Ring-Opening Reactions of 3-Aryl-1-benzylaziridine-2-carboxylates and Application to the Asymmetric Synthesis of an Amphetamine-Type Compound

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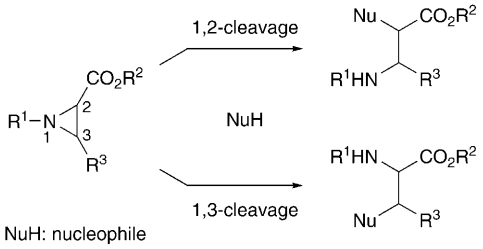
Nucleophilic ring-opening reactions of 3-aryl-1-benzylaziridine-2-carboxylates were examined by using O-nucleophiles and aromatic C-nucleophiles. The stereospecificity was found to depend on substrates and conditions used. Configuration inversion at C(3) was observed with O-nucleophiles as a major reaction path in the ring-opening reactions of aziridines carrying an electron-poor aromatic moiety, whereas mixtures containing preferentially the *syn*-diastereoisomer were generally obtained when electron-rich aziridines were used (*Tables 1–3*). In the reactions of electron-rich aziridines with C-nucleophiles, S_N2 reactions yielding *anti*-type products were observed (*Table 4*). Reductive ring-opening reaction by catalytic hydrogenation of (+)-*trans*-(2*S*,3*R*)-3-(1,3-benzodioxol-5-yl)aziridine-2-carboxylate (+)-*trans*-**3c** afforded the corresponding α-amino acid derivative, which was smoothly transformed into (+)-*tert*-butyl [(1*R*)-2-(1,3-benzodioxol-5-yl)-1-methylethyl]carbamate((+)-**14**) with high retention of optical purity (*Scheme 6*).

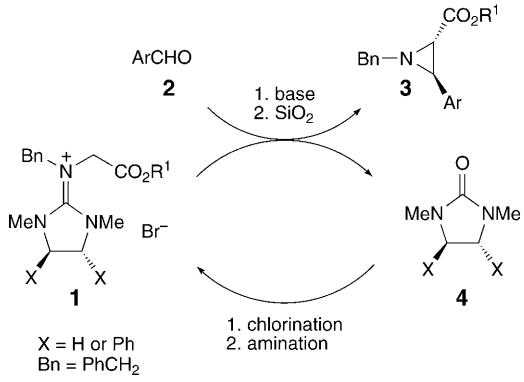
1. Introduction. – Aziridine-2-carboxylates are very versatile synthetic intermediates [1–3] for the preparation of biologically active N-containing compounds because they are convertible to α- or β-amino acid derivatives, including unnatural amino acids, by regioselective ring-opening reactions [1][4][5] (*Scheme 1*). Aziridines are classified into two groups, 'activated' and 'unactivated' (or nonactivated) aziridines, depending upon the substituent R^1 at the ring N-atom [1][4]; the former category includes electron-withdrawing substituents such as tosyl or acyl functions, whereas a H-atom and alkyl substituents are typical for the latter one. Although the reactivity of 'activated' aziridines has been well investigated, there are only limited reports [6–9] on 'unactivated' aziridines.

Recently, we have reported an atom-economical aziridine synthesis from guanidinium salts **1** (obtained from the ureas **4**) and arenecarboxaldehydes **2** [10] (or unsaturated aldehydes [11]) applicable to asymmetric synthesis, in which 1-alkyl-3-arylaziridine-2-carboxylates **3** (or the corresponding unsaturated derivatives) are produced, as shown in *Scheme 2*. In this paper, we present the ring-opening reactions of *N*-benzylaziridine-2-carboxylates, prepared by the above reaction, with O-nucleophiles and aromatic C-nucleophiles and application to the asymmetric synthesis of an amphetamine-type compound from the reductively ring-opened product.

Scheme 1. *Schematic Ring-Opening Reactions of Aziridine-2-carboxylates*



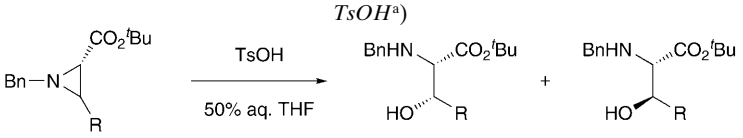
Scheme 2. *Aziridine Synthesis from Guanidinium Salts* **1** *and Arenecarboxaldehydes* **2**



2. Results and Discussion. – 2.1. *Ring-Opening Reactions with O-Nucleophiles.* In 1992, *Zwanenburg* and co-workers [6] reported the ring-opening reactions of *N*-unsubstituted *trans*-3-arylaziridine-2-carboxylates with various nucleophiles including AcOH and found that regio- and stereoselectivities in the reactions were dependent upon the characters of either the aziridine substrates or the nucleophiles used. Thus, the reaction of *trans*-3-phenylaziridine-2-carboxylate with AcOH quantitatively afforded the 2-(acetylamino)-3-hydroxy-3-phenylpropanoate with *anti*-configuration. Recently, *Hruby* and co-workers [7] observed the same result. In addition, in the course of the preparation of a chloramphenicol derivative, *Loncaric* and *Wulff* [8] also reported the formation of the *syn*-amino alcohol in the reaction of *cis*-1-benzyl-3-(4-nitrophenyl)aziridine-2-carboxylate with CF_3COOH in CH_2Cl_2 followed by alkaline hydrolysis. In these three ring-opening reactions, O-nucleophiles strictly attack at the C(3) position with inversion of configuration. However, *Cardillo et al.* [9] reported that a *syn*-amino alcohol was stereoselectively formed with retention of configuration in the Ac_2O-triggered ring-opening reaction on using the amide version of *Hruby*'s *trans*-aziridine. This result showed that the stereochemical course in the ring-opening reaction of 3-arylaziridine-2-carboxylates is partly confusing. Furthermore, there have been no reports on the ring-opening reaction of 3-arylaziridine-2-carboxylates carrying an electron-rich aromatic substituent with O-nucleophiles. We, therefore, examined the ring-opening reactions of some racemic 3-aryl-1-benzylaziridine-2-carboxylates **3** [12], including the 3-(1,3-benzodioxol-5-yl)- (**3c**), 3-(4-methoxyphenyl)- (**3d**),

and 3-{1-[(*tert*-butoxy)carbonyl]-1*H*-indol-4-yl}aziridine-2-carboxylate[1]) **3e** as electron-rich 3-arylaziridines, in 50% aqueous THF solution in the presence of *p*-toluenesulfonic acid monohydrate (TsOH) by using H_2O as an O-nucleophile (*Table 1*).

Table 1. *Ring-Opening Reaction of 3-Aryl-1-benzylaziridine-2-carboxylates* **3** *with* H_2O *in the Presence of TsOH*[a])



3a R = Ph
3b R = 4-ClC_6H_4
3c R = 1,3-benzodioxol-5-yl
3d R = 4-$MeOC_6H_4$
3e R = 1-[(*tert*-butoxy)carbonyl]-1*H*-indol-4-yl

anti-**5** *syn*-**5**

Entry	Starting material	Temp. [°]	Time [h]	Product **5**	
				Yield [%]	*anti*/*syn*[b])
1	*trans*-**3a**	45	2	97	1:0
2	*cis*-**3a**	45	16.5	94	0:1
3	*trans*-**3b**	45	9	99	1:0
4	*cis*-**3b**	45	72	72	0:1
5	*trans*-**3c**	r.t.[c])	2	quant.	1:1
6[d])	*trans*-**3c**	r.t.[c])	3	88	1:5
7	*trans*-**3d**	0	0.2	93	2:1
8[d])	*trans*-**3d**	r.t.[c])	17	96	1:3
9[d])	*cis*-**3d**	r.t.[c])	15	quant.	1:3
10[e])	*trans*-**3e**	r.t.[c])	0.5	quant.	1:6

[a]) Conditions: 0.1–0.19M **3**/50% aq. THF solution; TsOH, 1.0–1.2 mol-equiv. [b]) Estimated by ^{1}H-NMR. [c]) Room temperature. [d]) CH_2Cl_2 was used in place of THF. [e]) Ethyl ester and MeCN were used as aziridine and solvent, respectively.

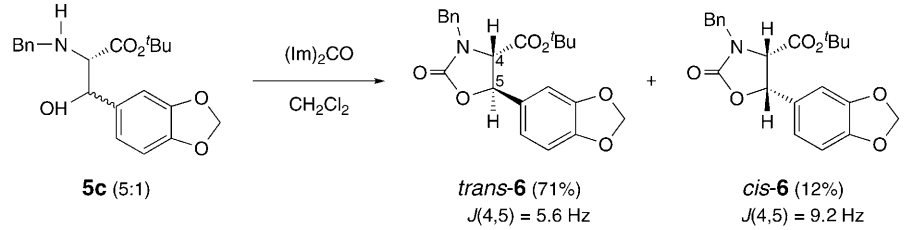
Examination of the ^{1}H-NMR spectra of the crude reaction products showed that, as expected, regioselective ring-opening and OH-incorporation at the C(3) position afforded products **5**. The diastereoselectivity was greatly dependent upon the aziridinecarboxylate used (*vide infra*). These results were confirmed by the isolation of pure products from the reactions described in *Entries 1–4*, *7*, and *8* of *Table 1*. Thus, strict inversion occurred in the cases of arylaziridinecarboxylates **3a** and **3b** carrying a Ph substituent (*Table 1*, *Entries 1* and *2*) or an electron-withdrawing-group(EWG)-substituted aryl substituent (*Entries 3* and *4*) at C(3). On the other hand, no or low diastereselectivity was observed when arylaziridines **3c** and **3d**, carrying an electron-donating-group-(EDG)-substituted aryl ring, were used as substrates (*Entries 5* and *7*). However, diastereoselectivity due to a solvent effect was observed since in CH_2Cl_2 instead of THF, *syn*-amino alcohols were the major ring-opening products (*Entries 6* and *8*). The predominance of *syn*-product was also observed in the ring-opening reaction of

[1]) The preparation of this compound will be reported elsewhere.

the *trans*-(1*H*-indol-4-yl)aziridinecarboxylate *trans*-**3e** in MeCN (*Entry 10*). Interestingly, in the reaction of *Entry 9* of *Table 1*, the *syn*-amino alcohol *syn*-**5d** was formed as the major product from *cis*-(4-methoxyphenyl)aziridinecarboxylate *cis*-**3d**, suggesting that the opening of the aziridine ring carrying an electron-rich aryl group at C(3) is independent of the relative configuration of the starting aziridines.

