107. Chiral 1,4-Benzodiazepin-2-one, Template for Enantioselective Synthesis of α-Amino Acids and their α-Deuterio Congeners

Preliminary communication

by **Enio Decorte, Roberto Toso, Alessandro Sega, Vitomir Šunjić**[1])
CRC, Chemical Research Company, 33048 San Giovanni al Natisone (UD), Italy

and **Živa Ružić-Toroš, Biserka Kojić-Prodić**
'Rudjer Bošković' Institute, P.O. Box 1016, 4100 Zagreb, Croatia, Yugoslavia

and **Nevenka Bresciani-Pahor, Giorgio Nardin** and **Lucio Randaccio**
Istituto di Chimica, Università degli studi di Trieste, 34127 Trieste, Italy

(21.IV.81)

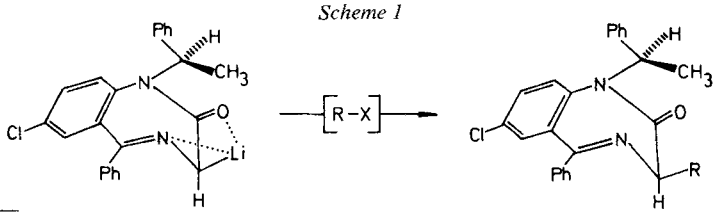
Summary

Absolute conformation of 7-chloro-5-phenyl-1-[(*S*)-α-phenylethyl]-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one (**1c**) in crystal, and its inversion rate in solution were determined, enabling prognosis of direction of asymmetric induction during C(3)-alkylation.

Alkylation of carbanions in the conformationally rigid chelates of the chiral molecules represents one of the most explored asymmetric syntheses. *Meyers* [1], *Yamada* [2] [3], and *Enders* [4] [5] amply demonstrated that lithium chelates of the chiral molecules gave high asymmetric induction. Tetrahedral oxygen within a methoxy group is a particularly effective coordinating site for lithium ions [1] though in some cases electron-rich N- [2] [3] and O-atom in amides [6] exhibit chelating abilities as well.

We anticipated that the amidic O-atom on C(2), and the N(4)-atom of 1,4-benzodiazepin-2-ones (**1a-1c**) may provide coordination sites for lithium (or potassium) ions. Another aspect of this rationale was the boat conformation, repeatedly established for these compounds in crystal [7], as well as in solution [8]

Scheme 1



[1]) Author to whom correspondence should be addressed.

0018-019X/81/4/1145-05$01.00/0

[9]. Their carbanions should be alkylated from the quasi-equatorial direction, proceeded by realignment and displacement of metal halides [10] *(Scheme 1)*. In view of these facts we initiated the study of asymmetric induction with chiral benzodiazepine **1c**, recently prepared in the course of another program [11].

Absolute configuration at the induced chiral centre C(3) in **1c** will be dictated by the *absolute conformation* of the 7-membered ring. The latter should in turn be predetermined by the absolute configuration of the incorporated α-phenylethyl moiety (*S* in **1c**). X-ray crystal structure determination of **1c** revealed a *P*-absolute conformation[2]) of the 7-membered ring appearing in boat form *(Fig.)*. The values of torsion angles: C(10)–N(1)–C(2)–C(3) −12.9(6)°, N(1)–C(2)–C(3)–N(4) [−68.4(5)°], C(2)–C(3)–N(4)–C(5) [74.6(5)°], C(3)–N(4)–C(5)–C(11) [2.9(6)°], N(4)–C(5)–C(11)–C(10) [−48.4(6)°], and displacements of C(3) (−0.763 Å), C(10) (−0.841 Å), C(11) (−0.859 Å) from the best least-squares plane defined by the N(1)-, C(2)-, N(4)- and C(5)-atoms are evidence for this conformation.

Since only weak *van der Waals* forces are expected to be the dominant interections the conformation of **1c** should be maintained in the solution, as confirmed by polarimetric determination of the temperature-dependent ring-inversion ($P \rightleftharpoons M$) rates *(Table 1)*.

