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Stereochemical assignment of the enantiomers of omeprazole from X-ray analysis of a fenchyloxymethyl derivative of (+)-(*R*)-omeprazole

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Abstract: The absolute configurations of the enantiomers of the H^+, K^+-ATPase inhibitor omeprazole **1** have been determined by an X-ray crystallographic study of a derivative of (+)-(*R*)-**1**. The examined compound 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(*R*)-sulfinyl]-1-[[[(1*R*-endo)-1,3,3-trimethylbicyclo[2.2.1]hept-2-yl]-oxy]methyl]-1*H*-benzimidazole **4** was synthesized from enantiomerically pure (1*R*-endo)-2-(chloromethoxy)-1,3,3-trimethylbicyclo[2.2.1]heptane **2** and enantiomerically pure (+)-(*R*)-**1**. Finally, enantiomerically, diastereomerically and regioisomerically pure **4** was converted back to (+)-(*R*)-**1** in order to verify that no stereomutation had occurred on sulfur during the synthesis of **4**. © 1997 Elsevier Science Ltd

Introduction

5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole **1**, which has the generic name omeprazole, is the prototypical compound of a class of highly potent gastric acid secretion inhibitors (Figure 1).[1] Unlike the histamine H_2-receptor antagonists, such as cimetidine and ranitidine, this class of anti ulcer agents acts as inhibitors of gastric H^+, K^+-ATPase, the gastric acid pump.[2]

Omeprazole — a chiral sulfoxide — was resolved analytically for the first time in 1984 by chromatography using bovine serum albumin[3] and then preparatively in 1991 by chromatography on a trisphenylcarbamoylcellulose-based stationary phase.[4] Resolutions, *via* diastereomerically N-substituted derivatives of omeprazole have afterwards been disclosed in two patent applications[5,6] and recently an asymmetric oxidation of the corresponding prochiral sulfide 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]thio]-1*H*-benzimidazole was described in the patent literature.[7]

In vitro tests on isolated gastric glands from rabbits showed that the two enantiomers of omeprazole, H 199/18 and H 199/19 (Figure 2) did not show significantly different inhibitory effect on acid formation.[4] An increased interest for studying *e.g.* the pharmacokinetics of the single enantiomers of omeprazole[8,9] and omeprazole analogues[10–12] makes an appropriate stereochemical assignment of the

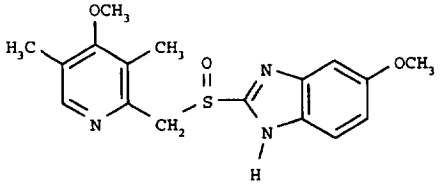

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Figure 1. Omeprazole.

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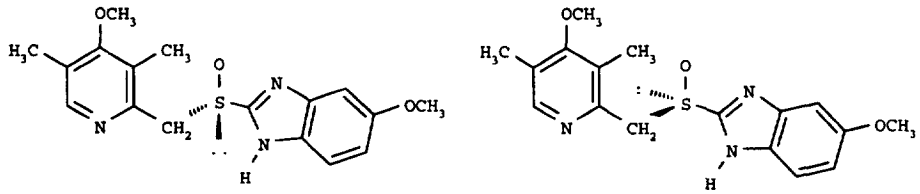

(-)-(*S*)-**1**, H 199/18 (+)-(*R*)-**1**, H 199/19

Figure 2. Enantiomers of omeprazole.

enantiomers of omeprazole necessary. Until now, we have not been able to determine the absolute configurations of the single enantiomers since these compounds, as opposed to the racemate, have hitherto not been obtained as crystalline products.[4–6]

Although, the sodium salts of these enantiomers have previously been obtained in crystalline forms,[6] X-ray studies of these salts have so far failed due to the small sizes of the crystals. The present paper describes the stereochemical assignment of the enantiomers of **1** by X-ray studies of a derivative of (+)-(*R*)-**1**, namely 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(*R*)-sulfinyl]-1-[[[(1*R*-endo)-1,3,3-trimethylbicyclo[2.2.1]hept-2-yl]oxy]methyl]-1*H*-benzimidazole **4**. This diastereomeric derivative of **1** has earlier been described in the patent literature as a synthetic intermediate when preparing (+)-(*R*)-**1** by a resolution procedure.[5]

Results and discussion

(1*R*-endo)-2-(chloromethoxy)-1,3,3-trimethylbicyclo[2.2.1]heptane **2**[13] was reacted with (+)-(*R*)-**1**[14] to give the regioisomeric mixture of **3** and **4** having the methoxy group in the benzimidazole moiety in 5 and 6 position respectively (Scheme 1).[15] Crystallization from ether afforded enriched regioisomer **4** and subsequently several successive recrystallizations from ethyl acetate/ether gave regioisomerically, enantiomerically and diastereomerically pure **4** as a white powder.[16] In order to verify that stereomutation had not occurred at the sulfur atom during the synthesis of **4**, a small amount of **4** was finally converted back to (+)-(*R*)-**1** by a hydrolytic reaction.[17] The formed enantiomer of omeprazole was shown to have the same absolute configuration as the omeprazole enantiomer that was originally alkylated with **2**.[18] The reason for performing this control reaction was that N-alkylated omeprazole analogues are prone to stereomutate at sulfur *via* a rearrangement reaction.[19,20]

The X-ray structure of **4** (Figure 3) shows that the sulfur atom in this molecule has the *R*-configuration and thus the sulfur atom in (+)-omeprazole must have the *R*-configuration. The correctness of the absolute crystal structure determination is confirmed by the fact that the fenchyl moiety in **4** has the same stereochemistry as the fenchyl moiety in (1*R*-endo)-(+)-fenchyl alcohol which was the starting material for obtaining compound **2**.[13]

Conclusions

The (+)-enantiomer of the neutral form of omeprazole as well as the (−)-enantiomer of the sodium salt[21] of said compound was found to have the *R*-configuration. Consequently, the (−)-enantiomer of the neutral form and the (+)-enantiomer of the sodium salt[21] of omeprazole have the *S*-configuration.

