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Enzymatic resolution of new carbonate intermediates for the synthesis of (*S*)-(+)-zopiclone

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Abstract—The lipase from *Candida antarctica* B catalyzes the enantioselective hydrolysis of (±)-6-(5-chloropyridin-2-yl)-7-chloromethyloxycarbonyloxy-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyrazin-5-one, a useful intermediate in the synthesis of (*S*)-(+)-zopiclone. This enzyme also catalyzes the resolution of the corresponding 2-chloroethylcarbonate derivative. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

The establishment of practical methods for stereoselective synthesis has become one of the most challenging tasks in modern organic chemistry and is especially important in the pharmaceutical industry. Of the methods for the production of enantiomerically pure drug compounds, industrial chemists have often chosen enzyme-catalyzed reactions and, of the available biocatalysts, lipases are the most frequently used.[1] This class of enzyme is very easy to handle and their availability, low cost and the low environmental impact of lipase-catalyzed processes are very important advantages from an industrial point of view.

Racemic zopiclone is a hypnotic agent of the cyclopyrrolone class, which has been commercialized for the treatment of insomnia. However, the (*S*)-configured enantiomer is more active[2] and less toxic[3] than the (*R*)-isomer. In a previous report we described a chemoenzymatic method for the preparation of enantiomerically pure (*S*)-(+)-zopiclone, **3** (Scheme 1).[4] The key step in this procedure is the resolution of the vinyl carbonate intermediate (±)-**2a** by lipase-catalyzed hydrolysis or transcarbonation (Scheme 1). The (*R*)-configured product **1** of the enzymatic reaction undergoes spontaneous racemization in the reaction medium. Therefore, it can be directly recycled after work-up of the enzymatic reaction. Thus, the overall formal yield of the enzymatic process is 100%, even though this enzymatic step is a kinetic resolution process.

Although the enzymatic step is efficient, two facts make the method expensive for the kilogram preparation of enantiopure (*S*)-(+)-zopiclone. Firstly, the high cost of vinyl chloroformate as a reagent and, secondly, the low 30% yield of the last step in the synthesis, i.e. the treatment of the vinyl carbonate (+)-**2a** with *N*-methylpiperazine. Herein, we describe an improvement of this method based on the preparation and enzymatic resolution of new carbonate intermediates.

2. Results and discussion

In our previous work,[4] we had tested the phenyl, ethyl, benzyl and 2,2,2-trichloroethyl carbonate derivatives (±)-**2** as substrates for the *Candida antarctica* lipase B (Novozym 435) catalyzed hydrolysis. In all cases, less than 10% conversion was achieved after 10 days of reaction. Only vinyl carbonate **2a** gave good conversion values (50% after 3 days at 60°C). It can be concluded from the previous results that the structure of the carbonate R substituent of substrate (±)-**2** has a marked effect on the enzymatic reaction (Scheme 1). We hypothesized that two properties of the carbonate substrate (±)-**2** were significant. Firstly, the carbonate should be activated by an electron withdrawing R group in order to achieve good reaction rates. However, apparently this may not be enough, because the

