Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 47 (2006) 5007–5011
Tetrahedron Letters

Salicylanilide esterification: unexpected formation of novel seven-membered rings

Aleš Imramovský, Jarmila Vinšová,* Juana Monreal Férriz, Jiří Kuneš, Milan Pour and Martin Doležal

Faculty of Pharmacy Charles University, 500 05 Hradec Králové, Czech Republic

Received 5 April 2006; revised 9 May 2006; accepted 18 May 2006

Abstract—Novel benzoxazepines were prepared upon esterification of biologically active salicylanilides with some N-protected amino acids. While the desired conjugates of the salicylanilides with the amino acids were obtained when sterically more demanding amino acids were used, benzoxazepines were formed as a result of a seven-*exo*-trig cyclization in the case of N-protected glycine and alanine. The structures of the products were confirmed by 2D NMR methods, and further transformations of the acyclic conjugates provided additional support for the proposed mechanism of cyclization.

1. Introduction

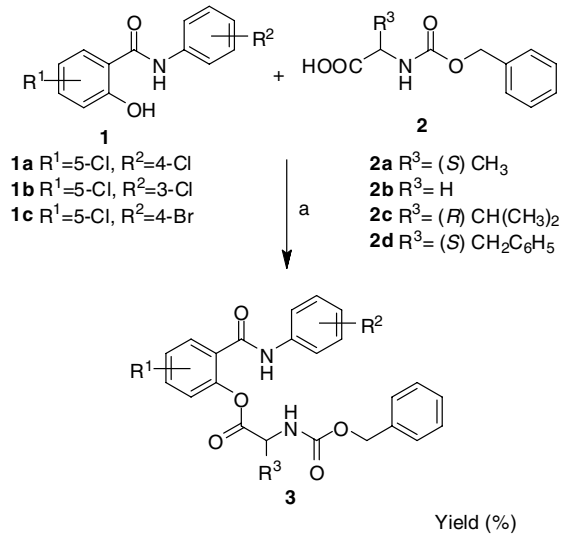
Salicylanilides display potent antifungal and antibacterial activity.[1] They have shown activity against gram-positive pathogens including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*, strains representing a significant problem in clinical practice.[2,3] Recently, antimycobacterial activity of salicylanilides has been reported.[4–6] They have shown activity not only against classical *Mycobacterium tuberculosis* $H_{37}Rv$, but also against atypical strains of mycobacteria, mainly *Mycobacterium avium*, *fortuitum* and *kansassii* where standard antituberculotics fail. In 1998, a new mechanism for their action based on the inhibition of two-component regulatory systems in bacteria was proposed.[7] Electron-accepting substituents on the salicylic moiety and hydrophobic groups on the anilide ring are essential for their activity.[8] Hydrophobicity is another factor that may influence biological activity: while the presence of phenolic hydroxyls seems necessary for the activity, and is probably responsible for oxidative phosphorylation cleavage,[9] they also add irritative properties to the compounds. Therefore, temporary masking of phenolic hydroxyls with hydrophilic moieties could be advantageous. The goal of this work was the preparation of esters of amino acids with highly active salicylanilides as a new group of prodrugs with high activity, improved solubility and low toxicity.

The starting salicylanilides **1** were routinely prepared by the reaction of substituted salicylic acids with the appropriate anilines in chlorobenzene with PCl_3.[4] Using a microwave reactor, we shortened the reaction times from several hours (5–8) to 10–15 min with yields of about 90%. As direct esterification of a non-protected amino acid with a salicylanilide or amino acyl derivative was not successful, we employed DCI-mediated condensation of salicylanilides **1** with N-protected amino acids **2** in the hope of obtaining the desired compounds **3** (Scheme 1).

