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Diastereoselectivity Enhancement in the 1,3-Cycloaddition of β-Lactam Aldehydes. Application to the Synthesis of Enantiopure Indolizidinone Amino Esters

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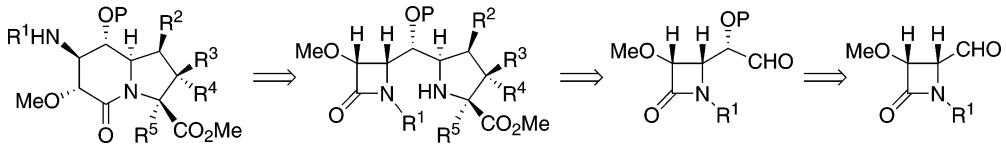

Enantiopure α-alkoxy β-lactam acetaldehydes were prepared via the thiazole-based one-carbon homologation. The 1,3-dipolar cycloaddition reaction involving α-alkoxy β-lactam acetaldehyde-derived azomethine ylides gave with excellent diastereoselectivity highly functionalized 2-azetidinone-tethered prolines, which were directly used for the first preparation of azabicyclo[4.3.0]-nonane (indolizidinone) amino esters from β-lactams.

Introduction

Indolizidine alkaloids are widely distributed in nature and frequently possess potent biological activity.[1] In recent years, indolizidine alkaloids as well as related unnatural compounds have become popular synthetic targets as a consequence of their bioactivity, moderate complexity, and the diversity of possible synthetic strategies for their construction.[2] In particular, azabicyclo-[4.3.0]nonane (indolizidinone) amino acids have proven to behave as conformationally restricted dipeptide mimetics.[3] 1,3-Dipolar cycloaddition employing azomethine ylides is an important process in organic synthesis, acquiring a prominent place of synthetic strategy for a variety of targets, including natural products such as azasugars and alkaloids.[4] Use of 2-azetidinones as chiral building blocks in organic synthesis is now well-established.[5] However, no information was available on the use of β-lactams as precursors for the synthesis of indolizidines until we entered this field.[6]

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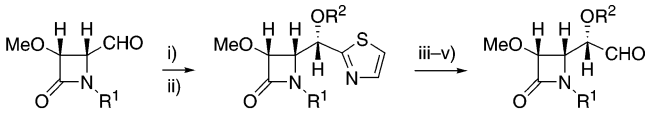
SCHEME 1[a]



(+)-1a R^1 = allyl
(+)-1b R^1 = benzyl

(–)-2a R^1 = allyl, R^2 = TBS (69%)
(–)-2b R^1 = benzyl, R^2 = TBS (42%)
(+)-2c R^1 = benzyl, R^2 = Me (52%)

(+)-3a (56%)
(+)-3b (52%)
(+)-3c (62%)

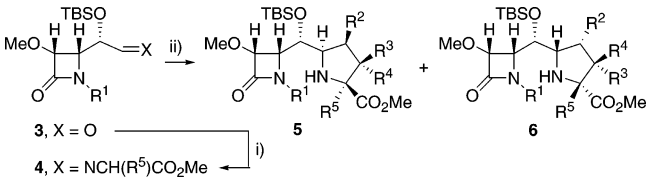
[a] Key: (i) TMST, DCM, 0 °C, 16 h. (ii) **2a**, **2b**: TBSOTf, Et_3N, DMAP, DMF, RT, 5 h; **2c**: Me_2SO_4, TBAI (cat), NaOH (aq 50%)/DCM (1:1), RT, 24 h. (iii) MeOTf, MeCN, RT, 15 min. (iv) $NaBH_4$, MeOH, RT, 10 min. (v) MeCN, $AgNO_3$, H_2O, RT, 10 min. Yields are for pure isolated products with correct analytical and spectroscopic data.

Recently, the 1,3-dipolar cycloaddition reaction involving 4-oxoazetidine-2-carbaldehyde-derived azomethine ylides has been examined.[7] However, disappointing diastereoselectivities (typically 40% de) were observed. We reasoned that installation of an extra stereocenter may improve the diastereoselectivity of the [3 + 2] cycloaddition. We wish to report here the intermolecular 1,3-dipolar cycloaddition reaction involving α-alkoxy β-lactam acetaldehyde-derived azomethine ylides, together with its application for the asymmetric synthesis of indolizidinone amino esters.