The configuration of the stereogenic centers in the H_2O adducts had been determined based on the ^{1}H-NMR spectra of known ring-opened products [6][7]; however, crucial information could not be obtained by this method in some cases. *Shiba* and coworkers [13] had assigned the configuration of diastereoisomeric α-amino-β-hydroxy acids by cyclization to oxazolidinones; the obtained *cis*-derivative showed a large coupling constant ($J = 9.6$ Hz) between H–C(4) and H–C(5), whereas the *trans*-isomer showed a small coupling constant ($J = 5.0$ Hz). We have independently determined the relative configuration of α-amino-β-hydroxy esters derived from 3-vinylaziridine-2-carboxylates in the synthesis of hydroxyleucinate and sphingosine [11] by application of *Shiba*'s procedure. This technique was also applied to product **5c** obtained in the reaction of *Entry 6* of *Table 1* (*Scheme 3*). Treatment of a *ca.* 5:1 mixture **5c** with carbonylbis[1*H*-imidazole] ($(Im)_2CO$) in CH_2Cl_2 afforded an inseparable mixture of isomeric oxazolidinone derivatives **6**, the ratio of which was determined by ^{1}H-NMR spectroscopy (major: 71%, minor: 12% yield). The coupling constants ($J(4,5) = 5.6$ Hz in the major isomer; $J(4,5) = 9.2$ Hz in the minor) indicated that the major isomer had the *trans* configuration. In other words, (2*RS*,3*SR*)-2-amino-3-aryl-3-hydroxypropanoate *syn*-**5c** can be assigned to the major isomer formed in the TsOH-catalyzed ring-opening reaction of *trans*-**3c**. This assignment was further supported by the NOE experiment with the minor oxazolidinone derivative *cis*-**6**, in which an NOE enhancement (15.3%) was observed between H–C(4) and H–C(5).

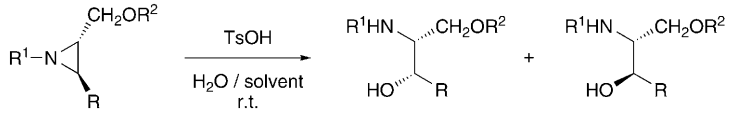
Scheme 3. *Derivatization of* **5c** *to Oxazolidinone Derivatives* **6** *for the Determination of Their Configuration*



Modification of the ester function to a [(silyloxy)methyl] or (hydroxymethyl) function in the aziridine derivatives afforded the same tendency of stereoselectivity in the TsOH-induced ring-opening reactions. *syn*-Amino alcohols *syn*-**8** were mainly formed from the reaction of the *trans*-aziridine derivatives[1]) carrying the 4-methoxyphenyl (**7d**) or 1*H*-indol-4-yl group (**7e**; *Table 2*).

Furthermore, we found that the diastereoselectivity was not influenced by the kind of nucleophiles (*Table 3*). Thus, *syn*-products *syn*-**9** were also obtained as the major product in the AcOH-induced ring-opening reactions of the EDG-substituted *trans*-3-arylaziridine-2-carboxylates *trans*-**3c** and *trans*-**3e**, by using either AcOH or MeOH as nucleophiles.

Table 2. *Ring-Opening Reactions of* trans-*(Silyloxy)methyl]- or* trans-*(Hydroxymethyl)aziridines* **7** *with H_2O in the Presence of TsOH*[a])

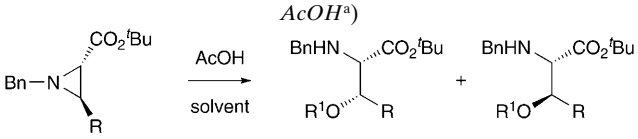


7 *anti*-**8** *syn*-**8**

Entry	Starting material	R^1	R^2	Solvent	Time [h]	Product **8**	
						Yield [%]	*anti*/*syn*[b])
1	**7d**	$PhCH_2$	$^iPr_3Si$	CH_2Cl_2	1	97	1:3
2	**7d**	$PhCH_2$	H	CH_2Cl_2	0.2	quant.	1:4
3	**7e**	$PhCH_2$	$^tBuMe_2Si$	MeCN	22	quant.	1:20
4	**7e**	CH_2=$CHCH_2$	$^tBuMe_2Si$	MeCN	14	92	1:7

[a]) The substituent R in **7** corresponds to that in **3** in *Table 1* (**d**: R = 4-$MeOC_6H_4$; **e**: R = 1-[(*tert*-butoxy)-carbonyl]-1*H*-indol-4-yl). Conditions: 0.09–0.17M **7**/solvent; TsOH, 1.1–1.2 mol-equiv. at room temperature (r.t.). [b]) Estimated by ^{1}H-NMR.

Table 3. *Ring-Opening Reactions of EDG-substituted* trans-*3-Aryl-1-benzylaziridine-2-carboxylates with AcOH*[a])



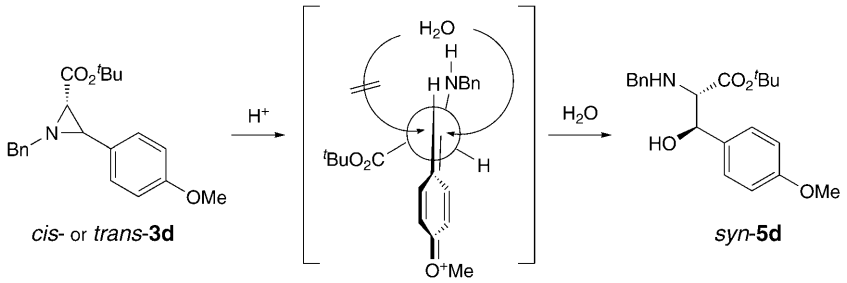
trans-**3** *anti*-**9** *syn*-**9**

Entry	Starting material	AcOH [mol-equiv.]	Solvent	Temp. [°]	Time [h]	Product **9**		
						R^1	Yield [%]	*anti*/*syn*[b])
1	*trans*-**3c**	81	none	0	0.5	Ac	88	1:3
2	*trans*-**3c**	48	CH_2Cl_2	r.t.[c])	2	Ac	81	1:10
3[d])	*trans*-**3c**	1.2	MeOH	r.t.[c])	22	Me[d])	78	1:10
4[e])	*trans*-**3e**	83	none	r.t.[c])	4	Ac	quant.	0:1

[a]) The substituent R in **3** corresponds to that in *Table 1* (**c**: R = 1,3-benzodioxol-5-yl; **e**:R = 1-[(*tert*-butoxy)carbonyl]-1*H*-indol-4-yl). [b]) Estimated by ^{1}H-NMR. [c]) Room temperature. [d]) An MeO group was incorporated in place of an AcO group. [e]) The ethyl ester was used.

Thus, ring-opening reactions of arylaziridinecarboxylates carrying an EDG-substituted aromatic ring with O-nucleophiles, except for the reactions in THF, proceed with the preferred formation of *syn*-amino alcohol derivatives, independently of the configuration of the starting aziridinecarboxylate or the kind of nucleophile. The production of *syn*-amino alcohol derivatives as a main course could be reasonably deduced by application of *Cram*'s model [14] for the transition state as shown in *Scheme 4*, in which the ring-opening reactions of *cis*- and *trans*-**3d** with H_2O is illustrated. Protonation of the aziridine N-atom followed by ring-opening should give a resonance-stabi-

Scheme 4. *Proposed Reaction Path for the Formation of* syn-**5d** *as the Major Product of the Ring-Opening Reactions of* cis- *and* trans-**3d** *with* H_2O



lized benzyl cationic species (*Scheme 4*) as a key intermediate, on which the H_2O attack on the less hindered side should give the *syn*-amino alcohol derivatives.

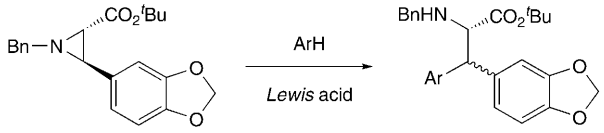
2.2. *Ring-Opening Reactions with Aromatic C-Nucleophiles. Zwanenburg* and co-workers [6] had also examined the ring-opening reactions of *N*-unsubstituted *trans*-3-arylaziridine-2-carboxylates using 1*H*-indole as a C-nucleophile in the presence of boron trifluoride etherate (BF_3), in which high regio- and stereoselectivities were observed when phenyl and 4-nitrophenyl groups were used as aromatic moiety, giving only *anti*-2-amino-3-aryl-3-(1*H*-indol-3-yl)propanoates[2]) as ring-opened products in 53% and 60% yields, respectively. On the other hand, (4-methoxyphenyl)aziridinecarboxylate gave, with 1*H*-indole, a mixture of *anti*- and *syn*-adducts at C(3) of the aziridine. Conversion to *anti*-2-amino-3-(1*H*-indol-3-yl)-3-phenylpropanoate from *trans*-3-phenylaziridine-2-carboxylate in the BF_3-induced ring-opening reaction had also been followed by *Hruby* and co-workers [7]. In addition, it had been reported that electron-rich aromatics such as 1*H*-indole and 1,2-dimethoxybenzene react with tosylaziridine, an 'activated' aziridine, to give ring-opened products in the presence of indium catalysts such as indium chloride ($InCl_3$) [15] or scandium perchlorate [16].

