7), 6.88 (d, 2 H, *J* = 8.6 Hz, H_m), 5.04 (d, 1 H, *J* = 6.6 Hz, SCH), 4.74 (m, 1 H, OH), 4.28 (t, 1 H, *J* = 6.6 Hz, C*H*OH), 3.74 (s, 3 H, PhOCH_3).

^{13}C NMR (DMSO, 50 MHz): δ = 172.6 (CO), 159.2 (C_p-OMe), 142.1 (C6), 134.0 (C10), 131.1 (C_o), 130.1 (C8), 128.6 (C12), 126.4 (C11), 125.7 (C9), 122.8 (C7), 113.5 (C_m), 69.7 (C3), 57.2 (C2), 55.3 (PhO*C*H_3).

MS (DCI, NH_3): *m*/*z* = 319 (100%, $[M + NH_4]^+$), 302 (23%, $[M + H]^+$).

HRMS (DCI^+) *m*/*z* calcd for $C_{16}H_{16}O_3N$: 302.0851; found: 302.0849.

***cis*-(+)-5-[2-(Dimethylamino)ethyl]-2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one (7)**

To a solution of benzothiazepinone **6** (5 mmol, 1.5 g) in EtOAc (15 mL) was added 2-(dimethylamino)ethyl chloride hydrochloride (6.4 mmol, 1.28 equiv, 922 mg). Under vigorous stirring were then added potassium carbonate (20 mmol, 4 equiv, 2.76 g) and H_2O (50 μL). The resulting mixture was heated at reflux for 7 h. After cooling, the mixture was filtered to remove salts and the solvent was concentrated under reduced pressure to give the crude benzothiazepinone **7**. The residue was purified by silica gel column chromatography (CH_2Cl_2–MeOH, 98:2) to afford *cis*-(+)-**7**.

Yield: 1.65 g (89%); white powder; $[\alpha]_D^{20}$ +147 (*c* 1.0, $CHCl_3$).

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.70 (dd, 1 H, *J* = 1.4, 7.7 Hz, H10), 7.39–7.46 (m, 4 H, H_o, H8, H9), 7.26 (m, 1 H, H7), 6.88 (dd, 2 H, *J* = 1.4, 8.6 Hz, H_m), 4.90 (d, 1 H, *J* = 7.3 Hz, SCH), 4.48 (m, 1 H, NCH_2), 4.30 (br dd, 1 H, *J* = 7.3, 9.9 Hz, C*H*OH), 3.82 (s, 3 H, PhOCH_3), 3.71 (m, 1 H, NCH_2), 2.85 (d, 1 H, *J* = 9.9 Hz, OH), 2.70 (m, 1 H, NCH_2), 2.48 (m, 1 H, NCH_2), 2.28 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 171.0 (CO), 159.5 (C_p-OMe), 144.7 (C6), 135.3 (C10), 131.3 (C_o), 130.5 (C8), 129.7 (C12), 127.5 (C9), 126.8 (C11), 124.5 (C7), 113.6 (C_m), 69.2 (C3), 56.7 (C14), 56.5 (C2), 55.2 (PhO*C*H_3), 47.6 (C13), 45.6 [$N(CH_3)_2$].

MS (DCI, NH_3): *m*/*z* = 373 (100%, $[M + H]^+$).

HRMS (DCI^+): *m*/*z* calcd for $C_{20}H_{25}O_3N_2S$: 373.1586; found: 373.1584.

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***cis*-(+)-3-Acetyloxy-5-[2-(dimethylamino)ethyl]-2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one (1)**

A mixture of benzothiazepinone **7** (4.45 mmol, 1.65 g), DMAP (0.22 mmol, 0.05 equiv, 27 mg) and Ac_2O (7.6 mmol, 1.7 equiv, 710 μL) in CH_2Cl_2 (25 mL) was heated at reflux for 5 h. After cooling, the reaction mixture was poured into iced H_2O (40 mL) and brine was added. The organic layer was separated and the aq layer was extracted with CH_2Cl_2 (2 ×). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to give the crude diltiazem (**1**). This latter was purified by silica gel column chromatography (EtOAc–MeOH, 1:1) to afford pure **1**.

Yield: 1.65 g (90%); white powder; $[\alpha]_D^{20}$ +112 (*c* 0.56, $CHCl_3$); mp 97–99 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.71 (dd, 1 H, *J* = 1.5, 7.7 Hz, H10), 7.51 (m, 2 H, H8, H9), 7.38 (d, 2 H, *J* = 8.6 Hz, H_o), 7.31 (m, 1 H, H7), 6.90 (d, 2 H, *J* = 8.6 Hz, H_m), 5.13 (d, 1 H, *J* = 7.7 Hz, SCH), 5.02 (d, 1 H, *J* = 7.7 Hz, C*H*OAc), 4.56 (m, 1 H, NCH_2), 4.27 (m, 1 H, NCH_2), 3.82 (s, 3 H, PhOCH_3), 3.32 (m, 1 H, NCH_2), 3.15 (m, 1 H, NCH_2), 2.32 [s, 6 H, N(CH_3)$_2$], 1,90 (s, 3 H, OCOCH_3).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 175.5 (NCO), 169.9 (O*C*OMe), 159.7 (C_p-OMe), 145.3 (C6), 135.4 (C10), 131.1 (C8), 130.7 (C_o), 128.4 (C12), 127.5 (C9), 126.5 (C11), 124.5 (C7), 113.7 (C_m), 71.1(C3), 55.7 (C14), 55.2 (PhO*C*H$_3$), 54.4 (C2), 47.1 (C13), 44.7 [N(CH$_3$)$_2$], 20.5 (OCO*C*H$_3$).

MS (DCI, NH_3): *m*/*z* = 415 (100%, $[M + H]^+$).

HRMS (DCI^+): *m*/*z* calcd for $C_{22}H_{24}O_4N_2S$: 415.1692; found: 415.1690.

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