Results and Discussion

The starting substrates were prepared with the service of thiazole as latent formyl group, via the thiazole-based one-carbon homologation.[8] Enantiopure 2-azetidinones (+)-**1a** and (+)-**1b** were obtained as single cis-enantiomers from imines of (*R*)-2,3-*O*-isopropylideneglyceraldehyde, through Staudinger reaction with methoxyacetyl chloride in the presence of Et_3N, followed by sequential acidic acetonide hydrolysis and oxidative cleavage.[9] The conversion of 4-oxoazetidine-2-carbaldehydes **1** into α-alkoxy β-lactam acetaldehydes **3** was carried out through a three-step reaction sequence involving 2-(trimethylsilyl)thiazole (TMST) addition,[10] hydroxyl protection to give ethers **2**, and aldehyde unmasking. Carbaldehydes **3** were obtained as single isomers in reasonable yields (Scheme 1). It deserves to be mentioned that TMST addition to 4-oxoazetidine-2-carbaldehydes **1** is not a trivial process, because we have recently reported that the addition reaction of TMST to *N*-aryl-4-oxoazetidine-2-carbaldehydes gave enantiopure α-alkoxy-γ-keto acid derivatives via a novel N1−C4 bond breakage of the β-lactam nucleus.[11]

SCHEME 2[a]



[a] Key: (i) $H_2NCH(R^5)CO_2Me$, 4 Å MS, DCM, RT, 2 h. (ii) AgOAc, Et_3N, dipolarophile, toluene, RT.

TABLE 1. Silver Acetate-Mediated 1,3-Dipolar Cycloaddition of α-Alkoxy β-Lactam Acetaldehyde-Derived Azomethine Ylides

aldehyde	R^2	R^3	R^4	R^5	adduct	**5/6** d.r.[b]	yield (%)[c]
(+)-**3a**	E[a]	H	H	H	(+)-**5a**	100:0	57
(+)-**3a**	E	H	H	Me	(+)-**5b**	95:5	74
(+)-**3a**	E	H	E	Me	(+)-**5c**	90:10	56
(+)-**3a**	*d*	*d*	H	Me	(+)-**5d**	100:0	78
(+)-**3a**	*e*	*e*	H	Me	(+)-**5e**	100:0	62
(+)-**3b**	E	H	H	H	(+)-**5f**	100:0	61

[a] E = CO_2Me. [b] The ratio was determined by integration of well-resolved signals in the ^1H NMR spectra of the crude reaction mixtures before purification. [c] Yields (%) are for pure isolated products with correct analytical and spectroscopic data. [d] Compound (+)-**5d** was prepared using *N*-methylmaleimide. [e] Compound (+)-**5e** was prepared using *N*-phenylmaleimide.

Aliphatic aldimines **4**, which were obtained in quantitative yields and were used for the next step without further purification, were achieved by reaction of α-alkoxy β-lactam acetaldehydes **3** with the corresponding α-amino ester in the presence of 4 Å molecular sieves. Treatment of alanine (glycine) aldimines **4** derived from the TBSO-protected aldehydes (+)-**3a** and (+)-**3b** with the appropriate dienophile (e.g., *N*-methylmaleimide, *N*-phenylmaleimide, methyl acrylate, and dimethyl fumarate) in the presence of AgOAc/Et_3N in toluene at room temperature gave cycloadducts **5** (Scheme 2, Table 1) in good yields (56−78%) with diastereoselectivities ranging from good (90:10) to complete (single isomer). No further improvement occurred when the reaction was carried out in other solvents, neither by using different reagents (LiBr) nor by using different bases (DBU). Much poorer diastereoselectivity was observed when the cycloaddition reaction was carried out in polar solvents (acetonitrile and DMSO). For example, (+)-**5b** and (+)-**6b** were obtained as a 85:15 mixture in 65% combined yield when DMSO was used as solvent and triethylamine as base, whereas in toluene with triethylamine as base the reaction afforded a 95:5 mixture (74%). The use of LiBr or DBU resulted in diminished yields. The imino esters derived from the MeO-protected aldehyde (+)-**3c** gave a complex mixture of unidentified products.

