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ASYMMETRIC SYNTHESIS OF cis 3-PHTHALIMIDO-4-STYRYL-2-AZETIDINONES. APPLICATION OF A NEW CHIRAL N-PROTECTING GROUP IN MONOBACTAM CHEMISTRY

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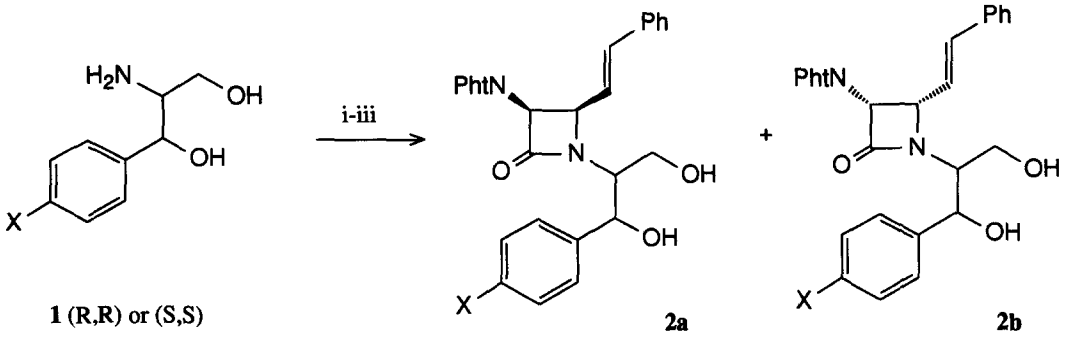
Abstract - 1-*N*-(1'-*p*-Nitrophenyl-1',3'-dihydroxy-2-propyl)-3-phthalimido-4-styrylazetidin-2-ones (**6a-d**), obtained in optically pure form *via* chiral Staudinger reactions, were transformed to the *N*-deprotected derivatives (**8a,b**) by means of a two-step oxidative procedure.

In a previous communication[1] we reported that optically active 2-amino-1-phenyl- or nitrophenyl-propane-1,3-diol is a good chiral auxiliary in the preparation of cis β-lactams. By condensation with cinnamaldehyde, the *O*-silyl protected amine was easily converted to its Schiff-base, which was reacted *in situ* with phthalimidoacetyl chloride to yield the desired *cis* lactams (**2a** and **2b**). The ratio of the two products depended on the protection groups used, but was always in favour of the configuration of type **2a**, starting from



