Pergamon

Tetrahedron, Vol. 53, No. 23, pp. 7985-7998, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00483-3

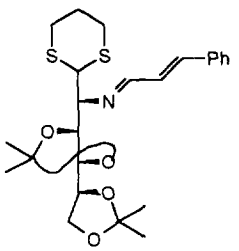
2-Amino-1-phenyl-propan-1,3-diol as Chiral Auxiliary. Application in the Synthesis of *cis* 3-Phthalimido-4-styryl-2-azetidinones

Tamas E. Gunda* and Ferenc Sztaricskai

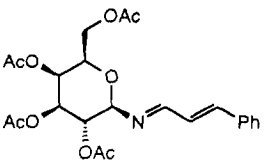
Research Group of Antibiotics, Hungarian Academy of Sciences, P.O.Box 70, H-4010 Debrecen, Hungary

Abstract - 3,4-*cis*-1-N-(1'-phenyl-1',3'-dihydroxy-2'-propyl)-3-phthalimido-4-styrylazetidinones were obtained in optically pure form by chiral Staudinger reaction. The *cis*-α/β-ratio could be influenced by the protective groups of the diol moiety. Removal of the chiral auxiliarity could be accomplished by direct oxidation, or by previous double bond formation, thus the 2-amino-1-phenyl-propan-1,3-diol can be regarded to a generally useful chiral auxiliary. © 1997 Elsevier Science Ltd.

The asymmetric ketene-imine cycloaddition route (Staudinger reaction) is of continual interest for the synthesis of the intermediates of β-lactam antibiotics, as well as for a source unnatural amino acid synthons, e.g. that present in taxol. In order to enhance the formation of one of the desired diastereomers of the 3,4-disubstituted azetidine-2-ones, different chiral starting materials may be used: Schiff-bases prepared from chiral aldehydes or amines, or optically active ketenes have been employed in a number of approaches described to date.[1] We have focused onto the role of chiral imines, when the asymmetric centre is attached directly to the N atom of the Schiff-base. Diastereoselectivity of the cycloadditon, i.e. selective formation of the α- or β-*cis* product is usually claimed to be less satisfactory in this case,[2,3] however, the results are contraversial: Barton *et al.* started from the acyclic D-glucosamine derivative (**1**) possessing 4 stereocentre and achieved complete diastereoselectivity,[4] while the galactose-imine (**2**) used by Gears *et al.*[5] with 5 chiral atoms yielded a *ca.* 2:3 mixture of α- and β-*cis* lactams.



1



2

Our preliminary results[6] appeared to be promising using the easily accessible (1S,2S)- and (1R,2R)-2-amino-1-phenyl (or 1-(p-nitrophenyl)) -propan-1,3-diol as chiral amine components. Since then another example was reported by utilizing this compound as a chiral auxuliary in addition reactions.[11] Only *cis*

β-lactams were formed, this is in accordance with the generally accepted two-step mechanism of the ketene addition, i.e. zwitterionic intermedier *via* the attack of the LUMO of the ketene carbonyl group by the imine, followed by conrotatory ring closure as depicted in Fig. 1. according to ref. 7h. The mechanism has been the subject of several recent studies on the semiempirical or *ab initio* MO level.[7]

RESULTS AND DISCUSSION

Cycloaddition

As discussed in our previous communication,[6a] the silylated Schiff-bases **5** react neatly with phthalimidoacetyl chloride in the presence of Et_3N yielding **6/8** and the end products **7/9**. Only the *cis* products were isolated and the β-isomer was always the major one, corresponding the 3*R*,4*S* configuration of the β-lactam ring, when starting from the L-*threo* (= 1*S*,2*S*) **3a** or **b**. Our assumption was that on starting from a more rigid chiral system there may be a more pronounced difference between the steric profile of the possible ionic intermediates, thus transition states with enhanced energy differences will increase the ratio of the desired diastereomers, especially if bulky protection groups are used. Different silyl derivatives were prepared from **3** by standard procedures, only the reaction of **3b** and Cl_2SiPh_2 providing **4d** required the use of more vigorous conditions, such as tBuLi/THF. However, attempted preparation of **4e** failed. When the TBDMS- protected **4b** was used, the **7/9** product ratio raised from the average 2:1 to 8:1 (Table 1.). Surprisingly, the cyclic **4c** did not produce the expected enhancement of **7b**, and the use of the diphenyl analogue **4d** was also somewhat less satisfactory as compared to **4b**. The assignment of the configurations of **7b** and **9b** was made on the basis of NOE experiments, as discussed in ref. 6a. In the case of the nitro-series the D-*threo* starting material (**3(R,R)a**) was also applied for obtaining the corresponding **7(R,R)a** and **9(R,R)a**.

