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Diastereoselective Synthesis of β-Lactam–Oxindole Hybrids Through a Three-Component Reaction of Azetidine-2,3-diones, α-Diazo-oxindoles, and Alcohols Catalyzed by $[Rh_2(OAc)_4]$

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β-Lactam–oxindole hybrids have been synthesized in good yields in a one-pot procedure through efficient and stereoselective capture of an oxonium ylide with azetidine-2,3-diones. The reaction allows high to moderate control of stereoselectivity, depending on the 3-diazo-oxindole precursor and the hydroxylic compound used. Two new quaternary stereogenic centers were formed; the stereochemistry at the C-3 quaternary center was controlled by a bulky substituent at C-4, whereas the stereoselectivity in the adjacent second quaternary stereogenic center was controlled by the α-diazo-oxindole. The stereochemistry of both quaternary centers has been unambiguously assigned by single-crystal X-ray diffraction.

Introduction

The 3-substituted 3-hydroxy β-lactam constitutes an efficient carboxylate mimic,[1] showing auspicious activity in acyl CoA-cholesterol acyltransferase inhibition assays.[2] Furthermore, it is found in different monobactams with interesting pharmacological activities such as sulfacezin (**A**; Figure 1) and related compounds.[3] On the other hand, the 3-substituted 3-hydroxyoxindole skeleton occurs in many biologically active molecules. Among them, oxindoles with heteroatoms at the stereogenic center are a useful class of compounds in the field of medicinal chemistry, including the potent growth hormone secretagogue SM-130686 (**B**; Figure 1).[4] Owing to the significance of this structural motif, several syntheses of these compounds have been reported.[5] In particular, special attention has been focused on asymmetric versions of these compounds.[6]

Generation of oxonium ylides by rhodium(II)-catalyzed decomposition of α-diazocarbonyl compounds have been extensively used in organic chemistry.[7] In this context, Hu and co-workers have described a novel reaction involving

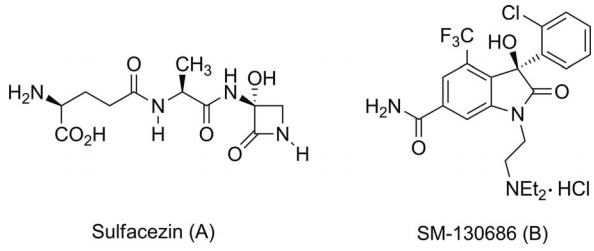
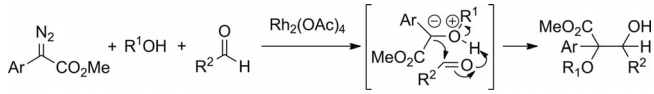


Figure 1. Representative compounds containing the 3-substituted 3-hydroxy β-lactam (A) and 3-substituted 3-hydroxyoxindole (B) skeletons.

the Rh^{II}-catalyzed aldol-type three-component reaction of methyl phenyldiazoacetate with an alcohol and an aldehyde, affording highly substituted hydroxy acid derivatives with several quaternary centers in a single step.[8] As shown in Scheme 1, an oxonium ylide, generated in situ from a rhodium carbenoid, is captured by an aldehyde (imine) to afford an aldol-type addition product.[8]



Scheme 1. Capture of oxonium ylides with aldehydes.

Following our interest in the asymmetric synthesis of nitrogenated compounds of biological significance,[9] in a previous report we described the rhodium-catalyzed synthesis of 3-hydroxy β-lactams through a three-component reaction between azetidine-2,3-diones, ethyl diazoacetate, and alcohols.[10] It was found that this multicomponent reaction proceeds in good to moderate stereoselectivity depending

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on the alcohol used. Due the importance of the 3-hydroxy-3-substituted β-lactam and 3-substituted 3-hydroxyoxindole skeletons, and because of our interest in the preparation of synthetic hybrid products combining the properties of different natural products, we thought that it could be rewarding to apply the previous methodology to the construction of β-lactam–oxindole hybrids in a single step through an efficient and stereoselective trapping of an oxonium ylide with azetidine-2,3-diones. Taking into account the current interest in using diazo-oxindoles for reaction development,[11] we were particularly interested in probing the process with these compounds.

Results and Discussion

Starting substrates, azetidine-2,3-diones **1a**–**c** were prepared both in racemic form and in optically pure form using our methodology. Enantiopure azetidine-2,3-diones (+)-**1a** and (–)-**1b** were obtained as single *cis*-enantiomers from imines of (*R*)-2,3-*O*-isopropylideneglyceraldehyde, through Staudinger reaction with acetoxyacetyl chloride in the presence of Et_3N, followed by sequential transesterification and Swern oxidation, as previously reported.[12] Racemic azetidine-2,3-dione **1c** was prepared from a tolyl-derived imine following our previous procedure.[13] Diazo-isatin **2c** was synthesized by *N*-acylation of compound **2a** with *p*-nitrobenzoyl chloride,[14] and *N*-methyl diazocarbonyl compounds **2b** and **2d**–**f** were prepared from the corresponding NH-isatin through *N*-alkylation under standard conditions (MeI, NaH, in DMF) followed by diazotization using a modification of Carreira's procedure (Figure 2).[14]

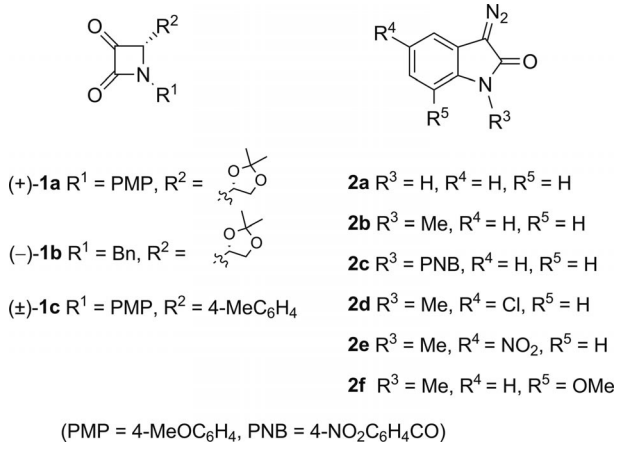


Figure 2. Starting materials used to study the multicomponent reaction.