The stereochemistry of the products (**5** and **6**) is based on the usual selectivity and endo-transition states via *E*,*E*-syn-dipole observed for metallo azomethine ylide cycloadditions.[4] In the current context, the *tert*-butyldimethylsilyloxy group comprises a large substituent. The reason for the great selectivity for endo-addition to give adducts **5** compared to endo-addition to give adducts **6** in the examples of Table 1 may be related to an increase ease of access of the dipolarophile to the metallodipole from the *Re*-face (trans to TBSO group). For example, the *E*,*E*-syn-dipoles derived from aldehydes **3** on reacting

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(10) The observed syn-diastereoselectivity for the TMST addition step might be tentatively explained by invoking the Felkin−Anh model, analogously to related addition processes described in our laboratories. See: (a) Alcaide, B.; Almendros, P.; Rodríguez-Acebes, R. *J. Org. Chem.* **2005**, *70*, 2713. (b) Alcaide, B.; Almendros, P.; Alonso, J. M. *J. Org. Chem.* **2004**, *69*, 993. (c) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem.−Eur. J.* **2002**, *8*, 1719.

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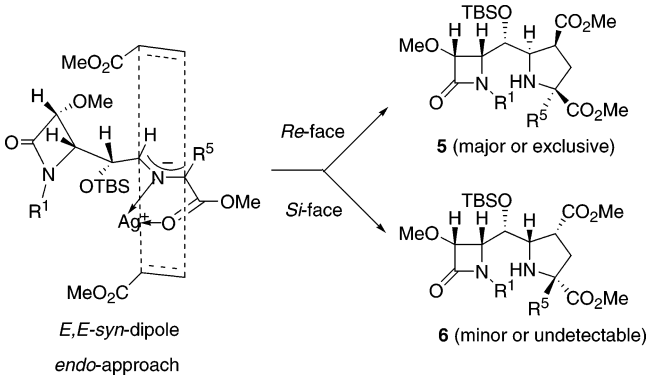
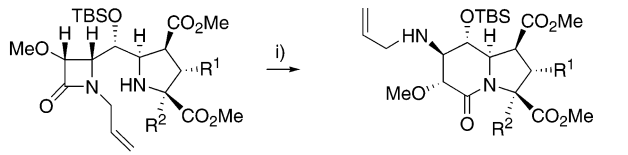
SCHEME 3

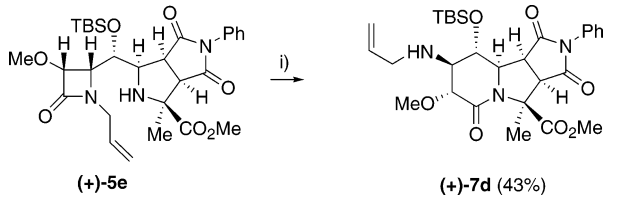


SCHEME 4[a]



[a] Key: (i) MeONa, MeOH, RT. Yields are for pure isolated products with correct analytical and spectroscopic data.

SCHEME 5[a]



[a] Key: (i) MeONa, MeOH, RT.

with methyl acrylate led to the corresponding cycloadducts **5** (Scheme 3).

With enantiopure highly functionalized 2-azetidinone-tethered prolines in hand, our aim was to find an expedient transformation of cycloadducts **5** into indolizidine systems. Transformation of pyrrolidine-*N*-allyl-*β*-lactams **5a**−**c** into indolizidinone amino acid derivatives **7a**−**c** was directly effected at room temperature via a sodium methoxide rearrangement reaction (Scheme 4). However, compound (+)-**5f** bearing a benzyl group at the N1 nitrogen was unreactive. It became evident that the group attached to the lactam nitrogen plays a crucial role in this reaction. The attempted transformation of adducts **5** into indolizidines by dissolution in a saturated solution of HCl(g) in 2-propanol resulted in complex reaction mixtures. The transformation of proline-*β*-lactams **5** into indolizidine derivatives **7** involves the selective amide bond cleavage of the four-membered ring, followed by cyclization of the resulting *β*-amino ester with concomitant ring expansion.

Fused indolizidinone (+)-**7d** was obtained in moderate yield from maleimide-derived cycloadduct (+)-**5e** after MeONa/MeOH treatment (Scheme 5). It deserves to be mentioned that the maleimide moiety is not altered under the basic rearrangement conditions.