We examined the $InCl_3$- or BF_3-induced ring-opening reactions of 'unactivated' aziridines with various aromatic C-nucleophiles, using the *trans*-(1,3-benzodioxol-5-yl)aziridine-2-carboxylate *trans*-**3c** (*Table 4*). Reactions with 1*H*-indole and 2-methyl-1*H*-indole were smoothly catalyzed with $InCl_3$ to afford 3-(1*H*-indol-3-yl)- and 3-(2-methyl-1*H*-indol-3-yl)-2-(benzylamino)propanoates **10a** and **10b** in 87 and 86% yield, respectively, as a single stereoisomer (*Table 4*, *Entries 1* and *3*). Interestingly, product **10a** was formed as a single isomer even in the absence of the catalyst albeit a longer reaction time was needed (*Entry 2*). Also 1*H*-pyrrole and furan reacted as nucleophiles in the $InCl_3$-catalyzed ring-opening reactions to give the corresponding ring-opened products **10c** and **10d**, in which the diastereoselectivity was dependent upon the nucleophile used (*Entries 4* and *6*). In the BF_3-induced reaction with 1*H*-pyrrole, a similar diastereoselectivity as with $InCl_3$ was observed (*Entry 5*).

As benzenoid C-nucleophiles, 1,3-dimethoxybenzene, *N*,*N*-dimethylaniline, and anisole (=methoxybenzene) were also examined. In the presence of $InCl_3$, the former

[2]) The configurational relation between the amino function and the aryl group inserted is adopted.

Table 4. Lewis *Acid Catalyzed Ring-Opening Reactions of* trans-*(1,3-Benzodioxol-5-yl)aziridine-2-carboxylate* (*trans*-**3c**) *with Aromatic C-Nucleophiles in* CH_2Cl_2



trans-**3c** **10**

Entry	ArH/*Lewis* acid ([mol-equiv.])	Temp. [°]	Time [h]	Product **10**			
					Ar	Yield [%]	d.r.[a])
1	1*H*-indole/$InCl_3$ (0.1)	r.t.[b])	20	**a**	1*H*-indol-3-yl	87	single
2	1*H*-indole/–	r.t.[b])	168	**a**	1*H*-indol-3-yl	73	single
3	2-methyl-1*H*-indole/$InCl_3$ (0.1)	30	12	**b**	2-methyl-1*H*-indol-3-yl	86	single
4	1*H*-pyrrole/$InCl_3$ (0.2)	r.t.[b])	5	**c**	1*H*-pyrrol-2-yl	66	4:1
5	1*H*-pyrrole/BF_3[c]) (1.0)	0	3	**c**	1*H*-pyrrol-2-yl	55	5:1
6	furan/$InCl_3$ (0.4)	r.t.[b])	36	**d**	1*H*-furan-2-yl	60	10:1
7	1,3-dimethoxybenzene/$InCl_3$ (0.5)	30	12	**e**	2,4-$(MeO)_2C_6H_3$	75	2:1
8	1,3-dimethoxybenzene/$MgBr_2$[c]) (1.1)	40	4	n.r.[d])	–	–	–
9	*N,N*-dimethylaniline/$InCl_3$ (0.5)	r.t.[b])	4	**f**	4-$(Me_2N)C_6H_4$	70	3.6:1
10	anisole/$InCl_3$ (0.3)	35	18	mixture[e])	–	–	–

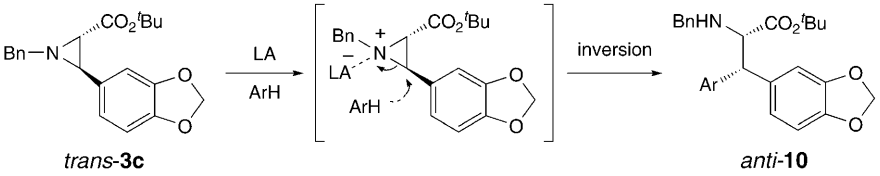
[a]) Diastereoisomeric ratio of the crude product estimated by ^{1}H-NMR. [b]) Room temperature. [c]) As an etherate. [d]) No reaction. [e]) A complex mixture was obtained containing the starting anisole as the main component.

two satisfactorily reacted with *trans*-**3c** to give the ring-opened products **10e** and **10f** (*Table 4*, *Entries 7* and *9*), but a complex mixture was obtained in the case of anisole (*Entry 10*). No reaction occurred when 1,3-dimethoxybenzene was treated with $MgBr_2 \cdot OEt_2$ (*Entry 8*). In general, low diastereoselectivity was observed with benzenoid C-nucleophiles as compared to heterocyclic ones in the $InCl_3$-catalyzed reactions.

Although the configuration of the products formed had been assigned by ^{1}H-NMR (chemical shift and coupling constant) in [6][7], this method could not be applied conclusively in this case. However, we succeeded in preparing a single crystal of **10a** (see *Table 4*, *Entry 1*). The X-ray crystallographic analysis (*Fig.*) indicated that it was *tert*-butyl (2*RS*,3*SR*)-3-(1,3-benzodioxol-5-yl)-2-(benzylamino)-3-(1*H*-indol-3-yl)propanoate with *anti*-configuration. In other word, inversion of configuration at C(3) of the aziridine ring occurred during the ring-opening reaction by the aromatic C-nucleophiles, as shown in *Scheme 5*, in contrast to the reactions with O-nucleophiles mentioned above (*Scheme 4*).

2.3. *Ring-Opening by Hydrogenation: Application to Asymmetric Synthesis of an Amphetamine-Type Compound.* In a previous paper [10], we reported the ring-opening reaction of aziridines by catalytic hydrogenation giving amino acid derivatives. *Quagliato et al.* [17] had reported the chemical conversion of the α-amino acid function

Scheme 5. *Proposed Mechanism for the Ring-Opening Reaction of* trans-*(1,3-Benzodioxol-5-yl)aziridine-2-carboxylate* trans-**3c** *with a C-Nucleophile*



LA: *Lewis* acid ArH: aromatics

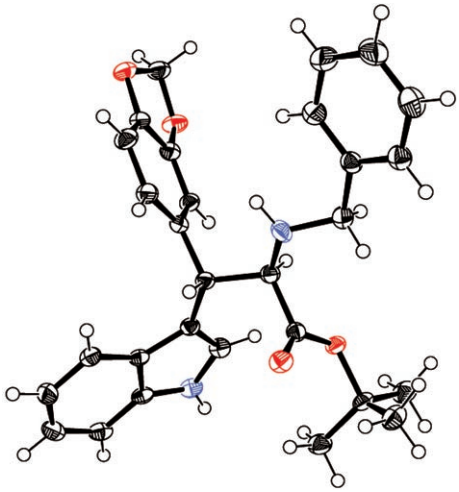
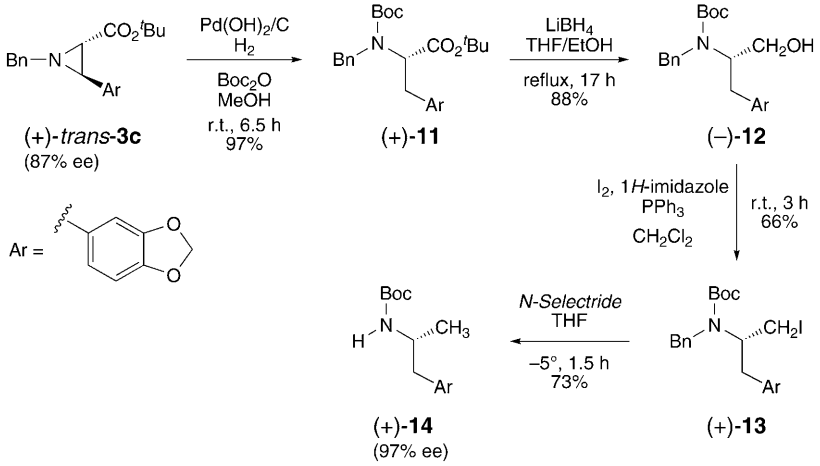


Figure. *ORTEP Drawing of product* **10a**

to a α-methylamine system. To show the utility of the 3-aryl-1-benzylaziridine-2-carboxylates as chiral tools for synthetic purposes, we independently carried out the asymmetric synthesis of an amphetamine-type compound (*i.e.*, 1-arylpropan-2-amines) from *tert*-butyl (+)-*trans*-3-(1,3-benzodioxol-5-yl)-1-benzylaziridine-2-carboxylate ((+)-*trans*-**3c**), obtained by the aziridination reaction [12] with (*R*,*R*)-guanidinium salt (*R*,*R*)-**1** (X = Ph, R^1 = Bn, R^2 = ^{t}Bu; see *Scheme 2*), after a slight modification of the reported method [17] (*Scheme 6*). Thus, a solution of (+)-*trans*-**3c** (87% ee) in MeOH was hydrogenated over $Pd(OH)_2/C$ in the presence of di(*tert*-butyl) dicarbonate ($(Boc)_2O$) to give the expected *N*-Boc-protected amino ester (+)-**11** in high yield, as reported earlier [10]. The absolute configuration of the chiral aziridinecarboxylate (+)-*trans*-**3c** was deduced to be (2*S*,3*R*) based on the fact that *trans*-(2*R*,3*S*)- and *cis*-(2*R*,3*R*)-aziridine derivatives were obtained when the (*S*,*S*)-guanidinium salt, the enantiomer of (*R*,*R*)-**1**, was used as a chiral template [10]. Reduction of the ester function in (+)-**11** with lithium borohydride ($LiBH_4$) afforded alcohol (−)-**12**, hydrogenolysis of which was achieved with *N-Selectride*® after conversion of the alcoholic function to an iodide (+)-**13**. Thus, (+)-*tert*-butyl [(1*R*)-2-(1,3-benzodioxol-5-yl)-1-methylethyl]-

Scheme 6. *Asymmetric Synthesis of the Amphetamine-Type Compound* (+)-**14**



carbanate ((+)-**14**) was smoothly and effectively produced in 41% overall yield from the (2*S*,3*R*)-aziridinecarboxylate (+)-*trans*-**3c**. The ee of (+)-**14** obtained was determined to be 97%, in spite of the 87% ee of the starting (+)-*trans*-**3c**, because of the purification procedures of crystalline synthetic intermediates by recrystallization.