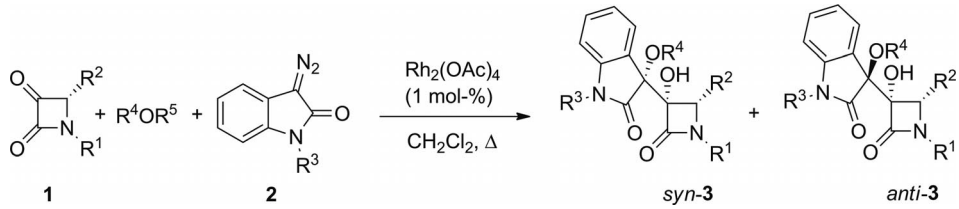
Our initial aim was to explore the reactivity of azetidine-2,3-dione **1a** as a model system for the study of the three-component reaction with alcohols. Thus, reaction of **1a** in the presence of 1.2 equivalents of 3-diazo-oxindole **2a** and 1.2 equivalents of methanol under rhodium catalysis (1 mol-%) afforded a complex reaction mixture. However, after purification by flash chromatography, compound **3a** was isolated as a single isomer in low yield (32%). Probably, the presence of the highly reactive NH bond, which forms an ylide intermediate after attack of the metal carbene to the lone pair of electrons on the heteroatom, is responsible for the formation of the complex mixture. Thus, our next experiments examined the multicomponent reaction using *N*-methyl-protected 3-diazo-oxindole **2b**. Reaction of **1a** in the presence of **2b** (1 equiv.), methanol (1.2 equiv.) and $[Rh_2(OAc)_4]$ (1 mol-%), cleanly afforded β-lactam–oxindole hybrid **3b** with moderate diastereoselectivity (*syn*/*anti*, 85:15) in good yield (89%). Fortunately, both isomers could be separated by flash chromatography. When azetidine-2,3-diones (–)-**1b** and (±)-**1c** were used instead of α-keto β-lactam **1a**, the reactions proceeded in a similar manner, giving the corresponding β-lactam–oxindole hybrids **3c** and **3d** (Table 1, entries 3A and 4A). Treatment of azetidine-2,3-dione (+)-**1a** and diazo-oxindole **2b** with allylic alcohol, under the same conditions, afforded compound **3e** in good yield but with low diastereoselectivity (65:35; Table 1, entry 5A).

To obtain better diastereoselectivity in the three-component reaction, the next stage was to treat azetidine-2,3-diones with a more bulky diazo compound, PNB diazo-isatin **2c**. When the reaction was performed with PNB diazo-isatin and alcohol under the conditions described above, similar diastereoselectivities and yields were obtained (Table 1, entries 9A–15A). Unfortunately, in some cases, the mixture of diastereoisomers could not be separated by flash chromatography (Table 1, entries 11A, 12A, and 13A–15A). To our delight, when titanium(IV) isopropoxide was used instead of alcohols,[15] the corresponding β-lactam–oxindole hybrids **3** were obtained in higher diastereoselectivities and with moderate to good yields (Table 1, entries 6B–8B and 13B–15B). In view of these results, we explored the role of titanium(IV) isopropoxide in influencing the diastereoselectivity of the reaction by adding a catalytic amount (20 mol-%) into the reaction of ketone **1a**, diazo-oxindole **2c**, and *i*PrOH. Thus, the expected compound **3m** was obtained as a mixture *syn*/*anti* (86:14) in 73% yield. On the other hand, when the reaction was performed under the same conditions using MeOH instead *i*PrOH, a 75:25 mixture of **3i** (*syn*/*anti* = 80:20; 52% yield) and **3m** (*syn*/*anti* >*95*:5; 4% yield) was obtained. The results obtained seem to indicate that both reagents, alcohol, and titanium(IV) isopropoxide react independently and that the use of a catalytic amount of $[Ti(iPrO)_4]$ does not control the diastereoselectivity in the reaction of alcohols.

In all reactions tested, a small amount of the insertion product, formed from reaction of 3-diazo-oxindole and the corresponding alcohol, was detected in 20 to 50 mol-% by ^1H NMR analysis of the crude product. However, when the reaction was carried out by slow addition of the 3-diazo-oxindole, a dramatic reduction in the amount (5–8 mol-%) of the insertion compound was observed.

Interestingly, the PNB group was easily removed by treatment of compound **3i** with sodium methoxide in methanol at –45 °C, affording β-lactam–oxindole hybrid **3a** in 58% yield (Scheme 2). Thus, the characterization data and

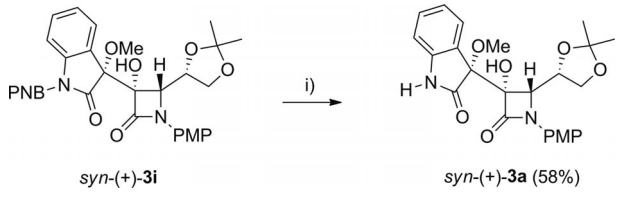
Table 1. Rh^{II}-catalyzed aldol-type three-component reaction of azetidine-2,3-diones **1a**–**c**.