^{1}H-NMR. spectroscopy revealed that equilibrium ratio *P*/*M* for **1c** at 35° in $CDCl_3$ is 55:45, *i.e.* that *P*-conformer remains as the more stable one in solution.

The first series of alkylations (*Table 2* and *Scheme 2*) afforded prevalently (3*R*)-diastereomers, as expected for quasi-equatorial attack on the *P*-conformer of **1c**.

Configuration at the induced chiral centre in compounds **2d**–**2f** was easily deduced by comparison of CD.-spectra of (+)-**2d** (minor diastereomer) with (+)-**2b**, the latter compound being prepared from (*S*)-alanine[3]). Both compounds

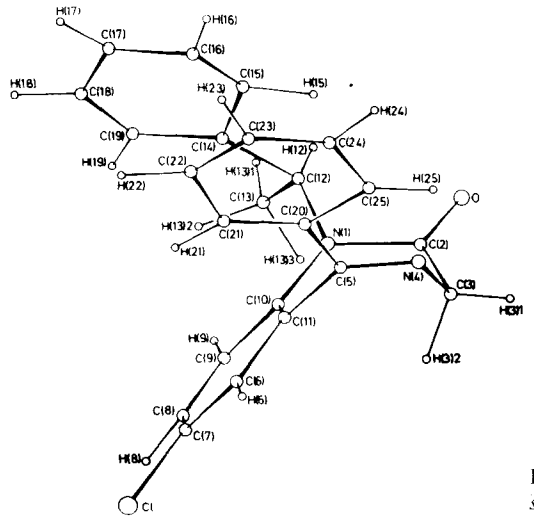


Figure. *Projection of the molecule of* **1c** *showing* P *boat conformation*

[2]) For the nomenclature see *Figure 1* in [12].

[3]) For preparation of (+)-**2b** (7-chloro-1,3-dimethyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one) see [14]. All new compounds exhibited expected analytical- (C,H,N) and spectral (IR., NMR.) data.

Table 1. *Ring inversion rates for* **1c** (in $CHCl_3$)

Entry	Temp. (°C) (±0.1°)	$k_{inv.} \times 10^3/s$[a])	Entry	Temp. (°C) (±0.1°)	$k_{inv.} \times 10^3/s$
1	10	1.17±0.02	5	30	12.51±0.20
2	15	2.16±0.04	6	35	16.51±0.20
3	20	4.06±0.14	7	40	24.03±0.39
4	25	7.44±0.09			
	$\Delta G^{\neq} = 14.35 \pm 0.93$[b]) kcal/mol		$\Delta S^{\neq} = 7.27 \pm 2.99$ e.u.		

[a]) Each value is the average of two polarimetric measurements.

[b]) This value reveals that the corresponding one for **1a** (7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one) is also high (17.6 kcal/mol, determined by *Linscheid et al.* using a less accurate ^{2}H-NMR. method [13]).

Table 2. *Alkylation of* **1c**

Entry	R-X	Reaction conditions	Product	Diastereomeric excess (%)[a])	Yield (%)	Configuration at C(3) of the prevalent diastereomer
1	Me-I	*t*-BuOK/THF/–10°	**2d**[b])	(31)	69.2	*R*
2	Me-I	*t*-BuOK/THF–65°	**2d**	(30)	80.1	*R*
3	Me-I	LDA/THF/–10°	**2d**	(3)	69.4	*R*
4	Me-I	LDA/THF–65°	**2d**	(6)	50.3	*R*
5	Et-Br	*t*-BuOK/THF/–65°	**2e**[c])	(6)	10.7	*R*
6	Et-I	*t*-BuOK/THF/–65°	**2e**	(9)	58.4	*R*
7	$PhCH_2$-Br	*t*-BuOK/THF/–65°	**2f**[d])	(26)	84.2	*R*
8	$PhCH_2$-Br	LDA/THF/–65°	**2f**	(21)	57.5	*R*
9	EtOOC-Cl	LDA/THF/RT.	**2g**	(85)	43.0	–

[a]) Indicated in the product mixture by NMR., determined quantitatively after separation of diastereomers on silica gel column (ethylacetate/heptane 1:6 as eluant).

