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SYNTHESIS OF β-LACTAMS OF HIGH ENANTIOMERIC PURITY BY CHIRAL LIGAND ACCELERATED OSMYLATION OF RACEMIC 4-(2-STYRYL)-AZETIDIN-2-ONES

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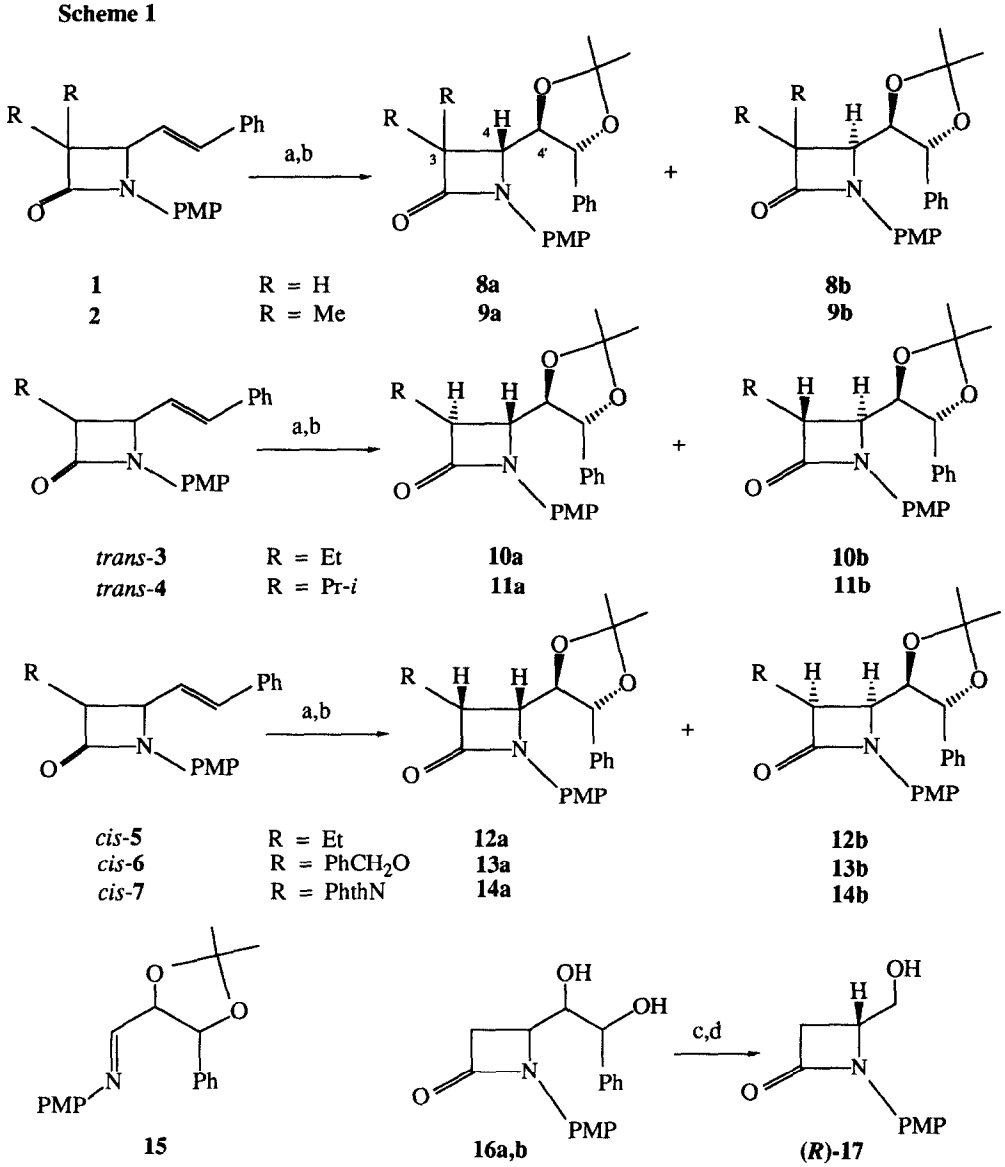
Abstract. The catalytic osmylation of a series of 4-(2-styryl)-azetidin-2-ones carried out in the presence of dihydroquinidine-*p*-chlorobenzoate opens access to synthetically useful precursors of β-lactam antibiotics of high enantiomeric purity (ee up to 97%).