Entry[a]	Substrate	R^1	R^2	R^3	R^4	Reagent	*t* [h][c]	Product	*syn*/*anti*[e]	Yield [%]
1A	(+)-**1a**	PMP	Diox[b]	H	Me	MeOH	6	**3a**	–[d]	32[f]
2A	(+)-**1a**	PMP	Diox[b]	Me	Me	MeOH	21	**3b**	85:15	76:13[g]
3A	(–)-**1b**	Bn	Diox[b]	Me	Me	MeOH	23	**3c**	60:40	50:33[g]
4A	(±)-**1c**	PMP	4-MeC_6H_4	Me	Me	MeOH	23	**3d**	83:17	73:14[g]
5A	(+)-**1a**	PMP	Diox[b]	Me	2-propenyl	allyl alcohol	21	**3e**	65:35	65:35[g]
6A	(+)-**1a**	PMP	Diox[b]	Me	*i*Pr	*i*PrOH	27	**3f**	80:20	68:16[g]
6B	(+)-**1a**	PMP	Diox[b]	Me	*i*Pr	[Ti(*i*PrO)$_4$]	5	**3f**	90:10	57[f]
7A	(–)-**1b**	Bn	Diox[b]	Me	*i*Pr	*i*PrOH	23	**3g**	60:40	46:33[g]
7B	(–)-**1b**	Bn	Diox[b]	Me	*i*Pr	[Ti(*i*PrO)$_4$]	6	**3g**	>95:5	60[f]
8A	(±)-**1c**	PMP	4-MeC_6H_4	Me	*i*Pr	*i*PrOH	23	**3h**	65:35	56:30[g]
8B	(±)-**1c**	PMP	4-MeC_6H_4	Me	*i*Pr	[Ti(*i*PrO)$_4$]	2	**3h**	>95:5	69[f]
9A	(+)-**1a**	PMP	Diox[b]	PNB	Me	MeOH	7	**3i**	80:20	77:19[g]
10A	(–)-**1b**	Bn	Diox[b]	PNB	Me	MeOH	6	**3j**	75:25	65:22[g]
11A	(±)-**1c**	PMP	4-MeC_6H_4	PNB	Me	MeOH	4	**3k**	75:25	92[h]
12A	(+)-**1a**	PMP	Diox[b]	PNB	2-propenyl	allyl alcohol	4	**3l**	86:14	96[h]
13A	(+)-**1a**	PMP	Diox[b]	PNB	*i*Pr	*i*PrOH	8	**3m**	85:15	95[h]
13B	(+)-**1a**	PMP	Diox[b]	PNB	*i*Pr	[Ti(*i*PrO)$_4$]	2	**3m**	90:10	54[f]
14A	(–)-**1b**	Bn	Diox[b]	PNB	*i*Pr	*i*PrOH	6	**3n**	85:15	89[h]
14B	(–)-**1b**	Bn	Diox[b]	PNB	*i*Pr	[Ti(*i*PrO)$_4$]	2	**3n**	> 95:5	42[f]
15A	(±)-**1c**	PMP	4-MeC_6H_4	PNB	*i*Pr	*i*PrOH	4	**3o**	80:20	79[h]
15B	(±)-**1c**	PMP	4-MeC_6H_4	PNB	*i*Pr	[Ti(*i*PrO)$_4$]	2	**3o**	>95:5	71[f]

[a] "A" refers to the use of an alcohol (Method A described in the Exp. Section for the preparation of hybrids **3**) and "B" refers to the use of [Ti(*i*PrO)$_4$] (Method B described in the Exp. Section for the preparation of hybrids **3**). [b] Diox = 2,2-dimethyl-1,3-dioxolan-4-yl. [c] Reaction progress was followed by TLC analysis. [d] A complex crude material was obtained; after purification, only the *syn* isomer was isolated. [e] The ratio was determined by integration of well-resolved signals in the ^{1}H NMR spectra (300 MHz) of the crude reaction mixtures before purification. [f] Yield of pure *syn* isomer. [g] Yield of pure, isolated isomers with correct analytical and spectra data. [h] Yield of pure, isolated mixture of isomers.

the stereochemistry of compound **3a**, obtained by reaction of azetidine-2,3-dione **1a**, diazo-oxindole **2a** and methanol, was confirmed by comparison of both products.



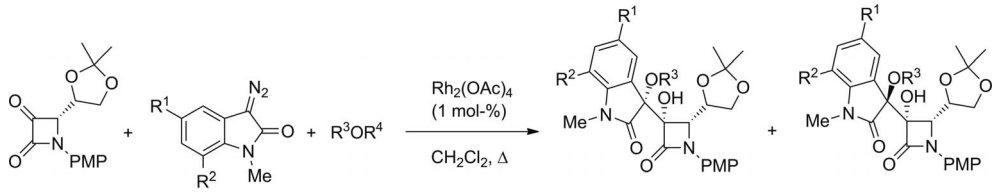
Scheme 2. Deprotection of the PNB group in compound *syn*-(+)-**3i**. *Reagents and conditions:* (i) MeONa, MeOH, –45 °C.

The scope of the three-component reaction was studied by using azetidine-2,3-dione (+)-**1a** and either methanol or [Ti(*i*PrO)$_4$] with different substituted α-diazo-oxindoles **2d**–**f** (Table 2). These experiments showed a similar behavior to reactions using α-diazo-oxindoles **2a**–**c** (see Table 1), and compounds **3p**–**r** were obtained in good yields with diastereoselectivity values in the range 65:35–85:15 when methanol was used (Table 2, entries 1–3). As expected, when the reaction was carried out with titanium(IV) isopropoxide, the diastereoselectivity of the reaction increased to 95:5–90:10, affording compounds **3s**–**u** in reasonable to excellent yields (Table 2, entries 4–6). 5-Chloro-diazo-oxindole **2d** was the least reactive α-diazo compound tested, and addition of four equivalents was necessary to achieve conversions of 73 and 80% (Table 2, entries 1 and 4, respectively).

Having established the optimal reaction conditions to carry out the multicomponent reaction with alcohols and titanium(IV) isopropoxide, our next aim was to evaluate the feasibility of the applying the process using phenols. Thus, the reaction was investigated with azetidine-2,3-dione **1a**, diazo-oxindole **2c**, and phenol. In the event, β-lactam–oxindole hybrid **3v** was isolated as a mixture of diastereoisomers (77:23) in moderate yield (50%; Scheme 3). Attempts to extend the scope of the process with other types of phenols were unsuccessful. In fact, when the reaction was tested with electron-withdrawing as well as electron-donating phenols, only complex crude reaction mixtures were observed. Unfortunately, formation of compound **3v** through this three-component methodology appears to be an isolated example and we have not yet found a reasonable explanation to account for this behavior.

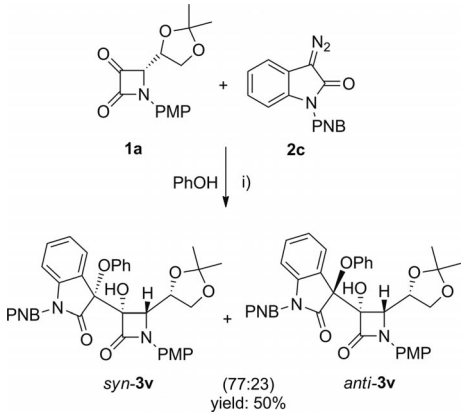
The stereoselectivity of the multicomponent reaction with azetidine-2,3-diones **1** is believed to be controlled by the bulky chiral auxiliary at C-4 and the substituent in the diazo-compound, in which one face of the carbonyl group

Table 2. Rh^{II}-catalyzed aldol-type three-component reaction of *N*-methyl-3-diazo-oxindoles **2d**–**f**.