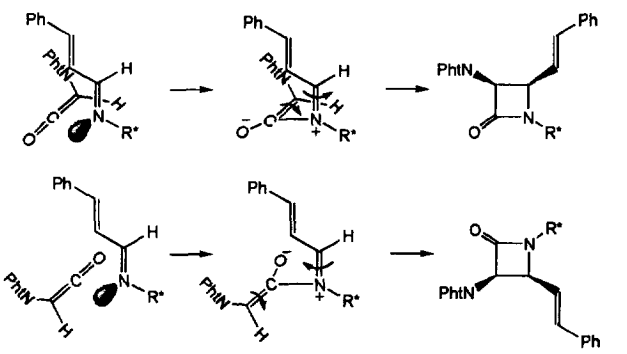


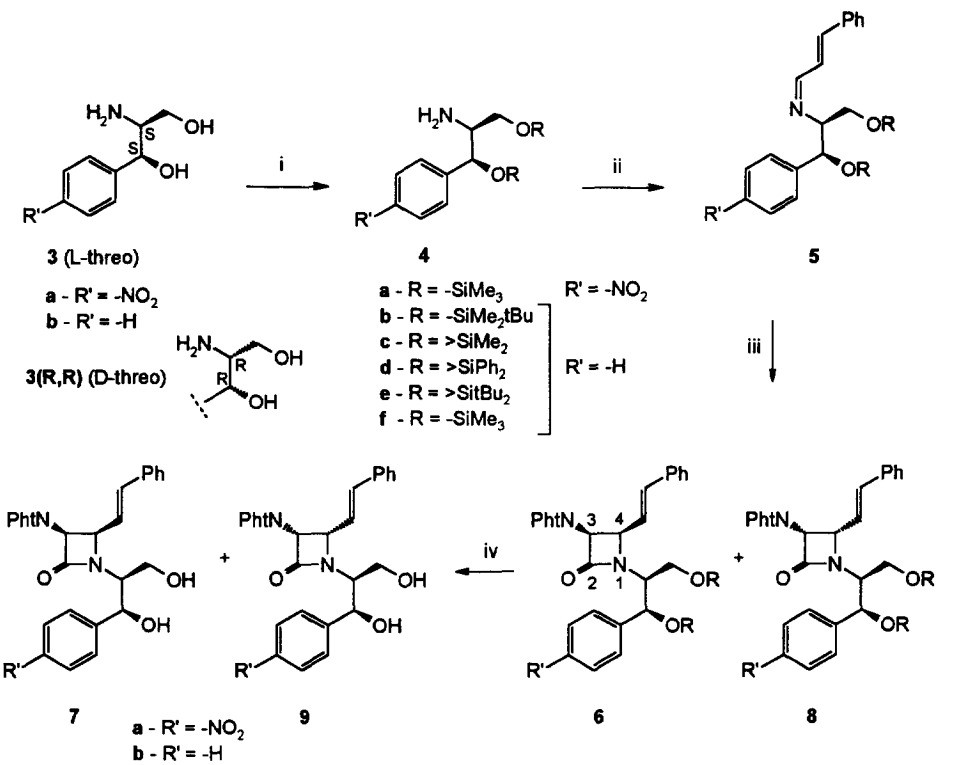
Figure 1

$-SiMe_3$:	2:1 (aver.)
$-SiMe_2tBu$:	8:1
$>SiMe_2$	3:1
$>SiPh_2$:	7:1

Table 1. Ratio of **7/9** *vs* protective groups used in **4**

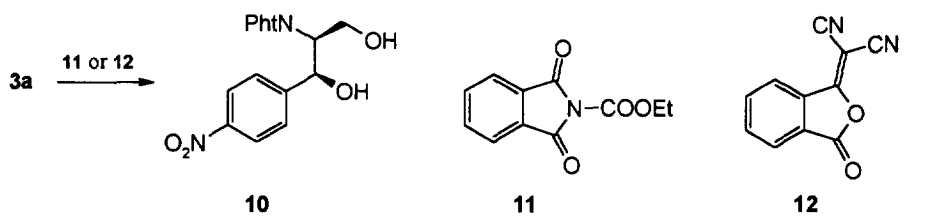
Removal of the propanediol moiety

To study the possibility of the removal of the propanediol moiety with a general the N-phthalimido protected **3a** was selected as a model compound (**3a** is the key compound in the industrial synthesis of the antibiotic chloramphenicol, therefore both enantiomers are easily available in optically pure form). The



i.silylation; ii. PhCH=CHCHO, Et_3N; iii. $PhtNCH_2COCl$, Et_3N; iv.deprotection

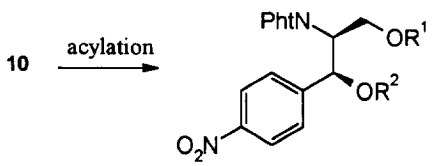
phthalimido derivative **10** was tried to prepare directly from **3a** and phthalic anhydride in boiling acetic acid[8], but this procedure always afforded two products. Employing the carbethoxy derivative **11** or the newer reagent **12**[9] yielded the desired **10**. In the case of **12** the yield of **10** was somewhat higher, but the product was more



coloured. Our first assumption was that after the acylation of the primary hydroxyl function and eliminating the resulting O-acyl group, the obtained double bond can be easily oxidized giving rise to a diketone or carbinol amide, which are possibly easily hydrolysable, regenerating the starting phthalimide.

Thus, a number of different reagents and methods were tried, but the selective acylation of the primary hydroxyl was not straightforward. For example the acetic anhydride – pyridine method yielded a *ca.* 1:1 mixture

of the 1,3-diacetyl and primary monoacetyl derivatives, together with a little secondary monoacetyl derivative. Somewhat better selectivity was achieved by using 2,6-collidine. In the case of aralkyl derivatives the use of the acid chlorides in THF in the presence of triethyl amine proved to be satisfactory. Several different acyl derivatives were prepared in order to find an optimal compound for the subsequent oxidation – elimination steps. The reactions with benzoyl chloride and phenylacetyl chloride were the most regiospecific ones and afforded the desired primary 3-monoacyl derivatives (**14g** and **14j**) in nearly pure form (although we needed only the primary monoacyl derivatives, for sake of completeness the data of all of the isolated products are included in the experimental section).

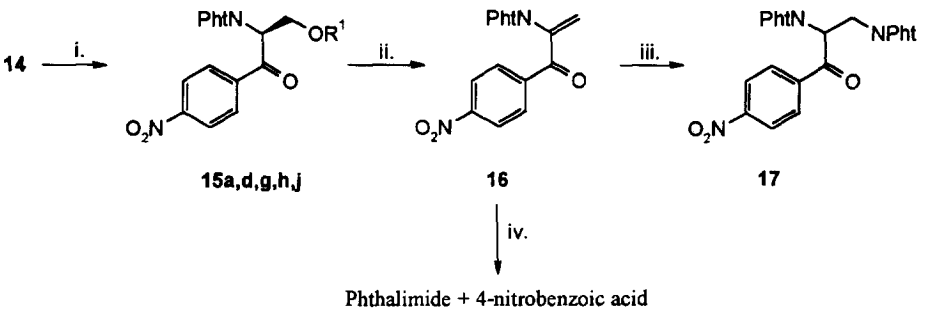


14a-k

	R^1	R^2
a -	$-COCH_3$	-H
b -	$-COCH_3$	$-COCH_3$
c -	-H	$-COCH_3$
d -	$-COC_2H_5$	-H
e -	$-COC_2H_5$	$-COC_2H_5$
f -	-H	$-COC_2H_5$
g -	$-COCH_2Ph$	-H
h -	$-COCH_2OPh$	-H
i -	$-COCH_2OPh$	$-COCH_2OPh$
j -	-COPh	-H
k -	-COPh	-COPh

In the years of the early chloramphenicol-chemistry it was found[10] that during the oxidation of chloramphenicol palmitate or similar esters in acetic acid by chromium trioxide at 50 °C, in addition to the oxidation a further elimination also occures and the reaction gives rise to the unsaturated ketone of type **16**. In our experiments the same behaviour was observed in the case of **14a**. However, under milder conditions (Jones reagent at room temperature) we could neatly prepare the ketones **15a,d,g,h** and **j**. These γ-keto esters eliminate very easily to the ketone **16**: in $CDCl_3$ it exhibits a clean ^1H NMR spectrum corresponding to the general structure of type **15**, but in DMSO-d_6 two peaks at 6.3 and 6.5 ppm, characteristic of the $=CH_2$ protons, appear and their ratio is slowly growing on allowing the sample to stand in room temperature. We could induce a complete conversion of **15** → **16** by slightly warming the compounds in wet DMSO in the presence of a catalytic amount of base (Et_3N or DBU) at 40-45 °C for 1 hour. **15a** and **15g** were difficult to prepare in pure form, but **15d,h** and **j** with an aromatic group in the side-chain could be purified by careful recrystallization.

