Synthesis of the Adrenergic Bronchodilators (*R*)-Terbutaline and (*R*)-Salbutamol from (*R*)-Cyanohydrins[1]

Franz Effenberger* and Jürgen Jäger[2]

Institut für Organische Chemie der Universität Stuttgart, Pfaffenwaldring 55, D-70569 Stuttgart, Germany

Received January 3, 1997

Stereoselective syntheses of (*R*)-terbutaline and (*R*)-salbutamol acetal, which are important bronchodilators, starting from O-protected (*R*)-cyanohydrins are described. (*R*)-Terbutaline hydrochloride (*R*)-**9**·HCl is obtained in an overall yield of 44% with >98% ee from the O-bisallyl-protected cyanohydrin (*R*)-**4k** via a Ritter N-tertiary butylation to the amide (*R*)-**6a**, hydrogenation to the amino alcohol (*R*)-**7a**, and deprotection of the hydroxyl functions. (*R*)-Salbutamol acetals (*R*)-**7b**,**c** can be obtained from the corresponding O-protected (*R*)-cyanohydrins either via the route described for (*R*)-terbutaline or via selective hydrogenation of the protected cyanohydrin (*R*)-**11** to the imino derivative, transimination with *tert*-butylamine, followed by hydrogenation with $NaBH_4$ to give the 2-amino alcohol derivative (*R*)-**12**. Desilylation of (*R*)-**12** to (*R*)-**7c** is performed with $LiAlH_4$. Hydrolytic cleavage of the acetals (*R*)-**7b** and **c** to (*R*)-salbutamol was not yet possible without racemization.

Introduction

The 2-amino alcohol skeleton is a structural unit found in a substantial number of bioactive natural products.[3] Since many of these compounds are of great importance as pharmaceuticals,[4] a variety of methods for their stereoselective synthesis have been developed.[3,5] Among the 2-amino alcohols, compounds which derive or are analogues of (*R*)-(−) adrenaline or of L-(−) ephedrine are widely used in the treatment of cardiovascular disease and as bronchodilators.[4] Although it is very well known,[4,6] that only the (*R*)-configuration in the adrenaline-type compounds and the (1*R*,2*S*)-configuration in the ephedrine-type compounds are of pharmacological relevance, today practically all of these pharmaceuticals are used as racemates. Because of possible side effects of the undesired stereoisomers,[7] the stereoselective synthesis of 2-amino alcohols became an important objective in the last years.

Optically active cyanohydrins, which became easily available in the last decade,[8] are excellent starting compounds for the stereoselective synthesis of 2-amino alcohols. (1*R*)-2-Amino alcohols can be prepared without any racemization either directly[9] from (*R*)-cyanohydrins or from their O-protected derivatives[10] with various hydrogenating agents. (1*R*,2*S*)-2-Amino alcohols are accessible with high diastereoselectivity from O-protected (*R*)-cyanohydrins by addition of a Grignard reagent to the nitrile group and subsequent hydrogenation of the primarily obtained imino intermediate.[11] Alkyl substituents at the amino group can be introduced either by a method involving the reaction of the imino intermediate with a primary amine (transimination) and subsequent hydrogenation[12] or alternatively—with the exception of the *tert*-butyl group—by reductive N-alkylation of the 2-amino alcohols.[13]

The biological activity and thus the pharmacological application of 2-amino-1-phenyl alcohols significantly depends on the kind of substituents at the amino group as well as in the phenyl ring. Particularly interesting sympathomimetics, i.e. substances that mimic the action of adrenaline and noradrenaline on sympathetic nerves, contain hydroxy groups in the ring which are required for the interactions with adrenergic receptors. On the other hand, the size of the N-substituents influences decisively the interaction with α- or *β*-receptors; an

⊗ Abstract published in *Advance ACS Abstracts,* May 15, 1997.

(1) Enzyme-catalyzed reactions, Part 28. Part 27: Effenberger, F.; Eichhorn, J. *Tetrahedron: Asymm.* **1997**, *8*, 469−476.

(2) Jäger, J. Part of Dissertation, Universität Stuttgart 1996.

(3) Kunieda, T.; Ishizuka, T. *Stud. Nat. Prod. Chem.* **1993**, *12*, 411−444.

(4) (a) Engel, J. *Chem.-Ztg.* **1982**, *106*, 169−183. (b) Kleemann, A.; Engel, J. *Pharmazeutische Wirkstoffe, Synthesen, Patente, Anwendungen*, 2nd ed.; Thieme: Stuttgart, 1982; and supplementary volume 1987.

(5) (a) Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1141−1143. (b) Reetz, M. T.; Drewes, M. W.; Lennick, K.; Schmitz, A.; Holdgrün, X. *Tetrahedron: Asymm.* **1990**, *1*, 375−378. (c) Yamashita, H. *Chem. Lett.* **1987**, 525−528. (d) Koppenhoefer, B.; Trettin, U.; Wächtler, A. *Synthesis* **1994**, 1141−1142. (e) Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629−631. (f) Corey, E. J.; Link, J. O. *J. Org. Chem.* **1991**, *56*, 442−444. (g) Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763−784. (h) Kawaguchi, T.; Saito, K.; Matsuki, K.; Iwakuma, T.; Takeda, M. *Chem. Pharm. Bull.* **1993**, *41*, 639−642. (i) Li, G.; Chang, H.-T.; Sharpless, K.-B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 451−454. (j) Hong, Y.; Gao, Y.; Nie, X.; Zepp, C. M. *Tetrahedron Lett.* **1994**, *35*, 5551−5554. (k) Oppolzer, W.; Tamura, O.; Sundarababu, G.; Signer, M. *J. Am. Chem. Soc.* **1992**, *114*, 5900−5902. (l) An, B.; Kim, H.; Cha, J. K. *J. Org. Chem.* **1993**, *58*, 1273−1275.

(6) (a) Hawkins, C. J.; Klease, G. T. *J. Med. Chem.* **1973**, *16*, 856−857. (b) Wetterlin, K. *J. Med. Chem.* **1972**, *15*, 1182−1183.

(7) Barberich, T. J.; Young, J. W. (Sepracor, Inc.), US Pat. No. 5,-362,755 (Nov. 8, 1994).

(8) (a) Effenberger, F. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1555−1564. (b) North, M. *Synlett* **1993**, 807−820. (c) Kanerva, L. T. *Acta Chem. Scand.* **1996**, *50*, 234−242.

(9) Ziegler, T.; Hörsch, B.; Effenberger, F. *Synthesis* **1990**, 575−578.

(10) (a) Elliott, J. D.; Choi, V. M. F.; Johnson, W. S. *J. Org. Chem.* **1983**, *48*, 2294−2295. (b) Ohta, H.; Miyamae, Y.; Tsuchihashi, G. *Agric. Biol. Chem.* **1986**, *50*, 3181−3184; *ibid* **1989**, *53*, 215−222. (c) Matsuo, N.; Ohno, N. *Tetrahedron Lett.* **1985**, *26*, 5533−5534.

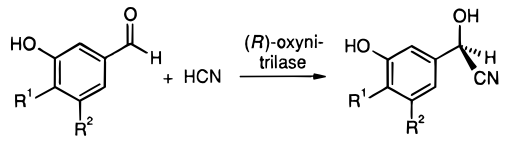
(11) (a) Brussee, J.; Dofferhoff, F.; Kruse, C. G.; van der Gen, A. *Tetrahedron* **1990**, *46*, 1653−1658. (b) Jackson, W. R.; Jacobs, H. A.; Matthews, B. R.; Jayatilake, G. S.; Watson, K. G. *Tetrahedron Lett.* **1990**, *31*, 1447−1450. (c) Effenberger, F.; Gutterer, B.; Ziegler, T. *Liebigs Ann. Chem.* **1991**, 269−273.