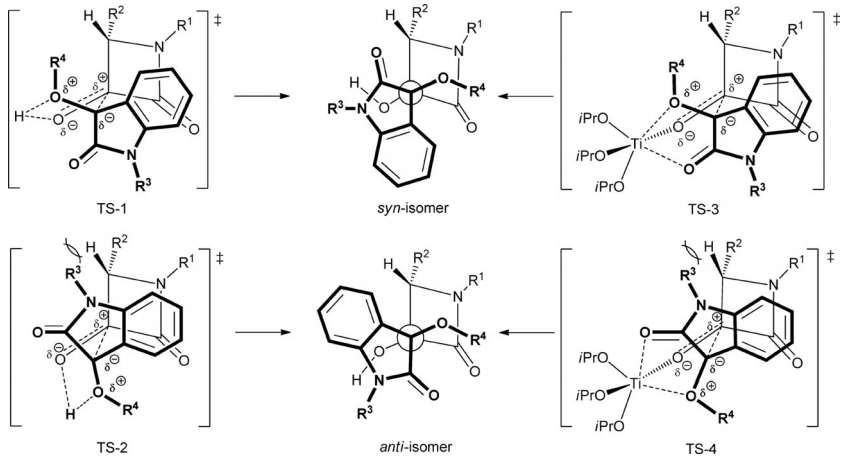
Entry	Substrate	R^1	R^2	R^3	Reagent	*t* [h][a]	Conversion [%][b]	Product	*syn*/*anti*[c]	Yield [%]
1	**2d**	Cl	H	Me	MeOH	48	73	**3p**	70:30	61:26[d]
2	**2e**	NO_2	H	Me	MeOH	23	100	**3q**	85:15	83[e]
3	**2f**	H	MeO	Me	MeOH	21	100	**3r**	65:35	57:31[d]
4	**2d**	Cl	H	*i*Pr	$[Ti(iPrO)_4]$	5	80	**3s**	90:10	63[f]
5	**2e**	NO_2	H	*i*Pr	$[Ti(iPrO)_4]$	2	100	**3t**	92:8	89[f]
6	**2f**	H	MeO	*i*Pr	$[Ti(iPrO)_4]$	2	100	**3u**	95:5	55[f]

[a] Reaction progress was followed by TLC. [b] The conversion was determined by integration of well-resolved signals in the ^{1}H NMR spectra (300 MHz) of the crude reaction mixtures before purification. [c] The ratio was determined by integration of well-resolved signals in the ^{1}H NMR spectra (300 MHz) of the crude reaction mixtures before purification. [d] Yield of pure, isolated isomers with correct analytical and spectral data. [e] Yield of pure, isolated mixture of isomers. [f] Yield of pure *syn* isomer.



Scheme 3. Multicomponent reaction of azetidine-2,3-dione **1a**, diazo-oxindole **2c**, and phenol in the presence of $[Rh_2(OAc)_4]$. *Reagents and conditions:* (i) $[Rh_2(OAc)_4]$ (1 mol-%), CH_2Cl_2, Δ.

is blocked preferentially, thus the oxonium ylide species is delivered to the less hindered face.[16] The stereochemical outcome of the overall reaction of oxonium ylides to azetidine-2,3-diones can be explained by the five-membered cyclic transitions states **TS1** and **TS2** (Scheme 4).[17] Interaction between the oxonium ylide, derived from diazo-isatin, with H-4 of the β-lactam ring would cause the reaction to take place mainly through **TS1**, in which the steric interactions are minimized compared to **TS2**, affording the *syn*-isomer. Analogously, when the reaction is performed in the presence of titanium(IV) isopropoxide, transition state **TS3** is found to be more favorable than **TS4**, because the coordination of the titanium atom to both functionalities of azetidine-2,3-dione and the oxonium ylide results in less pronounced steric interactions in **TS3** that in transition state **TS4**.



Scheme 4. Proposed transitions states used to explain the stereochemical outcome of the reaction of oxonium ylides with azetidine-2,3-diones.

The structural and configurational assignment of compounds **3** was unequivocally assigned by single-crystal X-ray analysis of compound *syn*-(+)-**3f** (Figure 3).[18]

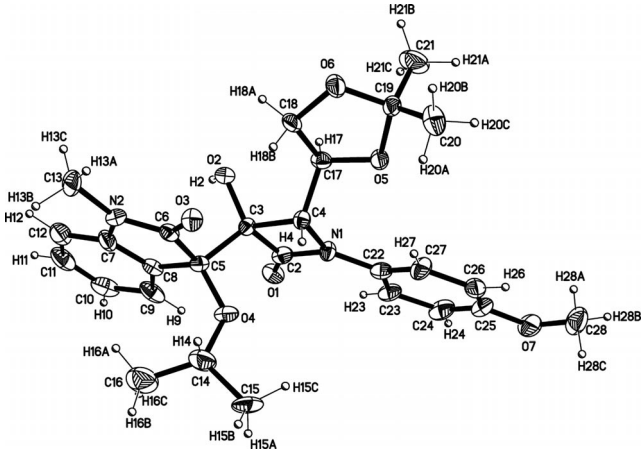


Figure 3. X-ray diffraction analysis of compound *syn*-(+)-**3f**.

Conclusions

The present study provides a rapid, stereoselective synthesis of β-lactam–oxindole hybrids through a multicomponent reaction between azetidine-2,3-diones, 3-diazo-oxindoles, and alcohols in the presence of catalytic amounts of $[Rh_2(OAc)_4]$. Interestingly, two new quaternary stereogenic centers are formed with moderate to high diastereoselectivities.

Experimental Section

General Methods: Melting points were measured with a Gallenkamp apparatus. IR spectra were recorded with a Perkin–Elmer 781 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded with a Bruker Avance-300 spectrometer. NMR spectra were recorded in $CDCl_3$ solutions, except where otherwise stated; chemical shifts are given in ppm relative to TMS (^1H, δ = 0.0 ppm), or $CDCl_3$ (^{13}C, δ = 77.0 ppm). IR spectra were recorded with a Bruker Tensor 27 spectrometer. Low- and high-resolution mass spectra were recorded with an AGILENT 6520 Accurate-Mass QTOF LC/MS spectrometer using electronic impact (EI) or electrospray modes (ES) unless otherwise stated. Specific rotation $[\alpha]_D$ is given in 10^{-1} deg cm^2 g^{-1} at 20 °C, and the concentration (*c*) is expressed in g per 100 mL. All commercially available compounds were used without further purification. Flame-dried glassware and standard Schlenk techniques were used for moisture-sensitive reactions. Flash chromatography was performed with Merck silica gel 60 (230–400 mesh). Reactions were monitored by TLC (Kiesegel 60F-254); UV light (λ = 254 nm) and a solution of phosphomolybdic acid in EtOH (1 g of phosphomolybdic acid hydrate, 100 mL) were used to develop the plates.

