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# Synthesis of *erythro*-α-Amino *β*-hydroxy Carboxylic Acid Esters by Diastereoselective Photocycloaddition of 5-Methoxyoxazoles with Aldehydes

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A new *photoaldol* route to α-amino-*β*-hydroxy carboxylic acid esters is initiated by the photocycloaddition of aromatic or aliphatic aldehydes to 5-methoxyoxazoles. The 4-unsubstituted 5-methyloxazole **1** gave the cycloadducts **8a**−**f** in high yields and excellent *exo*-diastereoselectivities. Hydrolysis of **8a**−**f** gives the *N*-acetyl α-amino-*β*-hydroxy esters **9a**−**f**, which could be subsequently converted into the corresponding *Z*-didehydro α-amino acids **10a**−**f**. Quartenary α-amino-*β*-hydroxy esters **12**, **14**, **16**, **18**, and **20**, which are stable against dehydration, were obtained from the 4-alkylated 5-methoxyoxazoles **2**−**6**, in most cases highly *erythro*-selective due to the high degree of stereocontrol (*exo*) at the photocycloaddition (to give **11**, **13**, **15**, **17**, and **19**) level. The relative configurations of the *N*-acetyl α-amino-*β*-hydroxy esters were determined by NMR spectroscopy and comparison with chiral pool-derived compounds as well as by X-ray structure determination of the ester **23**, formed by hydrolysis of the cycloadduct **22**, derived from photocycloaddition of propionaldehyde to the isoleucine-derived oxazole **21**.

## Introduction

*β*-Hydroxy-α-amino acids constitute an important class of amino acids that are found as building blocks in nature (threonine, serine, *β*-hydroxyproline) as well as constituents of more complex natural products. For example, *β*-hydroxytyrosine and *β*-hydroxyphenylalanine derivatives are found in the clinically important antibiotic glycopeptide vancomycin.[1] *β*-Hydroxyleucine 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 nonproteinogenic amino acids,[4] especially in view of their potential activity as enzyme inhibitors.[5] Incorporation of these components into peptide structures results in conformational restrictions and increased rigidity, leading to enhanced resistance toward protease enzymes[6] and to the preference of particular secondary structure motifs.[7] Numerous synthetic methods have been developed in the past decades to provide flexible access to these target molecules. Besides the α-alkylation of amino acid enolates, the aldol reaction is another suitable method to synthesize α,α-disubstituted amino acids. This reaction provides the important class of α-alkylated α-amino *β*-hydroxy acids which can also be found as substructures in biologically active molecules such as myriocin or lactacystin.[8] While various syntheses of α-amino-*β*-hydroxy acids by reaction of glycine with aldehydes are described in the literature,[9] only a few examples are known that provide α-alkylated α-amino *β*-hydroxy acids by reaction of other amino acid derivatives with aldehydes.[10]

Further, nonproteinogenic α-alkylated α-amino acids are playing an important role in natural product chemistry and for biological investigation. Because of the persubstituted central stereogenic carbon atom, they possess high configurational stability. They exert a remarkable influence on the configuration of the peptide into which they could be incorporated and, thus, are often used for the investigation of enzymatic mechanism and also as enzyme inhibitors.[11] These densely functionalized amino acids are also useful buliding blocks for the

(1) Rao, A. V. R.; Gurjar, M. K.; Reddy, K. L.; Rao, A. S. *Chem. Rev.* **1995**, *95*, 2135−2167. Vancomycin: Williams, D. H. *Acc. Chem. Res.* **1984**, *17*, 364−369. Harris, C. M.; Kopecka, H.; Harris, T. M. *J. Am. Chem. Soc.* **1983**, *105*, 6915−6922.

(2) Nagamitsu, T.; Sunazuka, T.; Tanaka, H.; Omura, S.; Sprengeler, P. A.; Smith, A. B., III. *J. Am. Chem. Soc.* **1996**, *118*, 3584−3590.

(3) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757−6761.

(4) Heimgartner, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 238−264.

(5) Rando, R. R. *Acc. Chem. Res.* **1975**, *8*, 281−288.

(6) Toniolo, C.; Crisma, M.; Pegoraro, S.; Valle, G.; Bonora, G. M.; Becker, E. L.; Polinelli, S.; Boesten, W. H. J.; Schoemaker, H. E.; Meijer, E. M.; Kamphuis, J.; Freer, R. *Peptide Res.* **1991**, *4*, 66−71.

(7) Paul, P. K. C.; Sukumar, M.; Bardi, R.; Piazzesi, A. M.; Valle, G.; Toniolo, C.; Balaram, P. *J. Am. Chem. Soc.* **1986**, *108*, 6363−6370.

(8) Rao, A. V. R.; Gurjar, M. K.; Devi, T. R.; Kumar, K. R. *Tetrahedron Lett.* **1993**, *34*, 1653−1656.

(9) (a) Sunazuka, T.; Nagamitsu, T.; Matsuzaki, K.; Tanaka, H.; Omura, S.; Smith, A. B., III. *J. Am. Chem. Soc.* **1993**, *115*, 5302. (b) Iwanowicz, E. J.; Blomgren, P.; Cheng, P. T. W.; Smith, K.; Lau, W. F.; Pan, Y. Y.; Gu, H. H.; Malley, M. F.; Gougoutas, J. Z. *Synlett* **1998**, 664−666. (c) Ooi, T.; Taniguchi, M.; Kameda, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 4542−4544.

(10) Schöllkopf, U.; Groth, U.; Hartwig, W. *Liebigs Ann. Chem.* **1981**, 2407−2418.

(11) (a) Kazmaier, U.; Grandel, R. *Synlett* **1995**, 945−946. (b) Grandel, R.; Kazmaier, U.; Nuber, B. *Liebigs Ann.* **1996**, 1143−1150. (c) Grandel, R.; Kazmaier, U. *Eur. J. Org. Chem.* **1998**, *409*, 9−417.

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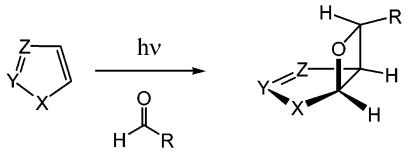
asymmetic synthesis of β-lactams.[12] As a consequence of the pivotal role that can be induced by these amino acids in biological systems and their utility as synthetic building blocks, a number of useful strategies have been devised for their preparation.[13] Most synthetic routes to these amino acids are based on 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 acceptable diastereoselectivities. Multistep stoichiometric preparation and careful purification of each reaction intermediate is therefore often requried for these syntheses.[14] Recently, catalytic enantioselective methods were added, such as the Sharpless asymmetric epoxidiation,[15] Sharpless asymmetric dihydroxylation,[16] electrophilic amination,[17] and hydroxylation,[18] stereoselective hydrolysis of aziridine carboxylate esters,[19] aldol condensation[20] involving oxazolidinone intermediates,[21] and the stereoselective reduction of α-amino ketones.[22]