(12) (a) Brussee, J.; van der Gen, A. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 25−26. (b) Zandbergen, P.; van den Nieuwendijk, A. M. C. H.; Brussee, J.; van der Gen, A.; Kruse, C. G. *Tetrahedron* **1992**, *48*, 3977−3982. (c) de Vries, E. F. J.; Brussee, J.; Kruse, C. G.; van der Gen, A. *Tetrahedron: Asymm.* **1994**, *5*, 377−386.

(13) (a) Effenberger, F.; Gutterer, B.; Jäger, J. *Tetrahedron: Asymm.* **1997**, *8*, 459−467. (b) Noe, C. R.; Knollmüller, M.; Gärtner, P.; Fleischhacker, W.; Katikarides, E. *Monatsh. Chem.* **1995**, *126*, 557−564.

S0022-3263(97)00032-7 CCC: $14.00

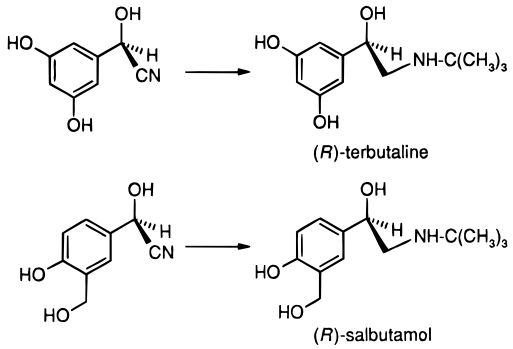
Scheme 1



1a-e	1, 2	a	b	c	d	e	(*R*)-2a-e
	R^1	H	CH_3	CH_3O	H	OH	
	R^2	H	H	H	OH	H	

exclusively β_2-adrenergic activity results by introduction of a *tert*-butyl substituent in the amino function. Therefore, many of the important adrenergic bronchodilators like terbutaline or salbutamol contain hydroxy groups in the phenyl ring and *tert*-butyl groups in the amino function.

For the synthesis of (*R*)-terbutaline and (*R*)-salbutamol, starting from optically active cyanohydrins, it is of interest first to see if the corresponding (*R*)-cyanohydrins can be prepared and if the *tert*-butylamino substituent can be introduced using the nitrogen of the cyanohydrins.



Jackson et al. have already synthesized successfully some biologically active 2-amino-1-phenylethanols starting from (*R*)-cyanohydrins,[14a] but in the preparation of (*R*)-terbutaline predominantly racemization was observed.[14b]

In contrast to the published results,[14b] in the present publication we describe the preparation of optically pure (*R*)-terbutaline starting from (*R*)-cyanohydrins. We also describe the synthesis of O-protected (*R*)-salbutamol. All attempts, however, to remove the acetal protecting groups have not been successful so far.

Results and Discussion

(*R*)-Oxynitrilase-Catalyzed Addition of HCN to Unprotected and O-Protected Hydroxybenzaldehydes. Previous publications[15,8a] have demonstrated that (*R*)-oxynitrilase [EC 4.1.2.10] accepts 3-hydroxybenzaldehyde as substrate but not 4-hydroxybenzaldehyde.

Now we have investigated the reaction of a variety of substituted hydroxy- and dihydroxybenzaldehydes **1** with HCN under (*R*)-oxynitrilase catalysis in diisopropyl ether as solvent as well as in aqueous citrate buffer to give the (*R*)-cyanohydrins (*R*)-**2** (Scheme 1). The chemical and optical yields obtained are summarized in Table 1.

As can be seen in Table 1, in diisopropyl ether relatively good chemical and high optical yields are attainable

Table 1. Formation of Hydroxybenzaldehyde Cyanohydrins (*R*)-2 by (*R*)-Oxynitrilase-Catalyzed HCN Addition to Aldehydes 1 in Diisopropyl Ether and Citrate Buffer, Respectively

			(*R*)-cyanohydrins **2**		
aldehydes **1**	(*R*)-oxynitrilase (U/mmol **1**)	reactn time(h)		conversion (%)[a]	*ee* (%)
1a	50 (100)[b]	25 (60)[b]	**2a**	76 (90)[b]	98 (97)[b]
1b	50	25	**2b**	67	98
1c	130	25	**2c**	35	90
1d	50 (100)[b]	40 (130)[b]	**2d**	58 (30)[b]	61 (54)[b]
	100	26		70	69
1e	100 (100)[b]	20 (85)[b]	**2e**	60 (29)[b]	0 (21)[b]

[a] Determined by ^{1}H NMR spectroscopy. [b] Conversion in citrate buffer (0.05 M, pH 3.25) in parentheses.

for the (*R*)-3-hydroxybenzaldehyde cyanohydrins (*R*)-**2a**,**b** whereas (*R*)-**2c** was obtained with only 35% conversion and 90% ee. (*R*)-3,5-Dihydroxybenzaldehyde cyanohydrin ((*R*)-**2d**), an important starting compound for the synthesis of (*R*)-terbutaline, is accessible, however, only with ee-values of 61−69% (Table 1). The enzyme-catalyzed reaction in aqueous citrate buffer (pH 3.25) generally requires higher amounts of enzyme and longer reaction times (Table 1), and moreover the substrate concentration is lower due to lesser solubility of the aldehydes **1** in water. Only with (*R*)-**2a** in citrate buffer were results comparable to those in diisopropyl ether. 3,4-Dihydroxybenzaldehyde **1e** is a poor substrate for (*R*)-oxynitrilase in both solvents (Table 1).

Because of these results we have investigated generally the acceptance of O-protected hydroxybenzaldehydes as substrates for (*R*)-oxynitrilase. In view of the different follow-up reactions of the cyanohydrins, compounds were chosen which are stable against both organometallic compounds and acids.

The protected hydroxy- and dihydroxybenzaldehydes **3b**,**c**,**f**,**k**,**n**,**o** were prepared based on known procedures for the protection of the hydroxybenzaldehydes **3a**,**d**,**e**,**g-j**,**l**,**m**[16] (see Experimental Section). The enzyme-catalyzed addition of HCN to the protected aldehydes **3a-o** to give the corresponding (*R*)-cyanohydrins (*R*)-**4a-o** was performed in diisopropyl ether (Scheme 2, Table 2).

With the exception of a few examples,[13a,17] the influence of protecting groups in hydroxybenzaldehydes in the (*R*)-oxynitrilase-catalyzed HCN addition has not been described so far. As can be seen from Table 2, protected hydroxybenzaldehydes in general are accepted as substrates by (*R*)-oxynitrilase. The conversion, however, is not complete in all cases. Since addition of more enzyme does not increase the conversion, the equilibrium concentration of the reaction obviously is reached in these cases. From donor-substituted benzaldehydes it is known that the equilibrium concentration of the HCN addition is not completely on the product side.[18]

(14) (a) Brown, R. F. C.; Donohue, A. C.; Jackson, W. R.; McCarthy, T. D. *Tetrahedron* **1994**, *50*, 13739−13752. (b) Donohue, A. C.; Jackson, W. R. *Aust. J. Chem.* **1995**, *48*, 1741−1746.

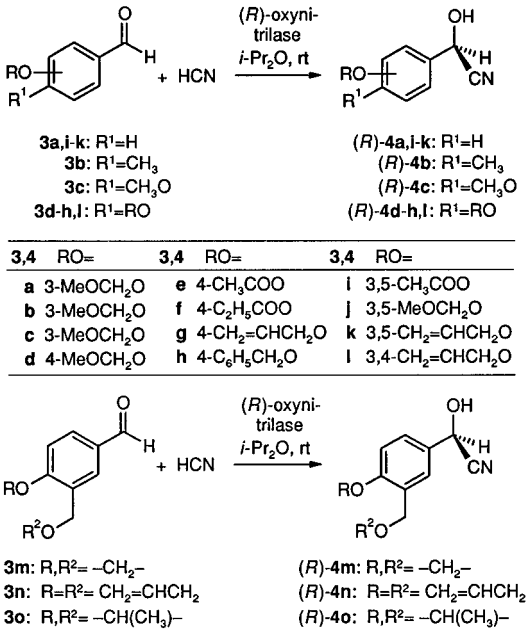
(15) Smitskamp-Wilms, E.; Brussee, J.; van der Gen, A.; van Scharrenburg, G. J. M.; Sloothaak, J. B. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 209−215.