As expected, the reactions proceeded uneventfully in most cases, affording esters **3a**–**d** in high yields. However, when Z-Gly and Z-L-Ala were used, the isolated products lacked the *N*-benzyloxycarbonyl group, while possessing the ester arrangement (ν CO 1764 cm^{-1}). The structures of the compounds were elucidated based on compounds **6a** and **6b** by spectral methods. The mass spectrum for **6b** showed a molecular ion at m/z 364, confirming the composition $C_{16}H_{10}Cl_2N_2O_4$. Hence, a complex cyclization process involving the loss of benzyl alcohol was strongly suspected. Two possible modes of cyclization could be envisaged: (1) attack of the amide

Keywords: Salicylanilide; Amino acid ester; Seven-membered ring; Benzoxazepines; 2D NMR.
* Corresponding author. Tel.: +420 495 067 343; fax: +420 495 514 330; e-mail: vinsova@faf.cuni.cz

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.05.110



	Yield (%)
3a R^1=4-Cl, R^2=4-Cl, R^3= (*R*) $CH(CH_3)_2$	36
3b R^1=4-Cl, R^2=4-Cl, R^3= (*S*) $CH_2C_6H_5$	52
3c R^1=4-Cl, R^2=3-Cl, R^3= (*S*) $CH_2C_6H_5$	62
3d R^1=4-Cl, R^2=4-Br, R^3= (*S*) $CH_2C_6H_5$	57

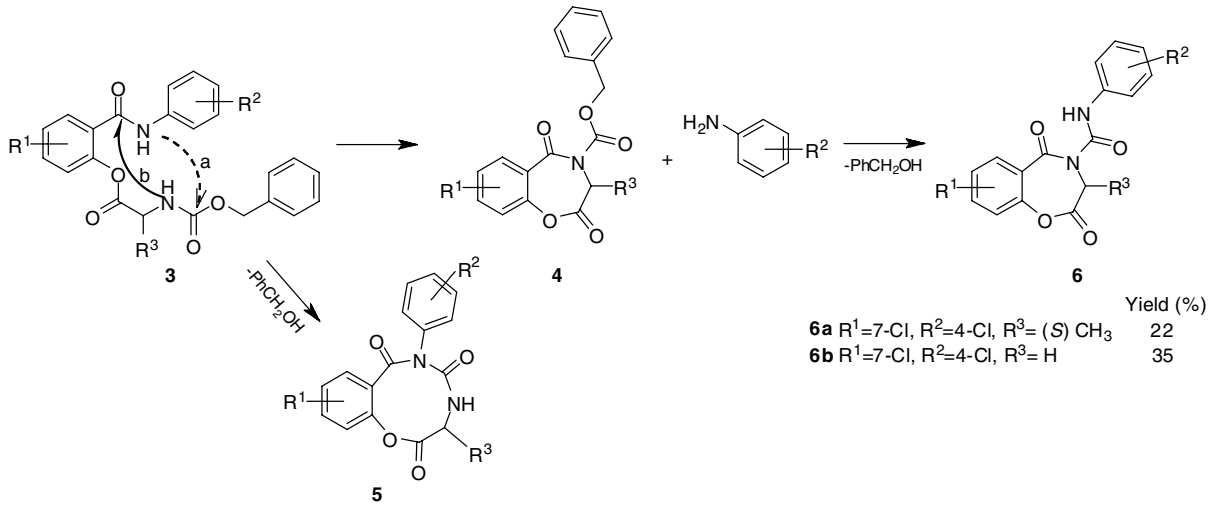
Scheme 1. Synthesis of *Z*-amino acid esters with substituted salicylanilides. Reagents and conditions: (a) DCI, DMF, −15 °C.