A possible photochemical approach to α-alkylated α-amino β-hydroxy acids is the photoaldol route. The thermal counterpart, the aldol reaction, is the archetype carbonyl reaction combining a CH-acidic carbonyl compound with an electrophilic carbonyl substrate. By this process, β-hydroxy carbonyl compounds are available that can be subsequently transformed into valuable product structures. An efficient photochemical route has been developed by Schreiber and co-workers for the synthesis of β-hydroxy carbonyl compounds by light-induced cycloaddition of aldehydes to furan and substituted furans.[23] Enol ethers are, however, not applicable as enolate equivalents in Paternò−Büchi reactions[24] because the regioselectivity of the excited-state carbonyl addition results in 3-alkoxyoxetanes that do not correspond to masked aldols. Furans as the alkene addends are more advantageous because the regioselectivity becomes reversed and protected aldols are formed with unusual high regio- and diastereoselectivity. The Paternò−Büchi reaction of furan and furan derivatives, respectively, with electronically excited aliphatic as well as aromatic aldehydes proceeds highly regioselective to give the 2,7-dioxabicyclo[3.2.0]hept-3-enes with the substituent at C-6 preferentially in *exo*-position. The *exo*/*endo* selectivity is remarkably high (e.g., 212:1 for the benzaldehyde/furan case) for a *triplet* photocycloaddition.[25] Aliphatic aldehydes react with slightly lower *exo*-selectivity, and a weak spin-selectivity effect[26] was also determined for aliphatic aldehydes: singlets favor the formation of the *exo*-diastereoisomer less pronounced than the corresponding triplets.[27] These photocycloadditions to furans have been extensively used for synthetic applications especially because of the extraordinary high degree of diastereocontrol (Scheme 1).[28]

**SCHEME 1. Photocycloaddition of Aldehydes to Five-Membered Heterocycles**




Several other five-membered aromatic heterocycles were used as alkene components in the Paternò−Büchi photocycloaddition.[29] Recently, we have reported on the oxazole-based route to α-amino β-hydroxy ketones. The commercially available 2,4,5-trimethyloxazole was used as our first model substrate, and excellent regio- and (*exo*-)diastereoselectivities were observed for the photocycloaddition with aldehydes.[30] Further extension of this concept is described in the present paper.[31]

## Results and Discussion

An attractive family of target molecules which might be available by the photoaldol route are derivatives of

(12) (a) Miller, M. J. *Acc. Chem. Res.* **1986**, *19*, 49−56. (b) Lotz, B. T.; Miller, J. J. *J. Org. Chem.* **1993**, *58*, 618−625.

(13) For leading references, see: (a) Blaskovich, M. A.; Evindar, G.; Rose, N. G. W.; Wilkinson, S.; Luo, Y.; Lajoie, G. A. *J. Org. Chem.* **1998**, *63*, 3631−3646. (b) Williams, R. M. *Synthesis of Optically Active* α-*Amino Acids*; Pergamon: Oxoford, U. K., 1989.

(14) (a) Bold, G.; Duthaler, R. O.; Riediker, M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 497−498. (b) Evans, D. A.; Sjogren, E. B.; Weber, A. E.; Conn, R. E. *Tetrahedron Lett.* **1987**, *28*, 39−42. (c) Schöllkopf, U. *Tetrahedron* **1983**, *39*, 2085−2091. (d) Seebach, D.; Juaristi, E.; Miller, D. D.; Schickli, C.; Weber, T. *Helv. Chim. Acta* **1987**, *70*, 237−261. (e) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757−6761.

(15) (a) Caldwell, C. G.; Bondy, S. S. *Synthesis* **1990**, 34−36. (b) Jung, M. E.; Jung, Y. H. *Tetrahedron Lett.* **1989**, *30*, 6637−6640.

(16) (a) Shao, H.; Rueter, J. K.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 5240−5244. (b) Shao, H.; Goodman, M. *J. Org. Chem.* **1996**, *61*, 2582−2583. (c) Rao, A. V. R.; Chakraborty, T. K.; Reddy, J. L.; Rao, A. S. *Tetrahedron Lett.* **1994**, *35*, 5043−5046. (d) Hale, K. J.; Manaviazar, S.; Delisser, V. M. *Tetrahedron* **1994**, *50*, 9181−9189.

(17) Guanti, G.; Banfi, L.; Narisano, E. *Tetrahedron* **1988**, *44*, 5553−5562.

(18) Fernandez-Megia, E.; Paz, M. M.; Sardina, F. J. *J. Org. Chem.* **1994**, *59*, 7643−7652.

(19) (a) Tomasini, C.; Vecchione, A. *Org. Lett.* **1999**, *1*, 2153−2156. (b) Davis, F. A.; Liu, H.; Reddy, G. V. *Tetrahedron Lett.* **1996**, *37*, 5473−5476. (c) Divas, F. A.; Reddy, G. V. *Tetrahedron Lett.* **1996**, *37*, 4349−4352. (d) Divas, F. A.; Zhou, P.; Reddy, R. E. *J. Org. Chem.* **1994**, *59*, 3243−3245.

(20) Blaser, D.; Seebach, D. *Liebigs Ann. Chem.* **1991**, 1067−1078.

(21) (a) Laib, T.; Chastanet, J.; Zhu, J. *Tetrahedron Lett.* **1997**, *38*, 1771−1772. (b) Williams, L.; Zhang, Z.; Shao, F.; Carroll, P. J.; Joullie, M. M. *Tetrahedron* **1996**, *52*, 11673−11694. (c) Kanemasa, S.; Mori, T.; Wada, E.; Tatsukawa, A. *Tetrahedron Lett.* **1993**, *34*, 677−680.

(22) (a) Maurer, P. J.; Takahata, H. *J. Am. Chem. Soc.* **1984**, *106*, 1095−1098. (b) Roemmele, R. C.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 1866−1875.

(23) Schreiber, S. L. *Science* **1985**, *227*, 857−863.

(24) Griesbeck, A. G.; Bondock, S. In *CRC Handbook of Photochemistry and Photobiology*; Horspool, W. M., Lenci, F., Eds.; CRC Press: Boca Raton, 2003; Chapter 60, pp 1−21.

(25) Griesbeck, A. G.; Buhr, S.; Fiege, M.; Schmickler, H.; Lex, J. *J. Org. Chem.* **1998**, *63*, 3847−3854.

(26) Griesbeck, A. G.; Fiege, M.; Bondock, S.; Gudipati, M. S. *Org. Lett.* **2000**, *2*, 3623−3625.

(27) Griesbeck, A. G.; Bondock, S. Unpublished results.

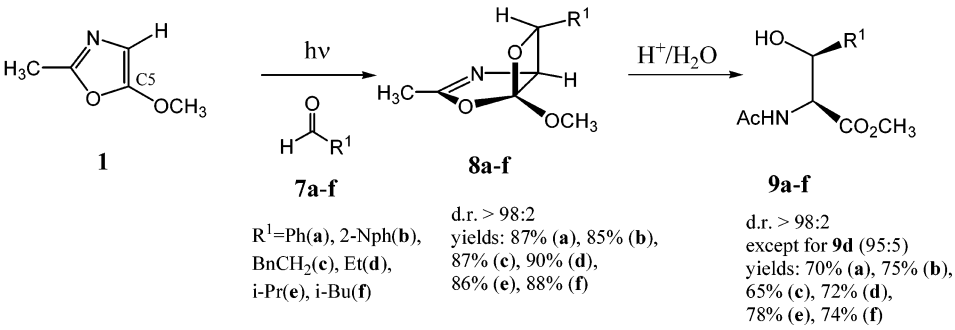
(28) (a) Schreiber, S. L.; Satake, K. *J. Am. Chem. Soc.* **1983**, *105*, 6723−6724. (b) Schreiber, S. L.; Hoveyda, A. H.; Wu, H. J. *J. Am. Chem. Soc.* **1983**, *105*, 660−661. (c) Schreiber, S. L.; Satake, K. *Tetrahedron Lett.* **1986**, *27*, 2575−2578. (d) Schreiber, S. L.; Desmaele, D.; Porco, J. A., Jr. *Tetrahedron Lett.* **1988**, *29*, 6689−6692.