(16) (a) Edwards, R. L.; Mir, I. *J. Chem. Soc. (C)* **1967**, 411−413. (b) Yardley, J. P.; Fletcher, H. *Synthesis* **1976**, 244. (c) Papadakis, P. E. *J. Am. Chem. Soc.* **1945**, *67*, 1799−1800. (d) Späth, E.; Liebherr, F. *Ber. Dtsch. Chem. Ges.* **1941**, *74*, 869−872. (e) Claisen, L.; Eisleb, O. *Liebigs Ann. Chem.* **1913**, *401*, 21−119. (f) Bergmann, E. D.; Sulzbacher, M. *J. Org. Chem.* **1951**, *16*, 84−89. (g) Nelson, W. L.; Burke, T. R. *J. Med. Chem.* **1979**, *22*, 1082−1088. (h) Duffley, R. P.; Handrick, G. R.; Uliss, D. B.; Lambert, G.; Dalzell, H. C.; Razdan, R. K. *Synthesis* **1980**, 733−736. (i) Denis, G.; Delmas, M.; Gaset, A. *J. Heterocycl. Chem.* **1984**, *21*, 517−519.

(17) Effenberger, F.; Gutterer, B.; Syed, J. *Tetrahedron: Asymm.* **1995**, *6*, 2933−2943.

(18) (a) Ching, W.-M.; Kallen, R. G. *J. Am. Chem. Soc.* **1978**, *100*, 6119−6124. (b) Young, P. R.; McMahon, P. E. *J. Am. Chem. Soc.* **1979**, *101*, 4678−4680.

Scheme 2



3,4	RO=	3,4	RO=	3,4	RO=
a	3-MeOCH$_2$O	**e**	4-CH$_3$COO	**i**	3,5-CH$_3$COO
b	3-MeOCH$_2$O	**f**	4-C$_2$H$_5$COO	**j**	3,5-MeOCH$_2$O
c	3-MeOCH$_2$O	**g**	4-CH$_2$=CHCH$_2$O	**k**	3,5-CH$_2$=CHCH$_2$O
d	4-MeOCH$_2$O	**h**	4-C$_6$H$_5$CH$_2$O	**l**	3,4-CH$_2$=CHCH$_2$O

Table 2. Formation of (*R*)-Cyanohydrins (*R*)-4a–o by (*R*)-Oxynitrilase-Catalyzed HCN Addition to the Protected Hydroxybenzaldehydes 3a–o in Diisopropyl Ether at Room Temperature

			(*R*)-cyanohydrins **4**		
aldehydes **3**	(*R*)-oxynitrilase (U/mmol **3**)	reactn time (h)		conversion (%)[a]	*ee* (%)
3a	100	24	**4a**	90	96.5
3b	40	40	**4b**	73	>98
3c	60	165	**4c**	54	81
3c	84	50[b]	**4c**	60	83
3d	42	26	**4d**[c]	85	94
3e	50	28	**4e**	90	93
3f	100	24	**4f**	92	95
3g	100	16	**4g**[d]	74	>99
3h	150	16	**4h**	48	>99
3i	100	43	**4i**	89	81
3j	50	45	**4j**	68	>99
3k	50	24	**4k**	92	>98
3l	100	24	**4l**	23	86.5
3m	60	18	**4m**	93	97
3n	100	72	**4n**	46	95
3o	60	17	**4o**	60	96

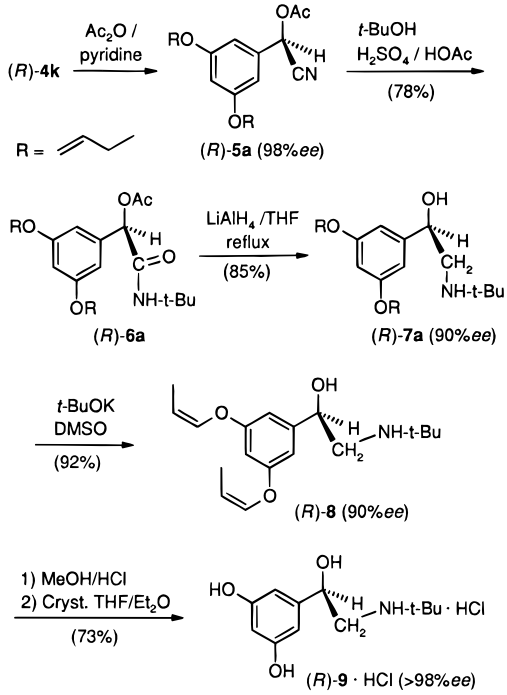
[a] Determined by ^{1}H NMR spectroscopy. [b] Reaction at 30 °C. [c] See ref 17. [d] Compare ref 22.

The (*R*)-cyanohydrins (*R*)-**4a**,**b**,**d**,**g** are accessible with high conversion (73–90%) and excellent enantiomeric excesses (94–99% ee) from the methoxymethyl-protected hydroxybenzaldehydes **3a**,**b**,**d** and 4-(allyloxy)benzaldehyde (**3g**).

Although 4-(benzyloxy)benzaldehyde (**3h**) is a poor substrate for (*R*)-oxynitrilase, the cyanohydrin (*R*)-**4h** is obtained with >99% ee. The conversion of 48%, however, is insufficient for a large scale preparation. The acyl-protected cyanohydrins (*R*)-**4e**,**f**,**i**, on the other hand, were obtained with lower ee-values (81–95% ee) but excellent conversion (Table 2).

The size of the protecting groups influences both the reaction rate and the conversion. So the conversion of aldehydes **3c** and **3n** with larger protecting groups is very slow, nevertheless (*R*)-**4n** was obtained even after long reaction time with 95% ee (Table 2). In the reaction of **3c**, however, neither the conversion nor the enantioselectivity could be improved by variation of reaction conditions (Table 2).

Scheme 3



With regard to the synthesis of (*R*)-terbutaline and (*R*)-salbutamol, the protected benzaldehydes **3k** and **3m** are the most suitable substrates. The corresponding (*R*)-cyanohydrins (*R*)-**4k** and (*R*)-**4m** can be obtained with high conversion and excellent optical yields >98% ee and 97% ee, respectively (Table 2).

Preparation of (*R*)-Terbutaline (*R*)-9 from (*R*)-3,5-Bis(allyloxy)benzaldehyde Cyanohydrin (*R*)-4k. Various procedures have been developed for preparing racemic terbutaline.[19] The most common route involves the reaction of 3,5-bis(benzyloxy)bromoacetophenone with benzyl-*tert*-butylamine and subsequent catalytic hydrogenation of the keto group to the corresponding alcohol with simultaneous removal of the *N*-benzyl group.[19a]

We have now synthesized optically active (*R*)-terbutaline (*R*)-**9** starting from the (*R*)-cyanohydrin (*R*)-**4k** as outlined in Scheme 3.

Our attempts[13a] to prepare 2-*N*-*tert*-butylamino alcohols starting from O-silylated cyanohydrins, according to a procedure described by Jackson,[14a] were unsuccessful. Jackson et al.[14a] applied the reaction sequence developed by Brussee et al.[12b] which includes selective hydrogenation of O-silylated cyanohydrins with DIBALH to the imino compounds, their transimination with *tert*-butylamine, and subsequent hydrogenation with $NaBH_4$.

We have chosen the Ritter reaction[20] for the introduction of the *N*-*tert*-butyl group in a nitrile function (Scheme 3), a methodology already applied by Jackson et al.[14b] to optically active cyanohydrins.