General Procedure for the Synthesis of β-Lactam–Oxindole Hybrids 3 Through Multicomponent Reaction

Method A: 3-Diazo-oxindole **2** (2.2 mmol) in anhydrous dichloromethane (11 mL) was added slowly over 5 h to a refluxing solution of the azetidine-2,3-dione **1** (1 mmol), the corresponding alcohol (2.2 mmol), and $[Rh_2(OAc)_4]$ (0.01 mmol) in anhydrous dichloromethane (8 mL). The reaction mixture was stirred at reflux temperature until disappearance of the starting material was observed (TLC). The reaction mixture was allowed to cool to room temperature and filtered through a short path of Celite. The solvent was removed under reduced pressure and the residue was purified by flash chromatography.

Method B: 3-Diazo-oxindole **2** (1.2 mmol) in anhydrous dichloromethane (2 mL) was added to a refluxing solution of azetidine-2,3-dione **1** (1 mmol), $[Ti(iPrO)_4]$ (1.2 mmol) and $[Rh_2(OAc)_4]$ (0.01 mmol) in anhydrous dichloromethane (8 mL). The reaction mixture was stirred at reflux temperature until disappearance of the starting material was observed (TLC). The reaction mixture was allowed to cool to room temperature, diluted with EtOAc (27 mL), washed with NH_4Cl (satd.) (18 mL), then extracted with EtOAc (2 × 18 mL). The organic extract was dried ($MgSO_4$), concentrated under reduced pressure, and the residue was purified by flash chromatography.

β-Lactam–oxindole Hybrid 3b: Method A; from azetidine-2,3-dione (+)-**1a** (39 mg, 0.13 mmol), the less polar compound *syn*-(+)-**3b** (42 mg, 76%) and the more polar compound *anti*-(+)-**3b** (14 mg, 13%) were obtained after flash chromatography (*n*-hexane/ethyl acetate, 2:1).

***syn*-(+)-3b:** White solid; m.p. 117–120 °C (*n*-hexane/ethyl acetate); $[\alpha]_D$ = +14.3 (*c* = 0.3, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.78 (dd, *J* = 7.4, 0.7 Hz, 1 H, Ar-H), 7.45 (*AA′*XX′, 2 H, Ar-H), 7.38 (td, *J* = 7.7, 1.3 Hz, 1 H, Ar-H), 7.12 (td, *J* = 7.7, 0.8 Hz, 1 H, Ar-H), 6.88 (AA′*XX′*, 2 H, Ar-H), 6.87–6.89 (m, 1 H, Ar-H), 5.16 (d, *J* = 4.1 Hz, 1 H, CH), 4.42 (td, *J* = 6.8, 4.1 Hz, 1 H, OCH), 4.15 (dd, *J* = 8.9, 6.6 Hz, 1 H, OC*H*H), 3.97 (dd, *J* = 8.9, 7.2 Hz, 1 H, OCH*H*), 3.80 (s, 3 H, Me), 3.26 (s, 3 H, Me), 3.04 (s, 3 H, Me), 1.32 (s, 3 H, Me), 1.37 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 173.9 (NC=O), 165.5 (NC=O), 156.8 (C), 145.0 (C), 130.6 (CH), 130.4 (C), 126.6 (CH), 123.3 (CH), 123.2 (C), 120.6 (CH), 114.1 (CH), 109.7 (C), 108.4 (CH), 87.2 (C), 82.3 (C), 76.0 (OCH), 66.4 (OCH_2), 60.8 (CH), 55.4 (OMe), 53.2 (OMe), 26.3 (Me), 26.2 (Me), 25.5 (Me) ppm. IR (KBr): $\tilde{\nu}$ = 3345, 1725 cm^{-1}; HRMS (ESI): calcd. for $C_{25}H_{29}N_2O_7$ $[M + H]^+$ 469.1975; found 469.1973.

***anti*-(+)-3b:** Colorless oil; $[\alpha]_D$ = +29.2 (*c* = 0.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.42 (d, *J* = 7.5 Hz, 1 H, Ar-H), 7.35 (*AA′*XX′, 2 H, Ar-H), 7.33–7.39 (m, 1 H, Ar-H), 7.00 (t, *J* = 7.5 Hz, 1 H, Ar-H), 6.90 (d, *J* = 7.9 Hz, 1 H, Ar-H), 6.76 (AA′*XX′*, 2 H, Ar-H), 4.41 (q, *J* = 7.1 Hz, 1 H, CH), 4.38 (s, 1 H, OH), 4.20 (dd, *J* = 9.1, 6.7 Hz, 1 H, OCH*H*), 3.92 (d, *J* = 7.4 Hz, 1 H, CH), 3.76 (s, 3 H, Me), 3.70 (dd, *J* = 9.1, 6.4 Hz, 1 H, OC*H*H), 3.21 (s, 3 H, Me), 3.13 (s, 3 H, Me), 1.37 (s, 3 H, Me), 1.29 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 172.8 (NC=O), 163.7 (NC=O), 156.6 (C), 144.3 (C), 131.0 (CH), 130.0 (C), 126.2 (CH), 123.4 (CH), 122.0 (C), 120.2 (CH), 113.8 (CH), 109.6 (C), 108.7 (CH), 86.4 (C), 82.6 (C), 76.6 (OCH), 66.6 (OCH_2), 62.7 (CH), 55.3 (OMe), 53.8 (OMe), 26.5 (Me), 26.3 (Me), 25.0 (Me) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3352, 1748, 1723 cm^{-1}; HRMS (ESI): calcd. for $C_{25}H_{28}N_2O_7$ $[M + Na]^+$ 491.1794; found 491.1797.

β-Lactam–Oxindole Hybrid 3c: Method A; from azetidine-2,3-dione (–)-**1b** (62 mg, 0.23 mmol), the less polar compound *syn*-(–)-**3c** (51 mg, 50%) and the more polar compound *anti*-(+)-**3c** (34 mg, 33%) were isolated after purification by flash chromatography (*n*-hexane/ethyl acetate, 3:1).