nitrogen on the carbonyl of the carbamic moiety resulting in nine-membered ring closure (path a), and (2) attack of the amide carbonyl by the carbamic NH group (path b). The latter process would give rise to a seven-membered cyclic intermediate **4**, which would further react with the substituted aniline released as a leaving group in the previous step, to furnish the final product **6**. MS fragmentation of **6b** led to intense signals at *m*/*z* 238 (loss of ClC_6H_4NH), and 210 (loss of ClC_6H_4NHCO). Strong correlation between the NH proton and carbons in the *ortho*-position on the *p*-chlorophenyl ring was observed in the gHMBC spectrum of **6a**. Thus, the initially formed esters **3** were converted to benzoxazepines **6** via a seven-*exo*-trig cyclization process depicted as path b in Scheme 2. Since cyclization was observed in the cases where $R^3 = H$ or CH_3, steric demand around the carbamic nitrogen appears to be the major factor influencing the formation of benzoxazepines **6** (Scheme 2).

It is also interesting to note that esters **3a–d** showed melting points in the range of 130–150 °C, while those of benzoxazepines **6** were substantially higher, in the range of 180–240 °C. Both types of compounds differed in solubility, esters **3** were soluble in ethyl acetate and chloroform, while heterocycles **6** were only slightly soluble in ethyl acetate and nearly insoluble in chloroform.

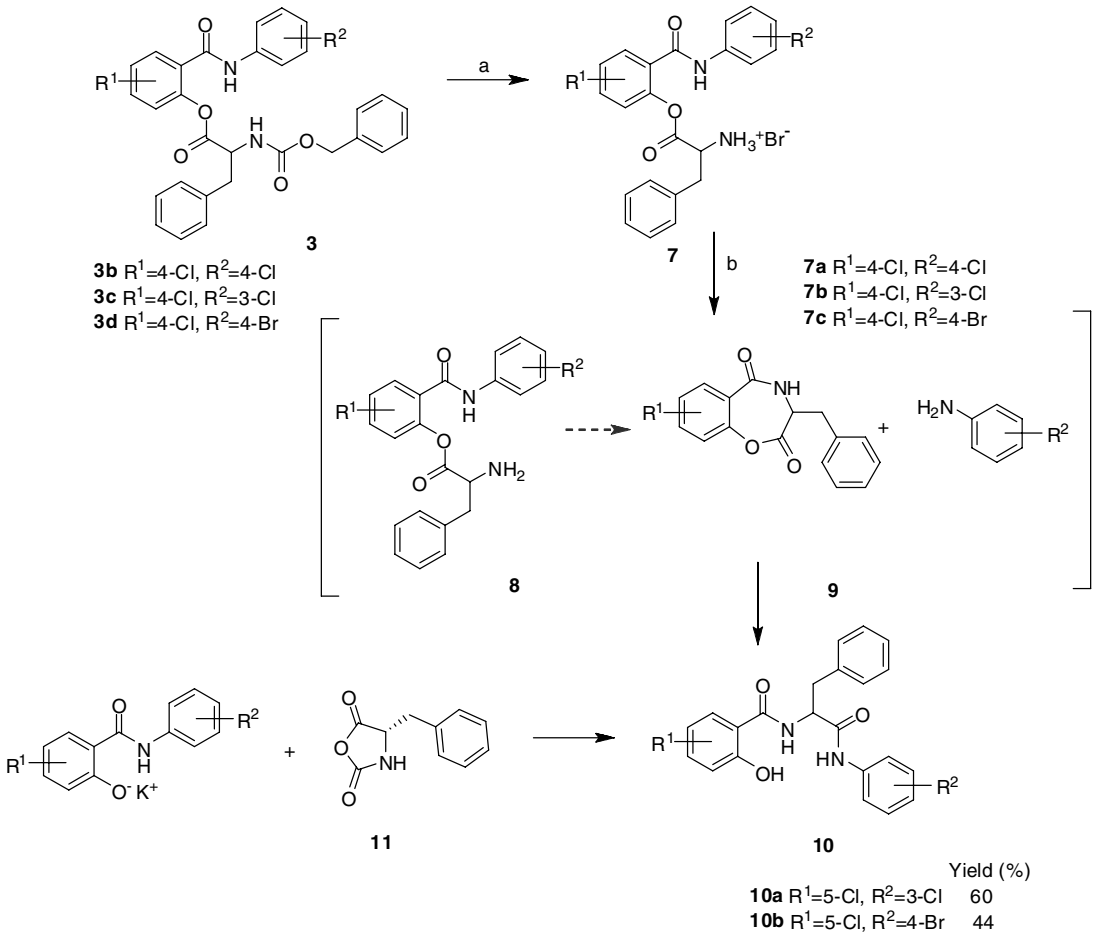
The proposed mechanism of cyclization is in accordance with the course of subsequent conversions of esters **3**. While N-deprotection of esters **3** ($R^3 = R/S$ CH_2Ph, R/S $CH(CH_3)_2$) by hydrogenolysis on Pd/C was unsuccessful, acidolysis (33% HBr in anhydrous acetic acid) gave hydrobromide amino salts **7** (Scheme 3). Subsequent amino group liberation by triethylamine under anhydrous conditions yielded product **10**. This compound possessed neither ester nor free amino groups, but the presence of a phenolic hydroxyl was clearly apparent. The structure of **10** was unequivocally corroborated by 2D NMR. All HMBC correlations are shown in Figure 1. The salicylic amide carbonyl at 166.3 ppm displayed cross-peaks to both the H6 salicylic and the NH proton observable as a doublet in the ^1H spectrum. Hence, this NH group must be adjacent to a CH moiety. The CH group, which was directly coupled to the benzylic protons, showed correlation to the other carbonyl at 170.1 ppm.

