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Stereoselective generation of vicinal stereogenic quaternary centers by photocycloaddition of 5-methoxy oxazoles to α-keto esters: synthesis of *erythro* β-hydroxy dimethyl aspartates

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The photocycloaddition of methyl pyruvate and methyl phenylglyoxylate, respectively, to 5-methoxy oxazoles bearing additional substituents at C-2 and C-4 leads to bicyclic oxetanes 2 and 3 with high to moderate (*exo*) diastereoselectivity that can be easily ring-opened to give bis-quaternary aspartic acid diester derivatives 4 and 5.

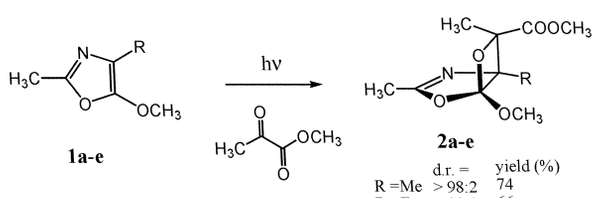
Introduction

As important building blocks in nature as well as constituents of more complex natural products, β-hydroxy α-amino acids constitute an important class of target molecules. For example, β-hydroxy tyrosine and β-hydroxy phenylalanine derivatives are found in the clinically important antibiotic glycopeptide vancomycin.[1] β-Hydroxy leucine is found in (+)-lactacystin[2] and *E*-2-butenyl-4,*N*-dimethyl-L-threonine is a prominent part of cyclosporine.[3] α,α-Disubstituted (quaternary) amino acids represent a highly interesting class of non-proteinogenic amino acids,[4] especially in view of their potential activity as enzyme inhibitors.[5] The synthesis of these target structures in diastereoisomerically pure form follows aldol routes or the alkylation of enolates from bislactim ethers, oxazolidinones, imidazolidinones or other chiral building blocks. In most of these approaches, the stereochemistry of alkylation steps can be perfectly controlled, whereas the formation of more than one new stereogenic center, *e.g. via* aldol addition to chiral enolates, proceeds only with moderate to good diastereoselectivities. Recently, catalytic enantioselective methods were added, such as the Sharpless asymmetric epoxidation,[6] and asymmetric dihydroxylation,[7] electrophilic amination,[8] and hydroxylation,[9] stereoselective hydrolysis of aziridine carboxylate esters,[10] aldol condensation involving oxazolidinone intermediates,[11] and the stereoselective reduction of α-amino ketones.[12]

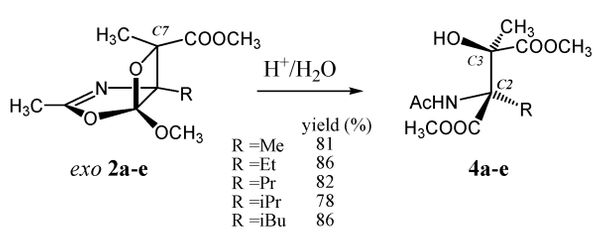
An efficient photochemical approach to α-alkylated α-amino β-hydroxy acids is the *photo aldol* route. Oxygen-containing five-membered heterocycles serve as enolate equivalents to which aldehydes are added photochemically in a highly regio- and diastereoselective manner. Photocycloaddition to oxazoles and subsequent hydrolytic ring-opening of the resulting bicyclic oxetanes leads to α-amino β-hydroxy carbonyl compounds.[13] Carboxylic acid esters were available from 5-methoxy substituted oxazoles.[14] The stereochemistry of these additions seems not to be determined by the spin state of the electronically excited carbonyl component, *i.e.* singlet as well as triplet excited aldehydes result in high *exo*-selectivity when irradiated in the presence of 5-methoxy oxazoles.