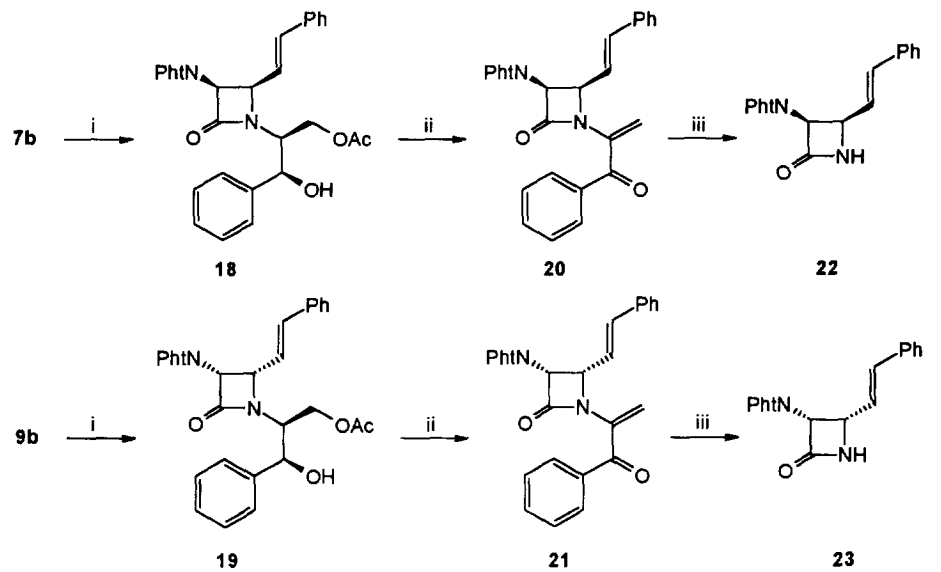
The oxidation of the double bond in **16** was accomplished with $KMnO_4$ under different conditions. Interestingly, when nonaqueous conditions were applied and the permanganate was solubilized with 18-crown-6 in CH_2Cl_2, the only product isolated was the adduct **17**. It is belived that the phthalimidate formed in the beginning of the oxidation might attack the starting material (**16**) by a Michael-type addition. In aqueous



i. Jones oxidation; ii. DMSO, Δ; iii. $KMnO_4$, CH_2Cl_2, 18-crown-6; iv. $KMnO_4$, H_2O-acetone

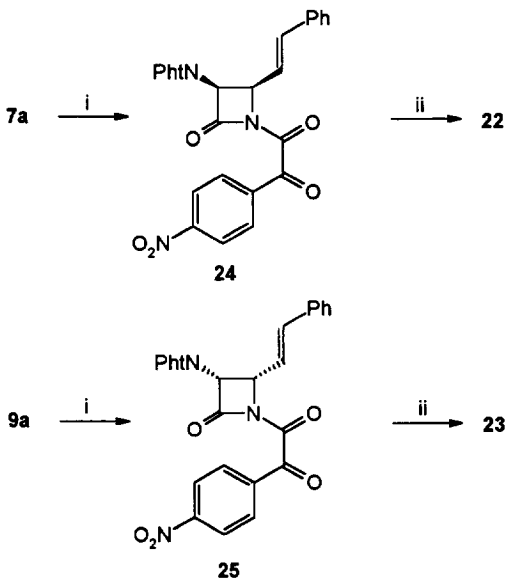
acetone, however, **16** was cleanly cleaved to phthalimide and 4-nitrobenzoic acid, the former was isolated in 76% yield.

When applying the above procedure to the β-lactam derivatives **7b** and **9b**, the regiospecifity of the acylation step proved to be more pronounced compared to the above model compound **10**, and the 3'-acetoxy mono derivatives **18** and **19** were formed nearly exclusively in collidine. There was no need to deal with separate oxidation and the elimination steps as during the next CrO_3 oxidation the elimination reaction has also occured and the β-lactam analogue of **15** could not be isolated. Careful slow oxidation of **20** and **21** with permanganate in the cold removed the N-side chain, as expected, without disturbing the styryl side chain and yielded **22** and **23**, albeit in low yields.



i. AcCl, collidine; ii. CrO_3; iii. $KMnO_4$

As an alternative to the above procedure, we found that the direct oxidation of **7** and **9** was also possible. We applied it in the nitro series. With an excess of the Jones reagent in the presence pyridine hydrochloride the diketones **24** and **25** were the main products in higher than 70% yields. Removal of the diketo moiety proceeded easily when **24** and **25** were kept in methanol - THF in the presence of a catalytic amount of sodium hydroxide.[6a]



i. Jones reag.; ii. NaOEt, THF/EtOH

EXPERIMENTAL

Melting points were determined on a Koffler-type hot-stage apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 283B spectrophotometer in KBr pellets. The ^{1}H NMR spectra were recorded at 200 MHz on a Bruker WP-SY instrument, with Me_4Si as internal standard.

The numbers and the corresponding compounds are concerning the S,S isomers of the amino-propandiol moiety, unless otherwise stated: **4a** *vs.* **4(R,R)a**.

(1S,2S)-1-(p-nitrophenyl)-2-amino-1,3-di(trimethylsilanyloxy)-propane (4a) To a mixture of 2.12 g of **3a** (0.01 mol), 1.4 ml of Et_3N and 60 ml of dry methylene chloride a solution of 2.52 ml (2 eq.) of chlorotrimethylsilane in 20 ml of methylene chloride was added dropwise at room temperature. The mixture was stirred overnight and was used immidiately for the next step.

(1S,2S)-1-phenyl-2-amino-1,3-di(trimethylsilanyloxy)-propane (4f) and **(4S,5S)-2,2-dimethyl-4-phenyl-5-amino-[1,3,2]-dioxasilanane (4c)** Both compounds were prepared as described for **4a** from the corresponding **3** with chloro-trimethylsilane and dichloro-dimethylsilane, respectively, and were used immidiately for the next step.

(1S,2S)-1-phenyl-2-amino-1,3-di(dimethyl-tert-butylsilanyloxy)-propane (4b) A mixture of 0.64 g of **3b**, 0.91 g of TBDMS-chloride, 10 ml of dry pyridine and a catalytic amount DMAP was kept at 60 °C for three days. The solvent was removed, the oily residue was taken up in chloroform and washed with water. The dried oily residue was used for the next step. Shorter reaction time yielded mainly the primary monosilylated product (m.p. 83-5 °C from hexane-chloroform).

(4S,5S)- 2,2,4-triphenyl-5-amino-[1,3,2]-dioxasilanane (4d) 1.67 g of **3b** was dissolved in 50 ml of freshly distilled abs. THF and a hexane solution of t-butyllithium (15 ml, 2 eq.) was added. Stirring was continued for 5 minutes under N_2 and then 2.1 ml of dichlorodiphenylsilane was added. Next day the solvent was removed and the oily product was used without purification for the next step. A small sample was purified by column chromatography (toluene – ethyl acetate 3:1), ^{1}H NMR ($CDCl_3$) δ 3.22 (H, m, J = 10, 5.45, 1.7 Hz), 3.86 (H, dd, J = 10, 11 Hz), 4.08 (H, dd, J = 5.5, 11 Hz), 5.58 (H, br s), 7.05-8.0 (m).