Consequently, the remaining 3-chloroaniline residue must have been a component of this amide fragment. Obviously, the deprotected amino group immediately attacked the amide carbonyl thus releasing substituted aniline, which opened cyclic ester **9** to furnish diamide **10**.



	Yield (%)
6a R^1=7-Cl, R^2=4-Cl, R^3= (*S*) CH_3	22
6b R^1=7-Cl, R^2=4-Cl, R^3= H	35

Scheme 2. Possible modes of cyclization.



Scheme 3. Reagents: (a) 33% HBr/CH_3COOH, (b) triethylamine.

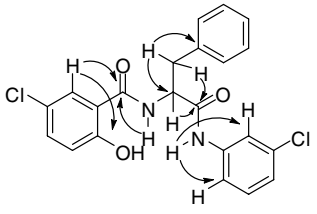


Figure 1. HMBC correlations present in **10**.

Diamide **10** was also obtained by the reaction of the Leuch anhydride of L-phenylalanine[10] **11** with the appropriate salicylanilide salt (Scheme 3).

2. General procedure for the synthesis of ester 3 or benzoxazepine 6

N-Benzyloxycarbonyl protected α-amino acid **2** (10 mmol) and substituted salicylanilide **1** (10 mmol) were dissolved in dry *N*,*N*′-dimethylformamide (DMF, 45 ml). The solution was cooled to −10 °C and *N*,*N*′-dicyclohexylcarbodiimide (DCI, 11 mmol) was added in three portions over 1 h. The mixture was then stirred for 3 h at the same temperature and stored at 4 °C for 20 h. The precipitate of *N*,*N*′-dicyclohexylurea was removed by filtration and the solvent was evaporated in vacuo. The crude product (**3** or **6)** was purified by crystallization from ethyl acetate–hexane.