Preliminary investigations of the Ritter reaction with (*R*)-mandelonitrile resulted in partial racemization under the strong acidic reaction conditions. With O-acetylated (*R*)-mandelonitrile, however, the reaction proceeds without racemization (see Experimental Section). On the basis of these results, (*R*)-**4k** was first acetylated to give

(19) (a) Ahuja, S.; Ashman, J. *Anal. Profiles Drug Subst.* **1990**, *19*, 601–625; *Chem. Abstr.* **1991**, *114*, 149988h. (b) Calzada Badia, J. M. Span. ES 498,812 (Cl. C07C83/04), 1.12.1981; *Chem. Abstr.* **1982**, *97*, 5970d.

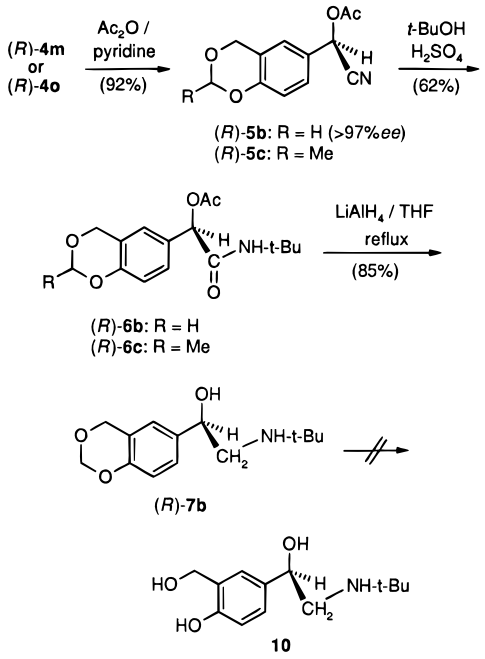
(20) Döpp, D.; Döpp, H. In *Houben Weyl, Methoden der Organischen Chemie*; Thieme: Stuttgart, 1985; vol. E5/2, pp 1032–1040.

(*R*)-**5a** followed by the Ritter reaction to yield after chromatography optically pure acid amide (*R*)-**6a**. In contrast to published results,[14b] a partial hydrolysis of the acetate was not observed. Hydrogenation of the acid amide (*R*)-**6a** was possible only under drastic conditions using $LiAlH_4$ in THF under reflux[14b] (24 h) to give the amino compound (*R*)-**7a** with 90% ee, indicating only minor racemization. These reaction conditions led also to removal of the acetyl protecting group. The hydrogenation of (*R*)-**6a** with sodium in alcohol[19b] as well as the catalytic hydrogenation for deprotection failed. Although numerous procedures for the cleavage of allyl ethers have been published,[21] the deprotection of (*R*)-**7a** turned out to be very difficult. Mild methods using Pd/C and *p*-toluenesulfonic acid[21b] as well as $PPh_3/PdAc_2$ in formic acid[21c] or $PdCl_2$ in acetic acid failed to isomerize (*R*)-**7a** to the bisenol ether (*R*)-**8**. The cleavage with $Pd(PPh_3)_4$ and tributyltin hydride,[21d] already used for the preparation of 2-amino alcohols,[22] was not applied because of the difficult isolation of the deprotected hydroxy compound. We therefore have applied a base-catalyzed isomerization.[23] Under base catalysis allyl ethers isomerize nearly exclusively to *cis*-enol ethers.[23b] By heating (*R*)-**7a** with *tert*-butanolate in DMSO at 100 °C the 3,5-bisenol ether (*R*)-**8** was isolated without racemization in 92% yield and 90% ee. The hydrolytic cleavage of (*R*)-**8** was performed with methanolic HCl solution to yield quantitatively (*R*)-terbutaline hydrochloride (*R*)-**9**·HCl. Optically pure (*R*)-**9**·HCl was obtained after recrystallization from THF/diethyl ether with 73% yield and >98% ee. (*R*)-**9**·HCl is extremely sensitive to oxidation,[19a] and crystallization is difficult. THF was incorporated in the crystals of the recrystallized (*R*)-**9**·HCl in a molar ratio of (*R*)-**9**·HCl:THF = 4:3. A similar effect was published already for racemic terbutaline sulfate which contains 6 mol of crystal water.[24]

Preparation of (*R*)-Salbutamol Acetals 7b,c from the Protected (*R*)-Cyanohydrins (*R*)-4m and (*R*)-4o. Synthetic approaches to racemic salbutamol have been comprehensively reported recently.[25] Possible routes to the optically active compound are also included in this report. Until now, only one procedure for the preparation of (*S*)-salbutamol has been published,[5j] including a stereoselective hydrogenation with an oxazaborolidine[26a] as the decisive step. Asymmetric hydrogenation of the carbonyl group of the corresponding halo ketone with chiral oxazaborolidines as catalysts has been applied successfully for the enantioselective syntheses of both enantiomers of salmeterol.[26b]

In this paper we describe our investigations of the preparation of (*R*)-salbutamol starting from O-protected (*R*)-cyanohydrins analogous to (*R*)-terbutaline, i.e. introduction of the *N*-*tert*-butyl group via the Ritter reaction followed by hydrogenation and deprotection, as summarized in Scheme 4.

Scheme 4



Starting from the (*R*)-cyanohydrin (*R*)-**4m** the formaldehyde acetal of (*R*)-salbutamol (*R*)-**7b** could be obtained via acetylation, Ritter reaction, and subsequent hydrogenation in a good overall yield without detectable racemization. The hydrolytic cleavage of the acetal (*R*)-**7b**, however, to accomplish the synthesis of (*R*)-salbutamol, was not possible so far. Acidic conditions in all cases led to racemization and partial decomposition. Under basic conditions, using sodium thioethoxide in DMF,[27] deacetalization did not occur.

Since the acid-catalyzed hydrolysis of acetaldehyde acetals is easier than the hydrolysis of formaldehyde acetals, we have also used the protected cyanohydrin (*R*)-**4o** to prepare (*R*)-salbutamol (Scheme 4). The O-acetylated cyanohydrin (*R*)-**5c**, however, which could be purified by chromatography, is less stable than (*R*)-**5b**, and thus only polymerization was observed under the conditions of the Ritter reaction. At lower temperature and lower concentration of sulfuric acid only traces of the amide (*R*)-**6c** could be obtained.

With regard to results described by Jackson et al.,[14a] who succeeded in the synthesis of 2-amino-1-phenylethanols, we have also tried the transimination method[12b] for the preparation of (*R*)-salbutamol. The reaction sequence, starting from the cyanohydrin (*R*)-**4o**, is represented in Scheme 5.

Under optimized reaction conditions using a threefold excess of DIBALH and a sixfold excess of *tert*-butylamine based on (*R*)-**11**, the acetal protected (*R*)-salbutamol (*R*)-**7c** was isolated in 93% yield (Scheme 5). From the measured specific rotations and previous experience of this procedure we assume that all reactions proceed nearly without racemization leading to the (*R*)-salbutamol acetal (*R*)-**7c** with an optical purity of >90% ee. Again, however, a hydrolytic cleavage of the acetal (*R*)-**7c** was not successful. While the acid-catalyzed hydroly-

(21) (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991. (b) Boss, R.; Scheffold, R. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 558−559. (c) Hey, H.; Arpe, H.-J. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 928−929. (d) Dangles, O.; Guibé, F.; Balavoine, G.; Lavielle, S.; Marquet, A. *J. Org. Chem.* **1987**, *52*, 4984−4993.

(22) Brown, R. F. C.; Jackson, W. R.; McCarthy, T. D. *Tetrahedron: Asymm.* **1993**, *4*, 2149−2150.

(23) (a) Prosser, T. J. *J. Am. Chem. Soc.* **1961**, *83*, 1701−1704. (b) Price, C. C.; Snyder, W. H. *J. Am. Chem. Soc.* **1961**, *83*, 1773.