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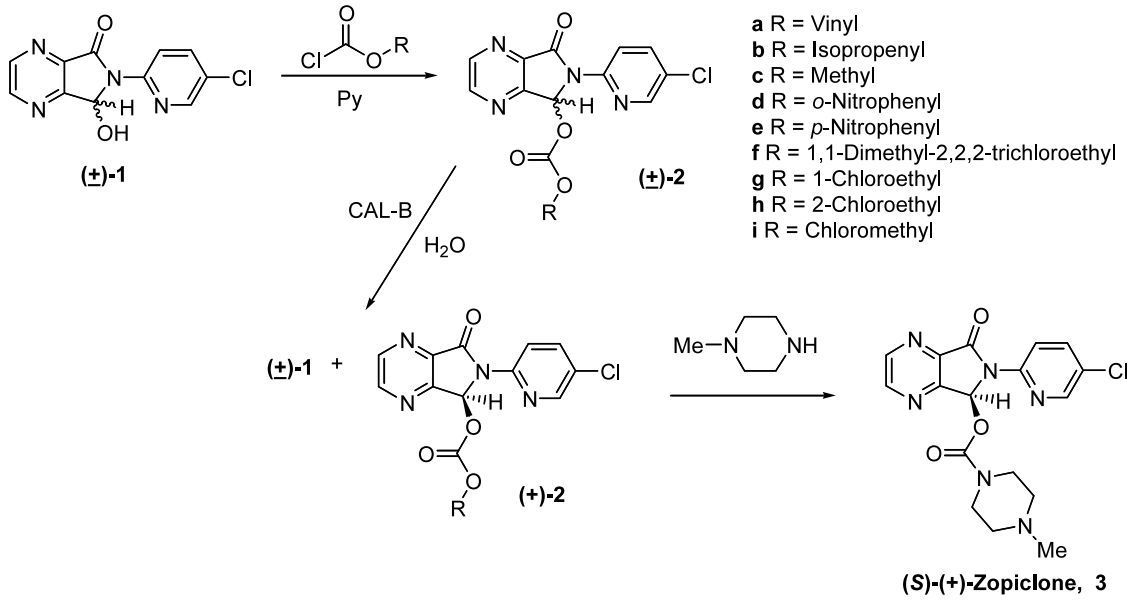

Scheme 1.

2,2,2-trichloroethyl derivative did not react, even though it is activated. Therefore, the size of the R group should also be considered. We expected that only substrates bearing small R groups would fit in the active site of the enzyme. In order to test these hypotheses, we synthesized eight new carbonates (±)-**2b**–**i**. Two steps were considered in the search for new substrates. The first goal was to find a set of substrates which reacted at a good rate in the enzyme catalyzed step, regardless of enantioselectivity. The best conditions already described for the vinyl carbonate (±)-**2a** (Novozym 435 as catalyst, 3 equiv. of H_2O in 1,4-dioxane at 60°C) were chosen as a standard for the screening. After that, different reaction conditions would be explored in order to improve the enantioselectivity with those reacting substrates.

We first studied the enzymatic hydrolysis of the isopropenyl and methyl derivatives (±)-**2b** and (±)-**2c**, but neither of them could be resolved.[4] As expected, being a non-activated carbonate, the methyl derivative (±)-**2c** did not react after 5 days. Compound (±)-**2b** reacted very slowly (only 15% conversion in 7 days) and with no enantioselectivity. As both vinyl and isopropenyl derivatives usually react in a similar way in enzymatic reactions,[5] the result with (±)-**2b** was rather unexpected—reaction of (±)-**2a** affords 50% conversion in 3 days and $E > 100$.[4]

The two derivatives possessing a deactivated aromatic ring as substituent, (±)-**2d** and (±)-**2e**, are also poor substrates for the Novozym 435 lipase and have the added inconvenience of their instability. The spontaneous hydrolysis product and other unidentified compounds could be detected by ^{1}H NMR after a few hours of storage of these compounds.

Finally, we studied the hydrolysis of the new chloro carbonates (±)-**2f**–**i**. Under standard conditions, substrates (±)-**2f** and (±)-**2g** were recovered unreacted after 15 days of incubation. On the other hand, 2-chloroethyl (±)-**2h** and chloromethyl (±)-**2i** carbonates yielded the corresponding racemic alcohol (±)-**1** with low conversion. Unfortunately, the blank reaction in the absence of enzyme showed that it was due to the spontaneous non-enzymatic reaction.