The di-tert-butyl derivative **4e** could not be prepared by the above procedures from **3b** and dichloro-di-tert-butylsilane.

1-[(1'S,2'S)-1'-phenyl-1',3'-dihydroxy-2-propyl]-3(R)-phthalimido-4(S)-styryl-azetidin-2-one (7b) and **1-[(1'S,2'S)-1'-phenyl-1',3'-dihydroxy-2-propyl]-3(S)-phthalimido-4(R)-styryl-azetidin-2-one (9b)** To a methylene chloride solution of **4f** (0.01 mol), obtained as above, 1.22 g of freshly distilled cinnamic aldehyde and 1.5 ml of Et_3N were added. The reaction mixture was stirred overnight, then evaporated. Dry methylene dichloride (30 ml) was added and the mixture was evaporated to dryness again. The residue was dissolved in 60 ml of dry methylene dichloride and 4.2 ml of Et_3N, cooled to -40 °C, and a solution of 2.7 g phthaloylglycyl chloride in 20 ml of dry methylene dichloride was added slowly. It was allowed to stay overnight without further cooling, then the solvent was changed to 100 ml of ethanol. To this mixture of **6f** and **8f** 10 ml of 2N aq. HCl was added, and was slightly warmed for 10 minutes. Column chromatographic work-up (toluene – ethyl acetate 5:1) yielded 0.95 g (19.0%) of **9b** and 2.0 g (39.0%) of **7b**.

7b: More polar compound, m.p.: 156-7 °C (methanol - ether); $[a]_D^{20}$ +109.44 (0.49, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.23 (m, H), 3.80 (m, 2H), 4.79 (dd, H, J = 5.2, 9.1 Hz), 5.12 (m, H), 5.58 (d, H, J = 5.2 Hz), 5.92 (dd, H, J = 9.1, 15.9 Hz), 6.58 (d, H, J = 15.9 Hz), 7.2-8 (m); IR (KBr) ν 1720 (br), 1380, 695 cm^{-1}; MS (EI) m$^+$ 468 (M^+, 0.2%), 281 (100%); analysis ($C_{28}H_{23}N_3O_7$, 513.51) N% calc.: 9.65%, found: 9.71%

9b: Less polar compound, m.p.: 190-2 °C (ethyl acetate); $[a]_D^{20}$ +66.48 (0.49, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.48 (m, H), 4.07 (m, 3H), 5.17 (m, H), 5.48 (d, H, J = 5.0 Hz), 6.04 (dd, H, J = 9.0, 15.8 Hz), 6.21 (d, H, J = 15.8 Hz), 7.2-8 (m); IR (KBr) ν 1728 (br), 1395, 691 cm^{-1}; analysis ($C_{28}H_{23}N_3O_7$, 513.51) N% calc.: 9.65%, found: 9.58%

When starting from **4c** the yields of **7b** and **9b** were 41% and 13%, respectively.

7b and **9b** from **4b**: The reaction was carried out as above giving rise to 52% of isomer mixture. This silylated mixture of **6b** and **8b** was deprotected with 5% aq. HF in CH_3CN yielding to a 8.1:1 mixture of **7a** and **9a**. Alternatively, a sample was separated by column chromatography (toluene – ethyl acetate 9:1) to characterize the components:

1-[(1'S,2'S)-1'-phenyl-1',3'-di(trimethylsilyloxy)-2'-propyl]-3(R)-phthalimido-4(S)-styryl-azetidin-2-one (**6b**) ^1H NMR ($CDCl_3$) δ 0.13, 0.14, 0.15, 0.24 (4 x s, 4 x 3 H), 1.04 (s, 18 H), 3.82-4.21 (m, 3H), 5.13 (dd, H, J = 5.4, 8.8 Hz), 5.27 (d, H, J = 2.8 Hz), 5.44 (d, H, J = 5.4 Hz), 6.32 (dd, H, J = 8.8, 16.1 Hz), 6.71 (d, H, J = 16.1 Hz), 7.26-7.93 (m)

1-[(1'S,2'S)-1'-phenyl-1',3'-di(trimethylsilyloxy)-2'-propyl]-3(S)-phthalimido-4(R)-styryl-azetidin-2-one (**8b**) ^1H NMR ($CDCl_3$) δ 0.13, 0.22 (2 x s, 2 x 6 H), 1.06 (s, 18 H), 3.8 (m, H), 4.4-4.7 (m, 3H), 4.86 (dd, H, J = 5.4, 9.0 Hz), 5.65 (d, H, J = 5.4 Hz), 6.28 (dd, H, J = 9.0, 16.0 Hz), 6.61 (d, H, J = 16 Hz), 7.21-7.95 (m)

Treatment of both compounds with 5% aq. HF in CH_3CN gave **7b** and **9b** in near quantitative yield, respectively.

7b and **9b** from **4d**: The reaction was carried out as above giving rise to 47% of isomer mixture. This silylated mixture of **6d** and **8d** was deprotected with 5% aq. HF in CH_3CN yielding to the 7.2:1 mixture of **7a** and **9a**. Alternatively, a sample was separated by column chromatography (toluene – ethyl acetate 9:1) to characterize the components:

1-[(4'S,5'S)-2',2',4'-triphenyl-[1',3',2']dioxasilanan-5'-yl]-3(R)-phthalimido-4(S)-styryl-azetidin-2-one (**6d**): solid foam; ^1H NMR ($CDCl_3$) δ 3.5-4.5 (m, 4H), 5.96 (d, H, J = 7.8 Hz), 6.16 (d, H, J = 6 Hz), 6.39 (dd, H, J = 15.9, 6 Hz), 6.87 (d, H, J = 15.9 Hz), 7.1-7.9 (m)

1-[(4'S,5'S)-2',2',4'-triphenyl-[1',3',2']dioxasilanan-5'-yl]-3(S)-phthalimido-4(R)-styryl-azetidin-2-one (**8d**): m.p.: 104-6 °C; ^1H NMR ($CDCl_3$) δ 4.2-4.6 (m, 3H), 5.16 (m, H) 6.08 ((d, H, J = 5.5 Hz), 6.40 (dd, H, J = 5.7, 16.1 Hz), 6.94 (d, H, J = 16.1 Hz), 7.2-7.9 (m); IR (KBr) ν 1958, 1764, 1718, 1671, 1418, 1194 cm^{-1}