[b]) **2d**: 7-Chloro-3-methyl-5-phenyl-1-(α-phenylethyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one.

[c]) **2e**: 7-Chloro-3-ethyl-5-phenyl-1-(α-phenylethyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one.

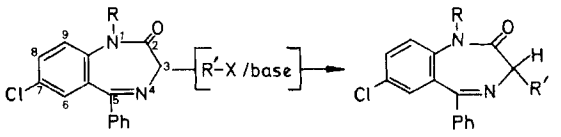
[d]) **2f**: 7-Chloro-5-phenyl-1-(α-phenylethyl)-3-(phenylmethyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one.

exhibited nearly superimposable CD. curves[4]). Configuration of (+)-**2g** (7-chloro-3-(ethoxycarbonyl)-5-phenyl-1-(α-phenylethyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one), obtained as the major product is not determined as yet, however, it was obtained in the highest diastereomeric excess.

In the course of this study we noticed an easy H/D-exchange process at C(3) in the ethoxycarbonyl substituted derivatives **2a** (7-chloro-3-(ethoxycarbonyl)-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one), and **2c** (7-chloro-3-(ethoxycarbonyl)-1-methyl-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one) affording **3a** (7-chloro-3-(ethoxycarbonyl)-5-phenyl-[3-$^2H_1$]-1,3-dihydro-2*H*-1,4-benzodiazepin-

[4]) (+)-(*S*)-α-Phenylethylamino-5-chloro-benzophenone could be recovered after hydrolytic cleavage of α-amino acids, and recyclized into **1c**. Model experiments with optically pure (±)-**2b** afforded 80–90% of (*S*)-alanine with 100% optical purity (after separation on *Dowex* 50, H^+-form column), thus, revealing that no racemization occurred in this step. Hydrolyses were performed in 1N NaOH at 80°, during 21 h. The authors are indebted to Dr. *B. Belin* for performing these experiments.

Scheme 2

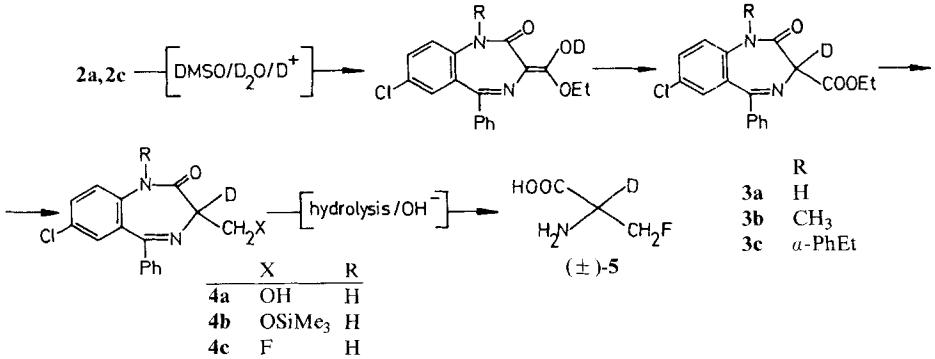


	R
1a	H
1b	Me
1c	α-PhEt

	R	R′
2a	H	COOEt
2b	Me	Me
2c	Me	COOEt
2d	α-PhEt	Me
2e	α-PhEt	Et
2f	α-PhEt	$PhCh_2$
2g	α-PhEt	COOEt

2-one) and **3b** (7-chloro-3-(ethoxycarbonyl)-1-methyl-5-phenyl-[3-$^2H_1$]-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one), respectively *(Scheme 3)*. Thus, **2a** underwent >98% H/D exchange when heated in DMSO/D_2O (molar ratio **2a**/D_2O being 1:18) for 4 h at 60°, or in THF/D_2O for 22 h at 90°. For **2c** the exchange rate $k_{ex} = 1.73 \pm 0.4 \times 10^{-3}$/s was determined by NMR. (at 35±0.1° in DMSO/D_2O; strong acid catalysis was noticed, however).