(29) Thiophenes: Rivas, C.; Pacheco, D.; Vargas, F.; Ascanio, J. *J. Heterocycl. Chem.* **1981**, *18*, 1065−1067. Pyrroles: Jones, G., II; Gilow, H. M.; Low, J. *J. Org. Chem.* **1979**, *44*, 2949−2951. Rivas, C.; Bolivar, R. A. *J. Heterocycl. Chem.* **1976**, *13*, 1037−1040. Imidazoles: Matsuura, T.; Banba, A.; Ogura, K. *Tetrahedron* **1971**, *27*, 1211−1219. Indoles: Julian, D. R.; Tringham, G. D. *J. Chem. Soc., Chem. Commun.* **1973**, 13−14. Thiazoles, isothiazoles, and isoxazoles: Nakano, T.; Rodriquez, W.; de Roche, S. Z.; Larrauri, J. M.; Rivas, C.; Pérez, *J. Heterocycl. Chem.* **1980**, *17*, 1777−1780.

(30) Griesbeck, A. G.; Fiege, M.; Lex, J. *Chem. Commun.* **2000**, 589−590.

(31) Preliminary communication: Griesbeck, A. G.; Bondock, S. *Can. J. Chem.* **2003**, *81*, 555−559.

**SCHEME 2. Photocycloaddition of a Series of Aromatic and Aliphatic Aldehydes 7a−f to Oxazole 1; Hydrolytic Ring Opening of the Oxetanes 8a−f Results in the 1,2-Acylamino Alcohols 9a−f**



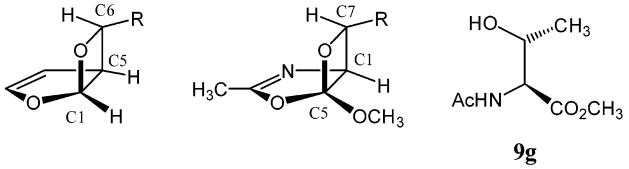




**FIGURE 1.** Structures of bicyclic oxetanes from photocycloaddition of aldehydes to furan and 5-methoxyoxazoles and the independently synthesized reference compound **9g**.

α-amino β-hydroxy carboxylic acids, either with a tertiary (from a corresponding glycine equivalent) or a quaternary stereogenic α-carbon center. To investigate this concept, we applied in a first series the 4-unsubstituted 5-methoxyoxazole **1**[32] as diene component in the photocycloaddition with aldehydes **7a**−**f**. Photolyses could be performed either in Rayonet photochemical reactors with coated mercury low-pressure lamps emitting at $\lambda = 300 \pm 10$ nm or in a XeCl-excimer falling-film reactor with a 3 kW XeCl ($\lambda = 308$ nm) emitter.[33] High conversions could be achieved (>90%) and in all cases only one regioisomeric bicyclic oxetane **8a**−**f** was detected in the crude photolysis mixture. Even more important, in all cases only one diastereoisomer was formed (Scheme 2).

The benzaldehyde adduct **8a** showed a strong ring-current-induced upfield shift in the $^1$H NMR for H-1 (Figure 1, R = H, note the switch in numbering of the bicyclohept[3.2.0]enes) in line with the results obtained for the furan/benzaldehyde adduct.[25] This effect corresponds also to the NMR data obtained for the trimethyloxazole photocycloadducts[30] as well as to effects detected for in β-lactams which resulted from Yang-cyclization of amino acid derived chiral butyrophenone derivatives[34] and confirmed the *exo*-configuration of the product **8a**.

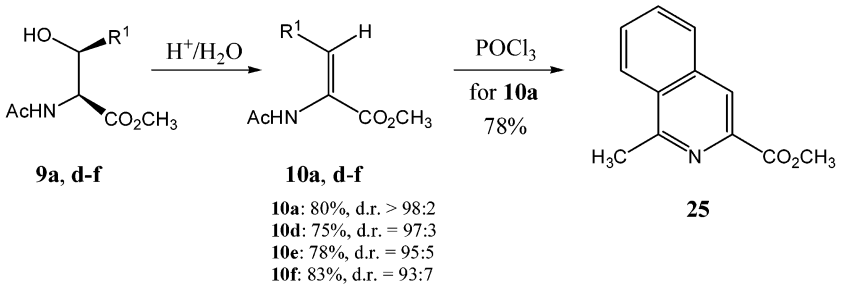
The *exo*/*endo* selectivity was excellent also when the aliphatic aldehydes **7c**−**f** were applied and the *exo*-diastereoisomers were formed in near-quantitative yields. Purification was, however, problematic because the primary photoproducts **8a**−**f** were hydrolytically unstable and underwent 2-fold ring opening to give the β-hydroxy α-amino acid esters **9a**−**f** even upon chromatography on silica. Except for the propionaldehyde adducts **8d**/**9d**, the diastereoisomeric ratio of the ring-opened products **9** matched the dr of the oxetane precursors **8**. From the relative configuration of the bicyclic oxetanes, assuming retention of configuration at C7, the *erythro* configuration for the α-amino β-hydroxy esters **9** was predicted. In fact, the relative configurations of the methyl esters of phenylserine (**9a**)[35] and β-hydroxyleucine (**9e**)[36] were elucidated in the literature, and by comparison with our data, the *erythro* (*S**,*S**) configuration for the major diastereoisomers of **9a**−**f** was established: for the *threo* β-hydroxyleucine derivative **9e** a chemical shift ($^{13}$C NMR) was reported for the β-carbon: 77.2 ppm for *R***S** (*threo*); 69.8 ppm was determined for the major diastereoisomer (*erythro*) **9e** obtained via the photoaldol route. Independent synthesis of the *threo*-diastereomer of *N*-acetyl methyl threoniate (**9g**) was also performed, and $^1$H NMR comparison revealed different relative configurations [values for $H_\alpha$ = for *erythro*-**9d**, 4.88 ppm; *erythro*-**9e**, 4.75 ppm; *erythro*-**9f**, 4.87 ppm, compared with the threonine derivative *threo*-**9g**, 4.35 ppm].