In a previous study,[6] we had observed a strong influence of the organic solvent, the amount of water as well as the pH of the aqueous solution employed, in the rate and enantioselectivity of the enzymatic hydrolysis of the vinyl carbonate (±)-**2a**. It has been suggested that water acts as a molecular lubricant, increasing enzyme flexibility in organic solvents, thus affecting to reaction rate and enantioselectivity.[7] According to this, we expected an increase in enzyme activity upon addition of water to the organic solvent. Indeed, addition of 0.1 M buffer to the dioxane solution—equivalent to a 40:1 molar excess of water—led to about 40% conversion of substrate (±)-**2h** in 6 days, affording the remaining substrate with 62% e.e. (Table 1, entry 1). The biocatalyzed reaction with substrate (±)-**2i** was also activated by addition of 0.1 M buffer, but in this case a higher amount was needed (equivalent to a 100:1 molar excess of water:substrate) and no enantioselectivity was observed (entry 7). Moreover, additional experiments in the absence of enzyme showed that the non-enzymatic hydrolysis of **2h** and **2i** was suppressed by addition of buffer to the organic solution, but not by addition of water alone. Hence, a certain amount of buffer was added to the organic solvent in all experiments thereafter. For the rest of carbonates **2b**–**g**, no improvement was observed neither with water nor with buffer.

It is noteworthy that, as expected, the two carbonates that reacted with the enzyme, namely **2h** and **2i**, are the

Table 1. Lipase hydrolysis of (±)-**2h** and (±)-**2i** in organic solvents, at 60°C

Entry	Substrate	Enzyme	H_2O (equiv.)[a]	Buffer conc. (M)	Solvent	Time (days)	Yield[b] (%)	c[c] (%)	e.e.$_s$[f] (%)
1	(±)-**2h**	Novozym 435	40	0.1	1,4-Dioxane	6		>40[d]	62
2	(±)-**2h**	Novozym 435	40	0.1	Acetonitrile	6		>30[d]	45
3	(±)-**2h**	Novozym 435	10	0.1	Toluene	4	39	61[e]	>99
4	(±)-**2h**	Chirazyme-L2	10	0.1	Toluene	4	45	55[e]	>99
5	(±)-**2h**	Chirazyme-L2	10	1	Toluene	4	47	53[e]	>99
6	(±)-**2h**	Chirazyme-L2	10	2	Toluene	4	48	52[e]	>99
7	(±)-**2i**	Novozym 435	100	0.1	1,4-Dioxane	5		>22[d]	0
8	(±)-**2i**	Novozym 435	10	0.1	Toluene	21		>27[d]	25
9	(±)-**2i**	Chirazyme-L2	10	0.1	Toluene	6		>24[d]	19
10	(±)-**2i**	Chirazyme-L2	10	0.2	Toluene	4		>20[d]	18
11	(±)-**2i**	Chirazyme-L2	10	1	Toluene	3		>25[d]	30
12	(±)-**2i**	Chirazyme-L2	30	1	Toluene	8		>45[d]	82
13	(±)-**2i**	Chirazyme-L2	30	2	Toluene	4		>50[d]	89
14	(±)-**2i**	Chirazyme-L2	60	2	Toluene	4	49	51[e]	96
15	(±)-**2i**	Chirazyme-L2	30	2	1,4-Dioxane	13			14
16	(±)-**2i**	Chirazyme-L2	30	1	Acetonitrile	2			48
17	(±)-**2i**	Chirazyme-L2	30	2	Acetonitrile	3		>50[d]	93
18	(±)-**2i**	Chirazyme-L2	30	2	Acetone[g]	13			8
19	(±)-**2i**	Chirazyme-L2	30	1	^{t}BuOMe[g]	2			60
20	(±)-**2i**	Chirazyme-L2	30	2	^{t}BuOMe[g]	3	37	63[e]	>99

[a] Referred to substrate **2**.
[b] Isolated yield of the remaining substrate. The isolation was carried out only when e.e.$_s$ >95%.
[c] Conversion.
[d] Determined from the reaction crude by ^{1}H NMR.[8]
[e] Estimated from the yield of the remaining substrate. In the absence of losses by purification, $c = 100 - \text{yield}$.
[f] Determined by HPLC.
[g] At 30°C.

less sterically hindered among the activated ones. On comparison of the results obtained with the couples of carbonates **2a**/**2b** and **2g**/**2i**, it is apparent that the presence of a methyl group in the 1′ position of the R moiety prevents the enzymatic reaction. If we assume that the reacting carbonyl is roughly equally activated within each couple, it can be concluded that the 1′-methyl group hinders the proper fitting of the substrate into the active site of the enzyme. This argument also explains why the phenyl[4] or the **2f** derivatives do not react either.