1-[(1'S,2'S)-1'-(p-nitrophenyl)-1',3'-dihydroxy-2'-propyl]-3(R)-phthalimido-4(S)-styryl-azetidin-2-one (**7a**) and **1-[(1'S,2'S)-1'-(p-nitrophenyl)-1',3'-dihydroxy-2'-propyl]-3(S)-phthalimido-4(R)-styryl-azet-**

idin-2-one (9a). Both compounds were prepared according to the previous method from **3a**:
7a: 35.7%, m.p.: 169-73 °C; $[a]_D^{20}$ +66.05 (1.589, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.6-3.9 (m, 3H), 4.95 (dd, H, J = 5.4, 8.5 Hz), 5.09 (br s, H), 5.45 (d, H, J = 5.4), 6.03 (dd, H, J = 8.5, 15.5 Hz), 7.2-8.3 (m, 2+4+2+5H); analysis ($C_{28}H_{23}N_3O_7$, 513.51) N% calc.:9.65%, found: 9.61%
9a: 21.1%, m.p.: 213-5 °C; $[a]_D^{20}$ +25.7 (0.202, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.6 (m, 2H), 3.8 (m, H), 4.64 (dd, H, J = 5.5, 8.5 Hz), 5.02 (d, H, J = 4.7 Hz), 5.49 (d, H, J = 5.5 Hz), 6.12 (dd, H, 8.5, 15.8 Hz), 6.50 (d, H, J = 15.8 Hz), 7.2-8.3 (m, 2+4+2+5H); analysis ($C_{28}H_{23}N_3O_7$, 513.51) N% calc.:9.65%, found: 9.70%

1-[(1'R,2'R)-1'-(p-nitrophenyl)-1',3'-dihydroxy-2'-propyl]-3(R)-phthalimido-4(S)-styryl-azetidin-2-one (7(R,R)a) and **1-[(1'R,2'R)-1'-(p-nitrophenyl)-1',3'-dihydroxy-2-propyl]-3(S)-phthalimido-4(R)-styryl-azetidin-2'-one (9(R,R)a)**. Both compounds were prepared according to the previous method from **3(R,R)a**:
7(R,R)a: 35.0%, m.p.: 169-73 °C; $[a]_D^{20}$ -69.6 (0.079, $CHCl_3$); spectroscopic properties were the same as those of the corresponding enantiomer **7a**.
9(R,R)a: 18.4%, m.p.: 217-20 °C; $[a]_D^{20}$ -24.9 (0.204, $CHCl_3$) ; spectroscopic properties were the same as those of the corresponding enantiomer **7a**.

(1S, 2S)-1-(p-nitrophenyl)-2-phthalimido-1,3-propandiol (10) *Method A.* 13.7 g of N-carb-ethoxyphthalimide, 13.1 g of **3a** and 0.6 ml of triethylamine in 140 ml of DMSO were stirred for 3 hours at ambient temperature. 300 ml of water was slowly added and the solvent was decanted from the gummy precipitation. This was digested several times with water, then 50 ml of n-butanol was added and it was brought to the boil. After cooling the collected material was dried over P_2O_5 in vacuo, yielding 13.1 g (62%) of **10**, m.p. 230-2 °C, m.p. lit[8] 228 °C
Method B. 10.6 g of **3a**, 9.8 g of **12**[9] and 140 ml of THF was allowed to react at 40 °C for 16 h. The solution was poured into water, and the product was extracted into ethyl acetate. After evaporation the residue was recrystallized from n-butanol, giving 12.8 g (75%) of pale yellow powder, m.p. 229-31 °C. ^1H NMR (DMSO-d_6) δ 3.18 (H, dd, J = 4.1, 11.3 Hz), 4.03 (H, dd, J = 10.0, 9.0 Hz), 4.36 (H, m), 5.22 (H, d, J = 9.4 Hz), 7.7-8.3 (8H, m)

Acylation of 10, *Method A* (acylation with anhydrides):
(1S,2S)-1-(p-nitrophenyl)-2-phthalimido-3-acetoxy-1-propanol (14a), (1S,2S)-1-(p-nitrophenyl)-2-phthalimido-1,3-diacetoxy-propane (14b) and **(1S,2S)-1-(p-nitrophenyl)-2-phthalimido-1-acetoxy-3-propanol (14c)** 1 g of **10** was acetylated with 0.35 ml of Ac_2O in 25 ml collidine at room temperature overnight. After usual work-up the obtained mixture was separated by column chromatography (toluene – ethyl acetate 5:1), yielding 0 .30 g of the desired **14a** as well as 0.32 g of **14b**, and a small amount of **14c**:
14a: m.p. 115-7 °C; ^1H NMR (DMSO-d_6) δ 1.81 (3H, s), 4.04 (H, m), 4.46, 4.57 (2H, ABq, J = 8.9 Hz), 5.28 (H, d, J = 7.7 Hz), 7.76, 8.30 (4H, 2 x d), 7.95 (4H, m); IR (KBr) ν 1774, 1744, 1710, 1390, 1350 cm^{-1};

analysis: $C_{19}H_{16}N_2O_7$ (384.35) N% calc.: 7.29, found: 7.39; **14b:** m.p. 139-41 °C; ^{1}H NMR (DMSO-d_6) δ 1.86 (3H, s), 1.98 (3H,s), 4.26 (H, dd, J = 11.4, 5.3 Hz), 4.56 (H, dd, J = 11.4, 8.5 Hz), 4.85 (H, m), 6.41 (H, d, J = 8.0 Hz), 7.82, 8.28 (4H, 2 x d), 7.94 (4H, m); IR (KBr) ν 1744, 1716, 1384, 1350 cm^{-1}; analysis: $C_{19}H_{16}N_2O_7$ (426.39) N% calc.: 6.57, found: 6.45 **14c:** m.p. 218-22 °C; IR (KBr) ν 1774, 1718, 1376, 1344, 1248 cm^{-1}; analysis: $C_{19}H_{16}N_2O_7$ (384.35) N% calc.: 7.29, found: 7.25.

(1S,2S)-1-(p-nitrophenyl)-2-phthalimido-3-propionyloxy-1-propanol (14d), (1S,2S)-1-(p-nitrophenyl)-2-phthalimido-1,3-di(propionyloxy)-propane (14e) and **(1S,2S)-1-(p-nitrophenyl)-2-phthalimido-1-propionyloxy-3-propanol (14f)** These were prepared according to the previous way by the use of propionic anhydride:

14d: 47%; m.p. 135-7 °C; ^{1}H NMR (DMSO-d_6) δ 0.81 (3H, t), 2.06 (2H, q), 4.02 (H, m), 4.48 (2H, m), 5.27 (H, m), 6.16 (H, d, J = 4.2 Hz, exch. D_2O), 7,78, 8,28 (4H, 2 x d), 7.9 (4H, m); IR ν (KBr) 1742, 1708, 1388, 1348 cm^{-1}; analysis: $C_{20}H_{18}N_2O_7$ (398.38) N% calc.: 7.03, found: 7.14; **14e:** 27%; m.p. 138-40 °C; ^{1}H NMR (DMSO-d_6) δ 0.85 (6H, m), 2.09 (2H, q), 2.25 (2H, q), 4.26 (H, dd, J = 5.3, 11.4 Hz), 4.55 (H, dd, J = 8.5, 11.4 Hz), 4.83 (H, m), 6.39 (H, d, J = 8.24 Hz), 7.9 (4H, m), 7.8, 8.28 (4H, 2 x d); IR ν (KBr) 142, 1708, 1388, 1348, 1170 cm^{-1}; **14f:** 5.2 %; m.p. 152-4 °C; ^{1}H NMR (DMSO-d_6) δ 0.82 (3H, t), 2.18 (2H, q), 3.32 (H, dd, J = 4.8, 11.2 Hz), 3.99 (H, dd, J = 11.2, 8.4 Hz), 4.55 (H, m), 6.27 (H, d, J = 8.3 Hz), 7.7, 8.25 (4H, 2 x d), 7.8 (4H, m)