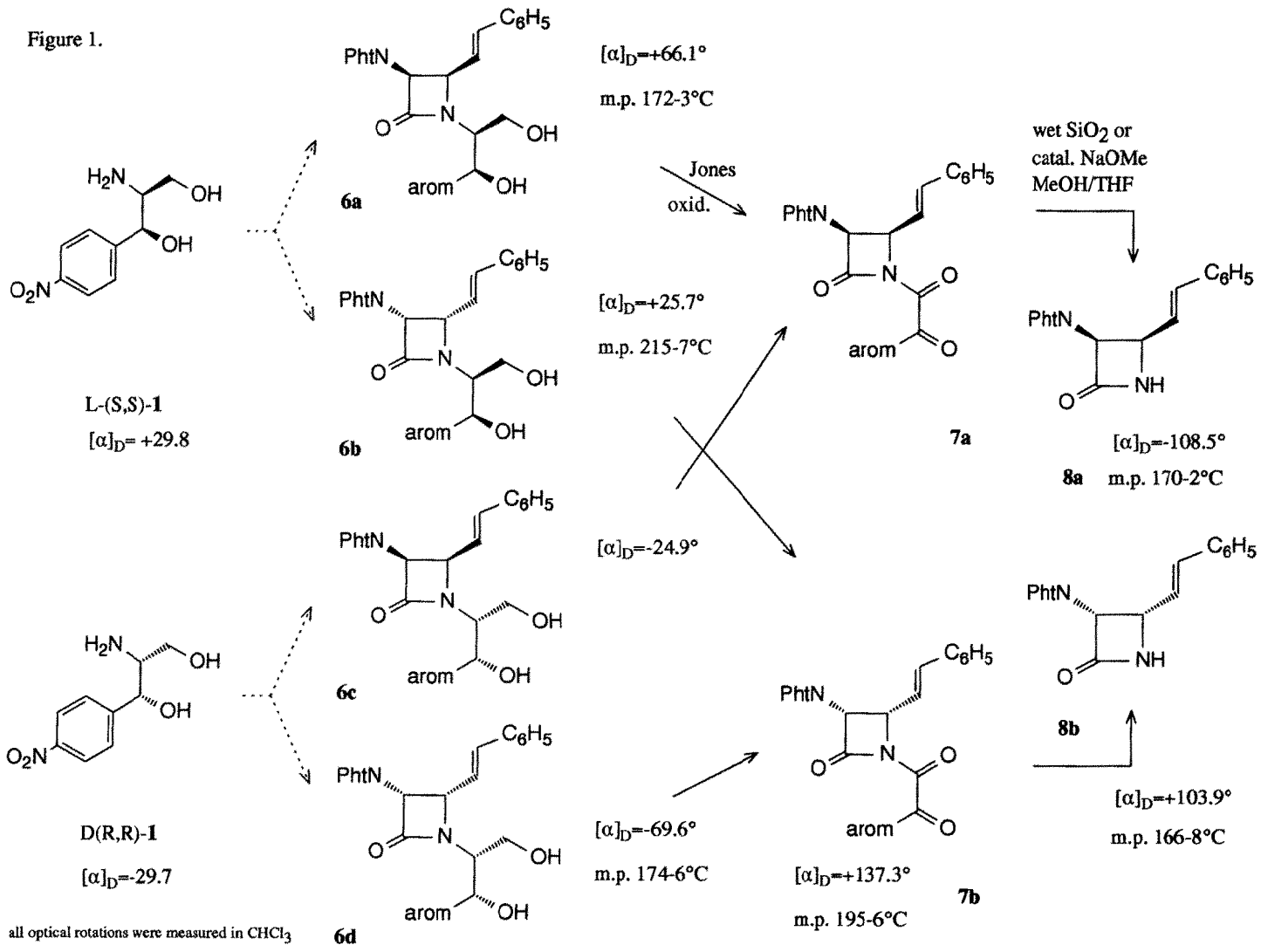
1 (R,R) or (S,S) **2a** **2b**

X= -H or $-NO_2$

i) TMSCl, TEA, CH_2Cl_2; ii) $C_6H_5CH{=}CHCHO$; iii) $PhtNCH_2COCl$, TEA; iv) F^-

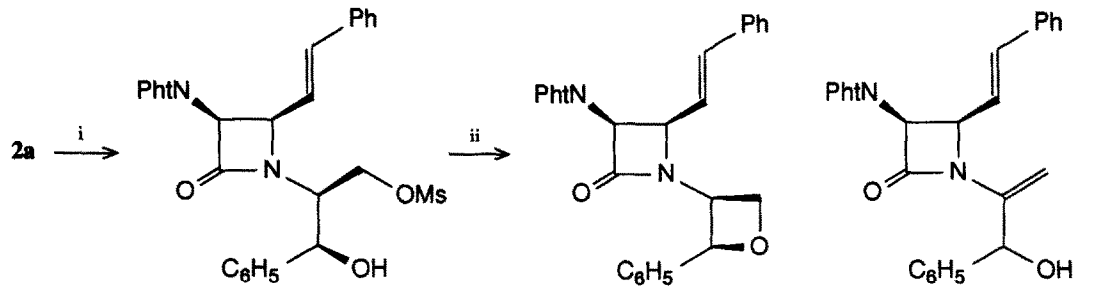
1(S,S). In order to obtain a usable starting material for further manipulations in the direction of monobactams or carbapenems, we had to find an efficient route to remove the *N*-auxiliary moiety. Utilization of the lability of carbinol amides is one possible approach: compounds possessing a double bond adjacent to the β-lactam

Figure 1.


L-(S,S)-1
[α]D= +29.8
D(R,R)-1
[α]D=-29.7
all optical rotations were measured in CHCl3
6a
6b
6c
6d
[α]D=+66.1°
m.p. 172-3°C
[α]D=+25.7°
m.p. 215-7°C
[α]D=-24.9°
[α]D=-69.6°
m.p. 174-6°C
Jones oxid.
7a
7b
[α]D=+137.3°
m.p. 195-6°C
wet SiO2 or
catal. NaOMe
MeOH/THF
8a
[α]D=-108.5°
m.p. 170-2°C
8b
[α]D=+103.9°
m.p. 166-8°C

nitrogen can be oxidized to hydroxy derivatives, which, in turn, spontaneously hydrolyze to the free lactam. Beyond this generally used route a few other examples can be found in the literature: an *N*-side chain with a hydroxy function beta to the nitrogen may be removed by conversion to the unsaturated derivative first, followed by oxidation.[2] To the best of our knowledge, there is only one example of direct oxidative removal,[3] and another one using a β-elimination process.[4]

We were not successful in elimination of the primary hydroxy group of any compunds of type **2** if a free secondary hydroxy group was present in the N-side-chain. For example, mesylation proceeded neatly to give the monomesylate (**3**),[5] but subsequent elimination of the mesyloxy group afforded a compound showing no characteristic unsaturated methylene protons in its ^{1}H-NMR spectrum, although its measured molecular weight (EI



i) MsCl; ii) TEA or DBU, THF

MS) was the same as that of the desired **5**. We assigned it the oxetan structure **4**.[6] More details concerning successful double bond formation will be provided in a forthcoming paper.