An unsaturated group containing a carbon-carbon double or triple bond has been frequently introduced at C-4 of an azetidin-2-one ring to provide an easy entry to 4-oxy substituted β-lactams (and to a variety of biologically important derivatives thereof) by oxidative degradation. The synthesis of enantiomerically enriched compounds featuring these unsaturated substituents, generally requires chiral enolates (in an enolate-imine condensation),[1] ketenes (in a Staudinger reaction),[2] or imines (in both processes)[3] as elements of stereocontrol. As an alternative to these methods, we here report that a 2-styryl substituent at C-4 can provide a convenient handle to prepare β-lactams in high enantiomeric excess (ee) by a conceptually different approach that involves Sharpless' chiral ligand accelerated osmylation reaction.[4]

The 4-(2-styryl)-azetidin-2-ones **1-7** (Scheme 1) were prepared by our recently reported[5] one-pot synthesis involving addition of trichlorotitanium enolates of 2-pyridylthioesters to *N*-4-methoxyphenyl-*E*-cinnamaldimine. These underwent osmylation reaction[4] with 0.02 mol equiv of OsO_4 in the presence of 0.5 mol equiv of commercially available dihydroquinidine *p*-chlorobenzoate[6] and of 3.0 mol equiv each of $K_3Fe(CN)_6$ and K_2CO_3 in a 1:1 mixture of water and *t*-BuOH (in the case of compounds **1-5**) or THF (in the case of compounds **6** and **7**, sparingly soluble in *t*-BuOH),[7] to afford a mixture of diastereoisomeric diols.[8] Flash chromatography allowed diastereoisomer separation and chiral ligand recovery. For ee determination the diols were converted into the corresponding acetonides **8a,b-14a,b** (2,2-dimethoxypropane, catalytic *p*-toluenesulfonic acid, 22 °C, 15h), that were obtained in the overall yields reported in the Table.[9] Ee's were determined in $CDCl_3$ by 300 MHz ^{1}H-NMR spectroscopy in the presence of the chiral shift reagent $Eu(hfc)_3$ in conditions pre-established on the racemic compounds. These were obtained by standard catalytic osmylation procedure (OsO_4, trimethylamine-*N*-oxide, THF:water 9:1, 22 °C, overnight), and diol protection, as mixtures of **a** (major) and **b** (minor) diastereoisomer.[10]

Scheme 1



Reagents: a, OsO_4, dihydroquinidine-*p*-Cl-benzoate; b, $(MeO)_2CMe_2$, *p*-TSA; c, $NaIO_4$; d, $NaBH_4$.
Abbreviations: PMP = 4-methoxyphenyl; Phth = phthaloyl.
For compounds **8-14** and **17** only major enantiomers are shown for simplicity.

The well recognized tendency of the osmylation reaction to preferentially afford products having the *anti* configuration[11] strongly suggested the indicated relative stereochemistry at C-4/C-4' of **8a,b-14a,b** (see Scheme 1 for numbering). This hypothesis was supported by the observation that **9b**, the minor isomer obtained by the osmylation of **2** and subsequent diol protection, was identical to the only product of the condensation of 2-pyridylthioisobutyrate with imine **15**, a process known to afford C-4/C-4' *syn* configurated compounds with high stereocontrol.[3b] Chemical shift trends found in the ^{1}H-NMR spectra for H-C4 and H-C4'[12] further supported the assignement.

The high facial selectivity generally observed for the AD process,[4] that should always occur on the same alkene diastereoface of **1-7**, strongly suggests that the major enantiomers of **8-14** have the same absolute configuration at C-4' and are epimers at C-4. This hypothesis was confirmed while establishing the configuration of compound **8** by chemical correlation. A 83:17 mixture of diastereoisomeric diols **16a** and **16b** (the precursors of **8a** and **8b**) was converted ($NaIO_4$, AcOEt : H_2O 1 : 1, 50 °C, 30 min; $NaBH_4$, EtOH, 22 °C, 2h; 60% overall yield) into alcohol (+)-(*R*)-**17**, $[\alpha]_D^{23}$ + 40.8 (*c* 1, CH_2Cl_2). By comparison of its optical rotation with that reported[13] for a >90% enantiomerically enriched sample of **17**, $[\alpha]_D^{30}$ + 91.7 (*c* 1, CH_2Cl_2), this compound was shown to have an ee of about 44%. Both the configuration and the ee of **17** are in satisfactory agreement with the structure indicated for **8a** and **8b**, and with the diastereoisomeric ratio and the ee that were observed.[14] Furthermore, the configuration of **8a,b** is the one expected on the basis of the model of stereoselection proposed by Sharpless for the AD reaction.[4] On the reasonable assumption that this facial selectivity is maintained for all the reported reactions, the stereochemistry of the major enantiomers of **8a,b** was extended to **9a,b-14a,b**.

