

STEREOSELECTIVE SYNTHESIS OF HIGHLY FUNCTIONALIZED γ -LACTONES VIA IODOLACTONIZATION

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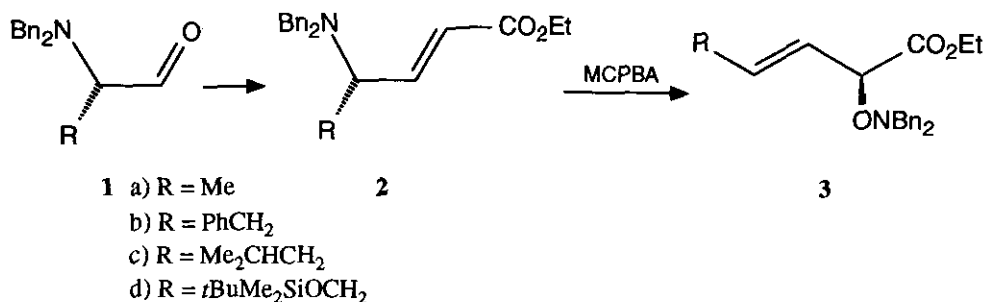
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Abstract - Chiral γ -amino α,β -unsaturated carboxylic acids (**5**) derived from L-amino acids undergo diastereofacially selective iodolactonization with formation of the highly functionalized lactones (**7**).

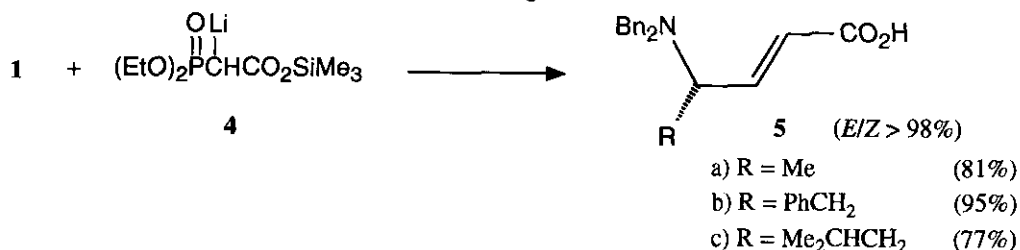
N,N-Dibenzylamino aldehydes (**1**) prepared in enantiomerically pure form from the corresponding amino acids are emerging as useful building blocks in organic synthesis.¹ They react with a variety of carbon nucleophiles, delivering Grignard-type adducts, aldols and cyanohydrins with unusually high degrees of non-chelation control. The corresponding aldimines² as well as the Wittig olefinations³ 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

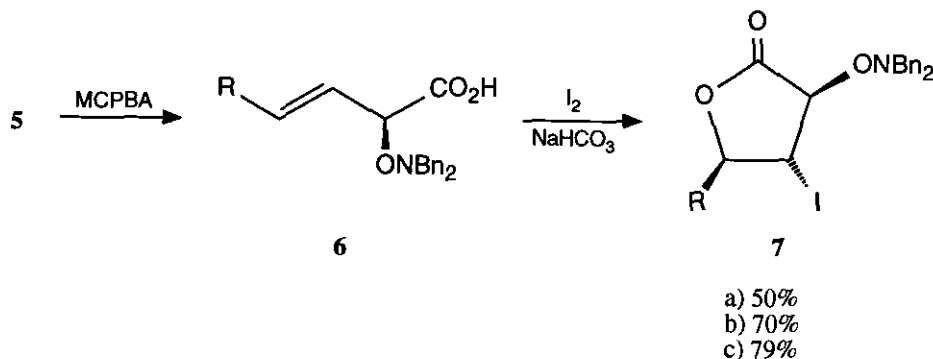
Dedicated to Prof. Edward C. Taylor on the occasion of his 70th birthday.



It was of interest to see if diastereoselective iodolactonization reactions⁵ 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

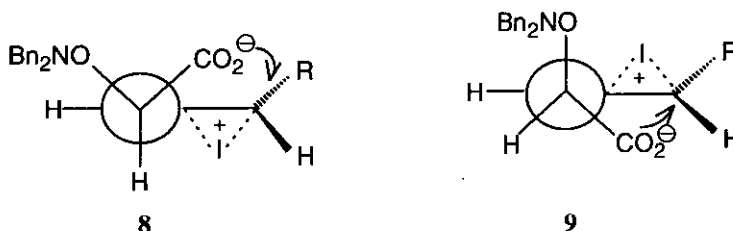


Compounds (5) were reacted with MCPBA as previously described for the esters (2).⁴ Indeed, >90% conversion to the acids (6) was observed, but isolation in analytically pure form proved to be difficult. The crude products were therefore subjected to iodolactonization. The conditions of choice turned out to be I₂/THF, ether/sat. NaHCO₃.⁷ 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).



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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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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