Method B (acylation with acyl chlorides):

(1S,2S)-1-(p-nitrophenyl)-2-phthalimido-3-phenylacetoxy-1-propanol (14g) To a cold solution of 1.0 g (0.0029 M) of **10** in 30 ml of dry THF 1.3 ml of triethyl amine and 0.62 ml of phenylacetyl chloride was added dropwise. Stirring was continued for 5 hours at 0 °C, and then 1/4 part of the reagents were added again. Next day the reaction mixture was evaporated to dryness and the residue was purified by column chromatography (toluene – ethyl acetate 3:1) yielding 0.6 g of product. M.p. 146-8 °C, ^{1}H NMR (DMSO-d_6) δ 3.97 (H, m), 4.52 (2H, m), 4.54 (2H, s), 5.24 (H, dd, J = 4.4, 8.4 Hz), 6.21 (H, d, J = 4.4 Hz, exch. with D_2O), 7.03 (5H, m), 7.91 (4H, m), 7.72, 8.26 (4H, 2 x d); IR (KBr) ν 1774, 1706, 1522, 1392, 1346 cm^{-1}; analysis: $C_{25}H_{20}N_2O_7$ (460.45) N% calc.: 6.08, found: 5.97.

The following derivatives were made analogously with the appropriate acyl chloride:

(1S,2S)-1-(p-nitrophenyl)-2-phthalimido-3-phenoxyacetoxy-1-propanol (14h) m.p. 129-31 °C; ^{1}H NMR (DMSO-d_6) δ 4.10 (H, dd, J = 4.0, 11.0 Hz), 4.54 and 4.65 (4H, two overlapping ABq), 5.25 (H, dd, J = 4.4, 8.6 Hz), 6.22 (H, d, J = 4.4 Hz , exch.), 6.69-7.17 (5H, m), 7.91 (4H, m), 7.74, 8.26 (4H, 2 x d); IR (KBr) ν 1766, 1710, 1522, 1388, 1350 cm^{-1}; analysis: $C_{25}H_{20}N_2O_8$ (476.45) N% calc.: 5.88, found: 5.81

(1S,2S)-1-(p-nitrophenyl)-2-phthalimido-1,3-di(phenoxyacetoxy)-propane (14i) m.p. 106-8 °C (slowly crystallizing oil); ^{1}H NMR (DMSO-d_6) δ 4.33 (H, dd, J = 4.8, 11.4 Hz), 4.5 – 5.1 (6H, m), 6.51 (H, d, J 7.8),

6.75 – 7.35 (10H, m), 7.91 (4H, m), 7.38, 8.25 (4H, 2 x d); IR (KBr) ν 1768, 1716, 1374, 1346, 1170 cm^{-1}

(1S,2S)-1-(p-nitrophenyl)-2-phthalimido-3-benzoyloxy-1-propanol (14j) m.p. 140-1 °C (EtOAc – hexane); ^1H NMR (DMSO-d_6) δ 4.41 (H, m), 4.71 (2H, m), 5.40 (H, d, J 8.2), 7.37-7.63 (5H, m), 7.79, 8.25 (4H, 2 x d), 7.94 (4H, m); IR (KBr) ν 1750, 1718, 1384, 1314, 1274 cm^{-1}; analysis: $C_{24}H_{18}N_2O_7$ (446.42) N% calc.: 6.28, found: 6.38

(1S,2S)-1-(p-nitrophenyl)-2-phthalimido-1,3-di(benzoyloxy)-propane (14k) m.p. 150-2 °C (EtOAc); ^1H NMR (DMSO-d_6) δ 4.86 (2H, m), 5.23 (H, m), 6.71 (H, d, J 7.6), 7.39-8.24 (m, aromatic); IR (KBr) ν 1776, 1720, 1452, 1384, 1346 cm^{-1}

(2S)-1-(p-nitrophenyl)-2-phthalimido-3-propionyloxy-1-propanone (15d) 100 mg of **14d**, dissolved in 2 ml of acetic acid, was oxidized with 0.1 ml of Jones reagent for 15 minutes at 40 °C. After removing the solvent the residue was partitioned between ethyl acetate and water. The organic phase was washed with $NaHCO_3$ solution, and after evaporation the residue was recrystallized from toluene, yielding 65 mg of product, m.p. 159-63 °C. ^1H NMR (DMSO-d_6) δ 0.88 (3H, t, J = 7.5), 2.19 (2H, q, J = 7.5 Hz), 4.69 (2H, m) 6.14 (H, m), 6.17 (H, m), 7.07 (4H, m), 7.92, 8.27 (4H, 2 x d); IR (KBr) ν 1778w, 1720, 1528, 1348, 1296 cm^{-1}.

(2S)-1-(p-nitrophenyl)-2-phthalimido-3-acetoxy-1-propanone (15a) could be prepared from **14a** as above in pure form by column chromatography followed by careful crystallization from benzene, m.p. 145-8 °C. However, its ^1H NMR spectrum always exhibited the presence of more or less **16**. ^1H NMR (DMSO-d_6) δ 1.93 (3H, s), 4.71 (2H, m), 6.08 (H, dd, J = 7.9, 8.0 Hz), 7.86 (4H, m), 7.95, 8.26 (4H, 2 x d); IR (KBr) ν 1752, 1716, 1606, 1528, 1384 cm^{-1}.