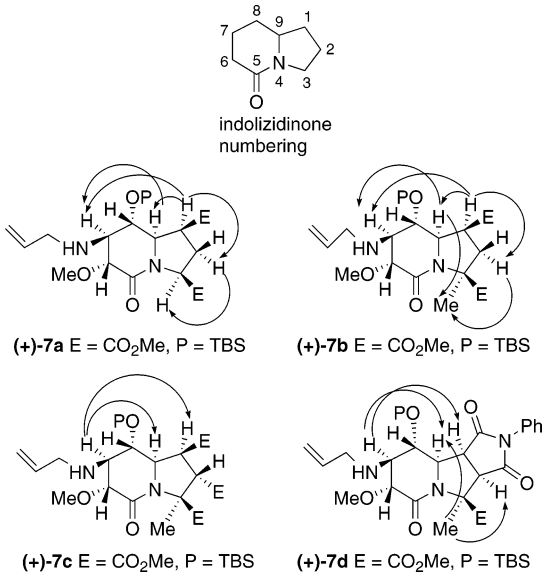


FIGURE 1. Selected NOE data for indolizidinone amino esters **7a**−**d**.

Configurational Assignment. The stereochemistry of indolizidinones **7** was established by NMR techniques, particularly by vicinal proton couplings and qualitative homonuclear NOE difference spectra. Taking into account that 2-azetidinone-tethered prolines **5** could be obtained and cyclized to indolizidinone amino esters **7**, the stereochemistry for compounds **5** was immediately deduced by comparison with the NOE results of the bicyclic systems. The cis-stereochemistry of the four-membered ring is set during the cyclization step to form the 2-azetidinone ring, and it is transferred unaltered during the further synthetic steps. Selected NOE enhancements that are in agreement with the proposed stereochemistries are shown in Figure 1. As an example, irradiation of the H9 hydrogen (indolizidinone numbering) in compound (+)-**7a** resulted in a 5% increment on the H7 proton. Irradiation of the H1 hydrogen in compound (+)-**7a** gave a 5% increment both on the H9 proton and on the less shielded proton of the methylene group. For (+)-**7a**, an additional NOE between the H1 hydrogen and the H7 proton confirmed the H1/H7/H9 all-syn stereochemical assignment. Besides, irradiation of the less shielded proton of the methylene group in compound (+)-**7a** gave a 5% increment on H3 hydrogen. Similar figures were observed on performing NOE experiments in bicycles (+)-**7b**, (+)-**7c**, and (+)-**7d**.

Conclusions

In conclusion, imino esters derived from enantiopure α-alkoxy *β*-lactam acetaldehydes gave the 1,3-dipolar cycloaddition reaction in a highly stereoselective fashion. The resulting 2-azetidinone-tethered prolines were directly used for the first preparation of azabicyclo[4.3.0]-nonane (indolizidinone) amino esters from *β*-lactams.

Experimental Section

General. The same experimental techniques were used as previously reported.[9−11]

General Procedure for the Reaction between Aldehydes 1 and TMST. A solution of TMST (94 mg, 0.60 mmol)

in anhydrous dichloromethane (0.35 mL) was added dropwise to a solution cooled at 0 °C of the corresponding 4-oxoazetidine-2-carbaldehyde **1** (0.50 mmol) in the same solvent (0.5 mL). The reaction was placed in a 0 °C freezer overnight. The mixture was extracted with EtOAc, washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave a more polar fraction containing the corresponding carbinol and a less polar compound, its trimethylsilyl ether. TBAF (0.63 mL, 2.88 mmol, 1 M solution in THF) was added dropwise to a solution cooled at 0 °C of the appropriate trimethylsilyl ether (1.8 mmol) in anhydrous THF (140 mL). The reaction was stirred a 0 °C for 30 min. The mixture was extracted with EtOAc, washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the corresponding free carbinol in quantitative yield. No further purification was necessary. Spectroscopic and analytical data for some representative forms of **2** follow.[12]