Thus, the photoaldol route serves as an efficient and highly diastereoselective route to *erythro* α-amino β-hydroxy esters. Furtheron, applying more harsh conditions, these products could be converted into the *Z*-didehydro α-amino acids **10a**,**d**−**f** (Scheme 3, not examined for **9b** and **9c**). For compounds **10d**−**f**, the *E*-isomers were also detected in the NMR spectra as minor diastereoisomers. The configuration of compound **10f** (derived from leucine) was determined by low-temperature ROESY and NOE spectroscopy (−63 °C, because of overlapping amide NH signals and rapid H/D exchange at room temperature). For the minor diastereoisomer, a strong enhancement of the vinylic hydrogen ($\delta_{=CH} = 6.95$ ppm) was observed during saturation of the amide hydrogen ($\delta_{NH} = 7.75$ ppm), whereas no such effect was observed for the major diastereoisomer during saturation of the amide hydrogen ($\delta_{NH} = 7.58$ ppm, $\delta_{=CH} = 6.75$ ppm). The acid-catalyzed elimination does not follow a E2 path but results in the thermodynamically more stable *Z*-isomers as described already for the para-hydroxy derivative of **9a** (β-p-hydroxyphenylserine).[37] The phenyl-substituted derivative **10a** could be cyclized by a Bischler−Napieralski reaction to give the literature-known isoquinoline **25**.[38]

In a next series of experiments, we investigated 5-methoxyoxazoles **2**−**6** as substrates with an additional

(32) Singh, R. S.; Singh, R. M. *Ind. J. Chem. Sect. B* **2000**, *39*, 688−693.
(33) Griesbeck, A. G.; Maptue, N.; Bondock, S.; Oelgemöller, M. *Photochem. Photobiol. Sci.* **2003**, *2*, 450−451.
(34) Griesbeck, A. G.; Heckroth, H. *Synlett* **2002**, 131−133.
(35) Legters, J.; Thijs, L.; Zwanenburg, B. *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 16−21.
(36) Cardillo, G.; Gentilucci, L.; Gianotti, M.; Tolomelli, A. *Tetrahedron: Asymmetry* **2001**, *12*, 563−569.
(37) Bolhofer, W. A. *J. Am. Chem. Soc.* **1953**, *75*, 4469−4473.
(38) Hickey, D. M. B.; Mackenzie, A. R.; Moody, C. J.; Ress, C. W. *J. Chem. Soc., Perkin Trans. 1* **1987**, 921−926.

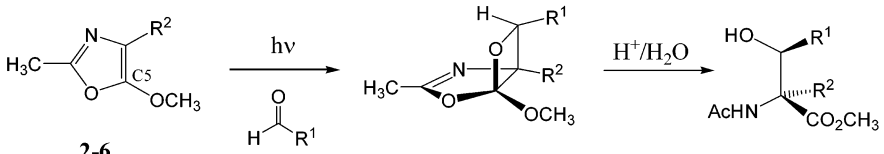
**SCHEME 3. Dehydration of 1,2-acylamino alcohols 9 Leads to *Z*-didehydro Amino Acids 10; Bischler−Napieralski Cyclization of 10a Gives the Isoquinoline 25**




**9a, d-f** **10a, d-f** **25**

**10a**: 80%, d.r. > 98:2
**10d**: 75%, d.r. = 97:3
**10e**: 78%, d.r. = 95:5
**10f**: 83%, d.r. = 93:7

**SCHEME 4. Photocycloaddition of Aldehydes 7a−f to 4-Substituted 5-Methoxy Oxazoles 2−6 and Subsequent Hydrolytic Ring-Opening of the Bicyclic Oxetanes**




**2-6**

$R^2$ =Me (**2**), Et (**3**), Pr (**4**), iPr (**5**), i-Bu (**6**).

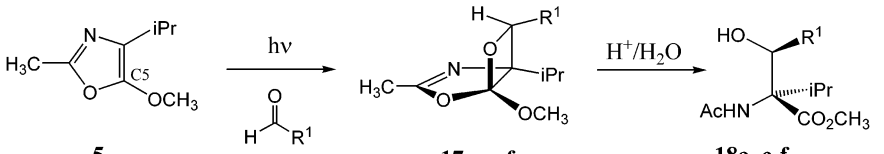
**7a-f**

$R^1$=Ph (**a**), 2-Nph (**b**), $BnCH_2$ (**c**), Et (**d**), i-Pr (**e**), i-Bu (**f**).

**11a-f** **13a,d-f** **15a,d-f** **17a,c-f** **19a,d-f**

$R^2$=Me **12a-f**
$R^2$=Et **14a,d-f**
$R^2$=Pr **16a,d-f**
$R^2$=iPr **18a,c-f**
$R^2$=iBu **20a,d-f**

**SCHEME 5. Photocycloaddition of Aldehydes 7 to 4-Isopropyl 5-Methoxy Oxazole 5 and Subsequent Hydrolytic Ring-Opening of the Bicyclic Oxetanes 17**




**5**

**7a, c-f**

$R^1$=Ph (**a**), $BnCH_2$ (**c**), Et (**d**), i-Pr (**e**), i-Bu (**f**).

**17a, c-f**

**17a**: 80%, d.r. = 73:27
**17c**: 86%, d.r. = 81:19
**17d**: 88%, d.r. > 98:2
**17e**: 83%, d.r. > 98:2
**17f**: 81%, d.r. = 81:19

**18a, c-f**

**18a**: 48%, d.r. = 90:10
**18c**: 55%, d.r. > 98:2
**18d**: 68%, d.r. = 95:5
**18e**: 73%, d.r. = 93:7
**18f**: 62%, d.r. > 98:2

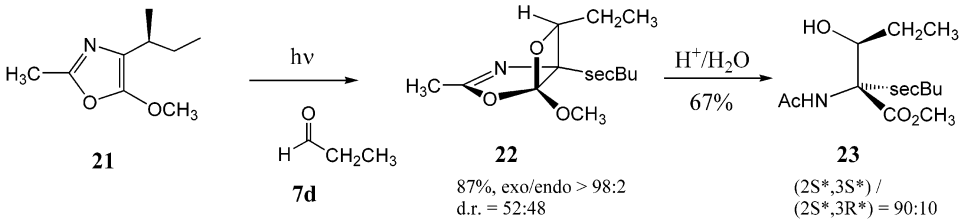
substituent at C-4. These substrates were available from the amino acids alanine, α-amino butyric acid, valine, norvaline, leucine, and isoleucine by a three-step procedure.[39] The photocycloadditions of **2**−**6** and the aldehydes **7a**−**f** were performed using equimolar amounts of the substrates in benzene, irradiations were performed in Rayonet photoreactors with lamps emitting at $\lambda = 300 \pm 10$ nm (Scheme 4). The primary photoadducts were formed with high to excellent diastereoselectivities except for the benzaldehyde additions to oxazole substrates with bulky substituents $R^2$ (vide infra). 2-Naphthaldehyde (**7b**) was applied only in the photocycloaddition to 2,4-dimethyl-5-methoxyoxazole (**2**), 3-phenylpropionaldehyde (**7c**) in the photocycloaddition to **2** and to 2-methyl-4-isopropyl-5-methoxy-oxazole (**5**).

Upon chromatography on silica, the photocycloaddition products were hydrolyzed to give the (*S**,*S**) α-acylamino *β*-hydroxy carboxylic acid esters **12**, **14**, **16**, **18**, and **20**. The relative configurations of the predeeding oxetanes were confirmed by NMR spectroscopy, and the relative configurations of the α-acylamino *β*-hydroxy carboxylic acid esters by spectral comparison with representative literature-known *anti*-products.[11,40] The photocycloadditions of propionaldehyde (**7d**) and isobutyraldehyde (**7e**) were *exo*-selectivitve with all oxazoles substrates investigated. The only remarkable drop in cycloaddition diastereoselectivity was observed with the isopropyl-substituted oxazole **5** (Scheme 5). In case of the vicinal bis-isopropyl-substituted oxetane **17e**, however, the *exo*-diastereoisomer was again the only detectable product in high yield. The serve strain generated in this product due to the cis-alignment of two bulky groups in a four-membered ring clearly indicates the kinetic control of oxetane formation. The marginal decline in *exo*-diastereoselectivity for **17a**,**c**, and **17f** might be due to triplet biradical geometries (vide infra), compensating the steric strain, and is, however, improved again in the (*S**,*S**)

(39) (a) Karrer, P.; Granacher, C. *Helv. Chim. Acta* **1924**, *7*, 740−758. (b) Doktorova, N. D.; Ionova, L. V.; Karpeisky, M. Y. A.; Padyukova, N. S.; Turchin, K. F.; Florentiev, V. L. *Tetrahedron* **1969**, *25*, 3527−3553. (c) Tolstikov, G. A.; Shul'ts, E. E. *J. Org. Chem. USSR* **1984**, *20*, 2230−2235.