3. Conclusions. – We found that ring-opening reactions of 'unactivated' 3-aryl-1-benzylaziridine-2-carboxylates carrying EWG-substituted aryl residues stereospecifically react with inversion at C(3) of the aziridine ring by an S_N2-type reaction, as reported earlier [6–8]. On the other hand, in the cases of the EDG-substituted arylaziridines, *syn*-amino alcohol derivatives were obtained as the major component of the diastereoisomer mixture, independently of the configuration of the starting aziridines[3]). These results could reasonably be explained by *Cram*'s transition-state model. In the reactions with the EDG-substituted arylaziridine-2-carboxylates with aromatic C-nucleophiles, an S_N2 reaction yielding *anti*-type products was observed as the preferred reaction. The reductively ring-opened product of (+)-*tert*-butyl (2*S*,3*R*)-*trans*-3-(1,3-benzodioxol-5-yl)aziridine-2-carboxylate ((+)-*trans*-**3c**) was effectively and smoothly converted to (+)-*tert*-butyl [(1*R*)-2-(1,3-benzodioxol-5-yl)-1-methylethyl]carbamate ((+)-**14**) with high retention of optical purity.

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[3]) *Zwanenburg* and co-workers [6] had also observed the formation of mixtures of diastereoisomeric products in the ring-opening reactions of *trans*-methyl 3-(4-methoxyphenyl)aziridine-2-carboxylate with hydrogen chloride and thiophenol.

Experimental Part

1. *General.* Anh. THF and CH_2Cl_2 were purchased from *Wako* and *Kanto Chemicals*, resp. DMF, Et_3N, MeCN, and EtOH were distilled from calcium hydride (CaH_2). Starting aziridines were prepared according to the reported procedure [12]. Column chromatography (CC): silica gel *60* (spherical, 70–230 mesh; *Fuji Silysia FL100D* or *Kanto Chemicals*). $[\alpha]_D$: *Jasco P-1020*. IR Spectra: *Jasco FT/IR-300E* spectrophotometer ATR = attenuated total reflectance; in cm^{-1}. NMR Spectra: *Jeol JNM-ECP400* spectrometer; at 400 (^1H) and 100 MHz (^{13}C); $CDCl_3$ solns. with $SiMe_4$ as an internal standard (^1H) and the middle resonance of $CDCl_3$ (δ 77.0) as an internal standard (^{13}C); δ in ppm, J in Hz; dif. = diffused. EI-MS: *Jeol GC-Mate* with direct inlet, or *Hewlett-Packard-5890 (*series *II*) gas chromatograph and *5971A* mass-selective detector for GC/MS. HR-FAB-MS: *JMS-HX110* with 3-nitrobenzyl alcohol as a matrix.

2. *Ring-Opening Reactions of Aziridine-2-carboxylates* **3** *in the Presence of TsOH* (*Table 1*). A soln. of **3** in 50% THF/H_2O in the presence of TsOH was stirred under the conditions given in the footnotes of *Table 1*, and in some cases CC (hexane/AcOEt) was carried out for the purification of ring-opened products.

tert-*Butyl (2*RS,*3*RS*)-2-(Benzylamino)-3-hydroxy-3-phenylpropanoate* (*anti*-**5a**): From *trans*-**3a** (*Entry 1*). Colorless needles. M.p. 95–96°. IR (KBr): 3290 (NH), 3064 (OH), 1726 (CO). ^1H-NMR: 1.33 (*s*, ^{t}Bu); 2.08 (br. *s*, NH); 3.57 (*d*, J = 5.1, H–C(2)); 3.68, 3.881 (2*d*, J = 12.9, PhCH_2); 3.880 (br. *s*, OH); 4.95 (*d*, J = 5.1, H–C(3)); 7.23–7.35 (*m*, 10 arom. H). ^{13}C-NMR: 27.9; 52.4; 66.2; 72.9; 81.9; 126.3; 127.2; 127.6; 128.0; 128.3; 128.4; 139.3; 140.3; 171.3. FAB-MS: 328 ($[M+H]^+$). Anal. calc. for $C_{20}H_{25}NO_3$: C 73.37, H 7.70, N 4.28; found: C 73.59, H 7.68, N 4.24.

tert-*Butyl (2*RS,*3*SR*)-2-(Benzylamino)-3-hydroxy-3-phenylpropanoate* (*syn*-**5a**): From *cis*-**3a** (*Entry 2*). Colorless needles. M.p. 45–47°. IR (KBr): 3437 (OH); 3287 (NH); 1720 (CO). ^1H-NMR: 1.22 (*s*, ^{t}Bu); 3.26 (*d*, J = 8.1, H–C(2)); 3.67, 3.78 (2*d*, J = 12.9, PhCH_2); 4.51 (*d*, J = 8.1, H–C(3)); 7.27–7.36 (*m*, 10 arom. H). ^{13}C-NMR: 27.7; 52.4; 68.3; 74.7; 81.7; 127.1; 127.3; 128.0; 128.1; 128.2; 128.5; 139.2; 140.1; 172.1. FAB-MS: 328 ($[M+H]^+$). Anal. calc. for $C_{20}H_{25}NO_3$: C 73.37, H 7.70, N 4.28; found: C 73.36, H 7.54, N 4.14.

tert-*Butyl (2*RS,*3*RS*)-2-(Benzylamino)-3-(4-chlorophenyl)-3-hydroxypropanoate* (*anti*-**5b**): From *trans*-**3b** (*Entry 3*). Colorless needles. M.p. 124–125°. IR (KBr): 3290 (NH); 3090 (OH); 1726 (CO). ^1H-NMR: 1.34 (*s*, ^{t}Bu); 3.53 (*d*, J = 5.1, H–C(2)); 3.67, 3.87 (2*d*, J = 13.0, PhCH_2); 4.91 (*d*, J = 5.1, H–C(3)); 7.21 (*d*, J = 8.4, 2 arom. H); 7.26–7.35 (*m*, 7 arom. H). ^{13}C-NMR: 27.9; 52.5; 66.0; 72.3; 82.2; 127.3; 127.7; 128.1; 128.3; 128.5; 133.3; 138.9; 139.1; 171.3. FAB-MS: 364 ($[M(^{37}Cl)+H]^+$), 362 ($[M(^{35}Cl)+H]^+$). Anal. calc. for $C_{20}H_{24}ClNO_3$: C 66.38, H 6.69, N 3.87; found: C 66.43, H 6.58, N 3.73.

tert-*Butyl (2*RS,*3*SR*)-2-(Benzylamino)-3-(4-chlorophenyl)-3-hydroxypropanoate* (syn-**5b**): From *cis*-**3b** (*Entry 4*). Colorless needles. M.p. 86–87°. IR (KBr): 3420 (OH); 3281 (NH); 1717 (CO). ^1H-NMR: 1.26 (*s*, ^{t}Bu); 2.25 (br. *s*, OH); 3.19 (*d*, J = 7.8, H–C(2)); 3.67, 3.78 (2*d*, J = 12.9, PhCH_2); 4.16 (br. *s*, NH); 4.50 (*d*, J = 7.8, H–C(3)); 7.25–7.36 (*m*, 9 arom. H). ^{13}C-NMR: 27.8; 52.5; 68.2; 73.9; 82.0; 127.3; 128.2; 128.3; 128.47; 128.52; 123.7; 138.8; 139.0; 171.9. FAB-MS: 364 ($[M(^{37}Cl)+H]^+$), 362 ($[M(^{35}Cl)+H]^+$). Anal. calc. for $C_{20}H_{24}ClNO_3$: C 66.38, H 6.69, N 3.87; found: C 66.50, H 6.75, N 3.81.

tert-*Butyl (2*RS,*3*RS*)/(2*RS,*3*SR*)-3-(1,3-Benzodioxol-5-yl)-2-(benzylamino)-3-hydroxypropanoate* (*anti*/*syn*-**5c**; *anti*/*syn* 1:5)*:* From *trans*-**3c** (*Entry 6*). Colorless prisms. M.p. 68–69°. IR (neat): 3422 (OH); 1725 (CO). ^1H-NMR: 1.27 (*s*, 9 H × 5/6, ^{t}Bu); 1.38 (*s*, 9 H × 1/6, ^{t}Bu); 3.19 (*d*, J = 8.0, 1 H × 5/6, H–C(2)); 3.52 (*d*, J = 5.2, 1 H × 1/6, H–C(2)); 3.66, 3.88 (2*d*, J = 13.2, 2 H × 1/6, PhCH_2); 3.68, 3.80 (2*d*, J = 13.2, 2 H × 5/6, PhCH_2); 4.42 (*d*, J = 8.0, 1 H × 5/6, H–C(3)); 4.87 (*d*, J = 5.2, 1 H × 1/6, H–C(3)); 5.93 (*s*, 2 H × 1/6, OCH_2O); 5.94 (*s*, 2 H × 5/6, OCH_2O); 6.73 (*s*, 2 H × 1/6, arom. H); 6.73–6.76 (*m*, 2 H × 5/6, arom. H); 6.87 (*s*, 1 H × 5/6, arom. H); 6.79 (*s*, 1 H × 1/6, arom. H); 7.27–7.34 (*m*, 5 H × 5/6, arom. H); 7.28–7.34 (*m*, 5 H × 1/6, arom. H). ^{13}C-NMR (major isomer): 27.8; 52.3; 68.5; 74.4; 81.8; 100.9; 106.8; 107.3; 107.8; 120.7; 127.3; 128.2; 128.5; 139.1; 147.3; 147.6; 172.1. EI-MS: 371 (1, M^+), 353 (11), 165 (100). Anal. calc. for $C_{21}H_{25}NO_5$: C 67.91, H 6.78, N 3.77; found: C 67.88, H 6.85, N 3.71.