Reaction between 4-Oxoazetidine-2-carbaldehyde (+)-1a and TMST. From 50 mg (0.42 mmol) of 4-oxoazetidine-2-carbaldehyde (+)-**1a** and after chromatography of the residue eluting with ethyl acetate/hexanes (1:1), two fractions were obtained. The less polar fraction contained the trimethylsilyl ether (57 mg, 60%) as a colorless oil. $[\alpha]_D$ −12.3 (*c* 1.4, $CHCl_3$). ^{1}H NMR: δ 0.00 (s, 9H), 3.37 (s, 3H), 3.56 (ddt, 1H, J = 15.4, 7.3, 1.0 Hz), 4.15 (ddt, 1H, J = 15.4, 5.1, 1.7 Hz), 4.32 (t, 1H, J = 4.9 Hz), 4.43 (d, 1H, J = 4.6 Hz), 5.00 (m, 2H), 5.12 (d, 1H, J = 5.2 Hz), 5.39 (m, 1H), 7.20 and 7.66 (d, each 1H, J = 3.2 Hz). ^{13}C NMR: δ 172.4, 167.5, 142.7, 131.0, 119.0, 118.2, 83.0, 70.8, 61.3, 59.2, 43.8, 0.0. IR ($CHCl_3$, cm^{-1}): ν 1742. MS (ES), *m/z*: 327 (M^+ + 1, 100), 326 (M^+, 30). (Anal. Calcd for $C_{14}H_{22}N_2O_3SSi$: C, 51.50; H, 6.79; N, 8.58. Found: C, 51.88; H, 6.72; N, 8.50.) The more polar fraction contained the free alcohol (24 mg, 32%) as a colorless oil. $[\alpha]_D$ −6.7 (*c* 1.9, $CHCl_3$). ^{1}H NMR: δ 3.18 (ddt, 1H, J = 15.3, 7.3, 1.2 Hz), 3.64 (s, 3H), 3.92 (m, 1H), 4.50 (dd, 1H, J = 4.9, 2.2 Hz), 4.62 (d, 1H, J = 4.9 Hz), 4.85 (m, 2H), 5.23 (t, 1H, J = 2.5 Hz), 5.29 (m, 1H), 7.23 and 7.65 (d, each 1H, J = 3.2 Hz). ^{13}C NMR: δ 170.8, 166.8, 142.3, 131.1, 119.1, 118.3, 83.4, 71.2, 61.8, 59.3, 43.9. IR ($CHCl_3$, cm^{-1}): ν 1741. MS (ES), *m/z*: 255 (M^+ + 1, 100), 254 (M^+, 20). (Anal. Calcd for $C_{11}H_{14}N_2O_3S$: C, 51.95; H, 5.55; N, 11.02. Found: C, 51.77; H, 5.49; N, 11.09.)

General Procedure for the TBS Protection of Alcohols. Preparation of Silyl Ethers (−)-2a and (−)-2b. Triethylamine (0.45 mL, 3.2 mmol) and *tert*-butyldimethylsilyl trifluoromethane sulfonate (0.50 mL, 2.4 mmol) were sequentially added dropwise via syringe to a solution of the corresponding alcohol (1.6 mmol) and a catalytic amount of 4-(dimethylamino)pyridine (DMAP) in DMF (4 mL) at 0 °C under argon. The resulting mixture was allowed to warm to room temperature and was stirred for 5 h. The crude mixture was diluted with CH_2Cl_2 (10 mL) and washed with brine (3 × 5 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave analytically pure silyl ethers **2**.

Silyl Ether (−)-2a. From 42 mg (0.16 mmol) of the corresponding alcohol, 44 mg (65%) of compound (−)-**2a** was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 2/1). $[\alpha]_D$ −13.5 (*c* 0.6, $CHCl_3$). ^{1}H NMR: δ 0.00 and 0.16 (s, each 3H), 0.96 (s, 9H), 3.43 (s, 3H), 3.69 (m, 1H), 4.26 (t, 1H, J = 4.9 Hz), 4.31 (m, 1H), 4.47 (d, 1H, J = 4.8 Hz), 5.09 (m, 2H), 5.33 (d, 1H, J = 5.1 Hz), 5.72 (m, 1H), 7.36 and 7.81 (d, each 1H, J = 3.2 Hz). ^{13}C NMR: δ 172.6, 167.6, 142.7, 131.1, 119.1, 118.4, 83.4, 71.2, 61.8, 59.3, 43.9, 25.8, 18.1, −4.5, −4.8. IR ($CHCl_3$, cm^{-1}): ν 1744. MS (ES), *m/z*: 369 (M^+ + 1, 100), 368 (M^+, 24). (Anal. Calcd for $C_{17}H_{28}N_2O_3SSi$: C, 55.40; H, 7.66; N, 7.60. Found: C, 55.68; H, 7.57; N, 7.69.)

(12) Full spectroscopic and analytical data for compounds not included in this Experimental Section are described in the Supporting Information.