(40) (a) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539−1650. (b) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708−2749.

**SCHEME 6. Photocycloaddition of Propionaldehyde to the Isoleucine-Derived Oxazole 21 and Hydrolytic Ring-Opening of 22 To Give the 1,2-Acylamino Alcohol 23**



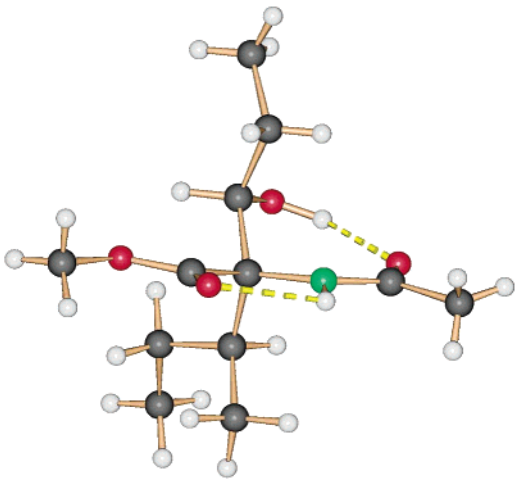



**FIGURE 2.** Crystal structure of **23**; internal hydrogen bonds are indicated by broken lines.

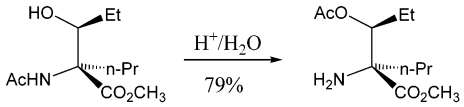
α-acylamino β-hydroxy carboxylic acid esters **18a**,**c**, and **18f**, obviously due to an enrichment effect during workup.

The ultimate proof for the relative configuration of the quaternary α-acylamino β-hydroxy carboxylic acid esters came from the X-ray structure analysis of compound **23**, which resulted from the hydrolytic ring-opening of the oxetane **22** (Scheme 6). In the crystal, conformational locking is achieved by strong internal hydrogen-bonding. The oxazole **21** was obtained from enantiomerically pure isoleucine by the standard procedure described above and was originally applied in order to study possible face-selectivity effects. The photocycloaddition of all aldehydes investigated herein proceeded with high *exo*-selectivity but with no particular facial selectivity. The hydrolytic ring-opening of the propionaldehyde adduct **22** resulted in the 1,2-acylamino alcohol **23** which was purified by chromatography (Figure 2). By fractional crystallization, one out of the two diastereoisomers resulting from different facial attack (both anti) was isolated and could be characterized by X-ray analysis. Enantiomerically pure products were obtained as also could be deduced from the chiral space group $P2_12_12_1$.

In contrast to the 1,2-amido alcohols **9**, the quaternary compounds isolated from photocycloaddition/hydrolysis of 4-substituted 5-methoxyoxazoles could not undergo dehydration. Prolonged treatment with aqueous HCl did, however, result in quantitative transacylation and the formation of β-acyloxy α-amino acid esters, as shown in Scheme 7 for the transacylation of **16d** into **24d**.

**Mechanistic Scenario.** The high *exo*-selectivity observed for the photocycloaddition of electronically excited aromatic as well as aliphatic aldehydes to the C4-unsubstituted oxazole **1** is analogous to Paternò–Büchi

**SCHEME 7. Trans-Acylation Observed for the 1,2-Acylamino Alcohol 16d To Give the 1,2-Acyloxyamine 24d**




reactions to furan and other heterocyclic dienes. It has been described as a consequence of spin–orbit-coupling geometries for triplet-1,4-biradicals in combination with secondary orbital interactions.[25] Aliphatic aldehydes, which can also react from their first excited singlet state, also show high *exo*-selectivity. When high concentrations of the trapping reagent (furan or oxazole, respectively) are used in the presence of aliphatic aldehydes, a drop in *exo*/*endo*-diastereoselectivity is observed.[27] Thus, the singlet excited carbonyl compounds add to oxazoles with slightly lower *exo*/*endo*-selectivity, albeit by a different mechanism.[26]

Surprisingly, also the trisubstituted oxazoles **2**–**6** and **21** gave the *exo*-diastereoisomers with high excesses upon photocycloaddition. This behavior was unprecedented, because in the triplet photocycloaddition to cycloalkenes,[41] ring alkylation always led to a *decrease* in selectivity and in some case to selectivity inversion due to interference with the spin–orbit-coupling geometries.[42] This is obviously not the case for the oxazole photocycloadditions described herein, which indicates that the secondary orbital interaction model originally applied for the benzaldehyde-furan reaction is operating.[25] Figure 3 shows the triplet 1,4-biradical conformers **A**–**C** with reactive spin–orbit coupling ("90°-conformers") geometries, as also expected from theoretical calculations.[43] If most of the spin inversion process is directed through the channel **C** due to high spin–orbit-coupling interaction and secondary orbital interactions, high *exo*-selectivity is expected. The *endo*-contribution from **A** only becomes relevant for bulky groups $R^1$ and $R^2$ (as for **17a**), because steric encumbrance is alreay substantial at the stage of the triplet biradical structure **C**. Also the singlet excited aldehydes do show high *exo*-selectivity and thus both mechanisms act cooperatively.

## Experimental Part

**Synthesis of the Oxazole Substrates. 2-Methyl-5-methoxyoxazole (1).** A mixture of 13.1 g of *N*-acetylglycine methyl

(41) Griesbeck, A. G.; Stadtmüller, S. *J. Am. Chem. Soc.* **1991**, *113*, 6923–6928.
(42) Griesbeck, A. G.; Stadtmüller, S.; Mauder, H. *Acc. Chem. Res.* **1994**, *27*, 70–75.
(43) Kutateladze, A. *J. Am. Chem. Soc.* **2001**, *123*, 9279–9282.