In order to improve the performance of the process, we studied exhaustively the enzymatic hydrolysis of the 2-chloroethyl (±)-**2h** and chloromethyl (±)-**2i** carbonates, which were the only substrates that had reacted so far. Substrate **2b** was disregarded at this point because it did not show any advantage over **2a** in terms of reactivity and its cost is also too high. We also tested other lipases as catalysts (from *C. antarctica*—A and B—, *Pseudomonas cepacia*, *Candida cylindracea* and *Candida rugosa*), but only the two immobilized forms of lipase B from *C. antarctica*, Novozym 435 and Chirazyme-L2, catalyzed the hydrolysis of these carbonates.

The results of the enzymatic hydrolysis of carbonate (±)-**2h** are summarized in Table 1 (entries 1–6). Comparable results were obtained in 1,4-dioxane and acetonitrile with Novozym 435 (entries 1 and 2). Interestingly, the influence of the addition of buffer to the solvent is much more favorable in toluene (entry 3). In this case, enantiopure compound was recovered with 61% conversion in only 4 days. The results were further improved by using Chirazyme-L2 as catalyst and increasing up to 2 M the concentration of the buffer added (entries 4–6). For the conditions in entry 6, an excellent value of E>100 can be estimated.[9]

In the case of chloromethyl carbonate (±)-**2i**, some enantioselectivity was observed when changing the solvent from dioxane to toluene (entries 7–8). As Chirazyme-L2 gave higher reaction rates than Novozym 435 in the same conditions (compare entries 8 and 9), the former was used as catalyst in the subsequent experiments. Conversion and enantioselectivity in toluene were improved by increasing the amount and concentration of buffer (entries 9–14). However, the effect was not as dramatic as in the case of (±)-**2h** (compare entries 5 and 11, or 6 and 14). The best result was obtained in toluene with 2 M buffer, affording (+)-**2i** in 49% yield and 96% e.e.$_s$, from which a value of $E = 97$ can be estimated. In other solvents, the reaction was slower or less enantioselective than in toluene (entries 15–20). It has to be pointed out that, due to the large amount of buffer added, a separate aqueous phase was formed in the reactions carried out in toluene.

It has been demonstrated that the use of certain additives in the reaction mixture may have a beneficial

influence on the reactivity and selectivity of the enzymatic processes.[10] For additional fine-tuning of the reaction conditions, we studied the effect of basic additives in the enzymatic hydrolysis of chloromethyl carbonate (±)-**2i**. Taking into account that hydrochloric acid is formed as a by-product, we expected an enhancement of the rate and enantioselectivity of this reaction by the addition of small amounts of amines to the reaction mixture. The results obtained are summarized in Table 2. In the absence of buffer (entries 1–4), the best result is obtained with triethylamine in ^{t}BuOMe, giving 33% yield of enantiopure (+)-**2i**. Much better results are obtained when the amine is employed together with the aqueous buffer in toluene (entries 5–7). In this case, the less basic pyrazine gives the best enantioselectivity, affording 50% yield of enantiopure (+)-**2i**, which corresponds to a value of $E>100$.

Finally, we carried out the reaction of enantiomerically pure substrates (+)-**2h** and (+)-**2i** with *N*-methylpiperazine, according to the usual procedure, to obtain the (*S*)-(+)-zopiclone **3**.[3] Treatment of carbonate (+)-**2i** with *N*-methylpiperazine afforded (*S*)-(+)-zopiclone **3**, with a yield higher than 90%. On the contrary, the reaction of carbonate (+)-**2h** did not afford the desired compound, but the substitution product at the 7 position of the dihydropirrolopyrazinone ring by *N*-methylpiperazine, together with the carbamate of 2-chloroethyl and *N*-methylpiperazine.