tert-*Butyl (2*RS,*3*RS*)-2-(Benzylamino)-3-hydroxy-3-(4-methoxyphenyl)propanoate* (*anti*-**5d**): From *trans*-**3d** (*Entry 7*). Colorless needles. M.p. 97–98°. Obtained as a major isomer after CC. IR (KBr): 3420 (OH); 3298 (NH); 1726 (CO). ^1H-NMR: 1.36 (*s*, ^{t}Bu); 2.02 (br. *s*, OH); 3.54 (*d*, J = 5.1, H–C(2)); 3.66, 3.87 (2*d*, J = 12.9, $PhCH_2$); 3.78 (*s*, MeO); 3.80 (br. *s*, NH); 4.90 (br. *d*, J = 5.1, H–C(3)); 6.83

(dif. *d*, *J* = 8.5, 2 arom. H); 7.19 (dif. *d*, *J* = 8.5, 2 arom. H); 7.24–7.35 (*m*, 5 arom. H). ^{13}C-NMR: 28.0; 52.6; 55.2; 66.3; 72.5; 81.9; 113.5; 127.2; 127.5; 128.3; 128.5; 132.4; 139.4; 159.1; 171.4. Anal. calc. for $C_{21}H_{27}NO_4$: C 70.56, H 7.61, N 3.92; found: C 70.59, H 7.59, N 3.87.

tert-*Butyl* (*2*RS,*3*SR)*-2-(Benzylamino)-3-hydroxy-3-(4-methoxyphenyl)propanoate* (*syn*-**5d**): From *cis*-**3d** (*Entry 9*). Colorless needles. M.p. 50–52°. Obtained as a major isomer after CC. IR (ATR): 3427 (OH), 3282 (NH), 1720 (CO). ^{1}H-NMR: 1.23 (*s*, ^{t}Bu); 2.18 (br. *s*, OH); 3.24 (*d*, *J* = 8.1, H–C(2)); 3.68, 3.80 (2*d*, *J* = 12.9, PhCH_2); 3.79 (*s*, MeO); 4.11 (br. *s*, NH); 4.45 (*d*, *J* = 8.1, H–C(3)); 6.86 (dif. *d*, *J* = 8.8, 2 arom. H); 7.24–7.35 (*m*, 7 arom. H). ^{13}C-NMR: 27.8; 52.4; 55.3; 68.5; 74.3; 81.6; 113.6; 127.3; 128.3; 128.4; 128.5; 132.1; 139.2; 159.5; 172.2. HR-FAB-MS: 357.1914 (M^+, $C_{21}H_{27}NO_4^+$; calc. 357.1940).

Ethyl (*2*RS,*3*RS)*/*(*2*RS,*3*SR)*-2-(Benzylamino)-3-{1-[(tert-butoxy)carbonyl]-1*H*-indol-4-yl}-3-hydroxypropanoate* (*anti*/*syn*-**5e**; *anti*/*syn* 1:6): From *trans*-**3e** (*Entry 10*). Colorless oil. IR (neat): 3338 (NH, OH); 1734 (CO). ^{1}H-NMR: 0.88 (*d*, *J* = 7.1, 3 H × 1/7, *Me*CH_2); 0.95 (*t*, *J* = 7.2, 3 H × 6/7, *Me*CH_2); 1.67 (*s*, 9 H, ^{t}Bu); 3.64 (*d*, *J* = 8.5, 1 H × 1/7, H–C(2)); 3.76 (*d*, *J* = 14.9, 2 H × 1/7, PhCH_2); 3.91 (*d*, *J* = 3.4, 1 H × 6/7, H–C(2)); 3.91–3.97 (*m*, 2 H, MeCH_2O); 4.07, 4.22 (2*d*, *J* = 12.8, 2 H × 6/7, PhCH_2); 5.14 (*d*, *J* = 8.5, 1 H × 1/7, H–C(3)); 5.78 (*d*, *J* = 3.4, 1 H × 6/7, H–C(3)); 6.58 (*d*, *J* = 3.5, 1 H × 1/7, H–C(3′)); 6.66 (*d*, *J* = 3.8, 1 H × 6/7, H–C(3′)); 7.17–7.29 (*m*, 5 arom. H); 7.44 (*d*, *J* = 6.8, 2 arom. H); 7.52 (*d*, *J* = 3.8, 1 H × 6/7, H–C(2′)); 8.06 (*d*, *J* = 6.8, 1 H, H–C(7′)). EI-MS: 438 (1, M^+), 91 (100).

tert-*Butyl* (*4*RS,*5*SR)*/*(*4*RS,*5*RS)*-5-(1,3-Benzodioxol-5-yl)-3-benzyl-2-oxooxazolidine-4-carboxylate* (*trans*/*cis*-**6**). The 5:1 mixture *syn*/*anti*-**5c** (0.034 g, 0.09 mmol: *syn*/*anti* = d.r. = 5:1), obtained as described in *Entry 6* of *Table 1*, and $(Im)_2CO$ (0.02 g, 0.12 mmol) in CH_2Cl_2 (1 ml) was stirred at 40° for 3 days. After evaporation of the solvent, purification of the residue by CC (hexane/AcOEt 3:1) afforded an inseparable mixture *trans*/*cis*-**6** as a colorless oil (0.030 g, 83%, *trans*/*cis* = d.r. = 6:1). IR (neat): 1763 (CO). ^{1}H-NMR: 1.18 (*s*, 9 H × 1/7, ^{t}Bu); 1.48 (*s*, 9 H × 6/7, ^{t}Bu); 3.76 (*d*, *J* = 5.6, 1 H × 6/7, H–C(4)); 4.12 (*d*, *J* = 9.2, 1 H × 1/7, H–C(4)); 4.24, 4.99 (2*d*, *J* = 14.8, 2 H × 6/7, PhCH_2); 4.99, 5.52 (2*d*, *J* = 14.8, 2 H × 1/7, PhCH_2); 5.32 (*d*, *J* = 5.4, 1 H × 6/7, H–C(5)); 5.52 (*d*, *J* = 9.1, 1 H × 1/7, H–C(5)); 5.94 (*s*, 2 H × 1/7, OCH_2O); 5.96 (*s*, 2 H × 6/7, OCH_2O); 6.68 (*d*, *J* = 1.6, 1 H × 6/7, arom. H); 6.72 (*dd*, *J* = 8.1, 1.6, 1 H × 6/7, arom. H); 6.75 (*d*, *J* = 8.1, 1 H × 6/7, arom. H); 6.80–6.82 (*m*, 3 H × 1/7, arom. H); 7.22–7.37 (*m*, 5 H, arom. H). ^{13}C-NMR (major isomer): 27.9; 47.2; 64.1; 77.1; 83.6; 101.4; 105.7; 108.3; 119.4; 128.2; 128.4; 128.9; 131.8; 134.9; 148.17; 148.20; 157.1; 168.1. EI-MS: 397 (28, M^+), 252 (54), 91 (100).

3. *Ring-Opening Reactions of* trans*-2-[(Silyloxy)methyl]- or 2-(Hydroxymethyl)aziridine* **7** *in the Presence of TsOH* (*Table 2*). *trans*-2-[(Silyloxy)methyl]- or 2-(hydroxymethyl)aziridine **7** was treated in either CH_2Cl_2 or MeCN under the conditions given in *Table 2*, and in some cases CC (hexane/AcOEt) was carried out for the purification of ring-opened products.

*(1*RS,*2*RS)*/(1*RS,*2*SR)*-2-(Benzylamino)-3-tris[(isopropylsilyl)oxy]-1-(4-methoxyphenyl)propan-1-ol* (*anti*/*syn*-**8d**; R^1 = $PhCH_2$, R^2 = ^{i}Pr$_3$Si; *anti*/*syn* 1:3): From *trans*-**7d** (R^1 = $PhCH_2$; R^2 = ^{i}Pr$_3$Si; *Entry 1*). Colorless oil. IR (neat): 3419 (NH, OH). ^{1}H-NMR: 0.97–1.13 (*m*, 21 H, ^{i}Pr); 2.68 (*ddd*, *J* = 8.6, 3.6, 3.6, 1 H × 3/4, H–C(2)); 2.90 (*ddd*, *J* = 7.2, 5.2, 5.2, 1 H × 1/4, H–C(2)); 3.46 (*dd*, *J* = 10.0, 5.2, 1 H × 1/4, CH_2(3)); 3.48 (*dd*, *J* = 10.4, 3.6, 1 H × 3/4, CH_2(3)); 3.66 (*dd*, *J* = 10.2, 7.2, 1 H × 1/4, CH_2(3)); 3.68 (*d*, *J* = 12.8, 1 H × 3/4, $PhCH_2$); 3.80 (*s*, 3 H × 3/4, MeO); 3.82 (*dd*, *J* = 10.2, 3.2, 1 H × 3/4, CH_2(3)); 3.89 (*d*, *J* = 12.8, 1 H, PhCH_2); 4.51 (*d*, *J* = 8.0, 1 H × 3/4, H–C(1)); 4.88 (*d*, *J* = 4.8, 1 H × 1/4, H–C(1)); 6.86 (dif. *d*, *J* = 8.4, 2 arom. H); 7.23–7.36 (*m*, 8 arom. H). HR-FAB-MS: 444.2918 ($[M+H]^+$, $C_{26}H_{42}NO_3Si^+$; calc. 444.2934).