Results and discussion

An additional attractive feature of this photochemical route is that quaternary centers can be easily generated by use of α-keto esters as carbonyl components.[15] This approach has not yet been investigated for nitrogen-containing heterocycles. Being aware of the excellent reactivity of oxazoles as alkene components, we first investigated the photocycloaddition of methyl pyruvate with 4-alkylated 5-methoxyoxazoles **1a**–**1e** (Scheme 1). The α-keto esters were excited in the long-wavelength region either using phosphor-coated mercury low-pressure lamps (λ = 350 ± 10 nm) in benzene or a XeCl excimer radiation source (λ = 308 nm)[16] using acetonitrile solution in the presence of a slight excess of oxazole. The crude reaction mixtures (yields and selectivities given in Scheme 1 are NMR-based) were treated with catalytic amounts of HCl in chloroform or directly chromatographed on silica in order to ring-open the thermally and acid sensitive bicyclic oxetanes. The diastereoselectivity of the [2+2]-photocycloaddition was remarkably high for all examples investigated: solely the *exo*-diastereoisomers were detected. Hydrolytic ring-opening of **2a**–**e** proceeded with retention of configuration at C7 and the *N*-acetyl β-hydroxy aspartic acid diesters **4a**–**e** were formed with the relative (2*S**,3*R**) configuration (Scheme 2). Careful analysis (NMR, GC) of **4a**–**e** revealed the high diastereocontrol (>98%) for both steps. The relative configuration of the aspartic acid diesters **4a**–**e** was also established by means of an X-ray structure analysis of the 2-ethyl derivative **4b** (Fig. 1).† Additional evidence for the proposed stereochemistry resulted from NOE measurements for **2a** (strong effects between the methyl groups at C3 and C7).



Scheme 1 Photocycloaddition of methyl pyruvate with 5-methoxy oxazoles **1a**–**e**.



Scheme 2 Hydrolytic ring-opening of oxetanes **2a**–**e** leading to dimethyl aspartate derivatives **4a**–**e**.

Phenylglyoxylates have been reported to add photochemically to electron-rich cycloalkenes with high diastereocontrol.[17] Thus, we also investigated the photocycloaddition of oxazoles **1a**–**e** with methyl phenylglyoxylate (Scheme 3). In contrast to the results with methyl pyruvate, the bicyclic

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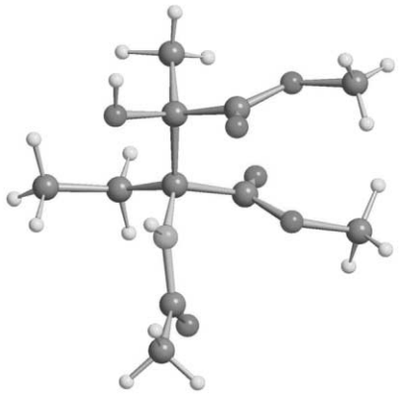
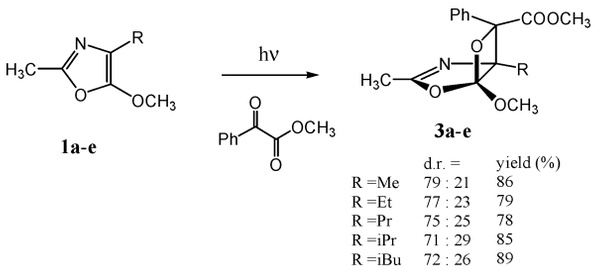
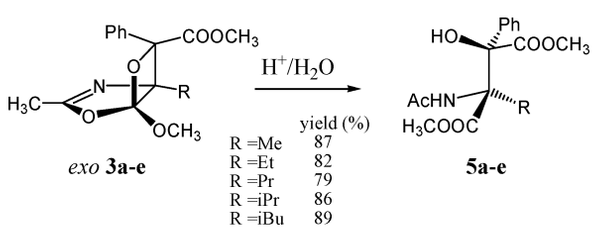


Fig. 1 Structure of the dimethyl aspartate derivative **4b** in the crystal.



Scheme 3 Photocycloaddition of methyl phenylglyoxylate with 5-methoxy oxazoles **1a**–**e**.

oxetanes **3a**–**e** were formed only with moderate simple diastereoselectivities. The adducts were stable under the reaction conditions and could even be separated by column chromatography on silica when pretreated with 1% of triethylamine in methylene chloride. Treatment of the major diastereoisomers *exo* **3a**–**e** with catalytic amounts of HCl in chloroform or direct chromatography on silica delivered (2*S**,3*R**) *N*-acetyl β-phenyl β-hydroxy aspartic acid diesters **5a**–**e** in high yields (Scheme 4). The diastereomeric oxetanes *endo* **3a**–**e** were likewise transformed into the (2*S**,3*S**) β-hydroxy aspartic acid diesters **5a**–**e**.