Scheme 3



	X	R
4a	OH	H
4b	$OSiMe_3$	H
4c	F	H

	R
3a	H
3b	CH_3
3c	α-PhEt

(±)-**5**

Regioselective hydrogenation of **3a** (OMH-1/toluene)[5]) afforded **4a** (7-chloro-3-(hydroxymethyl)-5-phenyl-[3-$^2H_1$]-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one) (82%)[6]) which was trimethylsilated into **4b** (7-chloro-5-phenyl-3-(trimethylsiloxymethyl)-[3-$^2H_1$]-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one) (100%). This compound was converted by fluorination to **4c** (7-chloro-3-(fluoromethyl)-5-phenyl-[3-$^2H_1$]-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one) and hydrolysis afforded (±)-3-fluoro[2-$^2H_1$]-alanine (**5**). (*S*)-Enantiomer of the latter was found to possess broad-spectrum antibacterial activity [16]. Compound (1′*R*,3*S*)-**2g** could be diastereoselectively deuteriated at C(3) affording (1′*R*,3*S*)-**3c** (7-chloro-3-(ethoxycarbonyl)-5-phenyl-1-(α-phenylethyl)-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one), an intermediate for new, enantioselective synthesis of (*S*)-3-fluoro[2-$^2H_1$]alanine. This approach to (*S*)-**5** is currently under investigation in our laboratories.

---

[5]) 'OMH-1' is an about 1M solution of $[(C_2H_5)_2AlH_2]Na$ supplied by *Ethyl Corp.*, Baton Rouge, Indiana.

[6]) For the modified procedure used see [15].

The authors are indebted to Prof. *G. Snatzke*, Ruhruniversität Bochum, F.R. Germany, for obtaining the CD. spectral data.

REFERENCES

[1] *A.I. Meyers*, Acc. Chem. Res. *11*, 375 (1980).
[2] *T. Oguri, T. Shioiri & S.I. Yamada*, Chem. Pharm. Bull. *25*, 2287 (1977).
[3] *T. Oguri, T. Kawai & S.I. Yamada*, Chem. Pharm. Bull. *26*, 803 (1978).
[4] *D. Enders & H. Eichenauer*, Angew. Chem. *88*, 579 (1976).
[5] *D. Enders & H. Eichenauer*, Chem. Ber. *112*, 2933 (1979).
[6] *W. Simon, E. Pretsch, D. Auman, W.E. Morf, H. Guggi, R. Bising & M. Kessler*, Pure Appl. Chem. *44*, 613 (1975).
[7] *G. Gilli, V. Bertolasi, M. Sacerdoti & P.A. Borea*, Acta Crystallogr. *B33*, 2664 (1977); iidem *B34*, 2826, 3793 (1978).
[8] *V. Šunjić, A. Sega, A. Lisini, T. Kovac, F. Kajfež & B. Ruščić*, J. Heterocycl. Chem. *16*, 757 (1979).
[9] *G. Romeo, M.C. Aversa, P. Gianetto, M.G. Vigorita & P. Ficarra*, Org. Magn. Reson. *12*, 593 (1979).
[10] *E.L. Eliel, A.A. Hartmann & A.G. Abatjoglou*, J. Am. Chem. Soc. *96*, 1807 (1974).
[11] *V. Šunjić, M. Oklobžija, A. Lisini, A. Sega, F. Kajfež, D. Srzić & L. Klasinc*, Tetrahedron *35*, 2531 (1980).
[12] *A. Konowa, G. Snatzke, T. Alebić-Kolbah, F. Kajfež, S. Rendić & V. Šunjić*, Biochem. Pharmacol. *28*, 3109 (1979).
[13] *P. Linscheid & J.M. Lehn*, Bull. Soc. Chim. Fr. *1967*, 992.
[14] *V. Šunjić, F. Kajfež, I. Štromar, N. Blaževič & D. Kolbah*, J. Heterocycl. Chem. *10*, 591 (1973).
[15] *D. Kolbah, N. Blaževič, M. Hannoun, F. Kajfež, T. Kovač, S. Rendić & V. Šunjić*, Helv. Chim. Acta *60*, 265 (1977).
[16] *J. Kollonitsch & L. Barash*, J. Org. Chem. *98*, 5591 (1976).