Next we tried the direct oxidation, similarly to the one described by Bose et al.,[3] who applied it to a threonine-derived β-lactam compound and obtained the *N*-unsubstituted lactam in low yield. In our case an excess of the Jones reagent was necessary for the full consumption of **6**. The reaction was not unequivocal, and the reaction mixture contained both **7** and **8** besides several minor components. In the presence of pyridine hydrochloride, the main product was the diketone (**7**) in better than 70% yield. Starting from both the threo and erythro isomers of **1**, two pairs of stereoisomers **6a/6b** and **6c/6d** were obtained, and each of them was oxidized either to **7a** or **7b**.[7] The physical data on **7a** and **7b** obtained in these two ways corresponded within 3%. The structure of **7** was unambiguously verified by the absence of the characteristic four-proton pattern in the ^{1}H-NMR spectrum of the 1,3-propanediol moiety; furthermore, instead of the three aliphatic carbon ^{13}C resonances, two new signals appeared in the carbonyl region. Removal of the diketo moiety occurred smoothly when **7** was allowed to stand in methanol–THF in the presence of catalytic amounts of sodium hydroxide or wet silica gel.[8] Compounds **8a** and **8b** are versatile intermediates for the synthesis of novel monobactam derivatives.[9]

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5. **3**: Prepared by standard mesylation with MsCl/Py. Slowly crystallizing oil, m.p. 61-65 °C; ^{1}H-NMR ($CDCl_3$) 3.09 (3H, s), 3.96 (H, m), 4.33 (H, dd, J=10.8, 4.5 Hz), 4.48 (H, d, J=10.8 Hz), 4.81 (H, dd, J=5.3, 9.2 Hz), 5.16 (H, m), 5.55 (H, d, J=5.2), 5.84 (H, dd, J=15.9, 9.2 Hz), 6.61 (H, d, J=15.9), 7.19-7.81 (aromatic)
6. **4**: Prepared from **3** with DBU in acetone (3 days, room temp.). MS (ei) 450.520 (calculated 450.496 for $C_{28}H_{22}N_2O_4$); ^{1}H-NMR ($CDCl_3$) 4.42-4.56 (2H, m), 4.85 (H, dd, J=5.4, 9.1 Hz), 5.22 (H, m), 5.48 (H, d, J=5.4 Hz), 5.79 (H, dd, J=9.1, 15.5 Hz), 5.95 (H, d, J=5.2 Hz), 6.55 (H, d, J=15.5 Hz), 7.1-7.82 (aromatic).
7. **7a**: 0.5 g (1.1 mmol) of **6** was dissolved in 10 ml of acetone and 1 ml of water, 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 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 equilibrated between water and ethyl acetate. The organic phase contained one main product, which was obtained in pure form after passage through a short silica gel column (EtOAc–toluene). A small amount of **8** was also eluted. For melting point and optical rotation ($CHCl_3$) data see Figure 1. ^{1}H-NMR (DMSO-d_6, TMS) 5.43 (H, dd, J= 6.7, 8.4 Hz), 6.05 (H, d, J=6.7 Hz), 6.26 (H, dd, J=16.1, 8.4 Hz), 6.85 (H, d, J=16.1 Hz), 7.24-8.06 (m, 13H); IR (KBr) 1814, 1780, 1722, 1690, 1390, 1346 cm^{-1}. In the ^{13}C-NMR spectrum, only two signals characteristic of sp^3 carbons were found, at 57.9 and 59.1 ppm. On the absolute configuration of the starting **6a** see ref. 1.
8. **8a**: 0.14 g of **7a** was dissolved in a mixture of 5 ml of THF and 2 ml of methanol. 0.15 ml of 0.1 N NaOH/EtOH was added, and the mixture was allowed to stand overnight in a refrigerator. The crude product was purified by flash chromatography. For data, seeFigure 1. ^{1}H-NMR (DMSO-d_6, TMS) 4.65 (H, overlapping dd), 5.53 (H, d, J=5.1 Hz), 6.18 (H, dd, J= 7.5, 16.O Hz), 6.66 (H, d, J= 16.0 Hz), 7.24 (5H, m), 7,86 (4H, m), 8.8 (H, s); IR(KBr) 1764 br, 1724, 1388 cm^{-1}
9. For a recent review on the Staudinger reaction, see: Georg, G. I.; Ravikumar, V. T., Stereocontrolled Ketene-Imine Cycloaddition Reactions; *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH 1993; chapter 6., pp. 296-368.