General Procedure for the Synthesis of α-Alkoxy β-Lactam Acetaldehydes 3. A mixture of the corresponding ether **2** (0.30 mmol), activated 4 Å powdered molecular sieves (0.3 g), and anhydrous acetonitrile (3 mL) was stirred at room temperature (RT) for 10 min, before methyl triflate (44 μL, 0.39 mmol) was added. The suspension was stirred at RT for 15 min and then concentrated to dryness without filtering off the molecular sieves. To a suspension cooled at 0 °C of the crude *N*-methylthiazolium salt in methanol (3 mL), $NaBH_4$ (23 mg, 0.60 mmol) was added. The mixture was stirred at RT for an additional 10 min, diluted with acetone, filtered through a pad of Celite, and concentrated. A solution of the residue in dichloromethane (50 mL) was washed with water (5 mL), dried ($MgSO_4$), and concentrated under reduced pressure. To a vigorously stirred solution of the resulting thiazolidine in acetonitrile (3 mL), water (0.3 mL) was added dropwise, and then $AgNO_3$ (51 mg, 0.30 mmol) was added in one portion. The mixture was stirred at RT for 10 min, then diluted with 1 M phosphate buffer at pH 7 (10 mL) and partially concentrated to remove the organic solvent (bath temperature not exceeding 40 °C). The suspension was extracted with dichloromethane (3 × 15 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. A solution of the residue in diethyl ether (30 mL) was filtered through a pad of Celite and concentrated to afford the corresponding α-alkoxy acetaldehydes **3** as a colorless oil. The crude product was used for the next step without any further purification. Spectroscopic and analytical data for some representative forms of α-alkoxy β-lactam acetaldehydes **3** follow.

α-Alkoxy β-Lactam Acetaldehyde (+)-3a. From 130 mg (0.30 mmol) of the precursor (−)-**2a**, 50 mg (56%) of compound (+)-**3a** was obtained as a colorless oil. $[\alpha]_D$ +9.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR: δ 0.09 (s, 6H), 0.92 (s, 9H), 3.51 (s, 3H), 3.55 (dd, 1H, J = 15.5, 7.2 Hz), 3.98 (dd, 1H, J = 4.4, 3.7 Hz), 4.09 (ddt, 1H, J = 15.4, 5.5, 1.5 Hz), 4.25 (dd, 1H, J = 3.6, 0.6 Hz), 4.52 (d, 1H, J = 4.7 Hz), 5.17 (m, 2H), 5.71 (m, 1H), 9.69 (d, 1H, J = 0.6 Hz). ^{13}C NMR: δ 210.7, 166.9, 131.1, 119.2, 83.4, 74.7, 59.3, 59.2, 43.7, 25.6, 18.0, −4.6, −5.1. IR ($CHCl_3$, cm^{-1}): ν 1760, 1746. MS (ES), *m/z*: 314 (M^+ + 1, 100), 313 (M^+, 15). (Anal. Calcd for $C_{15}H_{27}NO_4Si$: C, 57.47; H, 8.68; N, 4.47. Found: C, 57.66; H, 8.60; N, 4.53.)

General Procedure for the Synthesis of Cycloadducts 5. A solution of the appropriate α-alkoxy β-lactam acetaldehyde **3** (1.00 mmol) in dichloromethane (7 mL) was added dropwise to a stirred solution of 4 Å molecular sieves (2.0 g) and the corresponding α-amino ester (1.50 mmol) in dichloromethane (3 mL) at room temperature. After being stirred for 2 h at room temperature, the mixture was filtered through a plug of Celite. The solvent was removed under reduced pressure, giving in quantitative yield imines **4**. The crude product was used for the next step without any further purification. To a solution of the appropriate imine **4** (1.00 mmol) in toluene (6 mL) were sequentially added silver acetate (1.20 mmol), the dipolarophile (*N*-methylmaleimide, *N*-phenylmaleimide, methyl acrylate, and dimethyl fumarate) (1.50 mmol), and triethylamine (1.20 mmol), and the reaction mixture was stirred at room temperature for 40 h. Saturated aqueous NH_4Cl (1 mL) was added, and the mixture was partitioned between dichloromethane and water. The organic extract was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave analytically pure compounds **5**. Spectroscopic and analytical data for some representative pure forms of **5** follow.