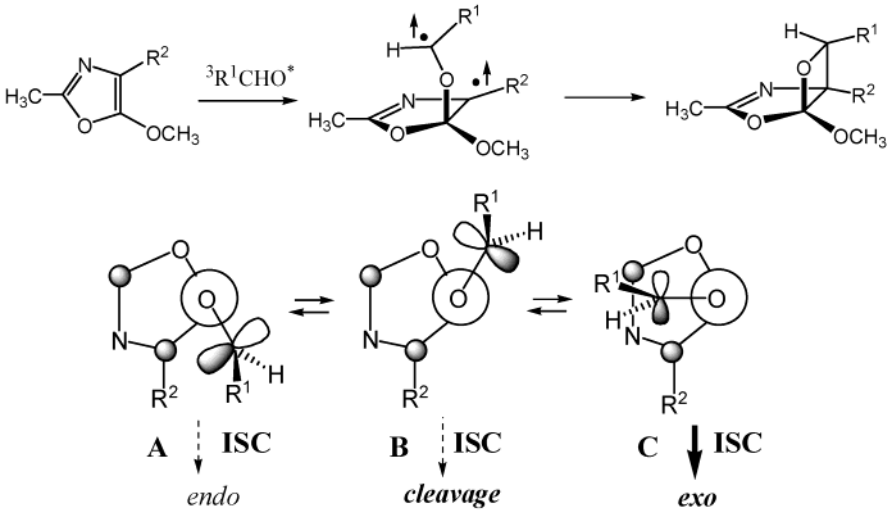



**FIGURE 3.** 1,4-Triplet biradical intermediates in the photocycloaddition of triplet RCHO to 4-substituted oxazoles.

ester (0.1 mol) and 40.0 g of phosphorus pentoxide (0.15 mol) in 100 mL of chloroform was heated to reflux with mechanical stirring for 24 h. After being cooled to room temperature, the residual phosphorus pentoxide was carefully crushed, and the resulting thick suspension was slowly added, in small portions, to ice-cold saturated sodium bicarbonate maintaining a pH of 6−7. The organic layer was separated, and the aqueous layer was extracted with 4 × 75 mL of methylene chloride. The combined extracts were then washed with brine, dried over anhydrous magnesium sulfate, concentrated and distilled to afford 10.0 g (80%) of **1**[32] as a colorless oil: bp 64−66 °C, 10 Torr; $^1$H NMR $\delta$ 2.27 (s, 3H), 3.79 (s, 3H), 5.87 (s, 1H); $^{13}$C NMR $\delta$ 13.9, 58.4, 97.8, 152.0, 160.5.

**Synthesis of Amino Acid Methyl Ester Hydrochlorides: General Procedure.** A 250 mL, two-necked, round-bottomed flask, containing a magnetic stirring bar, was equipped with a dropping funnel and reflux condenser, protected from moisture by a calcium chloride-filled drying tube and a rubber septum. The dropping funnel was charged with 4.2 mL of thionyl chloride (60 mmol). The flask was charged with 50 mL of absolute methanol and cooled with an ice−salt bath to −10 °C. Thionyl chloride was added dropwise over a period of 5 min. The solution was stirred for another 5 min, and then the solid L-amino acid (30 mmol) was added in one portion and the solution was slowly heated to reflux. Heating to reflux was continued for 3 h, and then the solution was allowed to cool to room temperature and the solvent was removed under reduced pressure to give the amino acid methyl ester hydrochloride as a colorless crystalline solid that was directly used without further purification.

**Synthesis of *N*-Acetylamino Acid Methyl Esters: General Procedure.** To a stirred suspension of the amino acid methyl ester hydrochloride (100 mmol) in 150 mL of chloroform was added 28 mL of triethylamine (200 mmol) at 0 °C, and the mixture was stirred for 15 min at room temperature. Acetyl chloride (7.2 mL, 100 mmol) was added dropwise, and stirring was continued for 45 min. The solvent was removed under reduced pressure, 750 mL of ethyl acetate was added, and the mixture was filtered through a pad of silica gel. Evaporation of the solvent under reduced pressure afforded the amide in high purity.

**Synthesis of 4-Substituted 2-Methyl-5-methoxyoxazoles 2−6: General Procedure.** *N*-Acetyl-L-amino acid methyl ester (0.1 mol) was dissolved in 20 mL of chloroform in a 250 mL flask, 20.8 g (0.1 mol) of phosphorus pentachloride was added, and the flask was fitted with a calcium chloride tube. The solution was gently warmed by means of a water bath (ca. 60 °C) with stirring until the HCl gas evolution ceased and the solution became intensively yellow. Then, the flask was cooled by an ice−salt bath, and 50 mL of absolute ether was added. To the cooled mixture was added 20% aqueous KOH dropwise until neutralization with vigorous stirring. The mixture was stirred at room temperature for 30 min. The organic layer was subsequently separated, and the aqueous layer was extracted with 2 × 200 mL of ether. The combined organic extracts were washed with water and brine and dried over anhydrous $MgSO_4$. After removal of the solvents under vacum, the remaining oil was distilled by a Büchi Kugelrohr apparatus to give the product **2**−**6**. Yields and spectroscopic data for **2**[44] and **3**−**6**[39] are given as Supporting Information.

**Photolyses of 2-Methyl-5-methoxyoxazole (1) with Aldehydes 7a−f: General Procedure.** 2-Methyl-5-methoxyoxazole (**1**) (0.56 g, 5 mmol) and the corresponding aldehyde (5 mmol) were dissolved in 50 mL of benzene, and the solution was transferred to a vacuum-jacket quartz tube and degassed with a steady stream of $N_2$ gas. The reaction mixture was irradiated at 10 °C in a Rayonet photoreactor (RPR 300 nm) for 24 h. The solvent was evaporated (40 °C, 20 Torr), and the residue was submitted to $^1$H NMR analysis for determination of the diastereomeric ratios. Purification was carried out by bulb-to-bulb distillation. The thermally and hydrolytically unstable primary products could in most cases not be fully characterized by combustion analysis and were hydrolyzed subsequently to the stable α-amino-β-hydroxy esters.

***exo*-5-Methoxy-3-methyl-7-phenyl-4,6-dioxa-2-azabicyclo[3.2.0]hept-2-ene (*exo*-8a).** From benzaldehyde (0.53 g, 5 mmol) according to the general procedure. Distillation of the solvent under vaccum afforded 0.82 g of the oxetane **8a** as a pale yellow oil: 75%; IR (Film) $\tilde{\nu}$(cm$^{-1}$) = 2987, 1635, 1600, 1558, 1440, 1341, 1012, 967; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.11 (s, 3H), 3.79 (s, 3H), 4.58 (d, $J$ = 7.7 Hz, 1H), 5.68 (d, $J$ = 7.7 Hz, 1H), 7.26−7.31 (m, 5H); $^{13}$C NMR $\delta$ 15.9, 52.8, 76.2, 83.0, 122.9, 125.4, 126.2, 128.1, 134.3, 167.7; HRMS ($C_{12}H_{13}NO_3$, M = 219.09 g/mol) calcd 219.0892, found 219.0886.

Yields and spectroscopic data for *exo*-**8b**−**f** are given as Supporting Information.

**Hydrolysis of the Bicyclic Oxetanes 8a−f: General Procedure.** To a solution of the oxetane **8a**−**f** (2 mmol) in 20 mL of methylene chloride was added 0.5 mL of concentrated HCl. The mixture was stirred in an open flask at room temperature for 2 h and the reaction controlled by TLC. After complete conversion, the reaction mixture was poured into 20 mL of water and extracted with 2 × 20 mL of methylene

(44) Suga, H.; Shi, X.; Ibata, T.; Kakehi, A. *Heterocycles* **2001**, *55*, 1711−1726.

chloride. The organic layer was washed with 5% $NaHCO_3$ and brine and dried over $MgSO_4$. The solvent was removed in vacuo, and the residue was purified by preparative chromatography using a mixture of ethyl acetate and *n*-hexane as eluent.