***syn*-(–)-3c:** Colorless oil; $[\alpha]_D$ = –46.4 (*c* = 0.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.83 (d, *J* = 7.0 Hz, 1 H, Ar-H),

7.37 (td, *J* = 7.8, 1.2 Hz, 1 H, Ar-H), 7.28–7.35 (m, 5 H, Ar-H), 7.12 (td, *J* = 7.6, 0.7 Hz, 1 H, Ar-H), 6.84 (d, *J* = 7.7 Hz, 1 H, Ar-H), 5.03 (d, *J* = 15.0 Hz, 1 H, NC*H*H), 4.43 (d, *J* = 3.8 Hz, 1 H, CH), 4.33–4.38 (m, 1 H, OCH), 4.21 (s, 1 H, OH), 4.12 (d, *J* = 15.1 Hz, 1 H, NC*H*H), 4.04 (dd, *J* = 9.0, 7.2 Hz, 1 H, OC*H*H), 3.80 (dd, *J* = 9.1, 4.8 Hz, 1 H, OCH*H*), 3.19 (s, 3 H, Me), 3.04 (s, 3 H, Me), 1.43 (s, 3 H, Me), 1.31 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 173.8 (NC=O), 168.0 (NC=O), 144.9 (C), 134.5 (C), 130.4 (CH), 128.7 (CH), 128.4 (CH), 127.5 (CH), 126.9 (CH), 123.42 (C), 123.38 (CH), 110.0 (*C*Me$_2$), 108.1 (CH), 88.1 (C), 82.2 (C3), 74.5 (OCH), 66.4 (OCH$_2$), 59.9 (CH), 52.8 (OMe), 44.7 (NCH$_2$), 26.21 (Me), 26.17 (Me), 24.8 (Me) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3327, 1751, 1725 cm^{-1}; HRMS (ESI): calcd. for $C_{25}H_{29}N_2O_6$ [M + H]$^+$ 453.2026; found: 453.2017.

***anti*-(+)-3c:** Colorless oil; $[\alpha]_D$ = +47.8 (*c* = 0.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.45 (dd, *J* = 7.4, 0.7 Hz, 1 H, Ar-H), 7.36 (td, *J* = 7.7, 1.2 Hz, 1 H, Ar-H), 7.10–7.18 (m, 3 H, Ar-H), 7.04 (td, *J* = 7.7, 0.7 Hz, 1 H, Ar-H), 6.84–6.86 (d, *J* = 7.2 Hz, 2 H, Ar-H), 6.84 (d, *J* = 7.6 Hz, 1 H), 4.69 (d, *J* = 14.9 Hz, 1 H, NC*H*H), 4.35–4.31 (m, 1 H, CH), 4.14 (br. s, 1 H, OH), 4.10 (d, *J* = 14.8 Hz, 1 H, NCH*H*), 4.06 (dd, *J* = 9.2, 6.6 Hz, 1 H, OC*H*H), 3.51 (dd, *J* = 9.2, 5.4 Hz, 1 H, OCH*H*), 3.19 (s, 3 H, Me), 3.12 (s, 3 H, Me), 3.03 (d, *J* = 8.3 Hz, 1 H, CH), 1.10 (s, 3 H, Me), 1.26 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 173.0 (NC=O), 165.9 (NC=O), 144.5 (C), 134.9 (C), 131.0 (CH), 128.4 (CH), 128.1 (CH), 127.2 (CH), 126.3 (CH), 123.7 (CH), 121.8 (C), 109.3 (*C*Me$_2$), 108.6 (CH), 87.0 (C), 82.2 (C), 76.2 (OCH), 66.5 (OCH$_2$), 60.8 (CH), 53.7 (OMe), 44.7 (NCH$_2$), 26.3 (Me), 26.1 (Me), 25.0 (Me) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3348, 1756, 1725 cm^{-1}; HRMS (ESI): calcd. for $C_{25}H_{29}N_2O_6$ [M + H]$^+$ 453.2026; found 453.2022.

β-Lactam–oxindole Hybrid 3f: Method A; from azetidine-2,3-dione (+)-**1a** (44 mg, 0.15 mmol), the less polar compound *syn*-(+)-**3f** (50 mg, 68%) and the more polar compound *anti*-(+)-**3f** (12 mg, 16%) were obtained after flash chromatography (*n*-hexane/ethyl acetate, 3:1).

Method B: From azetidine-2,3-dione (+)-**1a** (43 mg, 0.15 mmol), the less polar compound *syn*-(+)-**3f** (43 mg, 57%) was obtained after flash chromatography (*n*-hexane/ethyl acetate, 3:1).

***syn*-(+)-3f:** White solid; m.p. 156–157 °C (*n*-hexane/ethyl acetate); $[\alpha]_D$ = +40.7 (*c* = 0.7, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.80 (d, *J* = 7.4 Hz, 1 H, Ar-H), 7.41 (*AA*′XX′, 2 H, Ar-H), 7.37 (t, *J* = 7.7 Hz, 1 H, Ar-H), 7.10 (t, *J* = 7.2 Hz, 1 H, Ar-H), 6.88 (AA′*XX*′, 2 H, Ar-H), 6.86 (d, *J* = 7.6 Hz, 1 H, Ar-H), 5.19 (d, *J* = 3.8 Hz, 1 H, CH), 4.45 (td, *J* = 7.1, 3.8 Hz, 1 H, CH), 4.37 (br. s, 1 H, OH), 4.16 (dd, *J* = 8.8, 6.7 Hz, 1 H, OC*H*H), 3.95 (dd, *J* = 8.7, 7.2 Hz, 1 H, OCH*H*), 3.81 (s, 3 H, OMe), 3.48 (sept, *J* = 6.1 Hz, 1 H, C*H*Me$_2$), 3.25 (s, 3 H, Me), 1.37 (s, 3 H, Me), 1.32 (s, 3 H, Me), 1.04 (d, *J* = 6.1 Hz, 3 H, CH*Me*$_2$), 0.86 (d, *J* = 6.1 Hz, 3 H, CH*Me*$_2$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 175.0 (NC=O), 166.1 (NC=O), 156.7 (C), 144.5 (C), 130.5 (C), 130.3 (CH), 126.8 (CH), 124.6 (C), 123.0 (CH), 120.6 (CH), 114.1 (CH), 109.7 (*C*Me$_2$), 108.3 (CH), 87.8 (C), 81.0 (C), 75.8 (OCH), 69.6 (*C*HMe$_2$), 66.4 (OCH$_2$), 60.8 (CH), 55.4 (OMe), 26.3 (Me), 26.2 (Me), 25.5 (Me), 23.8 (Me), 23.1 (Me) ppm. IR (KBr): $\tilde{\nu}$ = 3347, 1723 cm^{-1}; HRMS (ESI): calcd. for $C_{27}H_{33}N_2O_7$ [M + H]$^+$ 497.2288; found 497.2285.