As can be seen from the data reported in the Table, the osmylation reaction occurs with a high level of facial selectivity. For each reaction, the ee's of *syn* and *anti* isomers are very similar . The ee's are very good in the case of 3-alkyl substituted compounds **9-12**. It is worth mentioning that *trans* β-lactams **10b** and **11b**, obtained in 86 and 93% ee, respectively, have the required configuration at C-3 and C-4 to be transformed into the carbapenem antibiotics (+)-PS-5 and (+)-PS-6. The reaction maintains a high stereoselectivity also when the β-lactam C-3/C-4 configuration is changed from *trans* to *cis*, and when a heteroatom containing substituent is introduced at C-3 as in **6** and **7**. Thus, this approach can be used as an entry to biologically important 3-azasubstituted azetidinones[3c,15] of high enantiomeric purity.

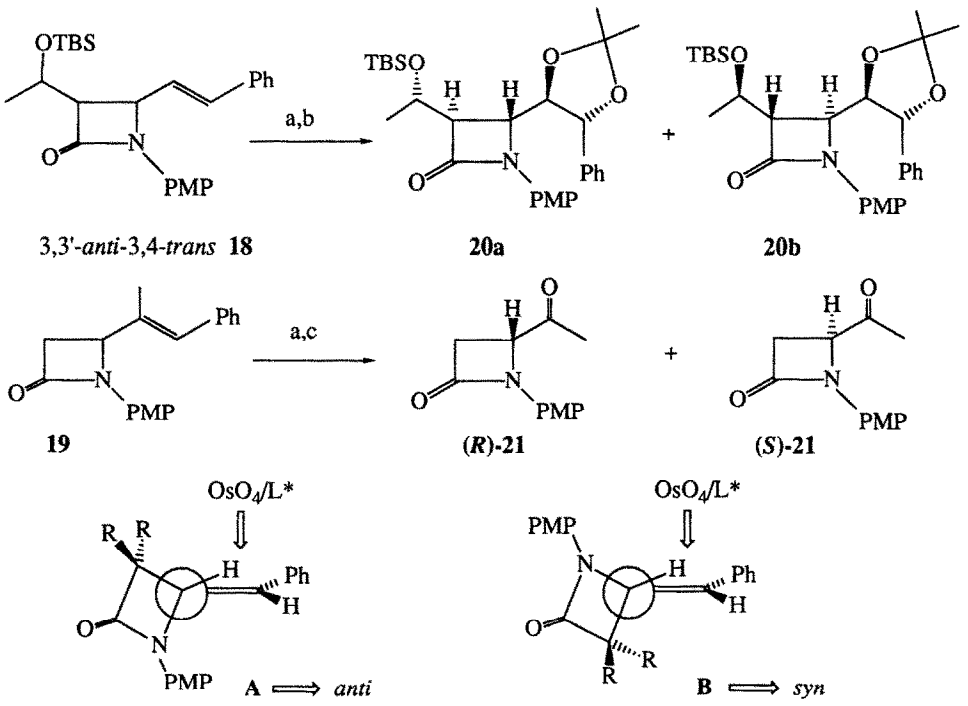
The osmylation of β-lactams **18** and **19** was also attempted to test the generality of this method. Racemic compound 3,3'-*anti*-3,4-*trans* **18** afforded, after diol protection, a 55 : 45 mixture of **20a** and **20b** with 87 and 86% ee, respectively, in 65% overall yield. Azetidinone **20b** is a precursor of carbapenem antibiotic thienamycin.[1c] From trisubstituted alkene **19** a 72 : 28 mixture of *anti* and *syn* diols, that were separated by flash chromatography, was obtained in 67% yield. $NaIO_4$ promoted oxidation of the diastereoisomerically pure materials gave (*R*) and (*S*)-4-acetylazetidin-2-one **21**, in 42% (from the major diol, 79% yield) and 78% ee (from the

Table. Synthesis of β-lactams **8a,b-14a,b** from 2-styryl derivatives **1-7.**

Starting material	Product	Overall yield %	ee *anti*	ee *syn*
1	**8a,b**	70	90	85
2	**9a,b**	61	90	91
3	**10a,b**	73	94	86
4	**11a,b**	72	94	93
5	**12a,b**	63	94	88
6	**13a,b**	68	93	97
7	**14a,b**	51	80	77

[a] As determined by 300 MHz ^{1}H-NMR spectroscopy by LSR technique.