*(1*RS,*2*RS)*/(1*RS,*2*SR)*-2-(Benzylamino)-1-(4-methoxyphenyl)propane-1,3-diol* (*anti*/*syn*-**8d**; R^1 = $PhCH_2$; R^2 = H; *anti*/*syn* 1:4): From *trans*-**7d** (R^1 = $PhCH_2$; R^2 = H; *Entry 2*). Colorless oil. IR (neat): 3419 (NH, OH). ^{1}H-NMR: 2.79 (*ddd*, *J* = 7.6, 3.7, 3.7, 1 H × 4/5, H–C(2)); 2.86 (*ddd*, *J* = 5.4, 5.4, 4.4, 1 H × 1/5, H–C(2)); 3.38 (*dd*, *J* = 11.2, 3.3, 1 H × 4/5, CH_2(3)); 3.56 (*dd*, *J* = 11.2, 4.4, 1 H × 1/5, CH_2(3)); 3.64 (*dd*, *J* = 11.2, 5.2, 1 H × 1/5, CH_2(3)); 3.66 (*dd*, *J* = 11.2, 4.0, 1 H × 4/5, CH_2(3)); 3.72, 3.84 (2*d*, *J* = 13.2, 2 H × 4/5, $PhCH_2$); 3.81 (*s*, 3 H, MeO); 4.63 (*d*, *J* = 7.6, 1 H × 4/5, H–C(1)); 4.82 (*d*, *J* = 5.7, 1 H × 1/5, H–C(1)); 6.89 (dif. *d*, *J* = 8.8, 2 arom. H); 7.23–7.35 (*m*, 8 arom. H). ^{13}C-NMR (major isomer): 51.4; 55.3; 59.7; 64.1; 73.3; 113.8; 127.1; 127.7; 128.1; 128.5; 133.9; 139.9; 159.2. HR-FAB-MS: 288.1600 ($[M+H]^+$, $C_{17}H_{22}NO_3^+$; calc. 288.1600).

tert-*Butyl 4-[(1*RS,*2*RS*)/(1*RS,*2*SR*)-2-(Benzylamino)-3-{[(*tert-*butyl)dimethylsilyl]oxy}-1-hydroxypropyl]indole-1-carboxylate* (*anti*/*syn*-**8e** $R^1 = PhCH_2$, $R^2 = {}^tBuMe_2Si$; *anti*/*syn* 1:20). From *trans*-**7e** ($R^1 = PhCH_2$, $R^2 = {}^tBuMe_2Si$; *Entry 3*). Colorless oil. IR (neat): 3339 (NH, OH), 1735. ^{1}H-NMR (major isomer): −0.14, −0.05 (each *s*, 3 H, MeSi); 0.78, 1.67 (each *s*, 9 H, ^{t}Bu); 3.33 (*m*, H−C(2)); 3.63 (*dd*, *J* = 11.7, 3.1, 1 H, CHCH_2O); 4.02 (*dd*, *J* = 11.7, 7.3, 1 H, CHCH_2O); 4.28, 4.42 (2*d*, *J* = 13.4, PhCH_2); 5.65 (*s*, H−C(1)); 6.39 (*d*, *J* = 4.0, H−C(3′)); 7.21–7.35 (*m*, 5 arom. H); 7.48 (*d*, *J* = 4.0, H−C(2′)); 7.61 (*d*, *J* = 6.8, 2 arom. H); 8.05 (*d*, *J* = 8.0, H−C(7′)). EI-MS: 511 (1, $[M+H]^+$), 265 (100), 91 (94).

tert-*Butyl 4-{(1*RS,*2*RS*)/(1*RS,*2*SR*)-3-{[(*tert-*Butyl)dimethylsilyl]oxy}-2-[(prop-2-enyl)amino]-1-hydroxypropyl}-1*H*-indole-1-carboxylate* (*anti*/*syn*-**8e**; $R^1 = CH_2=CHCH_2$, $R^2 = {}^tBuMe_2Si$; *anti*/*syn* 1:7): From *trans*-**7e** ($R^1 = CH_2=CHCH_2$, $R^2 = {}^tBuMe_2Si$; *Entry 4*): Colorless oil. IR (neat): 3337 (NH, OH), 1735. ^{1}H-NMR (major isomer): −0.19, −0.12 (each *s*, 3 H, MeSi); 0.75, 1.67 (each *s*, 9 H, ^{t}Bu); 3.38 (*m*, H−C(2)); 3.66 (*dd*, *J* = 12.0, 2.8, 1 H, CHCH_2O); 3.81 (*dd*, *J* = 13.6, 7.2, 1 H, NCH_2CH); 3.91 (*dd*, *J* = 13.6, 6.4, 1 H, NCH_2CH); 3.95 (*dd*, *J* = 12.0, 7.2, 1 H, CHCH_2O); 5.34 (*d*, *J* = 10.0, 1 H, CH=CH_2); 5.44 (*d*, *J* = 16.8, 1 H, CH=CH_2); 5.84 (*s*, H−C(1)); 6.15 (*dddd*, *J* = 16.8, 10.0, 7.2, 6.4, C*H*=CH_2); 6.85 (*d*, *J* = 3.6, H−C(3′)); 7.14 (*d*, *J* = 8.2, H−C(5′)); 7.26 (*dd*, *J* = 6.4, 6.4, H−C(6′)); 7.55 (*d*, *J* = 3.6, H−C(2′)); 8.07 (*d*, *J* = 8.2, H−C(7′)). EI-MS: 460 (0.1, M^+), 214 (100).

4. *Ring-Opening Reactions of EDG-Substituted* trans-*Aziridine-2-carboxylates* trans-**3** *with AcOH* (*Table 3*). EDG-Substituted *trans*-aziridine-2-carboxylate *trans*-**3c** or *trans*-**3e** was treated with AcOH under the conditions noted in *Table 1*, and in some cases, CC (hexane/AcOEt) was carried out for the purification of ring-opened products.

tert-*Butyl (2*RS,*3*RS*)/(2*RS,*3*SR*)-3-(Acetyloxy)-3-(1,3-Benzodioxol-5-yl)-2-(benzylamino)propanoate* (*anti*/*syn*-**9c**; R^1 = Ac; *anti*/*syn* 1:10): From *trans*-**3c** in CH_2Cl_2 (*Entry 2*). Colorless needles. M.p. 74–75°. IR (neat): 1733 (CO). ^{1}H-NMR: 1.38 (*s*, 9 H × 1/11, Me_3C); 1.45 (*s*, 9 H × 10/11, Me_3C); 2.03 (*s*, 3 H × 10/11, COMe); 2.09 (*s*, 3 H × 1/11, COMe); 3.41 (*d*, *J* = 5.6, 1 H × 1/11, H−C(2)); 3.48 (*d*, *J* = 7.2, 1 H × 10/11, H−C(2)); 3.58, 3.82 (2*d*, *J* = 13.6, 2 H × 1/11, PhCH_2); 3.63, 3.83 (2*d*, *J* = 13.4, 2 H × 10/11, PhCH_2); 5.79 (*d*, *J* = 7.2, 1 H × 10/11, H−C(3)); 5.94 (*d*, *J* = 5.6, 1 H × 1/11, H−C(3)); 5.95 (*s*, 2 H, OCH_2O); 6.74 (*s*, 1 H × 1/11, arom. H); 6.76 (*s*, 1 H × 10/11, arom. H); 6.80 (*d*, *J* = 1.6, 1 H × 10/11, arom. H); 6.82 (*d*, *J* = 1.6, 1 H × 1/11, arom. H); 6.83 (*d*, *J* = 1.6, 1 H × 10/11, arom. H); 6.90 (*d*, *J* = 1.6, 1 H × 1/11, arom. H); 7.19–7.29 (*m*, 5 arom. H). ^{13}C-NMR (major isomer): 21.0; 28.0; 51.9; 65.0; 75.8; 77.3; 81.7; 101.0; 107.9; 121.3; 128.1; 128.2; 131.0; 139.4; 147.5; 169.5; 171.2. FAB-MS: 414 ($[M+H]^+$). Anal. calc. for $C_{23}H_{27}NO_6$: C 66.81, H 6.58, N, 3.39: found: C 66.76, H 6.56, N 3.30.

tert-*Butyl (2*RS,*3*RS*)/(2*RS,*3*SR*)-3-(1,3-Benzodioxol-5-yl)-2-(benzylamino)-3-methoxypropanoate* (*anti*/*syn*-**9c**; R^1 = Me; *anti*/*syn* 1:10): From *trans*-**3c** in MeOH (*Entry 3*). Colorless oil. IR (neat): 1725. ^{1}H-NMR (major isomer): 1.44 (*s*, ^{t}Bu); 3.21 (*s*, MeO); 3.30 (*d*, *J* = 7.0, H−C(2)), 3.59, 3.78 (2*d*, *J* = 13.4, PhCH_2); 4.22 (*d*, *J* = 7.0, H−C(3)); 5.96 (*s*, OCH_2O); 6.77–6.80 (*m*, 3 arom. H); 7.16–7.26 (*m*, 5 arom. H). ^{13}C-NMR (major isomer): 28.0; 51.7; 57.0; 66.7; 75.8; 81.1; 84.6; 100.9; 107.6; 107.8; 121.4; 126.9; 128.1; 128.2; 132.4; 139.6; 147.3; 147.7; 172.4. EI-MS: 385 (1, M^+), 165 (100).

*Ethyl (2*RS,*3*SR*)-3-(Acetyloxy)-2-(benzylamino)-3-[1-{(*tert-*butoxy)carbonyl}-1H-indol-4-yl]propanoate* (*syn*-**9e**; R^1 = Ac): From *trans*-**3e** without solvent (*Entry 4*). Pale yellow oil. IR (neat): 3340 (NH), 1736 (CO). ^{1}H-NMR: 1.19 (*t*, *J* = 7.1, *Me*CH_2); 1.67 (*s*, ^{t}Bu); 2.05 (*s*, MeCO); 3.56, 3.77 (2*d*, *J* = 13.6, PhCH_2); 3.78 (*d*, *J* = 7.0, H−C(2)); 4.07–4.17 (*m*, MeCH_2O); 6.23 (*d*, *J* = 7.0, H−C(3)); 6.70 (*d*, *J* = 3.8, H−C(3′)); 7.09–7.11 (*m*, 2 arom. H); 7.18–7.21 (*m*, 4 arom. H); 7.25–7.29 (*m*, 1 arom. H); 7.57 (*d*, *J* = 3.8, H−C(2′)); 8.13 (*d*, *J* = 8.2, H−C(7′)). EI-MS: 480 (3, M^+), 246 (100).