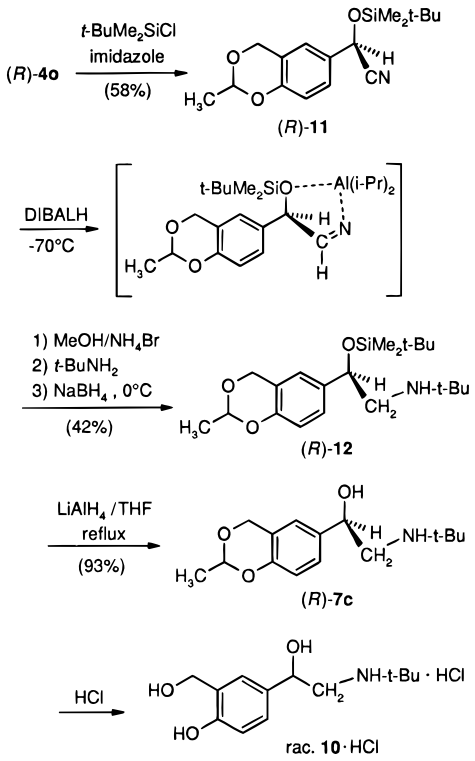
(24) Hickel, D.; Carpy, A.; Laguerre, M.; Leger, J. M. *Acta Crystallogr., Sect. B* **1982**, *B38*, 632−635.

(25) Bakale, R. P. *Spec. Chem.* **1995**, *15*, 249−250, 253; *Chem. Abstr.* **1996**, *124*, 175471k.

(26) (a) Corey, E. J.; Cimprich, K. A. *Tetrahedron Lett.* **1992**, *33*, 4099−4102. (b) Hett, R.; Stare, R.; Helquist, P. *Tetrahedron Lett.* **1994**, *35*, 9375−9378.

(27) Feutrill, G. I.; Mirrington, R. N. *Aust. J. Chem.* **1972**, *25*, 1731−1735.

Scheme 5



sis with 0.01 M HCl gives racemic salbutamol hydrochloride **10**·HCl (Scheme 5), deprotection of the acetal under neutral conditions, e.g., aqueous dimethyl sulfoxide,[28a] $PdCl_2(CH_3CN)_2$ in aqueous acetonitrile,[28b] $SnCl_2 \cdot 2H_2O$ in dichloromethane,[28c] or $CuSO_4$ adsorbed on silica gel,[28d] failed.

Conclusion

We were able to demonstrate, that optically active cyanohydrins are excellent starting compounds for the stereoselective synthesis of pharmacologically important 2-amino-1-arylethanols like (*R*)-terbutaline and (*R*)-salbutamol. The optically active cyanohydrins can be obtained by oxynitrilase-catalyzed addition of HCN to suitable benzaldehydes. Since most of the desired benzaldehydes are hydroxy substituted, it was necessary to investigate the influence of O-protecting groups on the substrate acceptance of the enzyme. For the introduction of a *tert*-butylamino group in the nitrile function of an optically active cyanohydrin without racemization, the Ritter reaction is the most suitable procedure.

Experimental Section

General Procedures. Melting points were determined on a Büchi SMP-20 apparatus and are uncorrected. ^{1}H NMR spectra were recorded with TMS as internal standard using a Bruker AC 250 F (250 MHz) instrument. Preparative chromatography was carried out on columns packed with silica gel S (Riedel-de Haen, size: 0.032−0.063 mm). Specific rotations were measured with a Perkin-Elmer polarimeter 241 LC. GC for ee-determination was performed on: (a) Carlo Erba HRGC 5300 Mega Series with FID, Carlo Erba Mega Series Integrator, 0.4−0.5 bar or 0.36 bar hydrogen, column 20 m, phases OV 1701 or PS086 with 10% permethylated β-cyclodextrin or Amid-Dex (amide phase); (b) Carlo Erba Fractovap 4160 with FID, Spectra Physics Minigrator, 0.5 bar hydrogen, column 50 m, phase OV 1701 with 10% permethylated β-cyclodextrin; (c) Hewlett Packard 5890 Series II with HP 7673-injector with FID, Software HP 3365 Series II, Chem Station, version A.03.21, hydrogen, columns FS-Lipodex C (50 m × 0.25 mm, Macherey Nagel), Chiraldex B-TA and Chiraldex G-TA (30 m × 0.32 mm, ITC), Permabond OV 1701-DF0.35 (25 m × 0.32 mm, Macherey Nagel). Capillary electrophoresis was performed using a BioFocus 3000 capillary electrophoresis system with BioFocus Software V3.10A (Bio-Rad) and uncoated glass capillary (50 μm × 50 cm). Avicel cellulose was purchased from Merck, hydroxybenzaldehydes **1a**,**c**,**d**,**e** from Fluka. All solvents were dried and distilled, and all reactions with organometallic compounds were carried out under an argon or nitrogen atmosphere in dried glassware.

The protected hydroxybenzaldehydes **3a**,**d**,**e**,**g**−**j**,**l**,**m** were prepared as described in the literature,[16b−i] 4-(propionyloxy)-benzaldehyde (**3f**) according to ref 16c, 3-hydroxy-4-methylbenzaldehyde (**1b**) according to ref 29, and (*R*)-oxynitrilase according to ref 30.

3-(Methoxymethoxy)-4-methylbenzaldehyde (3b). Potassium carbonate (5.0 g, 36 mmol) was suspended in a solution of **1b** (4.9 g, 36 mmol) in acetonitrile (50 mL), and chloromethyl methyl ether[31] (5 mL of a 65% ic solution) was added dropwise. After stirring for 18 h, the solid was filtered off and washed with acetonitrile. The combined filtrates were concentrated, and the residue was distilled in high vacuo: yield 6.1 g (94%); bp 71−75 °C/ 0.01 Torr; ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 3 H), 3.50 (s, 3 H), 5.28 (s, 2 H), 7.29−7.54 (m, 3 H), 9.95 (s, 1 H). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.43; H, 6.84.

3-(Methoxymethoxy)-4-methoxybenzaldehyde (3c). Potassium carbonate (43 g, 0.31 mol) was suspended in a solution of **1c** (15 g, 98 mmol) in acetone (200 mL), and chloromethyl methyl ether (25 mL of a 65% ic solution) was added dropwise. After stirring for 1 h at 50 °C, the solid was filtered off and washed with acetone, and the combined filtrates were concentrated in vacuo. The residue was dissolved in diethyl ether, washed with NaOH solution, dried ($MgSO_4$), and concentrated. The residue was distilled in high vacuo: yield 14.6 g (76%); bp 105 °C/0.001 Torr; mp 38−39 °C; ^{1}H NMR ($CDCl_3$) δ 3.53 (s, 3 H), 3.95 (s, 3 H), 5.33 (s, 2 H), 7.26−7.46 (m, 3 H), 9.87 (s, 1 H). Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.17; H, 6.24.

3,5-Bis(allyloxy)benzaldehyde (3k) According to Ref 16h. (a) A solution of allyl 3,5-bis(allyloxy)benzoate, prepared from 65 mmol of 3,5-dihydroxybenzoic acid,[32] (18.0 g, 37 mmol) in diethyl ether was added dropwise at 0 °C to a suspension of $LiAlH_4$ (1.5 g, 40 mmol) in diethyl ether (200 mL), and the reaction mixture was stirred for 16 h at rt. After hydrolysis, the organic phase was dried ($MgSO_4$) and concentrated: yield 8.07 g (99%) of 3,5-bis(allyloxy)benzyl alcohol which was used without further purification.