Scheme 2.



See Scheme 1 for reagents; only major enantiomers of **20a** and **20b** are shown.

minor diol, 73% yield), respectively.[16] Compound (*S*)-**21** is an intermediate for the synthesis of 1-β-methylthienamycin.[1b,17]

The stereochemical outcome of the osmylation reaction can tentatively be rationalized by models **A** and **B** (Scheme 2), leading to the major enantiomers of *anti* and *syn* diols, respectively. In both models the small hydrogen atom at the allylic stereocenter is in the "inside"[11b] position for steric reasons, and ligand directed osmylation occurs on the alkene face predicted by Sharpless' rationale for the AD reaction.[4]

In conclusion, we demonstrated that a 2-styryl group at C-4 of an azetidin-2-one can provide a simple entry to biologically relevant β-lactams of high enantiomeric purity, *via* an easy chiral ligand accelerated osmylation reaction.[18-20]

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1. Reviews: a) Hart, D. J.; Ha, D.-C. *Chem. Rev.* **1989**, *89*, 1447; b) Brown, M.J. *Heterocycles* **1989**, *29*, 2225. Leading references: c) Georg, G. I.; Kant, J.; Gill, H.S. *J. Am. Chem. Soc.* **1987**, *109*, 1129; d) Hart, D. J.; Lee, C.-S.; Pirkle, W. H.; Myung, N. H.; Tsipouras, A. *J. Am. Chem. Soc.* **1986**, *108*, 6054; e) Cainelli, G.; Panunzio, M.; Basile, T.; Bongini, A.; Giacomini, D.; Martelli, G. *J. Chem. Soc., Perkin Trans.1* **1987**, 2637.

2. Reviews: a) Koppel, G. A. *Heterocyclic Compounds* Hassner, A., Ed.; Wiley: New York, **1983**; Vol 42, Part 2, pp 219-441; b) Georg, G. I.; Ravikumar, V. T. in *The Organic Chemistry of β-Lactams* ; Georg, G. I., Ed.; Verlag Chemie: New York, **1993**; pp 295-368.

3. The use of chiral α-alkoxy-, α,β-dialkoxy-, and α-amino-β-alkoxy-imines represent a popular alternative for the introduction of oxygen-containing functionalities at C-4. For recent examples see: a) Andreoli, P.; Cainelli, G.; Panunzio, M.; Bandini, E.; Martelli, G.; Spunta, G.*J. Org. Chem.* **1991**, *56*, 5984; b) Annunziata, R.; Cinquini, M.; Cozzi, F.; Cozzi, P. G. *J. Org. Chem.* **1992**, *57*, 4155; c) Wagle, D. R.; Garai, C.; Chiang, J.; Monteleone, M.G.; Kurys, B. E.; Strohmeyer, T. W.; Hegde, V. R.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1988**, *53*, 4227; d) Frazier, J. W.; Staszak, M. A.; Weigel, L. O. *Tetrahedron Lett.* **1992**, 857; e) Palomo, C.; Cossio, F. P.; Cuevas, C.; Lecea, B.; Mielgo, A.; Roman, P.; Luque, A.; Martinez-Ripoll, M. *J. Am. Chem. Soc.* **1992**, *114*, 9360.

4. Since its original discovery (Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263) this process has been greatly improved over the last few years by Professor Sharpless and his group. For a recent report on this reaction, and for references to earlier work, see: Wang, L.; Sharpless, K.B. *J. Am Chem. Soc.* **1992**, *114*, 7568.

5. Cinquini, M.; Cozzi, F.; Cozzi, P. G.; Consolandi, E. *Tetrahedron* **1991**, *47*, 8767. The 4-methoxyphenyl substituent at nitrogen was selected because it can be easily removed by CAN degradation. In our hand this transformation was best performed by the procedure described by Georg, *et al.* in ref. 1c.

6. Opposite chiral discrimination can be achieved by the use of the "quasi" enantiomeric ligand derived from dihydroquinine.

7. This change in solvent, however, did not affect the stereoselectivity of the process, as was shown in the case of compounds **1** and **4** that were osmylated with almost identical ee and

comparable yields either in *t*-BuOH or THF. OsO_4 was always used as 0.039 M *t*-BuOH solution.

8. As determined by 300 MHz ^{1}H-NMR spectroscopy on the crude reaction mixture. Diastereoisomeric ratios ranged from 50 : 50 (compound **4** and **5**) to 60 : 40 (compound **1**).