5. *Reactions of* **3c** *with C-Nucleophiles* (*Table 4*). A mixture of *trans*-**3c** and a C-nucleophile in CH_2Cl_2 in either the presence or absence of a catalyst was stirred at r.t., 30°, 0°, or 40° for an appropriate time under Ar. Workup followed by purification by CC afforded a 3-aryl-3-(1,3-benzodioxol-5-yl)-2-(benzylamino)propanonate **10**.

tert-*Butyl (2*RS,*3*SR*)-3-(1,3-Benzodioxol-5-yl)-2-(benzylamino)-3-(1*H*-indol-3-yl)propanoate* (*anti*-**10a**): With 1*H*-indole in the presence of $InCl_3$ (*Entry 1*). Colorless solid. M.p. 170–172°. IR (neat): 3418 (NH); 1721, 1706 (CO). ^{1}H-NMR: 1.25 (*s*, ^{t}Bu); 3.64, 3.86 (2*d*, *J* = 13.2, PhCH_2); 3.84 (*d*, *J* = 7.2, H−C(2)); 4.51 (*d*, *J* = 7.2, H−C(3)); 5.88, 5.89 (2*d*, *J* = 1.2, OCH_2O); 6.68 (*d*, *J* = 7.9, 1 arom. H); 6.79 (*d*, *J* = 1.5, 1 arom. H); 6.81 (*dd*, *J* = 7.9, 1.6, 1 arom. H); 7.02 (*dd*, *J* = 7.5, 7.1, 1 arom. H); 7.13 (*dd*, *J* = 7.5, 7.1, 2 arom. H); 7.22–7.31 (*m*, 6 arom. H); 7.45 (*d*, *J* = 7.9, 1 arom. H); 7.99 (br. *s*, NH). ^{13}C-

NMR: 27.8; 45.3; 50.6; 52.3; 65.5; 81.0; 100.8; 107.8; 109.2; 110.9; 117.0; 119.2; 119.3; 121.9; 122.0; 126.9; 127.0; 128.2; 128.3; 134.9; 135.9; 139.9; 146.2; 147.4; 173.1. EI-MS: 470 (2, M^+); 250 (100), 91 (36). Anal. calc. for $C_{29}H_{30}N_2O_4$: C 74.02, H 6.43, N 5.95; found: C 74.01, H 6.39, N 5.76.

Crystal Data of **10a**: $C_{29}H_{30}N_2O_4$, M_r 470.55; monoclinic; $a=20.4716(12)$, $b=6.0519(4)$, $c=19.5419(12)$ Å, $\beta=93.2800(10)^\circ$, $V=2417.1(3)$ Å^3; $T=150$ K, space group $P2_1/c$ (no. 14); $Z=4$; μ(Mo-K_α) = 0.086 mm^{-1}; 13787 reflections measured, 5465 unique ($R_{int}=0.0407$); 327 parameters refined; $R_1(F^2>2\sigma(F^2))=0.0410$, $wR(F^2)=0.1057$. CCDC-614921 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif.

tert-*Butyl (2*RS,*3*SR*)-3-(1,3-Benzodioxol-5-yl)-2-(benzylamino)-3-(2-methyl-1*H*-indol-3-yl)propanoate* (*anti*-**10b**): With 2-methyl-1*H*-indole in the presence of $InCl_3$ (*Entry 3*). Yellow oil. IR (neat): 3407 (NH), 1718 (CO). ^{1}H-NMR: 0.89 (*s*, ^{t}Bu); 2.38 (*s*, MeC); 3.70, 3.86 (2*d*, *J* = 13.0, PhCH_2); 4.18 (*d*, *J* = 11.2, H–C(2)); 4.24 (*d*, *J* = 11.2, H–C(3)); 5.57, 5.87 (2*d*, *J* = 1.6, OCH_2O); 6.67 (*d*, *J* = 8.0, 1 arom. H); 6.81 (*dd*, *J* = 8.0, 1.6, 1 arom. H); 6.85 (*d*, *J* = 1.6, 1 arom. H); 6.96–7.05 (*m*, 2 arom. H); 7.19 (*d*, *J* = 8.0, 1 arom. H); 7.27–7.35 (*m*, 5 arom. H); 7.49 (*d*, *J* = 8.0, 1 arom. H); 7.70 (br. *s*, NH). ^{13}C-NMR: 12.2; 27.9; 45.4; 52.3; 63.8; 80.3; 100.7; 107.8; 109.0; 110.0; 112.1; 119.2; 119.8; 120.7; 121.1; 127.1; 127.8; 128.3; 128.6; 131.5; 135.1; 135.8; 139.6; 145.6; 147.4; 173.9. EI-MS: 484 (2, M^+), 264 (100), 91 (30). HR-FAB-MS: 485.2488 ([M+H]$^+$, $C_{30}H_{33}N_2O_4^+$; calc. 485.2440).

tert-*Butyl (2*RS,*3*RS*)/(2*RS,*3*SR*)-3-(1,3-Benzodioxol-5-yl)-2-(benzylamino)-3-(1*H*-pyrrol-2-yl)propanoate* (*anti*/*syn*-**10c**; *anti*/*syn* 4:1): With 1*H*-pyrrole in the presence of $InCl_3$ (*Entry 4*). Yellow oil. IR (neat): 3372 (NH); 1719 (CO). ^{1}H-NMR: 1.22 (*s*, 9 H×1/5, ^{t}Bu); 1.45 (*s*, 9 H×4/5, ^{t}Bu); 3.60, 3.86 (2*d*, *J* = 12.6, 2 H×4/5, PhCH_2); 3.65, 3.80 (2*d*, *J* = 12.8, 2 H×1/5, PhCH_2); 3.65 (*d*, *J* = 9.2, 1 H×1/5, H–C(2)); 3.73 (*d*, *J* = 4.5, 1 H×4/5, H–C(2)); 4.04 (*d*, *J* = 9.2, 1 H×1/5, H–C(3)); 4.44 (*d*, *J* = 4.5, 1 H×4/5, H–C(3)); 5.88, 5.90 (2*m*, 2 H×4/5, OCH_2O); 5.93 (*s*, 2 H×1/5, OCH_2O); 5.95 (br. *s*, 1 H×4/5, arom. H); 6.05 (*dd*, *J* = 2.8, 1 H×1/5, arom. H); 6.10 (*d*, *J* = 3.0, 1 H×4/5, arom. H); 6.59 (*dd*, *J* = 7.6, 1.6, 1 H×4/5, arom. H); 6.66–6.68 (*m*, 2 H×4/5, arom. H); 6.70–6.78 (*m*, 4 H×1/5, arom. H); 7.28–7.37 (*m*, 5 arom. H); 9.85 (br. *s*, 1 H×4/5, NH); 10.02 (br. *s*, 1 H×1/5, NH). ^{13}C-NMR (major isomer): 28.1; 45.7; 52.5; 65.0; 81.8; 100.9; 106.0; 107.8; 107.9; 109.0; 116.4; 121.7; 127.3; 128.4; 128.6; 132.5; 133.5; 139.4; 146.4; 147.5; 172.3. EI-MS: 420 (4, M^+), 200 (100). HR-FAB-MS: 421.2122 ([M+H]$^+$, $C_{25}H_{29}N_2O_4^+$; calc. 421.2127).

tert-*Butyl (2*RS,*3*RS*)/(2*RS,*3*SR*)-3-(1,3-Benzodioxol-5-yl)-2-(benzylamino)-3-(furan-2-yl)propanoate* (*anti*/*syn*-**10d**; *anti*/*syn* 10:1). With furan in the presence of $InCl_3$ (*Entry 6*). Light brown oil. IR (neat): 3338 (NH); 1719 (CO). ^{1}H-NMR (major isomer): 1.20 (*s*, ^{t}Bu); 3.60, 3.83 (2*d*, *J* = 13.4, PhCH_2); 3.69 (*d*, *J* = 8.8, H–C(2)); 4.16 (*d*, *J* = 8.8, H–C(3)); 5.90, 5.91 (2*d*, *J* = 1.2, OCH_2O); 6.13 (*d*, *J* = 3.2, 1 arom. H); 6.29 (*dd*, *J* = 3.0, 1.7, 1 arom. H); 6.70 (*d*, *J* = 8.0, 1 arom. H); 6.76 (*dd*, *J* = 8.0, 1.6, 1 arom. H); 6.86 (*d*, *J* = 1.6, 1 arom. H); 7.18–7.32 (*m*, 6 arom. H). ^{13}C-NMR (major isomer): 27.8; 48.5; 52.1; 64.9; 81.1; 100.9; 107.1; 107.9; 109.4; 110.2; 122.2; 126.9; 128.20; 128.24; 132.8; 139.7; 141.5; 146.5; 147.4; 154.4; 172.6. EI-MS: 421 (2, M^+), 220 (51), 164 (100), 91 (55). HR-FAB-MS: 422.1964 ([M+H]$^+$, $C_{25}H_{28}NO_5^+$; calc. 422.1967).

tert-*Butyl (2*RS,*3*SR*)/(2*RS,*3*RS*)-3-(1,3-Benzodioxol-5-yl)-2-(benzylamino)-3-(2,4-dimethoxyphenyl)propanoate* (*anti*/*syn*-**10e**; *anti*/*syn* 2:1): With 1,3-dimethoxybenzene in the presence of $InCl_3$ (*Entry 7*): Yellow oil. IR (neat): 3332 (NH); 1718 (CO). ^{1}H-NMR (major isomer): 1.25 (*s*, ^{t}Bu); 3.82, 3.59 (2*d*, *J* = 13.4, PhCH_2); 3.71, 3.78 (2*s*, 2 MeO); 3.75 (*d*, *J* = 10.4, H–C(2)); 4.47 (*d*, *J* = 10.4, H–C(3)); 5.84, 5.85 (2*d*, *J* = 1.5, OCH_2O); 6.35–6.41 (*m*, 2 arom. H); 6.63 (*d*, *J* = 8.4, 1 arom. H); 6.71–6.77 (*m*, 2 arom. H); 7.01 (*d*, *J* = 8.4, 1 arom. H); 7.19–7.32 (*m*, 6 arom. H). ^{13}C-NMR (major isomer): 27.8; 46.3; 51.9; 55.26; 55.29; 64.3; 80.8; 98.6; 100.6; 104.1; 107.7; 109.5; 122.0; 122.3; 126.9; 128.1; 128.4; 128.6; 135.5; 139.7; 145.8; 147.1; 158.2; 159.3; 173.7. EI-MS: 491 (0.2, M^+), 271 (100), 135 (33). HR-FAB-MS: 492.2421 ([M+H]$^+$, $C_{29}H_{33}NO_6^+$; calc. 492.2308).