3. Example of ester 3

3.1. 4-Chloro-2-{[(4-chlorophenyl)amino]carbonyl}phenyl (2*S*)-2-{[(benzyloxy)carbonyl]amino}-3-phenylpropanoate (3b)

White solid; yield 62%; mp 151–153 °C; $[\alpha]_D^{23}$ −13.2 (*c* 1; $CHCl_3$). IR (KBr): 3420, 1767, 1706, 1659, 1597, 1531, 1493, 1402, 1315, 1199, 1102. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (1H, br s, NH), 7.78 (1H, d, $J = 2.2$ Hz, H6), 7.59–7.46 (2H, m, H2′, H6′), 7.40 (1H, dd, $J = 8.8$ Hz, $J = 2.5$ Hz, H4), 7.36–7.21 (10H, m, H3′, H5′, Ar-phenyl), 7.19–7.11 (2H, m, Ar-phenyl), 6.92 (1H, d, $J = 8.5$ Hz, H3), 5.29 (1H, d, $J = 7.1$ Hz, NH), 5.04 (1H, d, $J = 12.1$ Hz, OCH_2), 4.96 (1H, d, $J = 12.1$ Hz, OCH_2), 4.75 (1H, q, $J = 7.4$ Hz, NCH), 3.23 (1H, dd, $J = 13.9$ Hz, $J = 6.3$ Hz, CH_2), 3.10 (1H, dd, $J = 13.9$ Hz, $J = 7.4$ Hz, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 162.1, 155.9, 145.7, 136.0, 135.7, 134.9, 132.2, 132.0, 129.9, 129.5, 129.1, 129.0, 128.9, 128.5, 128.3, 128.0, 127.5, 124.3, 121.9, 67.3, 55.3, 37.3. Anal Calcd for $C_{30}H_{24}Cl_2N_2O_5$ (563.43) C, 63.95; H, 4.29; N 4.97. Found: C, 63.83; H, 4.29; N, 4.69.

4. Ilustrative example of cycle 6

4.1. (3*S*)-7-chloro-*N*-(4-chlorophenyl)-3-methyl-2,5-dioxo-2,3- dihydro-1,4-benzoxazepine-4(5*H*)-carboxamide (6a)

White solid; yield 22%; mp 188–191 °C; $[\alpha]_D^{24}$ −67.8 (*c* 2.2; DMSO). IR (KBr): 3455, 1763, 1708, 1655, 1533, 1493, 1437, 1343, 1271, 1092, 827. ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 9.30 (1H, br s, NH), 7.97 (1H, d, $J = 2.6$ Hz, H6), 7.84 (1H, dd, $J = 8.8$ Hz, $J = 2.6$ Hz, H4), 7.58–7.52 (2H, m, AA′, BB′, H2′, H6′), 7.44 (1H, d, $J = 8.8$ Hz, H3), 7.30–7.24 (2H, m, AA′, BB′, H3′, H5′), 5.57 (1H, q, $J = 6.9$ Hz, CH), 1.66 (3H, d, $J = 6.9$ Hz, CH_3). ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 167.8, 160.4, 152.3, 138.6, 136.9, 131.0, 129.3, 128.8, 127.6, 122.4, 122.3, 119.3, 117.1, 53.4, 13.8. Anal Calcd for $C_{17}H_{12}Cl_2N_2O_4$ (379.19): C, 53.85; H, 3.19; N 7.39. Found: C, 53.98; H, 3.48; N, 7.50.

5. Preparation of hydrobromide salt 7

A solution of hydrogen bromide in acetic acid (33%) was slowly added to *N*-benzyloxycarbonyl-protected esters **3** with stirring. The suspension was stirred at room temperature for 30 min. Over this time, the suspension turned into a clear brown solution, and evolution of carbon dioxide was observed. When the gas evolution ceased, dry diethyl ether (DEE) was added. The precipitate was collected by filtration, washed with DEE (3×15 ml) and dried. The isolated crystals were suspended in dry chloroform at room temperature, filtered and dried in vacuo at room temperature. The yield of hydrobromide salt **7** was about 90%.