(b) A solution of the alcohol (8.07 g, 36.7 mmol) in dichloromethane (35 mL) was added dropwise at 10 °C to a suspension of pyridinium chlorochromate (16.2 g, 75 mmol) and sodium acetate (1.4 g, 17 mmol) in dichloromethane (70 mL). After stirring for 2 h, diethyl ether (200 mL) was added, and the formed solid was crushed. After being stirred for a further 1 h, the solid was filtered off and washed with diethyl ether. The combined filtrates were slurried with charcoal to remove color. After filtration the solvent was removed in vacuo, and the residue fractionally distilled in high vacuo: yield 9.23 g (65%, based on 3,5-dihydroxybenzoic acid) of **3k**:

(28) (a) Kametani, T.; Kondoh, H.; Honda, T.; Ishizone, H.; Suzuki, Y.; Mori, W. *Chem. Lett.* **1989**, 901−904. (b) Lipshutz, B. H.; Pollart, D.; Monforte, J.; Kotsuki, H. *Tetrahedron Lett.* **1985**, *26*, 705−708. (c) Ford, K. L.; Roskamp, E. J. *Tetrahedron Lett.* **1992**, *33*, 1135−1138. (d) Caballero, G. M.; Gros, E. G. *Synth. Commun.* **1995**, *25*, 395−404.

(29) Fukumi, H.; Kurihara, H.; Mishima, H. *Chem. Pharm. Bull.* **1978**, *26*, 2175−2180.

(30) (a) Hochuli, E. *Helv. Chim. Acta* **1983**, *66*, 489−493. (b) Kaul, R.; Mattiasson, B. *Biotechnol. Appl. Biochem.* **1987**, *9*, 294−302. (c) Lauble, H.; Müller, K.; Schindelin, H.; Förster, S.; Effenberger, F. *Proteins: Struct., Funct., Genet.* **1994**, *19*, 343−347.

(31) Löbering, J.; Fleischmann, A. *Ber. Dtsch. Chem. Ges.* **1937**, *70*, 1680−1683.

(32) Coqueret, X.; Wegner, G. *Makromol. Chem.* **1992**, *193*, 2929−2943.

bp 115 °C/0.01 Torr; ^{1}H NMR ($CDCl_3$) δ 4.55−4.59 (m, 4 H), 5.29−5.47 (m, 4 H), 5.97−6.13 (m, 2 H), 6.75 (t, J = 2.3 Hz, 1 H), 7.02 (d, J = 2.3 Hz, 2 H). Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.64; H, 6.47. Found: C, 71.33; H, 6.38.

Introduction of Protecting Groups in 5-Bromo-2-hydroxybenzyl Alcohol. (a) A solution of 5-bromo-2-hydroxybenzyl alcohol (10.15 g, 50 mmol) in THF (20 mL) was added dropwise at 0 °C to a suspension of NaH (3.7 g, 154 mmol) in THF (80 mL). After stirring for 30 min at rt, allyl bromide (13 mL, 154 mmol) was added dropwise, and the reaction mixture was stirred for further 16 h and then refluxed for 8 h. Sodium bromide was filtered off, the filtrate concentrated in vacuo, and the residue distilled in high vacuo: yield 10.8 g (76%) 3-[(allyloxy)methyl]-4-(allyloxy)bromobenzene: bp 115−120 °C/0.001 Torr; ^{1}H NMR ($CDCl_3$) δ 4.06−4.10 (m, 2 H), 4.55 (s, 2 H), 4.67 (d, J = 6.4 Hz, 2 H), 5.10−5.40 (m, 4 H), 5.90−6.10 (m, 2 H), 6.73 (d, J = 8.7 Hz, 1 H), 7.34 (dd, J = 8.7, 2.5 Hz, 1 H), 7.53 (d, J = 2.5 Hz, 1 H).

(b) Ethyl vinyl ether (15 mL, 157 mmol) was added dropwise to a stirred solution of 5-bromo-2-hydroxybenzyl alcohol (22 g, 108 mmol) and *p*-toluenesulfonic acid (100 mg) in DMF (100 mL). The reaction mixture was stirred for 17 h, and after addition of the double volume of NaOH solution (0.1 N) extracted with diethyl ether. The combined extracts were dried ($MgSO_4$) and concentrated in vacuo, and the residue was distilled in high vacuo: yield 22.8 g (92%) of 6-bromo-2-methyl-1,3-benzodioxin: bp 94 °C/0.02 Torr; ^{1}H NMR ($CDCl_3$) δ 1.54 (d, J = 5.1 Hz, 3 H), 4.78 and 4.94 (AB system, J = 14.8 Hz, 2 H), 5.14 (q, J = 5.1 Hz, 1 H), 6.73 (d, J = 8.7 Hz, 1 H), 7.09−7.10 (m, 1 H), 7.24 (dd, J = 8.7, 2.3 Hz, 1 H).

Preparation of Compounds 3n and 3o. A small amount of the respective bromo compound (see above) was added to Mg in THF, and the Grignard reaction was started by heating to 50 °C and addition of 1,2-dibromoethane as entrainer. The residual educt was added dropwise with stirring, and the reaction mixture was heated to 60 °C for 1 h and after addition of DMF at 0 °C stirred for further 16 h. The reaction mixture was hydrolyzed with HCl (5%) and extracted with diethyl ether. The combined extracts were dried ($MgSO_4$) and concentrated, and the residue was distilled in vacuo.

3-[(Allyloxy)methyl]-4-(allyloxy)benzaldehyde (3n). From Mg (50 mmol), bromo compound (10.5 g, 37 mmol), and DMF (50 mmol): yield 4.6 g (54%); bp 115−120 °C/0.001 Torr; ^{1}H NMR ($CDCl_3$) δ 4.09−4.10 (m, 2 H), 4.61 (s, 2 H), 4.64−4.67 (m, 2 H), 5.20−5.50 (m, 4 H), 5.90-6.10 (m, 2 H), 6.95 (d, J = 8.5 Hz, 1 H), 7.80 (dd, J = 8.5, 2.1 Hz, 1 H), 7.97 (d, J = 2.1 Hz, 1 H), 9.93 (s, 1 H). MS (EI 70 eV) m/z 232 (20), 202 (15), 174 (65), 135 (100).

6-Formyl-2-methyl-1,3-benzodioxin (3o). From Mg (150 mmol), bromo compound (22 g, 96 mmol), and DMF (150 mmol): yield 10.5 g (61%); bp 95−100 °C/0.01 Torr, mp 68 °C; ^{1}H NMR ($CDCl_3$) δ 1.58 (d, J = 5.1 Hz, 3 H), 4.90 and 5.03 (AB system, J = 14.7 Hz, 2 H), 5.26 (q, J = 5.1 Hz, 1 H), 6.96 (d, J = 8.4 Hz, 1 H), 7.54−7.55 (m, 1 H), 7.71 (dd, J = 8.4, 1.9 Hz, 1 H), 9.85 (s, 1 H). Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.40; H, 5.65. Found: C, 67.49; H, 5.73.

Preparation of (*R*)-Cyanohydrins 4. General Procedure. A solution of (*R*)-oxynitrilase (100 U/0.2 g support) was added to the support (2 g, soaked in 50 mL of 0.02 M sodium acetate solution, pH 3.3 or 4.5, filtered off and centrifuged) followed by addition of a solution of **3** (0.5−51 mmol) in diisopropyl ether and a two- to fourfold excess of HCN. After stirring for the time given in Table 2, the support was filtered off and the filtrate dried ($MgSO_4$) and concentrated in vacuo.

Determination of Enantiomeric Excess of (*R*)-4. Acetic anhydride (50 μL) and pyridine (10 μL) were added to a solution of crude (*R*)-**4** (5 μL) in dichloromethane (200 μL). After heating to 60 °C for 2−3 h, the reaction mixture was filtered through a silica gel column (0.5 × 3 cm) with dichloromethane (3 mL). The enantiomeric excess was directly determined from the filtrate.

Acetylation of (*R*)-4k,m,o to Compounds (*R*)-5a−c. General Procedure. As described for the ee-determination, from (*R*)-**4k**, -**4m**, or -**4o** in dichloromethane, acetic anhydride, and pyridine. After stirring for 2 h at 60 °C, solvent and the excess of pyridine were removed in vacuo, and the products were reacted without further purification.