**Methyl (2*S**,3*S**) 2-Acetylamino-3-hydroxy-3-phenylpropionate (*erythro*-9a).** According to the general procedure, oxetane **8a** (0.44 g, 2 mmol) was hydrolyzed in 3 h. Preparative chromatography yielded 0.33 g of **9a** as a colorless oil: 70%; $^1$H NMR $\delta$ 2.07 (s, 3H), 3.97 (s, 3H), 4.45 (d, $J$ = 9.7 Hz, 1H), 5.85 (d, $J$ = 9.7 Hz, 1H), 6.37 (bs, 1H), 7.28−7.35 (m, 5H); $^{13}$C NMR $\delta$ 23.7, 52.4, 75.4, 81.6, 126.2, 128.9, 129.6, 134.3, 169.3, 170.3. Anal. ($C_{12}H_{15}NO_4$, $M$ = 237.10 g/mol) Calcd: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.86; H, 6.52; N, 6.00.

Yields and spectroscopic data for *erythro*-**9b**−**f** are given as Supporting Information.

**Independent Synthesis of Methyl (2S*,3R*) 2-Acetylamino-3-hydroxybutanoate (threo-9g).** A 100 mL, three-necked, round-bottomed flask, containing a magnetic stirring bar, was equipped with a dropping funnel and reflux condenser. The dropping funnel was charged with 7.8 mL of acetyl chloride. The flask was subsequently charged with 50 mL of methanol and cooled with an ice bath to 0 °C. Acetyl chloride was added dropwise over a period of 10 min. The solution was stirred for a further 5 min, L-threonine (4.5 g, 38 mmol) was added in one portion, and the solution was slowly heated to reflux. Reflux was continued for 3 h, and then the solution was allowed to cool to room temperature and the solvent removed under reduced pressure to give 4.8 g (94%) of methyl threoniate hydrochloride. A 250 mL two-necked flask was equipped with a magnetic stirring bar, a reflux condenser, and a pressure-equalizing dropping funnel that was charged with acetyl chloride (2.1 mL, 30 mmol). Methyl threoniate hydrochloride (4.6 g, 30 mmol) was placed in the flask and suspended in 100 mL of chloroform and triethylamine (7.6 mL, 60 mmol). The resulting white suspension was cooled with an ice bath, and the solution of acetyl chloride was added dropwise over a period of 30 min. After 15 min of additional stirring, the ice bath was removed and the suspension stirred for a further 2 h. The solvent was removed under vacuo, ethyl acetate (150 mL) was added, and the mixture was filtered through a pad of silica gel. Evaporation of the solvent under reduced pressure afforded 4.9 g (89%) of *N*-acetyl methyl threoniate as colorless crystals: mp 106−108 °C (lit.[45] mp 105−106 °C); $^1$H NMR $\delta$ 0.92 (d, $J$ = 6.4 Hz, 3H), 1.97 (s, 3H), 3.59 (s, 3H), 4.16 (ddq, $J$ = 2.6, 6.0, 6.4 Hz, 1H), 4.35 (dd, $J$ = 8.8, 2.6 Hz, 1H). $^{13}$C NMR $\delta$ 13.4, 20.2, 52.1, 57.6, 67.3, 171.3, 171.4.

**Synthesis of (*Z*)-α,β-Didehydroamino Acid Derivatives 10a−f: General Procedure.** The photoaldol product (1 mmol) was added to 10 mL of methylene chloride, presaturated with concentrated HCl, for 5 min and the solution stirred at room temperature until Tlc indicated completion of the reaction. The reaction mixture was then washed with saturated $NaHCO_3$ and saturated NaCl, dried over anhydrous $Na_2SO_4$, and then evaporated. The residue was purified by preparative thick-layer chromatography.

**Methyl 2-Acetylamino-3-phenylacrylate (*Z*-10a).** According to the general procedure, methyl 2-acetylamino-3-hydroxy-3-phenylpropionate **9a** (0.24 g, 1 mmol) was dehydrated in 20 h. Preparative chromatography yielded 0.17 g of the product as a colorless oil which was solidified from a mixture of chloroform and petroleum ether as a colorless powder: 80%; mp 122−124 °C (ref 125 °C).[46]

Yields and spectroscopic data for ***Z*-10d**,[47] ***Z*-10e**,[48] and ***Z*-10f**[49] are given as Supporting Information.

**Photolyses of 4-Substituted 2-Methyl-5-methoxyoxazoles 2−6 with Aldehydes 7a−f: General Procedure.** A solution of the 5-methoxyoxazole **2**−**6** (5 mmol) and the aldehyde **7a**−**f** (5 mmol) in 50 mL of benzene was transferred to a vacuum-jacket quartz vessel and degassed with a steady stream of $N_2$ gas. The reaction mixture was irradiated at 10 °C in a Rayonet photoreactor (RPR 300 nm) for 24 h. The solvent was evaporated (40 °C, 20 Torr), and the residue was analyzed by $^1$H NMR analysis. Purification was carried out by bulb-to-bulb distillation. The thermally and hydrolytically unstable primary products could in most cases not be characterized by combustion analysis and were hydrolyzed subsequently to the corresponding α-amino-β-hydroxy esters.

***exo*-5-Methoxy-1,3-dimethyl-7-phenyl-4,6-dioxa-2-azabicyclo[3.2.0]hept-2-ene (*exo*-11a).** From benzaldehyde (0.53 g, 5 mmol) and 2,4-dimethyl-5-methoxyoxazole (**2**) (0.64 g, 5 mmol). Distillation of the solvent under vaccum afforded 0.96 g of the oxetane **11a** as a pale yellow oil: 82%; $^1$H NMR $\delta$ 0.79 (s, 3H), 1.99 (s, 3H), 3.52 (s, 3H), 5.19 (s, 1H), 7.21−7.25 (m, 5H); $^{13}$C NMR $\delta$ 13.4, 14.8, 51.2, 75.8, 89.3, 124.5, 125.7, 128.6, 129.3, 136.9, 164.9; HRMS ($C_{13}H_{15}NO_3$, $M$ = 233.1 g/mol) calcd 233.0762, found 233.0758.

Yields and spectroscopic data for further bicyclic oxetanes are given as Supporting Information.

**Synthesis of *erythro*-(2S*,3S*)-α-Acetamido-α-alkylated-β-hydroxy Esters: General Procedure.** To a solution of the oxetane (2 mmol) in 20 mL of methylene chloride, 0.5 mL of concentrated HCl was added. The mixture is stirred in an open flask at room temperature for 2 h and the reaction was controlled by TLC. The reaction mixture was quenched with water and extracted with methylene chloride (3 × 20 mL). The organic layer was washed with 5% $NaHCO_3$ and brine and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo, and the residue was purified by preparative chromatography.

***erythro*-Methyl (2S*,3S*)-2-(*N*-Acetylamino)-3-hydroxy-2-methyl-3-phenylpropanoate (*erythro*-12a).** Following the general procedure, oxetane **11a** (0.47 g, 2 mmol) was hydrolzed in 3 h. Preparative chromatography yielded 0.33 g of **12a** as a colorless oil: 65%; IR (film) $\tilde{\nu}$(cm$^{-1}$) = 3350, 3320, 2988, 1720, 1680, 1580, 1440, 1340, 1062, 987; $^1$H NMR $\delta$ 1.23 (s, 3H), 2.12 (s, 3H), 3.79 (s, 3H), 4.06 (s, 1H), 7.32 (m, 5H); $^{13}$C NMR $\delta$ 13.5, 21.4, 23.4, 47.7, 49.1, 52.9, 127.6, 128.4, 133.5, 169.9, 179.4; MS (EI, 70 eV) *m*/*z* 249 ($M^+ - H_2$, 4), 236 ($M^+ -$ Me, 8), 202 (8), 192 ($M^+ - CO_2Me$, 15), 191 (78), 160 (10), 132 (12), 131 (100), 105 (50), 91 (20), 77 (30), 51 (10); HRMS ($C_{13}H_{17}NO_4$, $M$ = 251.12 g/mol) calcd 251.1254, found 251.1249.