5.1. 4-Chloro-2-{[(4-chlorophenyl)amino]carbonyl}phenyl (2*S*)-2-amino-3-phenylpropanoate hydrobromide (7a)

Yield 92%; mp 214–216 °C. IR (KBr): 3421, 1763, 1658, 1595, 1493, 1400, 1204, 1102, 825, 701, 507. ^{1}H NMR (300 MHz, DMSO) δ 10.72 (1H, br s, NH), 8.61 (3H, br s, NH_2·HBr) 7.87 (1H, d, $J = 2.7$ Hz, H6), 7.78–7.73 (2H, m, AA′, BB′ overlapped, H2′, H6′), 7.73 (1H, dd overlapped, $J = 8.5$ Hz, $J = 2.7$ Hz, H4), 7.45–7.39 (2H, m, AA′, BB′, H3′, H5′), 7.33–7.21 (6H, m H3, H2″, H3″, H4″, H5″, H6″), 3.20 (1H, dd, $J = 14.4$ Hz, $J = 6.7$ Hz, CH_2), 3.13 (1H, dd, $J = 14.4$ Hz, $J = 6.7$ Hz, CH_2). ^{13}C NMR (75 MHz, DMSO) δ 167.5, 162.6, 146.1, 137.9, 134.8, 132.0, 131.0, 130.8, 129.7, 129.4, 128.9, 128.8, 127.9, 127.5, 125.2, 121.7, 53.5, 35.6. MS (ESI) *m*/*z* 511.2 $[M^+H]^+$.

6. General procedure for the synthesis of diamide 10

Triethylamine (0.95 mmol) was added to a stirred suspension of hydrobromide salt **7** (1 mmol) in dry chloroform (10 ml) at room temperature. After 30 min of stirring, insoluble material was filtered off and the filtrate was purified by using a Chromatotron® Harrison Research Model 7924T (toluene/ethyl acetate 4:1) or flash chromatography (toluene/ethyl acetate 9:1).

6.1. (*S*)-5-chloro-*N*-(1-(3-chlorophenylamino)-1-oxo-3-phenylpropan-2-yl)-2-hydroxybenzamide (10a)

White solid; yield 60%; mp 181–183 °C; $[\alpha]_D^{25}$ 38.25 (*c* 1; ethyl acetate). IR (KBr pellet): 3297, 1672, 1633, 1594, 1536, 1483, 1416, 1288, 1236, 1180, 865, 823, 746, 693, 675, 535. ^{1}H NMR (300 MHz, DMSO) δ 12.03 (1H, br s, NH), 10.45 (1H, br s, OH), 9.09 (1H, d, $J = 7.4$ Hz, NH) 7.97 (1H, d, $J = 2.5$ Hz, H6), 7.79 (1H, t, $J = 1.9$ Hz, H2′), 7.49–7.09 (9H, m, H4, H4′, H5′, H6′, H2″, H3″, H4″, H5″, H6″), 6.94 (1H, d, $J = 8.8$ Hz, H3), 4.95–4.81 (1H, m, CH), 3.24–3.03 (2H, m, CH_2). ^{13}C NMR (75 MHz, DMSO) δ 170.1, 166.4, 157.6, 140.3, 137.4, 133.5, 133.3, 130.7, 129.4, 128.6, 128.5, 126.8, 123.5, 122.9, 119.4, 119.1, 118.0, 117.7, 55.6, 37.5. Anal Calcd for $C_{22}H_{18}Cl_2N_2O_3$ (429.30): C, 61.55; H, 4.23; N, 6.53. Found: C, 61.48; H, 4.41; N 6.57. MS (ESI) *m*/*z* 428.9 $[M^+]$.

In conclusion, we have shown that depending on the structure of the amino acids, their conjugates with bioactive salicylanilides may undergo an interesting cyclization reaction leading to novel benzoxazepines. The scope and limitations of this reaction as well as its synthetic potential and biological activity of the products are now being intensively studied and the results will be reported in due course.

Acknowledgements

This study was supported by IGA of the Ministry of Health of the Czech Republic No. 1A/8238–3 and by the Ministry of Education of the Czech Republic (MSM 0021620822).