Cycloadduct (+)-5a. From 50 mg (0.16 mmol) of the α-alkoxy β-lactam acetaldehyde (+)-**3a**, 43 mg (57%) of compound (+)-**5a** was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 2/1). $[\alpha]_D$ +15.4 (*c* 1.7, $CHCl_3$). ^{1}H NMR: δ 0.00 and 0.10 (s, each 3H), 0.73 (s, 9H), 2.35 (m, 2H), 2.52 (br s, 1H), 2.88 (m, 1H), 3.39 (dd, 1H, J = 9.7, 6.6 Hz), 3.54 (s, 3H), 3.59 (m, 1H), 3.61 and 3.74 (s, each 3H), 3.80 (m, 1H), 3.85 (dd, 1H, J = 4.9, 1.9 Hz),

3.94 (dd, 1H, J = 9.7, 1.9 Hz), 4.28 (ddt, 1H, J = 15.4, 4.1, 1.7 Hz), 4.33 (d, 1H, J = 4.9 Hz), 5.16 (m, 2H), 5.73 (m, 1H). ^{13}C NMR: δ 173.8, 173.4, 167.6, 132.1, 118.6, 83.2, 69.9, 67.5, 59.0, 58.9, 58.1, 52.2, 51.7, 44.7, 44.1, 33.6, 26.3, 18.5, −3.8, −3.9. IR ($CHCl_3$, cm^{-1}): ν 3334, 1750, 1736. MS (ES), *m/z*: 471 (M^+ + 1, 100), 470 (M^+, 22). (Anal. Calcd for $C_{22}H_{38}N_2O_7Si$: C, 56.14; H, 8.14; N, 5.95. Found: C, 56.35; H, 8.07; N, 5.88).

Sodium Methoxide-Promoted Reaction of 2-Azetidinone-Tethered Prolines. General Procedure for the Preparation of Indolizidinone Amino Esters 7. Sodium methoxide (108.3 mg, 2.0 mmol) was added in portions at 0 °C to a solution of the appropriate 2-azetidinone-tethered proline (0.50 mmol) in methanol (10 mL). The reaction was stirred at room temperature until complete disappearance of the starting material (TLC), and then water was added (1 mL). The methanol was removed under reduced pressure, and the aqueous residue was extracted with ethyl acetate (10 × 3 mL). The organic extract was washed with brine and dried over $MgSO_4$, and the solvent was removed under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixtures gave analytically pure compounds **7**.

Indolizidinone Amino Ester (+)-7a. From 30 mg (0.06 mmol) of the cycloadduct (+)-**5a**, 16 mg (55%) of compound (+)-**7a** was obtained as a colorless oil after purification by flash chromatography (hexanes/ethyl acetate, 2/1). $[\alpha]_D$ +33.6 (*c* 0.9, $CHCl_3$). ^{1}H NMR: δ 0.14 (br s, 6H), 0.94 (s, 9H), 2.07 (ddd, 1H, J = 13.1, 9.7, 7.1 Hz), 2.46 (ddd, 1H, J = 13.0, 8.8, 7.5 Hz), 2.79 (dt, 1H, J = 10.0, 7.1 Hz), 3.17 (d, 1H, J = 8.1 Hz), 3.55 (s, 3H), 3.65 (m, 1H), 3.71 and 3.76 (s, each 3H), 3.88 (m, 1H), 4.00 (d, 1H, J = 5.6 Hz), 4.21 (ddt, 1H, J = 15.6, 5.4, 1.2 Hz), 4.28 (dd, 1H, J = 5.8, 1.9 Hz), 4.42 (d, 1H, J = 5.2 Hz), 5.18 (m, 2H), 5.75 (m, 1H). ^{13}C NMR: δ 174.0, 173.9, 168.3, 131.5, 118.7, 83.3, 69.1, 67.3, 65.1, 59.2, 58.7, 52.4, 52.1, 45.0, 44.9, 29.8, 26.2, 18.3, −3.7, −3.8. IR ($CHCl_3$, cm^{-1}): ν 3336, 1739, 1647. MS (EI), *m/z*: 471 (M^+, 6), 186 (M^+ − 284, 100). (Anal. Calcd for $C_{22}H_{38}N_2O_7Si$: C, 56.14; H, 8.14; N, 5.95. Found: C, 55.98; H, 8.08; N, 6.01.)

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Supporting Information Available: General experimental procedures as well as spectroscopic and analytical data for compounds (+)-**1a**, (+)-**1b**, (−)-**2b**, (+)-**2c**, (+)-**3b**, (+)-**3c**, (+)-**5b**−**f**, and (+)-**7b**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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