tert-*Butyl (2*RS,*3*SR*)/(2*RS,*3*RS*)-3-(1,3-Benzodioxol-5-yl)-2-(benzylamino)-3-[4-(dimethyamino)-phenyl]propanoate* (*anti*/*syn*-**10f**; *anti*/*syn* 3.6:1). With *N*,*N*-dimethylaniline in the presence of $InCl_3$ (*Entry 9*): Yellow oil. IR (neat): 3394 (NH); 1708 (CO). ^{1}H-NMR (major isomer): 1.23 (*s*, ^{t}Bu); 2.86 (*s*, Me_2N); 3.62, 3.84 (2*d*, *J* = 13.2, PhCH_2); 3.75 (*d*, *J* = 9.6, H–C(2)); 3.96 (*d*, *J* = 9.6, H–C(3)); 5.88, 5.89 (2*d*, *J* = 1.5, OCH_2O); 6.61 (*d*, *J* = 8.8, 2 arom. H); 6.68–6.70 (*m*, 3 arom. H); 7.11 (*d*, *J* = 8.8, 2 arom. H); 7.21–7.31 (*m*, 5 arom. H). ^{13}C-NMR (major isomer): 27.9; 46.3; 51.9; 55.3; 64.2; 80.8; 98.6; 100.6;

104.1; 107.7; 109.4; 122.2; 126.9; 128.1; 128.5; 135.5; 139.7; 145.8; 147.0; 158.2; 159.3; 173.7. EI-MS: 474 (1, M^+), 254 (100), 91 (17). Anal. calc. for $C_{29}H_{34}N_2O_4$: C 73.39, H 7.22, N 5.90; found: C 73.33, H 7.18, N 5.68.

6. *Synthesis of the Amphetamine-Type Compound (+)-***14**. *(+)-*tert*-Butyl (2*S*)-3-(1,3-benzodioxol-5-yl)-2-{[(*tert*-butoxy)carbonyl]amino}propanoate* ((+)-**11**). A mixture of (+)-*trans*-**3c** (0.457 g, 1.29 mmol; 87% ee), Boc_2O (0.300 g, 1.37 mmol), and 20% $Pd(OH)_2/C$ (0.134 g) in MeOH (8 ml) was stirred at r.t. for 6.5 h under H_2. After filtration of the mixture through a *Celite* pad, the filtrate was concentrated. Purification of the residue by CC (hexane/AcOEt 10:1) afforded (+)-**11** (0.457 g, 97%), a part of which was recrystallized from hexane. Colorless prisms. M.p. 118–119° $[\alpha]_D^{24} = +26.1$ ($c = 1.0$, $CHCl_3$). IR (neat): 3343 (NH), 1720 (CO), 1702 (CO). ^{1}H-NMR: 1.43 (*s*, 2 ^{t}Bu); 2.97 (br. *s*, CH_2(3)); 4.38 (*q*-like, $J = 7.2$, H–C(2)); 4.97 (br. *d*, $J = 8.8$, NH); 5.92, 5.93 (2*d*, $J = 0.8$, OCH_2O); 6.61 (*dd*, $J = 7.6$, 1.6, 1 arom. H); 6.66 (*d*, $J = 1.6$, 1 arom. H); 6.72 (*d*, $J = 7.6$, 1 arom. H). EI-MS: 365 (54, M^+), 236 (100). Anal. calc. for $C_{19}H_{27}NO_6$: C 62.45, H 7.45, N 3.83; found: C 62.24, H 7.51, N 3.81.

*(–)-(2*S*)-3-(1,3-Benzodioxol-5-yl)-2-{[(*tert*-butoxy)carbonyl]amino}propan-1-ol* (=*(–)-*tert*-Butyl [(1*S*)-2-(1,3-Benzodioxol-5-yl)-1-(hydroxymethyl)ethyl]benzylcarbamate*; (–)-**12**). To a soln. of (+)-**11** (0.456 g, 1.25 mmol) and $LiBH_4$ (0.123 g, 5.64 mmol) in THF (6 ml) was added anh. EtOH (0.2 ml, 3.41 mmol). The mixture was stirred at r.t. for 1 h and then refluxed for 17 h. After addition of H_2O (1 ml) and 20% NaOH soln. (1 ml), the mixture was extracted with AcOEt (50 ml). The org. soln. was dried ($MgSO_4$) and concentrated: (–)-**12** (0.325 g, 88%). Colorless prisms. M.p. 76–77° (hexane). $[\alpha]_D^{24} = -21.6$ ($c = 1.0$, $CHCl_3$). IR (neat): 3357 (NH, OH), 1685 (CO). ^{1}H-NMR: 1.43 (*s*, ^{t}Bu); 2.27 (br. *s*, NH or OH); 2.75 (*d*, $J = 7.1$, CH_2(3)); 3.52–3.70 (*m*, CH_2(1)); 3.79 (br. *s*, H–C(2)); 4.71 (br. *s*, NH or OH); 5.93 (*s*, OCH_2O); 6.65 (*dd*, $J = 8.0$, 1.6, 1 arom. H); 6.71 (*d*, $J = 1.6$, 1 arom. H); 6.74 (*d*, $J = 8.0$, 1 arom. H). EI-MS: 295 (100, M^+), 239 (100), 178 (99). Anal. calc. for $C_{15}H_{21}NO_5$: C 61.00, H 7.17, N 4.74; found: C 60.93, H 7.27, N 4.60.

*(+)-(2*S*)-3-(1,3-Benzodioxol-5-yl)-2-{[(*tert*-butoxy)carbonyl]amino}propyl Iodide* (=*(+)-*tert*-Butyl [(1*S*)-2-(1,3-Benzodioxol-5-yl)-1-(iodomethyl)ethyl]benzylcarbamate*; (+)-**13**). A soln. of PPh_3 (0.582 g, 2.2 mmol), I_2 (0.567 g, 2.23 mmol), and 1*H*-imidazole (0.153 g, 2.2.5 mmol) in CH_2Cl_2 (5 ml) was stirred at 0° for 0.5 h. To the soln. was added a soln. of (–)-**12** (0.299 g, 1.01 mmol) in CH_2Cl_2 (7 ml) at r.t., and then the mixture was stirred at r.t. for 3 h. After addition of sat. aq. $Na_2S_2O_3$ soln. (5 ml), the mixture was extracted with CH_2Cl_2 (2×5 ml). The org. soln. was dried (Na_2SO_4) and concentrated. Purification of the residue by CC (hexane/AcOEt 3:1) afforded (+)-**13** (0.269 g, 66%). Colorless prisms. M.p. 86–87° (hexane). $[\alpha]_D^{24} = +16.2$ ($c = 1.0$, $CHCl_3$). IR (neat): 3361 (NH), 1676 (CO). ^{1}H-NMR: 1.44 (*s*, ^{t}Bu); 2.68 (*dd*, $J = 13.3$, 8.2, 1 H, CH_2(3)); 2.82 (*dd*, $J = 13.3$, 5.6, 1 H, CH_2(3)); 3.18 (*dd*, $J = 10.0$, 3.8, 1 H, CH_2(1)); 3.35–3.45 (*m*, H–C(2)); 3.52 (br. *s*, 1 H, CH_2(1)); 4.66 (br. *s*, NH); 5.94 (*s*, OCH_2O); 6.70–6.76 (*m*, 3 arom. H). EI-MS: 405 (19, M^+), 135 (100). Anal. calc. for $C_{15}H_{20}INO_4$: C 44.46, H 4.97, N 3.46; found: C 44.93, H 5.04, N 3.23.

*(+)-(2*R*)-1-(1,3-Benzodioxol-5-yl)-2-{[(*tert*-butoxy)carbonyl]amino}propane* (=*(+)-*tert*-Butyl [(1*R*)-2-(1,3-Benzodioxol-5-yl)-1-methylethyl]carbamate*; (+)-**14**). *N-Selectride*® (0.51 ml, 0.51 mmol) was added to a soln. of (+)-**13** (0.172 g, 0.42 mmol) in THF (5 ml) at –20°, and the mixture was stirred at –5° for 1.5 h. After addition of H_2O (0.4 ml), followed by a mixture of H_2O (3.5 ml), 30% H_2O_2 soln. (0.5 ml), and K_2CO_3 (0.150 g), the mixture was stirred at r.t. for 1 h. After evaporation, the residue was extracted with $CHCl_3$ (30 ml). The org. soln. was dried (Na_2SO_4) and concentrated. Purification of the residue by CC (hexane/AcOEt 30:1) afforded (+)-**14** (0.104 g, 88%). Colorless prisms. M.p. 60–62°. Chiral HPLC: *Daicel ChiralCel AS-H*; hexane/^{i}PrOH 9:1, 1 ml/min, 254 nm): t_R 6.6 (minor) and 10.9 min (major); 97% ee. $[\alpha]_D^{23} = +5.6$ ($c = 1.0$, $CHCl_3$). IR (neat): 3342 (NH), 1701 (CO). ^{1}H-NMR: 1.08 (*d*, $J = 6.6$, Me–C(2)); 1.43 (*s*, ^{t}Bu); 2.57 (*dd*, $J = 13.4$, 7.3, 1 H, CH_2(1)); 2.75 (*dd*, $J = 13.4$, 5.4, 1 H, CH_2(1)); 3.83 (br. *s*, H–C(2)); 4.35 (br. *s*, NH); 5.93 (*s*, OCH_2O); 6.62 (*d*, $J = 7.8$, 1 arom. H); 6.68 (*s*, 1 arom. H); 6.74 (*d*, $J = 7.8$, 1 arom. H). EI-MS: 279 (32, M^+), 162 (32), 135 (100). HR-FAB-MS: 280.1559 ($[M+H]^+$, $C_{15}H_{22}NO_4^+$; calc. 280.1548).

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