Acknowledgements

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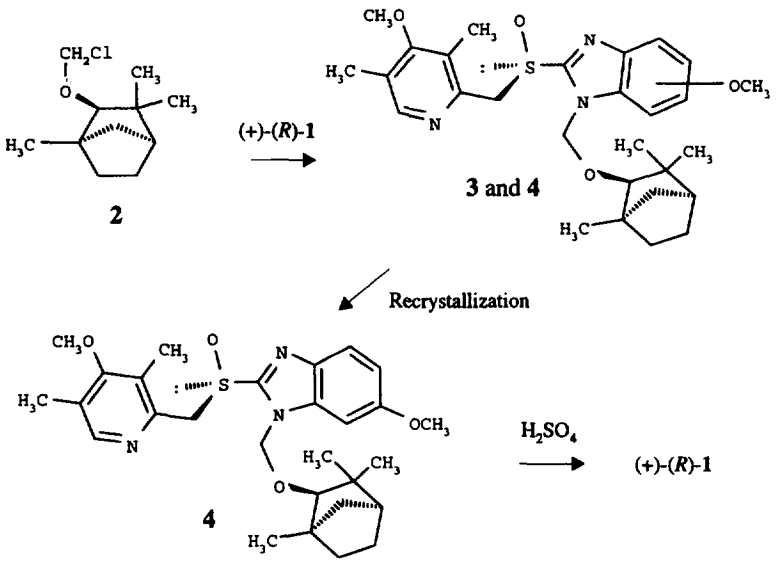

Scheme 1. Synthesis of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(*R*)-sulfinyl]-1-[[[(1*R*-endo)-1,3,3-trimethylbicyclo[2.2.1]hept-2-yl]oxy]methyl]-1*H*-benzimidazole **4** followed by hydrolysis thereof.

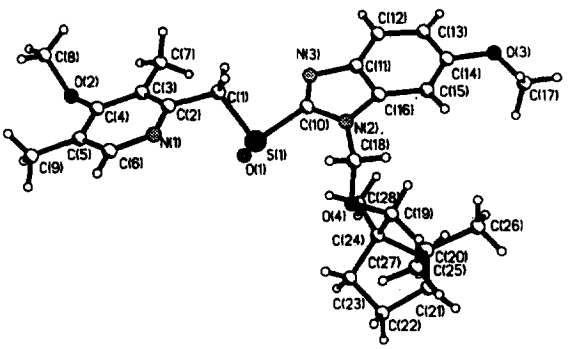

Figure 3. Perspective drawing of **4** derived from the X-ray coordinates.

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13. (1*R*-endo)-2-(Chloromethoxy)-1,3,3-trimethylbicyclo[2.2.1]heptane **2** was derived from (1*R*-endo)-(+)-fenchyl alcohol (Aldrich) according to the method described by Shipov, A. G.; Savostyanova, I. A.; Baukov, Y. I., *Zh. Obshch. Khim.* **1989**, 59, 1204–1205.
14. (+)-*(R)*-**1** was synthesized from the corresponding prochiral sulfide by a titanium catalyzed asymmetric oxidation (see reference 7).
15. Alkylation of (+)-(*R*)-**1** with **2** was performed as described in reference 5 except that (+)-*(R)*-**1** was used instead of racemic **1**.
16. Data for **4**: $[\alpha]_D^{20}$=+102.4 (c 0.5, $CHCl_3$), ^{1}H-NMR (300 MHz, $CDCl_3$) δ ppm, J Hz: 0.74 (3H, s, CH_3), 0.86 (3H, s, CH_3), 0.96 (3H, s, CH_3), 0.8–1.7 (7H, m, fenchylic CH_2 and CH), 2.21 (3H, s, $ArCH_3$), 2.27 (3H, s, $ArCH_3$), 3.25 (1H, s, CHO), 3.68 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 4.93 and 4.98 (2H, AB, J=13.5, $PyCH_2$), 5.73 and 5.79 (2H, AB, J=11.0, OCH_2), 6.95–6.99 (2H, m, ArH), 7.68 (1H, d, J=9.0, ArH), 8.15 (1H, s, PyH).
17. Hydrolysis of **4** was carried out as described in reference 5. Although omeprazole and omeprazole analogues are acid labile, they are stable in 90% sulfuric acid (see *e.g.* Senn-Bilfinger, J.; Krüger, U.; Sturm, E.; Figala, V; Klemm, K.; Kohl, B.; Rainer, G.; Schaefer, H.; *J. Org. Chem.*, **1987**, 52, 4582–4592).
18. Determination that the omeprazole enantiomers had the same configuration was achieved by chiral HPLC.
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21. Note! The sign of the optical rotation is reversed in relation to that of the neutral form when the measurement of the optical rotation is performed with the enantiomers of omeprazole as sodium salts dissolved in water. Thus, the *R*-enantiomer as *sodium salt* has the following optical rotation: $[\alpha]_D^{20}$= −44.1 (c 0.5, H_2O), whereas the *R*-enantiomer in *neutral form* has the following optical rotation: $[\alpha]_D^{20}$=+181.5 (c 0.5, $CHCl_3$).

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