STEREOSELECTIVE SYNTHESIS OF HIGHLY FUNCTIONALIZED γ-LACTONES VIA IODOLACTONIZATION

Manfred T. Reetz* and Erik H. Lauterbach

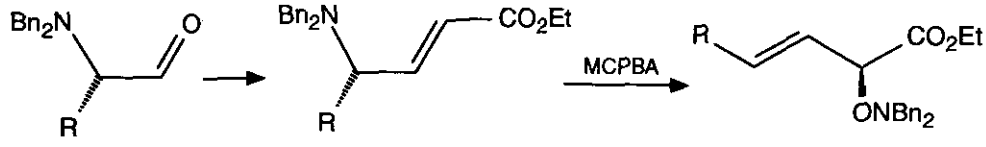
Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1,
4330 Mülheim/Ruhr, Germany
and
Fachbereich Chemie der Universität, Hans-Meerwein-Strasse, 3550 Marburg, Germany

Abstract - Chiral γ-amino α,β-unsaturated carboxylic acids (**5**) derived from L-amino acids undergo diastereofacially selective iodolactonization with formation of the highly functionalized lactones (**7**).

N,N-Dibenzylamino aldehydes (**1**) prepared in enantiomerically pure form from the corresponding amino acids are emerging as useful building blocks in organic synthesis.[1] They react with a variety of carbon nucleophiles, delivering Grignard-type adducts, aldols and cyanohydrins with unusually high degrees of non-chelation control. The corresponding aldimines[2] as well as the Wittig olefinations[3] products are also key compounds in various stereoselective C-C- bond forming reactions.[1]

Recently we reported that the Wittig products (**2**) react with *m*-chloroperbenzoic acid (MCPBA) to form intermediate amine oxides which undergo spontaneous [2,3]-sigmatropic rearrangements with complete 1,3-transfer of chirality.[4]

Dedicated to Prof. *Edward C. Taylor on the occasion of his 70th birthday.*

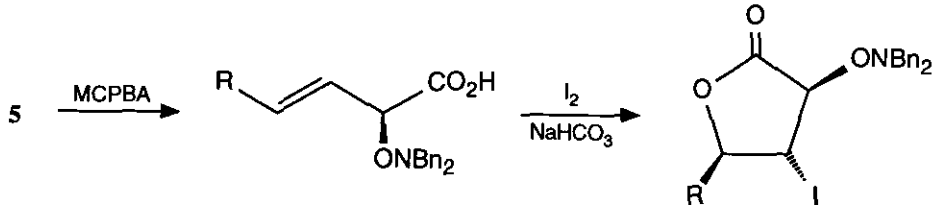


1 a) R = Me **2** **3**
b) R = $PhCH_2$
c) R = Me_2CHCH_2
d) R = tBuMe$_2$SiOCH$_2$

It was of interest to see if diastereoselective iodolactonization reactions[5] are possible using the acids corresponding to (**3**), because this would make highly functionalized γ-lactones accessible, possibly in a stereochemically uniform manner. In this paper we report on the results of these efforts. Attempts to hydrolyze the esters (**3**) to the acids resulted in only 30% conversion. Therefore, the acids (**5**) were prepared directly from the aldehydes (**1**) using the olefination reagent (**4**):[6]

4 **5** (*E*/*Z* > 98%)
a) R = Me (81%)
b) R = $PhCH_2$ (95%)
c) R = Me_2CHCH_2 (77%)

Compounds (**5**) were reacted with MCPBA as previously described for the esters (**2**).[4] Indeed, >90% conversion to the acids (**6**) was observed, but isolation in analytically pure form proved to be difficult. The crude products were therefore subjected to iodolactonization. The conditions of choice turned out to be I_2/THF, ether/sat. $NaHCO_3$.[7] In this way acceptable yields of isolated lactones (**7**) were obtained (50 - 79% based on the two steps).[8] In all cases essentially a single diastereomer was observed (diastereoselectivity >95% on the basis of nmr spectroscopy).

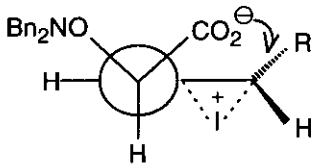


6 **7**

a) 50%
b) 70%
c) 79%

The stereochemical assignment is tentative (an X-ray structure analysis has not been possible to date). Nevertheless, the all trans arrangement of the vicinal substituents of the lactone ring is plausible on the basis of nmr data.[9] The vicinal coupling constants of the ring protons are all about 9 Hz. Generally, trans vicinal hydrogens in γ-lactones show coupling constants of 9 - 12 Hz, whereas cis vicinal hydrogens in the analogous molecules show coupling constants of less than 7.5 Hz.[10] A NOESY-experiment also speaks for this assignment.[9]

Most of the highly stereoselective iodolactonization reactions known in the literature were carried out under reversible (thermodynamic) conditions using a non-basic medium.[5] Fewer cases are known in which stereoselectivity is >95% under basic conditions, which appear to be examples of kinetic control.[5,7] Mechanistically and stereochemically they are not well understood. Although we have not yet studied those aspects in detail in the present system, we speculate that the usual trans-stereospecific addition of $I^{\oplus}$ and $RCO_2^{\ominus}$ occurs with complete diastereofacial selectivity according to (**8**), which in fact leads to the observed products (**7**). In the species (**8**) the C-O sigma bond of the electronegative substituent has the "outside" position. In the alternative intermediate (**9**) it occupies a position which allows for maximum π-σ* interaction (electron withdrawal from the olefinic π-system), which is not conducive for electrophilic attack.[11]



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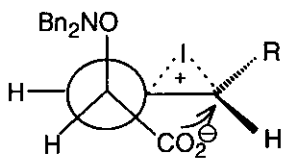

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8. Procedure: A suspension of MCPBA (1.21 g, 7 mmol) and 2.5 g $NaHCO_3$ in 75 ml of CH_2Cl_2 is cooled to 0°C and 5 mmol of an acid **5** in 10 ml of CH_2Cl_2 is added. The mixture is stirred for 10 h, quenched with 5 ml of a sat. acetone solution of NaI and allowed to reach room temperature. Following treatment with a 5% solution of $NaHSO_3$, the organic phase is washed twice with H_2O and dried over $MgSO_4$. The solvent is removed and the residue (**6**) is dissolved in 20 ml of THF/ether (1 : 1). Sat. $NaHCO_3$ (40 ml) is added, followed by iodine (3.8 g, 15 mmol). The mixture is rapidly stirred over night and treated with a 5% $NaHSO_3$ solution until excess iodine has been consumed. The mixture is poured on 200 ml H_2O/ether (1 : 1) and the aqueous phase is extracted twice with ether. The combined org. phases are washed with H_2O and dried over $MgSO_4$. The solvent is removed and the product (**7**) is chromatographed over SiO_2 (pet. ether/ether, 10 : 1). ^1H Nmr ($CDCl_3$, 300 MHz) of a typical compound (**7a**): δ = 1.33 (d, J = 6.2 Hz, 3H), 3.48 (dd, J = 8.9, 9.4 Hz, 1H), 4.08 (AB-system, J_{AB} = 13.0 Hz, 4H), 4.47 (dq, J = 8.9 Hz, J = 6.2 Hz, 1H), 4.56 (d, J = 9.4 Hz, 1H), 7.3 - 7.4 (m, 10H). ^{13}C Nmr ($CDCl_3$, 75 MHz): δ = 18.3, 22.5, 62.3, 81.0, 86.4, 127.8, 128.5, 130.2, 136.6. FDms: m/z = 437 (M^+, 100%).

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