***anti*-(+)-3f:** Colorless oil; $[\alpha]_D$ = +8.5 (*c* = 0.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.43 (d, *J* = 7.3 Hz, 1 H, Ar-H), 7.36 (*AA*′XX′, 2 H, Ar-H), 7.32–7.37 (m, 1 H, Ar-H), 6.97 (t, *J* = 7.2 Hz, 1 H, Ar-H), 6.89 (d, *J* = 8.2 Hz, 1 H, Ar-H), 6.76 (AA′*XX*′, 2 H, Ar-H), 4.37–4.44 (m, 1 H, OCH), 4.22 (dd, *J* = 9.1, 6.6 Hz, 1 H, OC*H*H), 4.18 (s, 1 H, OH), 3.86 (d, *J* = 7.6 Hz, 1 H, CH), 3.76 (s, 3 H, OMe), 3.74 (dd, *J* = 9.0, 6.4 Hz, 1 H, OCHH), 3.45 (sept, *J* = 6.1 Hz, 1 H, C*H*Me$_2$), 3.22 (s, 3 H, Me), 1.29 (s, 3 H, Me), 1.16 (d, *J* = 6.1 Hz, 3 H, CH*Me*$_2$), 1.05 (d, *J* = 6.0 Hz, 3 H, CH*Me*$_2$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 173.7 (NC=O), 163.7 (NC=O), 156.5 (C), 144.0 (C), 130.8 (CH), 130.2 (C), 126.5 (CH), 123.2 (C, CH), 120.0 (CH), 113.8 (CH), 109.5 (*C*Me$_2$), 108.6 (CH), 86.5 (C), 81.9 (C), 76.8 (OCH), 70.8 (*C*HMe$_2$), 66.7 (OCH$_2$), 62.8 (CH), 55.4 (OMe), 26.6 (Me), 26.3 (Me), 25.1 (Me), 23.9 (Me), 23.2 (Me) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3362, 1734 cm^{-1}; HRMS (ESI): calcd. for $C_{27}H_{33}N_2NaO_7$ [M + Na]$^+$ 519.2107; found 519.2112.

β-Lactam–oxindole Hybrid 3i: Method A; from azetidine-2,3-dione (+)-**1a** (54 mg, 0.19 mmol), the less polar compound *syn*-(+)-**3i** (82 mg, 77%) and the more polar compound *anti*-(–)-**3i** (21 mg, 19%) were isolated after purification by flash chromatography (*n*-hexane/ ethyl acetate, 4:1).

***syn*-(+)-3i:** White solid; m.p. 142–144 °C (*n*-hexane/ethyl acetate); $[\alpha]_D$ = +182.0 (*c* = 0.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.33 (*AA*′XX′, 2 H, Ar-H), 7.97 (d, *J* = 7.4 Hz, 1 H, Ar-H), 7.95 (AA′*XX*′, 2 H, Ar-H), 7.89 (dd, *J* = 7.6, 0.9 Hz, 1 H, Ar-H), 7.50 (td, *J* = 7.9, 1.3 Hz, 1 H, Ar-H), 7.40 (*AA*′XX′, 2 H, Ar-H), 7.35 (td, *J* = 7.6 Hz, 1 H, Ar-H), 6.90 (AA′*XX*′, 2 H, Ar-H), 5.05 (d, *J* = 3.4 Hz, 1 H, CH), 4.57 (s, 1 H, OH), 4.31 (td, *J* = 6.7, 3.4 Hz, 1 H, OCH), 4.11 (dd, *J* = 8.8, 6.6 Hz, 1 H, OC*H*H), 3.87 (dd, *J* = 8.8, 6.9 Hz, 1 H, OCH*H*), 3.81 (s, 3 H, Me), 3.11 (s, 3 H, Me), 1.37 (s, 3 H, Me), 1.34 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 175.4 (NC=O), 166.7 (NC=O), 164.8 (NC=O), 157.2 (C), 150.1 (C), 141.2 (C), 139.7 (C), 131.1 (CH), 130.0 (C, CH), 126.9 (CH), 125.9 (CH), 123.5 (CH), 122.7 (C), 120.8 (CH), 115.1 (CH), 114.3 (CH), 110.2 (*C*Me$_2$), 87.9 (C), 82.9 (C), 75.5 (OCH), 66.2 (OCH$_2$), 60.4 (CH), 55.4 (OMe), 57.8 (OMe), 26.1 (Me), 25.6 (Me) ppm. IR (KBr): $\tilde{\nu}$ = 3268, 1757, 1711 cm^{-1}; HRMS (ESI): calcd. for $C_{31}H_{30}N_3O_{10}$ [M + H]$^+$ 604.1931; found 604.1926.

***anti*-(–)-3i:** Colorless oil; $[\alpha]_D$ = –152.3 (*c* = 0.4, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.98 (d, *J* = 8.0 Hz, 1 H, Ar-H), 7.71 (dd, *J* = 7.6, 0.9 Hz, 1 H, Ar-H), 7.60 (*AA*′XX′, 2 H, Ar-H), 7.53–7.58 (m, 1 H, Ar-H), 7.51 (AA′*XX*′, 2 H, Ar-H), 7.40 (*AA*′XX′, 2 H, Ar-H), 7.37 (td, *J* = 7.6, 0.9 Hz, 1 H, Ar-H), 6.95 (AA′*XX*′, 2 H, Ar-H), 4.93 (d, *J* = 5.0 Hz, 1 H, CH), 4.50 (q, *J* = 6.1 Hz, 1 H, OCH), 4.27 (s, 1 H, OH), 4.19 (dd, *J* = 8.8, 6.8 Hz, 1 H, OC*H*H), 3.96 (dd, *J* = 9.0, 6.6 Hz, 1 H, OCH*H*), 3.92 (s, 3 H, Me), 3.13 (s, 3 H, Me), 1.38 (s, 3 H, Me), 1.35 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 173.7 (NC=O), 166.9 (NC=O), 163.3 (NC=O), 157.6 (C), 149.7 (C), 140.2 (C), 139.2 (C), 131.4 (CH), 129.6 (C), 129.5 (CH), 127.2 (CH), 125.8 (CH), 123.3 (CH), 122.4 (C), 120.7 (CH), 115.6 (CH), 114.5 (CH), 110.3 (CMe$_2$), 86.8 (C), 83.3 (C), 75.8 (OCH), 66.4 (OCH$_2$), 60.9 (CH), 55.5 (OMe), 53.8 (OMe), 26.3 (Me), 25.2 (CH$_3$) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3361, 1759, 1706 cm^{-1}; HRMS (ESI): calcd. for $C_{31}H_{29}N_3NaO_{10}$ [M + Na]$^+$ 626.1751; found 626.1748.