References and notes

1. Vinšová, J.; Imramovský, A. *Ces. Slov. Farm.* **2004**, *53*, 294–299.
2. Hiramatsu, K.; Hanaki, H.; Ino, T.; Yabuta, K.; Oguri, T.; Tenover, F. C. *J. Antimicrob. Chemother.* **1997**, *40*, 135–136.
3. Chu, D. T. W.; Plattner, J. J.; Katz, L. *J. Med. Chem.* **1996**, *39*, 3853–3874.
4. Waisser, K.; Bures, O.; Holy, P.; Kunes, J.; Oswald, R.; Jiraskova, L.; Pour, M.; Klimesova, V.; Kubicova, L.; Kaustova, J. *Arch Pharm.* **2003**, *336*, 53–71.
5. Kunes, J.; Balsanek, V.; Pour, M.; Waisser, K.; Kaustova, J. *Il Farmaco* **2002**, *57*, 777–782.
6. Waisser, K.; Hladuvkova, J.; Kunes, J.; Kubicova, L.; Klimesova, V.; Karajannis, P.; Kaustova, J. *Chem. Pap.-Chem. Zvesti* **2001**, *55*, 121–129.
7. Hlasta, D. J.; Demers, J. P.; Foleno, B. D.; Fraga-Spano, S. A.; Guan, J.; Hilliard, J. J.; Macielag, M. J.; Ohemeng, K. A.; Sheppard, C. M.; Sui, Z.; Webb, G. C.; Weidner-Wells, M. A.; Barret, J. F. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1923–1928.
8. Macielag, M. J.; Demers, J. P.; Fraga-Spano, S. A.; Hlasta, D. J.; Johnson, S. C.; Kanojia, R. M.; Eussell,

R. K.; Sui, Z.; Widner-Wells, M. A.; Werblood, H.; Folen, B. D.; Goldschmidt, R. M.; Loeloff, M. J.; Webb, G. C.; Barrett, J. F. *J. Med. Chem.* **1998**, *41*, 2939–2945.

9. Terada, H.; Goto, S.; Yamamoto, K.; Takeuchi, I.; Hamada, Y.; Miyake, K. *Biochim. Biophys. Acta* **1988**, *936*, 504–512.
10. L-*Phenylalanine-N-carboxyanhydride* (**11**) A solution of 0.89 g (3 mmol) of bis(trichloromethyl)carbonate in THF (25 ml) was added to a suspension of 0.83 g (5 mmol) of L-phenylalanine in tetrahydrofuran (10 ml). The reaction mixture was stirred for 3 h at 50 °C under an argon atmosphere (the suspension became a transparent solution), the solvent was evaporated under reduced pressure, and the oil recrystallized from a mixture of THF/petroleum ether and dried at room temperature. Yield 78%, mp 91–93 °C.[11] $[\alpha]_D^{23.3}$ −23.8 (*c* 8; DMF); IR 1847 cm^{-1} and 1784 cm^{-1}.
N-(1S)-1-Benzyl-2-[(3-chlorophenyl)amino]-2-oxoethyl-5-chloro-2-hydroxybenzamide To a solution of 5-chloro-*N*-(3-chlorophenyl)-2-hydroxybenzamide potassium salt (4.2 mmol) in dry THF (20 ml), cetyltrimethylammonium bromide (0.4 mmol) and a solution of L-phenylalanine-*N*-carboxyanhydride (4.2 mmol) in THF (20 ml) were added. The reaction was performed under direct sonication at 40 °C for 1 h. The solvent was then evaporated under reduced pressure, the residue suspended in dry ethyl acetate and heated at reflux for 1 h. Insoluble material was filtered off, and the filtrate was evaporated and purified by flash chromatography (toluene/ethyl acetate 4:1).
11. Wilder, R.; Mobashery, S. *J. Org. Chem.* **1992**, *57*, 2755–2756, mp 91–93 °C.