(*R*)-2-Acetoxy-2-[3,5-bis(allyloxy)phenyl]acetonitrile (5a). From (*R*)-**4k** (30 mmol), acetic anhydride (10 mL), pyridine (5 mL): bp 125−130 °C/0.001 Torr; $[\alpha]^{20}_{578}$ +7.2 (*c* 1.0, MeOH); ^{1}H NMR ($CDCl_3$) δ 2.17 (s, 3 H), 4.50−4.56 (m, 4 H), 5.26−5.46 (m, 4 H), 5.95−6.13 (m, 2 H), 6.32 (s, 1 H), 6.55 (t, J = 2.2 Hz, 1 H), 6.65 (d, J = 2.2 Hz, 1 H). Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.87. Found: C, 66.69; H, 6.10; N, 4.91.

(*R*)-2-Acetoxy-2-(1,3-benzodioxin-6-yl)acetonitrile (5b): From (*R*)-**4m** (15 mmol), acetic anhydride (4 mL), pyridine (1.6 mL): $[\alpha]^{20}_{578}$ −7.5 (*c* 1.5, CH_2Cl_2), 97% ee; ^{1}H NMR ($CDCl_3$) δ 2.14 (s, 3 H), 4.92 (s, 2 H), 5.26 (s, 2 H), 6.32 (s, 1 H), 6.93 (d, J = 8.5 Hz, 1 H), 7.16 (d, J = 2.0 Hz, 1 H), 7.31 (dd, J = 8.5, 2.0 Hz, 1 H). Anal. Calcd for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.75; N, 6.00. Found: C, 61.58; H, 4.75; N, 5.92.

(*R*)-2-Acetoxy-2-(2-methyl-1,3-benzodioxin-6-yl)acetonitrile (5c): From (*R*)-**4o** (34 mmol), acetic anhydride (10 mL), pyridine (2.7 mL): bp 110−115 °C/0.01 Torr; $[\alpha]^{20}_{578}$ −17.0 (*c* 1.0, CH_2Cl_2), 96% ee; ^{1}H NMR ($CDCl_3$) δ 1.56 (d, J = 5.1 Hz, 3 H), 2.15 (s, 3 H), 4.81 and 4.98 (AB system, J = 14.8 Hz, 2 H), 5.19 (q, J = 5.1 Hz, 1 H), 6.35 (s, 1 H), 6.90 (d, J = 8.5 Hz, 1 H), 7.15 (s, 1 H), 7.30 (d, J = 8.5 Hz, 1 H). Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.66. Found: C, 63.09; H, 5.39; N, 5.43.

Ritter Reaction to *tert*-Butyl Amides (*R*)-6. General Procedure. At 15 °C H_2SO_4 (80 mmol) was slowly added to a stirred solution of **5** in acetic acid (80 mL) and *tert*-butyl alcohol (80 mmol). The reaction mixture, allowed to warm up to 30 °C, was diluted after 4−5 h with water to the double volume and extracted with diethyl ether. The combined extracts were concentrated, and the residue was chromatographed on silica gel with ethyl acetate/petroleum ether (3:7).

(*R*)-2-Acetoxy-2-[3,5-bis(allyloxy)phenyl]-*N*-*tert*-butylacetamide (6a). From (*R*)-**5a** (obtained from 43.5 mmol of **3k** as starting compound): yield 12.2 g (78% based on **3k**); $[\alpha]^{20}_{D}$ −25.0 (*c* 1.46, MeOH); ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 9 H), 2.17 (s, 3 H), 4.49−4.52 (m, 4 H), 5.25−5.44 (m, 4 H), 5.79 (s, 1 H), 5.85 (s, 1 H), 5.95−6.11 (m, 2 H), 6.46 (t, J = 2.2 Hz, 1 H), 6.58 (d, J = 2.2 Hz, 2 H). Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.87. Found: C, 66.31; H, 7.64; N, 3.65.

(*R*)-2-Acetoxy-2-(1,3-benzodioxin-6-yl)-*N*-*tert*-butylacetamide (6b). From (*R*)-**5b** (40 mmol): yield 7.80 g (63%); mp 125 °C; $[\alpha]^{20}_{578}$ −29.6 (*c* 1.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 9 H), 2.16 (s, 3 H), 4.89 (s, 2 H), 5.23 (s, 2 H), 5.86 (s, 1 H), 5.94 (bs, 1 H), 6.86 (d, J = 8.5 Hz, 1 H), 7.05 (d, J = 2.1 Hz, 1 H), 7.18 (dd, J = 8.5, 2.1 Hz, 1 H). Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.88; N, 4.56. Found: C, 62.33; H, 6.91; N, 4.42.

Reduction to Amino Alcohols (*R*)-7. General Procedure. A solution of **6** or **12** in THF was added dropwise at 0 °C under Ar to a suspension of $LiAlH_4$ in dry THF, and the reaction mixture was refluxed for 20 h (**6**) or 5 h (**12**). After cooling to 0 °C, the reaction mixture was diluted with diethyl ether and hydrolyzed with a small volume of water. The ethereal phase was decanted from precipitated aluminum hydroxide, and the aqueous phase was washed several times with diethyl ether. The combined organic phases were dried ($MgSO_4$) and concentrated, and the residue was crystallized from diethyl ether/hexane or diethyl ether/petroleum ether.

(*R*)-1-[3,5-Bis(allyloxy)phenyl]-2-(*tert*-butylamino)-ethanol (7a). From (*R*)-**6a** (5.4 g, 15 mmol), $LiAlH_4$ (2.3 g, 60 mmol), and THF (100 mL): yield 4.35 g (85%) as hydrochloride; mp 143 °C; $[\alpha]^{20}_{D}$ −28.0 (*c* 1.0, MeOH), 90% ee; ^{1}H NMR ($CDCl_3$) δ 1.09 (s, 9 H), 2.58 (ABX system, J = 11.8, 8.4 Hz, 1 H), 2.88 (ABX system, J = 11.8, 3.8 Hz, 1 H), 4.50−4.55 (m, 5 H), 5.24−5.45 (m, 4 H), 5.97−6.12 (m, 2 H), 6.41 (t, J = 2.3 Hz, 1 H), 6.55 (d, J = 2.3 Hz, 2 H). Anal. Calcd for $C_{18}H_{27}NO_3$·HCl: C, 63.24; H, 8.25; N, 4.10; Cl, 10.37. Found: C, 63.25; H, 8.33; N, 3.97; Cl, 10.62.

(*R*)-1-(1,3-Benzodioxin-6-yl)-2-(*tert*-butylamino)ethanol (7b). From (*R*)-**6b** (3.6 g, 11.7 mmol), $LiAlH_4$ (1.8 g, 47 mmol), THF (60 mL): yield 2.50 g (85%); mp 129−130 °C; $[\alpha]^{20}_{D}$ −24.0 (*c* 1.10, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.10 (s, 9 H), 2.53 (ABX system, J = 11.8, 9.0 Hz, 1 H), 2.85 (ABX system,

J = 11.8, 3.6 Hz, 1 H), 4.50 (dd, J = 3.6, 9.0 Hz, 1 H), 4.90 (s, 2 H), 5.23 (s, 2 H), 6.85 (d, J = 8.4 Hz, 1 H), 7.00 (d, J = 1.2 Hz, 1 H), 7.13 (dd, J = 8.4, 1.2 Hz, 1 H). Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.82; H, 8.39; N, 5.46.