β-Lactam–Oxindole Hybrid 3v: Method A; from azetidine-2,3-dione (+)-**1a** (52 mg, 0.18 mmol), an inseparable mixture of *syn*/*anti* isomers (ratio 77:23, 60 mg, 50%) was obtained after flash chromatography (*n*-hexane/ethyl acetate, 3:1).

***syn*-3v:** Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.25 (*AA*′XX′, 2 H, Ar-H), 8.07 (d, *J* = 6.9 Hz, 1 H, Ar-H), 7.90 (d, *J* = 8.2 Hz, 1 H, Ar-H), 7.64 (AA′*XX*′, 2 H, Ar-H), 7.48–7.52 (m, 1 H, Ar-H), 7.45 (*AA*′XX′, 2 H, Ar-H), 7.35 (td, *J* = 7.5 Hz, 1 H, Ar-H), 7.13–7.18 (m, 2 H, Ar-H), 7.04–7.09 (m, 1 H, Ar-H), 6.93 (AA′*XX*′, 2 H, Ar-H), 6.62–6.67 (m, 2 H, Ar-H), 5.32 (d, *J* =

2.6 Hz, 1 H, CH), 4.70 (s, 1 H, OH), 4.37 (td, *J* = 6.7, 2.7 Hz, 1 H, OCH), 4.12 (dd, *J* = 9.0, 6.0 Hz, 3 H, OC*H*H), 3.92 (dd, *J* = 9.4, 6.4 Hz, 1 H, OCH*H*), 3.82 (s, 3 H, Me), 1.36 (s, 3 H, Me), 1.35 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 173.8 (NC=O), 166.6 (NC=O), 164.9 (NC=O), 157.3 (C), 154.3 (C), 150.0 (C), 140.5 (C), 139.4 (C), 131.3 (CH), 130.0 (CH), 129.9 (C), 129.6 (CH), 127.4 (CH), 126.1 (CH), 124.5 (CH), 123.8 (C), 123.4 (CH), 120.8 (CH), 120.2 (CH), 114.9 (CH), 114.6 (CH), 110.3 (*C*Me$_2$), 88.3 (C), 83.2 (C), 75.3 (C), 66.1 (OCH$_2$), 60.4 (C), 55.4 (OMe), 26.0 (Me), 25.6 (Me) ppm. HRMS (ESI): calcd. for $C_{36}H_{31}N_3O_{10}$ $[M + H]^+$ 665.2082; found 665.2100.

Deprotection of the PNB Group in *syn*-(+)-3i. Synthesis of the β-Lactam–Oxindole *syn*-(+)-3a: Sodium methoxide (3.5 mg, 0.06 mmol) was added to a well-stirred solution of *syn*-(+)-**3i** (32 mg, 0.05 mmol) in MeOH (1.3 mL) at –45 °C. After 15 min, brine (2.5 mL) was added and the methanol was removed under reduced pressure. The mixture was extracted with EtOAc (5 × 5 mL), dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (*n*-hexane/ethyl acetate, 1:1) to give pure *syn*-(+)-**3a** (14 mg, 58%). White solid; m.p. 126–128 °C (*n*-hexane/ethyl acetate); $[\alpha]_D$ = +50.9 (*c* = 0.6, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.87 (br. s, 1 H, NH), 7.78 (d, *J* = 7.4 Hz, 1 H, Ar-H), 7.47 (*AA′*XX′, 2 H, Ar-H), 7.31 (td, *J* = 7.7, 1.2 Hz, 1 H, Ar-H), 7.11 (td, *J* = 7.6, 0.9 Hz, 1 H, Ar-H), 6.89 (AA′*XX′*, 2 H, Ar-H), 6.88 (d, *J* = 7.7 Hz, 1 H, Ar-H), 5.11 (d, *J* = 4.2 Hz, 1 H, CH), 4.40–4.46 (m, 1 H, CH), 4.40 (br. s, 1 H, OH), 4.15 (dd, *J* = 8.8, 6.6 Hz, 1 H, OC*H*H), 3.92 (dd, *J* = 8.8, 7.2 Hz, 1 H, OC*H*H), 3.81 (s, 3 H, Me), 3.11 (s, 3 H, Me), 1.37 (s, 3 H, Me), 1.33 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 175.6 (NC=O), 165.5 (NC=O), 156.9 (C), 142.0 (C), 130.7 (CH), 130.4 (C), 127.1 (CH), 123.5 (C), 123.4 (CH), 120.7 (CH), 114.2 (CH), 110.3 (CH), 109.8 (*C*Me$_2$), 87.1 (C), 82.6 (C), 76.0 (OCH), 66.4 (OCH$_2$), 60.8 (CH), 55.4 (OMe), 33.4 (OMe), 26.2 (Me), 25.5 (Me) ppm. IR (KBr): $\tilde{\nu}$ = 3362, 1731 cm^{-1}; HRMS (ESI): calcd. for $C_{24}H_{27}N_2O_7$ $[M + H]^+$ 455.1818; found 455.1818.

Supporting Information (see footnote on the first page of this article): Full spectroscopic and analytical data for compounds not included in the Exp. Section above are described. Characterization data and experimental procedures for compounds **2**, **3d**, **3e**, **3g**, **3h** and **3j**–**u**, as well as X-ray data for compound *syn*-(+)-**3f**, and copies of NMR spectra for all new compounds are provided.

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