(2S)-1-(p-nitrophenyl)-2-phthalimido-3-phenoxyacetoxy-1-propanone (15h) Prepared as **15d**. M.p. 115-8 °C (toluene); ^1H NMR (DMSO-d_6) 4.70 (2H, s), 4.76 (2H, m), 6.21 (H, m), 6.76 – 7.22 (5H, m), 7.86 (4H, m), 7.94, 8.31 (4H, 2 x d); IR (KBr) ν 1770, 1720, 1528, 1348, 1296 cm^{-1}

(2S)-1-(p-nitrophenyl)-2-phthalimido-3-benzoyloxy-1-propanone (15j) Prepared as **15d**. M.p. 128-30 °C (toluene); ^1H NMR (DMSO-d_6) δ 4.91 (2H, m), 6.36 (H, dd, J = 4.8, 7.8), 7.45 – 7.68 (5H, m), 7.84 (4H, m), 7.96, 8.30 (4H, 2 x d); IR (KBr) ν 1778, 1722, 1528, 1384, 1272 cm^{-1}

(2S)-1-(p-nitrophenyl)-2-phthalimido-3-phenylacetoxy-1-propanone (15g) Prepared as **15d**. M.p. 148-52 °C; ^1H NMR (DMSO-d_6) 3.58 (2H, s), 4.71 (2H, m), 6.19 (H, dd, J = 7.1, 7.0 Hz), 7.11 (5H, m), 7.86 (4H, m), 7.91, 8.26 (4H, 2 x d); IR (KBr) ν 1754, 1714, 1524, 1386, 1346, 1296 cm^{-1}

(2S)-1-(p-nitrophenyl)-2-phthalimido-2-propen-1-one (16) 1.2 g of raw **14a** was dissolved in 5 ml of DMSO, 0.3 ml of water and 0.05 ml of Et_3N were added, and the mixture was kept at 50 °C for 2 hours. It was diluted with water and the precipitate was collected, washed with water, and recrystallized from ethyl acetate, 0.94 g (78%) of **16** was obtained, m.p. 191-4 °C. ^{1}H NMR (DMSO-d_6) δ 6.34 (H, d, J = 1.6 Hz), 6.53 (H, d, J = 1.6 Hz), 8.01 (4H, m), 8.09 and 8.41 (4H, 2 x d). $C_{17}H_{10}N_2O_5$ (322.28) MS 322, 305, 232, 190, 172 (100%), 150, 132, 104; analysis N% calc.: 8.69, found: 8.88. Similarly, the same compound was obtained from **15d,g,h,** or **j.**

Oxidation of 16:

Method A. To a solution of 0.25 g of **16** (0.00078 M) in 40 ml of methylene chloride 0.12 g of $KMnO_4$ (0.00076 M) and a catalytic amount of 18-crown-6 were added. The mixture was stirred at room temperature overnight and then another 0.12 g of $KMnO_4$ was added. Next day the suspension was passed through a short Silicagel 60 column. The main product **1-(p-nitrophenyl)-2,3-di(phthalimido)-propanone (17)** was isolated as fine needles, 0.11 g, m.p. 260-2 °C. ^{1}H NMR (DMSO-d_6) δ 4.19 (H, dd, J = 10.1, 14.5 Hz), 4.41 (H, dd, J = 3.8, 14.5 Hz), 6.04 (H, dd, J = 3.8, 10.1 Hz), ~7.85 (10H, m), 7.87, 8.25 (4H, 2 x d); ^{13}C NMR (DMSO-d_6) δ 36.1, 53.1, 122.7, 123.0, 123.6, 128.8, 130.4, 134.1, 134.5, 134.9, 139.6, 149.7, 166.5, 167.4; $C_{25}H_{15}N_3O_7$ (469.41) MS (EI) m^+ 319 (M-nitrobenzoyl), 292, 172, 147, 120, 104, 103, 76 (100%)

Method B. To a solution of 0.25 g of **16** in 20 ml of acetone 0.36 g of $KMnO_4$ was slowly added, dissolved in 30 ml of water. It was allowed to react 1 hour, then the suspension was filtered through celite, and extracted with CH_2Cl_2 at pH 8 and pH 3. From the basic extract phthalimide was isolated (0.099g, 87%), from the acidic extract 4-nitrobenzoic acid, as identified by comparison with authentic samples (tlc, m.p., mixed m.p.)

1-[(1'S,2'S)-1'-phenyl-1'-hydroxy-3'-acetoxy-2-propyl]-3(R)-phthalimido-4(S)-styryl-azetidin-2-one (18) 0.47 g of **7b** was dissolved in 10 ml of 2,6-collidine and after cooling to 0-5 °C 0.086 ml of acetyl chloride was added. Stirring was continued for 3 hours at room temperature, and then the solvent was removed *in vacuo.* The residue was taken up in ethyl acetate and was washed with dilute aq. HCl and water. After evaporation the obtained oil was passed through a small silicagel column, using toluene – ethyl acetate as solvent. 0.253 g of oily **18** was obtained, which crystallized slowly on standing, m.p. 180-1°C. ^{1}H NMR ($CDCl_3$) δ 2.11 (s ,3H), 3.80 (ddd, H, J = 4.4, 6.7, 4.2 Hz), 4.12, 4.32 (m, J = 4.4, 7.2 Hz), 4.70 (dd, H, J = 5.3, 9.0 Hz), 5.20 (d, H, J = 6.7 Hz), 5.33 (d, H, J = 5.2 Hz), 5.91 (dd, H, J = 9.0, 15.9 Hz), 6.60 (d, H, J = 15.9 Hz) 7.6-8.0 (m). Correct nitrogen analysis could not be obtained, presumably owing to the lability of the compound.

1-[(1'S,2'S)-3'-phenyl-propen-3'-on-2'-yl]-3(R)-phthalimido-4(S)-styryl-azetidin-2-one (20) To 0.2 g of **18**, dissolved in 3 ml of AcOH and 0.5 ml of H_2O, 30 mg of CrO_3 was added at 55-60 °C. After stirring for 5 hours at this temperature, the mixture was evaparated, the residue was partitioned between H_2O and ethyl acetate. The organic layer was separated, washed with H_2O, and the resulting oil was pure enough for the

immediate next step. A sample was chromatographed over silicagel (toluene – ethyl acetate 5/1), yielding crystals with m.p. 148-50 °C (dec.); ^{1}H NMR ($CDCl_3$) δ 5.31 (dd, H, J = 8.9, 5.3 Hz), 5.71 (d, H, J = 5.3 Hz); 6.25 (dd, H, J = 8.9, 15.3 Hz); 6.66 (d, H, J = 15.3 Hz); 7.2-8.0 (m); analysis: $C_{28}H_{20}N_2O_4$ (448.48) N% calc.: 6.25, found: 6.30

1-[(4-nitro-phenyl)-oxo-acetyl]-3(R)-phthalimido-4(S)-styryl-azetidin-2-one(24): 0.5 g of **7a** was dissolved in 10 ml of acetone and 1 ml of H_2O, and 220 mg of pyridine hydrochloride was added, followed by 1.7 ml of Jones reagent. After 1 hour at ambient temperature, the same amount of the reagent was added. Next day the reagent was destroyed by the addition of a few drops of isopropanol. After evaporation of the solvent, the residue was partitioned between water and ethyl acetate. The oily residue obtained by evaporating the organic phase was purified by passing through a short silica column (toluene – ethyl acetate). A small amount of **22** was also eluted. M.p. 197-8°C, $[a]_D^{20}$ -140.5 (0.605, $CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 5.43 (dd, H, J = 6.7, 8.4 Hz), 6.05 (d, H, J = 6.7 Hz), 6.26 (dd, H, J = 16.1, 8.4 Hz), 6.85 (d, H, J = 16.1 Hz), 7.2-8 (m, 13H); ^{13}C NMR ($CDCl_3$) δ 57.9, 59.1, 120.8, 123.8, 126.4, 128.4, 128.6, 129.5, 129.6, 130.6, 131.3, 135.2, 135.7, 136.9, 162.4, 162.8, 166.6, 188.2; IR (KBr) ν 1814, 1780, 1722, 1690, 1390, 1346 cm^{-1}. The same compound was obtained from **7a(R,R)** by the same procedure, m.p. 195-7 °C, $[a]_D^{20}$ -137.6 (0.509, $CHCl_3$)

(25): As **24**, from **8a**: m.p.: 195-6°C, $[a]_D^{20}$ +137.3 (0.873, $CHCl_3$), or from **8a(R,R)**: m.p. 191-2 °C.