3. Conclusion

We have described the resolution of two new carbonate derivatives (±)-**2h** and (±)-**2i**, via *C. antarctica* lipase-catalyzed hydrolysis. Carbonate (±)-**2i** is a useful intermediate in the synthesis of (*S*)-(+)-zopiclone. It is noteworthy the low cost of the reagents employed in the synthesis of (±)-**2i** as well as the high yield of the last step in the synthesis of (*S*)-(+)-zopiclone by the reaction of the enantiomerically pure carbonate (+)-**2i** with *N*-methylpiperazine.

4. Experimental

Enzymatic reactions were carried out in a Gallenkamp incubatory orbital shaker. Immobilized *C. anctarctica* lipase B Novozym 435 was a gift from Novo Nordisk. *Candida antarctica* lipase B Chirazyme-L2, c.-f., lyo. was purchased from Roche Diagnostics.

Melting points were taken using a Gallenkamp apparatus and were uncorrected. Optical rotations were measured using a Perkin–Elmer 241 polarimeter and are quoted in units of 10^{-1} deg cm^2 g^{-1}. ^{1}H and ^{13}C NMR spectra were obtained with TMS (tetramethylsilane) as internal standard using a Bruker AC-300 (^{1}H 300 MHz and ^{13}C 75.5 MHz) spectrometer. Mass spectra were recorded on a Hewlett–Packard 1100 LC/MSD. All reagents were purchased from Aldrich Chemie. Solvents were distilled over an adequate desiccant and stored under nitrogen. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh).

The enantiomeric excesses were determined by chiral HPLC analysis on a Shimadzu LC liquid chromatograph, using a CHIRALPAK AS column (4.6×250 mm).

4.1. Synthesis of (±)-7-(2-chloroethyloxycarbonyloxy)-6-(5-chloropyridin-2-yl)-6,7-dihydro-5*H*-pyrrolo-[3,4-*b*]-pyrazin-5-one, (±)-2h

2-Chloroethyl chloroformate (0.8 ml, 7.61 mmol) was slowly added to a solution of alcohol (±)-**1** (1 g, 3.8 mmol) and anhydrous pyridine (1.2 ml) in anhydrous CH_2Cl_2 (20 ml) under nitrogen at 0°C. The resulting mixture was allowed to warm to rt, stirred for 7 h and then extracted with CH_2Cl_2. The organic extract was

Table 2. Chirazyme-L2 catalyzed hydrolysis of (±)-**2i** in the presence of additives

Entry	Additive	Additive (equiv.)[a]	Solvent	*T* (°C)	H_2O (equiv.)[a]	Buffer conc. (M)	*t* (days)	Yield[b] (%)	*c*[c] (%)	e.e.$_s$[f] (%)
1	Pyrazine	3:1	Toluene	60	30:1	–	4		>23[d]	28
2	Triethylamine	3:1	Toluene	60	30:1	–	4		>47[d]	84
3	Triethylamine	1:1	Acetonitrile	60	30:1	–	2		>45[d]	72
4	Triethylamine	1:1	^{t}BuOMe	30	30:1	–	2	33	67[e]	>99
5	Pyrazine	2:1	Toluene	60	60:1	2	4	50	51[e]	>99
6	Pyridine	2:1	Toluene	60	60:1	2	4	32	68[e]	>99
7	Triethylamine	2:1	Toluene	60	60:1	2	4	30	70[e]	>99

[a] Referred to substrate **2**.
[b] Isolated yield of the remaining substrate. The isolation was carried out only when e.e.$_s$ >95%.
[c] Conversion.
[d] Determined from the reaction crude by ^{1}H NMR.[8]
[e] Estimated from the yield of the remaining substrate. In the absence of losses by purification, $c=100-$yield.
[f] Determined by HPLC.

dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was washed with diethyl ether to afford compound (±)-**2h** as a white solid (>95% yield). No further purification was necessary. Mp 177–178°C; ^{1}H NMR ($CDCl_3$) δ 8.86 (dd, 2H, 2 CH), 8.52 (d, 1H, CH, $^3J_{HH}$ = 8.98 Hz), 8.39 (d, 1H, CH, $^4J_{HH}$ = 2.58 Hz), 7.99 (s, 1H, CH), 7.82 (dd, 1H, CH, $^3J_{HH}$ = 8.98 Hz, $^4J_{HH}$ = 2.58), 4.53 (m, 2H, CH_2), 3.74 (t, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ (ppm): 162.8 (C=O), 154.6 (C=O), 153.6 (C), 148.6 (CH), 148.6 (CH), 147.8 (C), 147.1 (CH), 144.3 (C), 138.6 (CH), 128.9 (C), 116.3 (CH), 80.8 (CH), 68.5 (CH_2), 41.3 (CH_2). MS (ESI$^+$) m/z (%): 391 [(M+Na)$^+$, 100%].

4.2. Synthesis of (±)-7-chloromethyloxycarbonyloxy-6-(5-chloropyridin-2-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]-pyrazin-5-one, (±)-2i

Chloromethyl chloroformate (1.02 ml, 11.42 mmol) was slowly added to a solution of the alcohol (±)-**1** (1 g, 3.8 mmol) and anhydrous pyridine (1.2 ml) in anhydrous CH_2Cl_2 (8 ml) under nitrogen at 0°C. The resulting mixture was allowed to warm to rt, stirred for 17 h and then extracted with CH_2Cl_2. The organic fraction was dried over Na_2SO_4, filtered and evaporated under reduced pressure to afford compound (±)-**2i** as a white solid (86% yield). No further purification was necessary. Mp 55–58°C; ^{1}H NMR ($CDCl_3$) δ 8.89 (dd, 2H, 2 CH), 8.50 (d, 1H, CH, $^3J_{HH}$ = 8.85 Hz), 8.37 (d, 1H, CH, $^4J_{HH}$ = 2.52 Hz), 7.97 (s, 1H, CH), 7.80 (dd, 1H, CH, $^4J_{HH}$ = 2.52 Hz, $^3J_{HH}$ = 8.85 Hz), 5.81 (dd, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ (ppm): 163.0 (C=O), 154.5 (C=O), 152.8 (C), 149.1 (CH), 148.0 (C), 147.4 (CH), 144.5 (C), 139.0 (CH), 129.2 (C), 116.3 (CH), 81.6 (CH), 73.2 (CH_2). MS (ESI$^+$) m/z (%): 377 [(M+Na)$^+$, 100%], 355 [(M+H)$^+$, 68%].

4.3. General procedure for lipase-catalyzed hydrolysis of carbonates

The reaction mixture contained the carbonate (±)-**2h** or (±)-**2i** (0.2 g), the immobilized lipase (0.2 g) and phosphate buffer pH 7 (amount indicated in Tables 1 and 2) in the corresponding organic solvent (40 ml). In the enzymatic hydrolysis carried out in the presence of an additive, the amount indicated in Table 2 was also added to the reaction mixture. The resulting mixture was shaken at 250 rpm in a rotatory shaker. The progress of the reaction was monitored by TLC using the solvent system hexane:ethyl acetate 1:1. The enzyme was removed by filtration and washed with ethyl acetate. The solvent was evaporated under reduced pressure and the crude residue was purified by flash chromatography on silica gel to afford the corresponding remaining substrate (*S*)-(+)-**2h** (hexane:ethyl acetate 6:4) or (*S*)-(+)-**2i** (hexane:ethyl acetate 1:1), and the racemic product (±)-**1**.

4.3.1. (*S*)-(+)-7-(2-Chloroethyloxycarbonyloxy)-6-(5-chloropyridin-2-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]-pyrazin-5-one, (*S*)-(+)-2h. $[\alpha]_D^{20}$ +87 (*c* 1.1, $CHCl_3$), e.e. >99%. Determination of the e.e. by HPLC analysis: two well resolved peaks were obtained for the racemic compound (1 mg in 4 ml mobile phase; 20 μl sample) at 20°C in hexane:*i*-propanol (60:40), 0.8 cm^3 min^{-1}, Rs 2.8. (*S*)-(+)-**2h**, t_R 26.0.4 min; (*R*)-(−)-**2h**, t_R 32.89 min.