9. The conversion of the diols into the acetonides did not affect the diastereoisomeric ratio.

10. Diastereoisomeric ratios ranged from 64 : 36 (compound **7**) to 82 : 18 (compound **2**).

11. a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 224; b) Houk, K. N.;Paddon-Row, M. N.; Rondan, N. G.; Wu, Y.-D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R.J. *Science* **1986**, *231*, 1108; c) Vedejs, E.; McClure, C. K. *J. Am. Chem. Soc.* **1986**, *108*, 1094.

12. In the case of *trans* β-lactams **10**, **11**, and **19** (see text) HC-4 and HC-4' resonate at lower field in the syn than in the anti isomer. The opposite is true for *cis* β-lactams **12-14**. C-3 disubstituted compound **9** behaved like a *cis* and C-3 unsubstituted compound **8** like a *trans* β-lactam.

13. Palomo, C.; Cossio, F. P.; Ontoria, J. M.; Odriozola, J. M. *Tetrahedron Lett.* **1991**, 3105.

14. The opposite configuration at C-4 of **8a** and **8b** was also demonstrated by the low degree of kinetic resolution observed by recovering unreacted **1** from the osmylation reaction in 23% ee at 75% conversion.

15. Van Der Steen, F. H.; Van Koten, G. *Tetrahedron* **1991**, *47*, 7503.

16. The enantiomeric excesses were determined by comparison of the optical rotation of (*R*)-**21**, $[\alpha]_D^{23}$ + 46.7 (*c* 1.25, $CHCl_3$), and of (*S*)-**21**, $[\alpha]_D^{23}$ - 86.0 (*c* 0.7, $CHCl_3$) with that reported[1b] for a > 95% enantiomerically enriched sample of (*S*)-**21**, $[\alpha]_D^{23}$ -110.5 ($CHCl_3$). From this reaction unreacted **19** was recovered with an ee of 45%.

17. a) Fuentes, L. M.; Shinkai, I.; King, A.; Purick, R.; Reamer, R. A.; Schmitt, S. M.; Cama, L.; Christensen, B. *J. Org. Chem.* **1987**, *52*, 2563; b) Gurjar, M. K.; Bhanu, M. N.; Khare, V. B.; Bhandari, A.; Deshmukh, M. N.; Rao, A. V. R. *Tetraedron* **1991**, *47*, 7117.

18. For a recently reported kinetic resolution of azetidin-2-ones see: Coggins, P.; Simpkins, N. S. *Synlett* **1992**, 313.

19. A typical procedure for the osmylation reaction is as follows: To a stirred solution of 4-(2-styryl)-azetidin-2-one (0.5 mmol) in *t*-BuOH or THF (15 mL) and water (15 mL), $K_3Fe(CN)_6$ (0.510 g, 1.5 mmol), K_2CO_3 (0.207 g, 1.5 mmol), dihydroquinidine-*p*-chlorobenzoate (0.116g, 0.25 mmol), and 0.256 mL of a 0.039 M solution of OsO_4 in *t*-BuOH were added in this order. After 15h stirring at 22 °C the reaction was quenched by the addition of solid $NaHSO_3$, and the resulting mixture was extracted three times with Et_2O. The combined organic extracts were dried, concetrated in vacuum, and the residue chromatographed to give the diols, that were converted into the corresponding acetonides for ee determination.

20. All new compounds gave satisfactory analytical and spectral data. Some selected ^{1}H-NMR data for compounds **8a,b-14a,b** and **19a,b** are here reported in this order: HC-4 and HC-4' (ppm), $J_{4\text{-}4'}$ (Hertz). The data were collected at 300 MHz in $CDCl_3$ solutions: **8a**: 4.22, 4.11, 7.0; **8b**: 4.25, 4.27, 2.0; **9a**: 3.98, 4.24, 3.8; **9b**: 3.84, 4.03, 4.7, **10a**: 3.90, 4.21, 6.0; **10b**:3.95, 4.28, 2.0; **11a**: 3.95, 4.26, 5.8; **11b**: 4.02, 4.28, 7.0; **12a**: 4.41, 4.22, 3.2; **12b**: 4.23, 3.97, 2.0; **13a**: 4.53, 4.38, 2.8; **13b**: 4.40, 4.36, 4.8; **14a**: 4.76, 4.67, 8.5; **14b**: 4.48, 4.55, 8.0; **19a**: 4.28, 4.24, 6.5; **19b**: 4.46, 4.27, 1.5.