3(R)-phthalimido-4(S)-styryl-azetidin-2-one (22) *Method A*: To a cold acetone solution (10 ml) of **20** (obtained from 0.2 g of **18**) $KMnO_4$ solution (100 mg / 5 ml H_2O) was added very slowly dropwise, until tlc showed the disappearence of the starting material. The reaction mixture was filtered through a short silicagel column (toluene – ethyl acetate 5/1), and the obtained crystalline material was recrystallized from isopropanol. 71 mg (52%), $[a]_D^{20}$ -103.9 (0.611, $CHCl_3$); other properties are the same as those of the compund obtained by other method.

Method B: To a solution of 0.14 g of **24** in 5 ml of THF and 2 ml of EtOH an ethanolic NaOH solution was added (0.1 N, 0.15 ml) in the cold. The reaction mixture was placed into a refrigerator overnight. Next day it was neutralized with dil. HCl, evaporated, and the residue was purified on a small silicagel column. M.p. 170-2 °C, $[a]_D^{20}$ -108.5 (0.517, $CHCl_3$); ^{1}H NMR (DMSO-d_6) δ 4.65 (overlapping dd, H), 5.53 (d, H, J = 5.1 Hz), 6.18 (dd, H, J = 7.5, 16.0 Hz), 6.66 (d, H, J = 16.0 Hz), 7.24 (m, 5H), 7.86 (m, 4H), 8.78 (s, H, exch.); IR (KBr) ν 1764 br, 1724, 1388 cm^{-1}; analysis: $C_{19}H_{14}N_2O_3$ (318.34) C% calc.: 71.69, found: 72.0, H% calc.: 4.43, found: 4.51; N% calc.: 8.80, found: 8.88

3(S)-phthalimido-4(R)-styryl-azetidin-2-one (23) It was prepared as **22**, method B, from **25.** M.p. 169-70 °C, $[a]_D^{20}$ +103.9 (0.618, $CHCl_3$).

ACKNOWLEDGEMENT

This work was partly funded by the grant OTKA T 23592.

REFERENCES

1. For recent reviews see: (a) Georg, G. I.; Ravikumar, V. T.: "Stereocontrolled Ketene-Imine Cycloaddition Reactions" in: The Organic Chemistry of ß-Lactams (Georg, G.I. ed.), ch. 6., VCH, 1992; (b) Backer, J.: "2-Oxo-azetidine (ß-Lactame)" in: Methoden der Organischen Chemie (Klagman, D. ed.) vol 16b, pp 295-381, Georg Thieme Verl., Stuttgart, 1971; (c) van der Steen, F. H.; van Kosten, G. *Tetrahedron* **1991** *47*, 7503-7524; (d) Labia, R.; Morii, C. *J. Antibiotics* **1984,** *37*, 1103-1129; (e) Cooper, R. D. G.; Daugherty, B. W.; Boyd, D. B. *Pure Appl. Chem.* **1987**, *37*, 485-492
2. Just, G.; Liak, T.-J. *Can. J. Chem.* **1978**, *56*, 211-217
3. Bose, A. K.; Manhas, M. S.; Vincent, J. E.; Gula, K.; Fernandez, I. F. *J. Org. Chem.* **1982**, 47, 4075-4081
4. Barton, D. H. R.; Gatean-Odesker, A.; Anaya-Mateos, J.; Cleophax, J.; Gero, S. D.; Chiaroni, A.; Riche, A. *J. Chem. Soc. Perkin Trans. I* **1990**, 3211-3212
5. Georg, G. I.; Akgün, E.; Mashava, P. M.; Milstead, M.; Ping, H.; Wu, Z.-j.; Vedde, D. V. *Tetrahedron Lett.* **1992**, *33*, 2111-2114
6. (a) Gunda, T. E.; Vieth, S.; Kövér, K. E.; Sztaricskai, F. *Tetrahedron Lett.* **1990**, *31*, 6707-6710; (b) Gunda, T. E. and Sztaricskai, F.: *Bioorg. Med. Chem. Letters* **1993,** *3*, 2379-2382
7. β-Lactams via ketene – imine cycloaddition with theoretical discussions on the stereochemistry: (a) López, R.; Suárez, D.; Ruiz-López, M. F.; Gonzáles, J.; Sordo, J. A.; Dordo, T. L. *J. Chem. Soc. Chem. Commun.* **1995**, 1677-1678; (b) Arrieta, A.; Ugalde, J. M.; Cossío, F. P.; Lecea, B. *Tetrahedron Lett.* **1994**, *35*, 4465-4468; (c) Cossío, F. P.; Arrieta, A.; Lecea, B.; Ugalde, J. M. *J. Amer. Chem. Soc.* **1994**, *116*, 2085-2093; (d) Dumas, S.; Hegedus, L. S. *J. Org. Chem.* **1994,** *59*, 4967-4971; (e) Cossio, F. P.; Ugalde, J. M.; Lopez, X.; Lecea, B.; Palomo, C. *J. Amer. Chem. Soc.* **1993**, *115*, 995-1004 (f) Brady, W. T.; Dad, M. M. *J. Org. Chem.* **1991**, *56*, 6118-6122; (g) Araki, K.; Wichtowski, J. A.; Welch, J. T. *Tetrahedron Lett.* **1991**, *32*, 5461-5464; (h) Hegedus, L. S.; Montgomery, J.; Narukawa, Y.; Snustad, D. C. *J. Am. Chem. Soc.* **1991**, *113*, 5784-5791
8. Fischer, F.; Tidet, H.-J.; Wolf, K.; Platz, K.-H., *J. Prakt. Chem.* **1965**, *28*, 157-168
9. Moore, J. A.; Kim, J.-H., *Tetrahedron Lett.* **1991**, *32*, 3449-3452
10. Edgerton, W. H.; Maddox, V. H.; Controulis, J. *J. Amer. Chem. Soc.* **1955**, *77*, 27-29
11. Fujisawa, T.; Itoh, S.; Shimizu, M. *Chem. Letters* **1994**, 1777-1780

(*Received in UK* 24 *February* 1997; *revised* 21 *April* 1997; *accepted* 1 *May* 1997)