4.3.2. (*S*)-(+)-7-Chloromethyloxycarbonyloxy-6-(5-chloropyridin-2-yl)-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]-pyrazin-5-one, (*S*)-(+)-2i. $[\alpha]_D^{20}$ +94 (*c* 1.1, $CHCl_3$), e.e. >99%. Determination of the e.e. by HPLC analysis: two well resolved peaks were obtained for the racemic compound (1 mg in 4 ml mobile phase; 20 μl sample) at 20°C in hexane:ethanol:*i*-propanol (60:35;5), 1 cm^3 min^{-1}, Rs 4.1. (*S*)-(+)-**2i**, t_R 10.34 min; (*R*)-(−)-**2i**, t_R 15.28 min.

4.4. Synthesis of (*S*)-(+)-6-(5-chloropyridin-2-yl)-7-[(4-methyl-1-piperazinyl)carbonyloxy]-6,7-dihydro-5*H*-pyrrolo[3,4-*b*]pyrazin-5-one, (*S*)-(+)-Zopiclone, (*S*)-(+)-3

N-Methylpiperazine (0.48 ml, 4.2 mmol) was slowly added to a solution of the carbonate (*S*)-(+)-**2i** (0.5 g, 1.4 mmol) in anhydrous acetone (6 ml) under nitrogen at 0°C. The resulting mixture was allowed to warm to rt, stirred for 2 h and then the solvent was evaporated under reduced pressure and the crude residue was purified by flash chromatography on silica gel to afford the corresponding (*S*)-(+)-**3** (acetone) as a white solid (90% yield). No further purification was necessary. Mp 176–178°C; ^{1}H NMR ($CDCl_3$) δ 8.85 (dd, 2H, 2 CH), 8.48 (d, 1H, CH, $^3J_{HH}$ = 8.85 Hz), 8.36 (d, 1H, CH, $^4J_{HH}$ = 2.49 Hz), 7.99 (s, 1H, CH), 7.77 (dd, 1H, CH, $^4J_{HH}$ = 2.49 Hz, $^3J_{HH}$ = 8.85 Hz), 3.56 (bd, 2H, CH_2), 3.22 (bs, 2H, CH_2), 2.33 (bs, 2H, CH_2), 2.22 (s, 3H, CH_3), 2.08 (sa, 2H, CH_2); ^{13}C NMR ($CDCl_3$) δ (ppm): 162.7 (C=O), 155.2 (C=O), 153.2 (C), 148.2 (CH), 147.6 (CH), 146.5 (CH), 143.6 (C), 137.9 (CH), 128.0 (C), 115.8 (CH), 78.8 (CH), 54.2 (2 CH_2), 45.9 (CH_3), 43.8 (2 CH_2). MS (ESI$^+$) m/z (%): 411 [(M+Na)$^+$, 100%], 389 [(M+H)$^+$, 72%]. $[\alpha]_D^{20}$ +176 (*c* 1.1, $CHCl_3$), e.e. >99%. Determination of the e.e. by HPLC analysis: two well resolved peaks were obtained for the racemic compound (1 mg in 4 ml mobile phase; 20 μl sample) at 20°C in hexane:ethanol:*i*-propanol (60:35:5), 1 cm^3 min^{-1}, Rs 3.9. (*S*)-(+)-**3**, t_R 8.08 min; (*R*)-(−)-**3**, t_R 12.83 min.

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8. Values of conversion calculated by ^{1}H NMR are only approximate due to the insolubility of the product (±)-**1** in the NMR solvent. Unfortunately, the calculation of the conversion and the enantiomeric ratio *E* (see Ref. 9) from the enantiomeric excesses of the substrate and product is not possible due to the racemization of the reaction product **1**. In those cases in which reactions were worked up, a lower limit for the enantiomeric ratio *E* can be evaluated according to Ref. 9 by taking into account the value of e.e.$_s$ and the yield of the remaining substrate, which have been isolated almost quantitatively (see Tables 1 and 2).
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