(*R*)-2-(*tert*-Butylamino)-1-(2-methyl-1,3-benzodioxin-6-yl)ethanol (7c). From (*R*)-**12** (1.4 g, 3.69 mmol), $LiAlH_4$ (0.3 g, 7.9 mmol), THF (47 mL): yield 0.91 (93%); mp 103 °C; $[\alpha]^{20}_D$ −73.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 1.10 (s, 9 H), 1.54 (d, J = 5.1 Hz, 3 H), 2.45−2.58 (m, 1 H), 2.82−2.89 (m, 1 H), 4.60 (dd, J = 3.5, 8.9 Hz, 1 H), 4.83 and 4.99 (AB system, J = 14.6 Hz, 2 H), 5.16 (q, J = 5.1 Hz, 1 H), 6.80 (d, J = 8.4 Hz, 1 H), 7.00 (bs, 1 H), 7.12 (d, J = 8.4 Hz, 1 H). Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.89; H, 8.74; N, 5.28. Found: C, 67.68; H, 8.60; N, 5.36.

Isomerization of (*R*)-7a to Compound (*R*)-8. Potassium *tert*-butanolate (90 mg, 0.8 mmol) was added under Ar to a solution of **7a** (2.4 g, 7.8 mmol) in dry DMSO (30 mL). After heating to 120 °C for 16 h, DMSO was removed at 10 Torr, and the residue was mixed with water (50 mL) and extracted with diethyl ether. The combined extracts were dried ($MgSO_4$) and concentrated: yield 2.20 g (92%); as sulfate: mp 243 °C dec; $[\alpha]^{20}_D$ −25.4 (*c* 0.5, MeOH), 90% ee; ^{1}H NMR ($CDCl_3$) δ 1.10 (s, 9 H), 1.70 (d, J = 6.9 Hz, 3 H), 1.71 (d, J = 6.9 Hz, 3 H), 2.57 (ABX system, J = 11.9, 8.5 Hz, 1 H), 2.90 (ABX system, J = 11.9, 3.6 Hz, 1 H), 4.53 (dd, J = 8.5, 3.6 Hz, 1 H), 4.83−4.94 (m, 2 H), 6.35−6.39 (m, 2 H), 6.55 (t, J = 2.2 Hz, 1 H), 6.71 (d, J = 2.2 Hz, 2 H). Anal. Calcd for $C_{18}H_{27}NO_3 \cdot {}^1/_2 H_2SO_4$: C, 60.99; H, 7.96; N, 3.95; S, 4.52. Found: C, 60.79; H, 8.10; N, 3.97; S, 4.59.

Preparation of (*R*)-Terbutaline Hydrochloride (*R*)-9·HCl. An ethereal solution of HCl (1 mL) was added dropwise under N_2 at rt to a solution of **8** (1.0 g, 3.28 mmol) in methanol (50 mL), and the reaction mixture was stirred for 18 h. The solvent was removed in vacuo, and the residue was recrystallized from THF/diethyl ether and dried at 40 °C in high vacuo: yield 0.63 g (73%); mp 215 °C dec; $[\alpha]^{20}_D$ −32.5 (*c* 0.76, MeOH), >98% ee; ^{1}H NMR (CD_3OD) δ 1.27 (s, 9 H), 2.86 (ABX system, J = 12.4, 10.1 Hz, 1 H), 2.98 (ABX system, J = 12.4, 3.2 Hz, 1 H), 4.65 (dd, J = 10.1, 3.2 Hz, 1 H), 6.10 (t, J = 2.2 Hz, 1 H), 6.27 (d, J = 2.2 Hz, 1 H). Anal. Calcd for $C_{12}H_{19}NO_3 \cdot HCl$: C, 55.06; H, 7.70; N, 5.35; Cl, 13.54. Found: C, 55.12; H, 7.62; N, 5.44; Cl, 13.22.

Determination of Enantiomeric Excess of (*R*)-7a, 8, and 9. By capillary electrophoresis according to ref 33 using the conditions 20 kV; 20 mM β-cyclodextrin, 150 mM $(N(C_4H_9)_4)_3PO_4$, 10% MeOH, pH 2.5; uncoated capillary column (50 cm × 50 μm); 40 °C and detection at 214 nm.

Preparation of (*R*)-11 According to Ref 34. At 0 °C *tert*-butyldimethylchlorosilane (6.78 g, 45 mmol) was added to imidazole (5.4 g, 80 mmol) in DMF (80 mL). After stirring for 15 min, (*R*)-**4o** (prepared from 42 mmol **3o**) in DMF (5 mL) was added dropwise, and the reaction mixture was stirred for 3 h at rt. After hydrolysis with water (150 mL), the aqueous phase was extracted with diethyl ether. The combined extracts were dried ($MgSO_4$) and concentrated, and the residue fractionally distilled in high vacuo: yield 7.70 g (58%); bp 125 °C/0.005 Torr; $[\alpha]^{20}_D$ −7.86 (*c* 1.4, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.13, 0.21 (each s, 6 H), 0.92 (s, 9 H), 1.55 (d, J = 5.1 Hz, 3 H), 4.84 (AB system, J = 14.7 Hz, 1 H), 5.00 (AB system, J = 14.7 Hz, 1 H), 5.19 (q, J = 5.1 Hz, 1 H), 5.42 (s, 1 H), 6.87 (dd, J = 8.5, 2.1 Hz, 1 H), 7.08 (dd, J = 7.4, 1.7 Hz, 1 H), 7.19−7.26 (m, 1 H). Anal. Calcd for $C_{17}H_{25}NO_3Si$: C, 63.91; H, 7.89; N, 4.38. Found: C, 63.63; H, 7.93; N, 4.25.

Preparation of Silylated Amino Alcohol (*R*)-12 According to Ref 14a. A 1.5 M solution of DIBALH in toluene (10 mL) was added at −70 °C under Ar via syringe to a solution of (*R*)-**11** (1.7 g, 5.3 mmol) in dry diethyl ether (60 mL). After stirring for 4 h, a solution of NH_4Br (1.35 g, 13.7 mmol) in methanol (25 mL) was added dropwise via syringe followed after 10 min by *tert*-butylamine (3.2 mL, 30 mmol). The stirred reaction mixture was allowed to warm to 0 °C within 2 h and cooled to −50 °C, and $NaBH_4$ (0.4 g, 10.5 mmol) was added in two portions. The reaction mixture was stirred for 16 h at rt and hydrolyzed with 1 N HCl (80 mL), and the aqueous phase was extracted twice with diethyl ether. The combined extracts were washed with NaOH solution (1 N), dried ($MgSO_4$), and concentrated, and the residue was chromatographed on silica gel with ethyl acetate/petroleum ether (7:3): yield 0.85 g (42%) as colorless oil; $[\alpha]^{20}_D$ −77.8 (*c* 1.1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ −0.17 and 0.45 (each s, 6 H), 0.88 (s, 9 H), 1.07 (s, 9 H), 1.54 (d, J = 5.1 Hz, 3 H), 2.52 (ABX system, J = 10.8, 3.8 Hz, 1 H), 2.67 (ABX system, J = 10.8, 8.8 Hz, 1 H), 4.66 (dd, J = 3.8, 8.8 Hz, 1 H), 4.83 and 4.98 (each AB system, J = 14.6 Hz, 2 H), 5.18 (q, J = 5.1 Hz, 1 H), 6.80 (d, J = 8.4 Hz, 1 H), 6.91 (d, J = 1.8 Hz, 1 H). MS (CI methane) m/z 408 (10), 380 (60), 364 (80), 336 (90), 248 (100).

Acknowledgment. This work was generously supported by the Bundesministerium für Bildung und Forschung (Zentrales Schwerpunktprogramm Bioverfahrenstechnik, Stuttgart) and the Fonds der Chemischen Industrie. We thank Katja Sovarasteanu for her experimental contributions.

JO970032D

(33) (a) Quang, C.; Khaledi, M. G. *Anal. Chem.* **1993**, *65*, 3354−3358. (b) Quang, C.; Khaledi, M. G. *J. Chromatogr.* **1995**, *692*, 253−265.

(34) Brussee, J.; Loos, W. T.; Kruse, C. G.; van der Gen, A. *Tetrahedron* **1990**, *46*, 979−986.