Yields and spectroscopic data for further *erythro*-(2*S**,3*S**)-α-acetamido-α-alkylated-β-hydroxy esters are given as Supporting Information.

**4-*sec*-Butyl-2-methyl-5-methoxyoxazole (21).** Reaction of methyl *N*-acetylamino isoleucinate (18.7 g, 0.1 mol) and $PCl_5$ (20.8 g, 0.1 mol) according to the general procedure afforded 12.7 g (75%) of **21** as a colorless liquid: bp 89−93 °C, 10 Torr; $^1$H NMR $\delta$ 0.77 (t, $J$ = 7.4 Hz, 3H), 1.12 (d, $J$ = 7.1 Hz, 3H), 1.50 (m, 2H), 2.26 (s, 3H), 2.42 (m, 1H), 3.79 (s, 3H); $^{13}$C NMR $\delta$ 11.9, 14.1, 19.3, 28.6, 31.5, 61.3, 119.9, 152.1, 154.1.

***exo*-1-*sec*-Butyl-7-ethyl-5-methoxy-3-methyl-4,6-dioxa-2-azabicyclo[3.2.0]hept-2-ene (*exo*-22).** A solution of propionaldehyde (0.29 g, 5 mmol) and 4-*sec*-butyl-2-methyl-5-methoxyoxazole (**21**) (0.84 g, 5 mmol) in benzene (50 mL) was irradiated for 24 h. Distillation of the solvent under vaccum afforded 1.0 g of the oxetane **22** as a pale yellow oil. The product was thermally unstable and was subsequently hydrolyzed to give the corresponding α-amino-β-hydroxy ester **23**: 88%; $^1$H NMR $\delta$ 0.76 (d, $J$ = 6.6 Hz, 3H), 0.83 (m, 3H), 0.92 (t, $J$ = 7.4 Hz, 3H), 1.43 (m, 1H), 1.83 (m, 2H), 2.10 (s, 3H), 3.47 (s, 3H), 4.16 (dd, $J$ = 3.7, 7.5 Hz, 1H); $^{13}$C NMR $\delta$ 9.0, 11.5, 12.9, 13.9, 23.5, 24.9, 32.0, 51.8, 80.4, 91.0, 124.6, 164.9; MS

(45) Pfister, K.; Robinson, C. A.; Shabica, A. C.; Tishler, M. *J. Am. Chem. Soc.* **1949**, *71*, 1101−1103.
(46) Cook, A. H.; Harris, G.; Heilbron, I.; Shaw, G. *J. Chem. Soc.* **1948**, 1056−1060.
(47) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125−10138.
(48) Poisel, H.; Schmidt, U. *Chem. Ber.* **1975**, *108*, 2547−2553.
(49) Kuwano, R.; Sawamura, M.; Ito, Y. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2571−2578.

(EI, 70 eV) *m*/*z* 216 ($M^+ - Et$, 10), 196 (5), 186 (18), 170 (20), 169 (35), 168 (52), 155 (32), 144 (75), 126 (100), 112 (43), 99 (20), 95 (15), 84 (55), 70 (18), 57 (60).

***erythro*-Methyl (2S*,3S*) 2-Acetylamino-2-(1-hydroxypropyl)-3-methylpentanoate (*erythro*-23).** Following the general procedure, oxetane **22** (0.45 g, 2 mmol) was hydrolyzed in 3h. Preparative chromatography yielded 0.37 g of **23** as a colorless oil. Single crystals suitable for X-ray crystal structure analysis were obtained by recrystallization from chloroform: 75%; mp 43−45 °C; $^1$H NMR $\delta$ 0.76 (d, $J$ = 6.9, Hz, 3H), 0.85 (t, $J$ = 7.2, Hz, 3H), 0.96 (t, $J$ = 7.1 Hz, 3H), 1.21 (m, 1H), 2.08 (s, 3H), 2.42 (m,1H), 3.77 (s, 3H), 4.62 (dd, $J$ = 11.7, 1.7 Hz, 1H), 6.90 (bs, 1H); $^{13}$C NMR $\delta$ 10.8, 12.3, 13.3, 13.9, 23.7, 27.3, 37.4, 52.9, 73.7, 74.2, 170.8, 172.8. Anal. ($C_{12}H_{23}NO_4$, $M$ = 245.32 g/mol) Calcd: C, 58.75; H, 9.45; N, 5.71. Found: C, 59.03; H, 9.38; N, 5.62.

**Transacylation: General Procedure.** To a solution of the α-acetamido-β-hydroxy ester (approximately 300 mg, 15 mmol) in 15 mL of chloroform was added 0.2 mL of 1 N aq HCl at room temperature and the mixture stirred overnight. After the reaction was quenched with water (15 mL), the mixture was extracted with methylene chloride (3 × 15 mL), the organic extract was washed with 5% sodium bicarbonate solution and dried over $MgSO_4$, and the solvent was removed under vacuum. The residue was purified by preparative thin-layer chromatography.

**Methyl (2*S**,3*S**)-3-Acetoxy-2-amino-2-propylpentanoate (*erythro*-24d).** From **16d** following the gernal procedure. Preparative chromatography yielded 0.24 g of the product as a colorless oil: 79%; $^1$H NMR $\delta$ 0.78 (t, $J$ = 7.4, Hz, 3H), 0.84 (t, $J$ = 6.0 Hz, 2H), 1.10 (t, $J$ = 7.6 Hz, 3H), 1.42 (m, 2H), 1.75 (m, 2H), 1.98 (s, 3H), 3.69 (s, 3H), 5.30 (dd, $J$ = 10.9, 2.6 Hz, 1H), 6.38 (bs, 2H); $^{13}$C NMR $\delta$ 9.2, 11.3, 13.3, 17.6, 23.7, 36.0, 52.8, 67.8, 77.6, 172.9, 173.6; HRMS ($C_{11}H_{21}NO_4$, $M$ = 231.15 g/mol) calcd 231.1473, found 231.1471.

**Cyclization of the *Z*-Amidoacrylate 10a. Methyl 1-Methyl-isoquinoline-3-carboxylate (25).** To an ice-cooled solution of 210 mg (1 mmol) of methyl (*Z*)-2-acetylamino-3-phenylacrylate (**10a**) in 20 mL of methylene chloride was added 200 mg (1.5 mmol) of phosphorus oxychloride, and the solution was heated to 60 °C for 2 h. After being cooled to room temperature and quenched with 25 mL of saturated sodium bicarbonate, the mixture was extracted with methylene chloride (3 × 10 mL) and dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by column chromatography to give 290 mg (78%) of the isoquinoline 25 as a colorless powder with mp 105−107 °C (lit.[38] mp 104−105 °C).

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**Supporting Information Available:** Yields and spectroscopic data for substrates, bicyclic oxetanes, and α-acetamido-β-hydroxy esters, $^{13}$C NMR spectra of bicyclic oxetanes, and X-ray crystallographic data for compound **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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