Scheme 4 Hydrolytic ring-opening of oxetanes **3a**–**e** leading to dimethyl aspartate derivatives **5a**–**e**.

The decrease in diastereoselectivity for the Paternò–Büchi cycloaddition of methyl pyruvate *versus* methyl phenylglyoxylate is in good agreement with our recently published mechanism of triplet carbonyl reaction with five-membered heterocyclic dienes.[18] In the case of the formation of the *exo*-oxetanes **2a**–**e**, secondary orbital interactions at the stage of the triplet 1,4-biradical might induce the formation of the *exo* isomers *via* the biradical geometry **A** favoring intersystem crossing (ISC, see Fig. 2).[19,20] Spin inversion (ISC) is coupled with a torque and directly leads to the formation of the terminal C–C bond. Thus, ISC is expected to proceed concerted with the formation of a new bond (or the cleavage of the primarily formed single bond). In the presence of the sterically more encumbering substituents phenyl and COOR, the ISC-reactive conformer **B** controls the reaction (similar for cyclic monoalkenes)[19] and directs the phenyl group into the *endo* position. The conformationally more flexible **B**, however, exhibits less stereocontrol than the more stringent orbital arrangement in **A**.

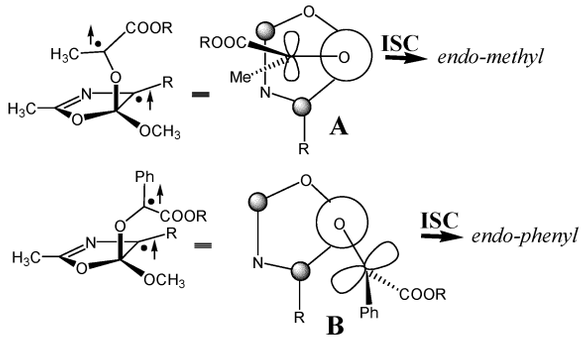


Fig. 2 Triplet 1,4-biradical as the diastereoselectivity determining species: ISC-favourable geometries **A** and **B** following the 90° orbital orientation rule.

Conclusion

In summary, we have reported an efficient and stereoselective approach to α-alkylated β-hydroxy aspartic acid diesters **4** and **5**, respectively, with vicinal stereogenic quaternary centers.

Experimental

Synthesis of (2*S**,3*R**)-dimethyl 2-acetamido-2-ethyl-3-hydroxy-3-methylsuccinate (4b)

A solution of 706 mg (5 mmol) of 4-ethyl-5-methoxy-2-methyloxazole (**1a**) and 510 mg (5 mmol) of methyl pyruvate in 50 ml of benzene was irradiated in a vacuum-jacket quartz tube with constant nitrogen purging at 15 °C in a Rayonet photochemical reactor equipped with phosphor-coated mercury low-pressure lamps (λ = 350 ± 10 nm) for 14 h. After evaporation of the solvent and purification of the residue by preparative thin layer chromatography, 900 mg (74%) of oxazole **2a** were isolated in diastereoisomerically pure (*endo*-methyl) form. This product was dissolved in 20 ml of methylene chloride, cooled to 0 °C and 0.5 ml of conc. aqueous HCl were added. The mixture was stirred in an open flask and the reaction progress was followed by TLC. After completion of the reaction (2 h), the reaction mixture was poured in 100 ml of water and extracted with 2 × 50 ml of methylene chloride. The organic layer was separated, washed with 2 × 50 ml of aqueous 5% sodium bicarbonate and 50 ml of brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residual oil was purified by preparative thin layer chromatography or by flash column chromatography on silica resulting in 782 mg (81%) of the dimethyl aspartate derivative **4b**. Slow crystallization from acetone delivered colorless needles suitable for X-ray structure analysis.†

Acknowledgements

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Notes and references

† *Crystal data* for **4b**: $C_{11}H_{19}NO_6$ (from acetone), M = 261.27, monoclinic, a = 7.319(1), b = 21.573(1), c = 8.799(1) Å, β = 108.02(1)°, space group P-$2_1/c$, Mo-Kα, 5302 reflections measured, 1023 reflections with $I > 2\sigma(I)$, R_1 = 0.0559, wR_2 = 0.0997. CCDC reference number 231106. See http://www.rsc.org/suppdata/ob/b4/b401990c/ for crystallographic data in .cif or other electronic format.

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