Polyfunctionalized Pyrrolidines by Stereoselective 1,3-Dipolar Cycloaddition of Azomethine Ylides to Chiral Enones

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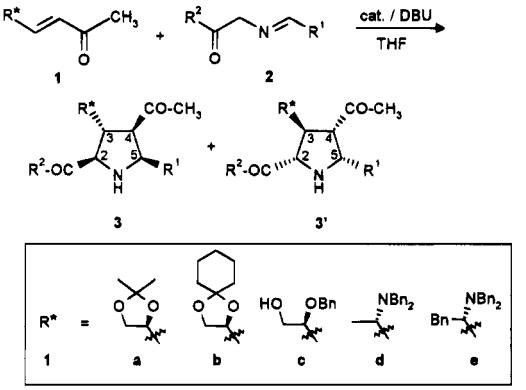
The cycloaddition reactions of chiral α,β-unsaturated ketones substituted by alkoxy or amino groups in the γ-position to azomethine ylides (obtained from glycine imines) were investigated in the presence of a base, LiBr and AgOAc. High regioselectivities were observed in most cases, resulting in the formation of a single diastereomer, particularly if a DBU/AgOAc catalyst system was employed. The influence of reaction conditions and olefin structure on the stereoselectivity of the reaction was investigated, and models rationalizing stereocontrol are proposed. In addition, an interesting deconjugation reaction of acetals derived from γ,δ-dihydroxy α,β-unsaturated enones or esters is described.

Introduction

The dipolar cycloaddition of an azomethine ylide to an alkene is a very useful synthetic method for the synthesis of pyrrolidines. Two carbon–carbon bonds are formed in a single operation, usually with a high degree of regioselectivity, while up to four new stereocenters are created, often in a highly stereoselective manner.[1,2] Therefore, this method has also been used as an effective tool for the assembly of biologically relevant highly functionalized proline derivatives.

It has been shown by the groups of Grigg[3] and Kanemasa[4] that azomethine ylides can be conveniently prepared from acceptor-substituted imines by deprotonation in the presence of a metal salt and a tertiary amine. The resulting stabilized metalloazomethine ylides occasionally provided high levels of stereocontrol in asymmetric syntheses.[4,5] For example, Cinquini et al.[6] have recently reported a cycloaddition of azomethine ylides derived from glycine imines to enantiomerically pure *E*-α,β-unsaturated esters with an alkoxy substituent in the γ-position. High regioselectivity and diastereomeric ratios ranging from 75:25 to 95:5 were observed if a combination of DBU/LiBr was used for the ylide generation. To the best of our knowledge, only esters were employed as dipolarophiles based on γ-chiral α,β-unsaturated carbonyl compounds in dipolar cycloadditions with azomethine ylides.

Scheme 1



In a preliminary communication, we reported on the application of this reaction to chiral α,β-unsaturated ketones **1** bearing alkoxy or amino substituents in the γ-position.[7] In the present paper, we report on experimental details and spectroscopic data as well as on investigations of the influence of catalyst, temperature, and chiral controller on the stereochemical outcome of these reactions. The extension of the substituent patterns of the imine component **2** and interesting deconjugation reactions of enones **1** with an acetal moiety are also included. Models of transition states are shown to rationalize the observed stereochemistry.

Results and Discussion

The chiral α,β-unsaturated enones **1**[7,8] were reacted with azomethine ylides under various conditions (Scheme 1). The metalloazomethine ylides (see Figure 3) were generated in THF from the corresponding azomethines **2** with DBU in the presence of a metal salt (LiBr or AgOAc). Whereas LiBr gave diastereomeric mixtures in most cases even at low temperatures, the reactions with AgOAc (0.15 equiv, 1:1 ratio of imine **2** and dipolarophile **1**) proceeded with remarkable regio- and diastereoselectivity (see Table 1). Only one detectable stereoisomer (according to ^1H and ^{13}C NMR spectroscopy) was obtained at room temperature in most cases.

[⊗] Abstract published in *Advance ACS Abstracts,* July 15, 1995.

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(8) Galley, G.; Pätzel, M.; Jones, P. G. *Tetrahedron* **1995**, *51*, 1631.

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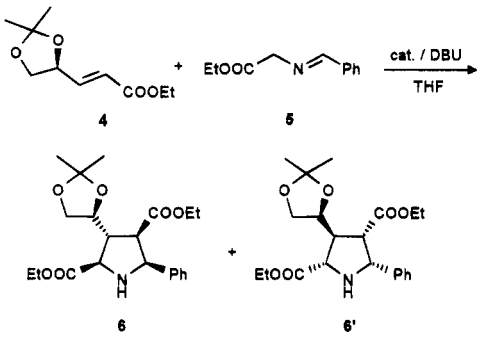
Table 1. Synthesis of Pyrrolidines 3 from Enones 1 and Glycine Imines 2

entry	enone	R^1	R^2	product	metal salt	temp	time (h)	yield (%)	3:3′
1	**1a**	Ph	OEt	**3a**	LiBr	rt	2	63	70:30
2	**1a**	Ph	OEt	**3a**	AgOAc	rt	2	90	95:5
3	**1a**	Ph	OEt	**3a**	LiBr	−78 °C	4	53	85:15
4	**1a**	Ph	OEt	**3a**	AgOAc	−78 °C	4	91	>95:5
5	**1a**	3-Py	OEt	**3b**	LiBr	rt	2	60	75:25
6	**1a**	3-Py	OEt	**3b**	AgOAc	rt	2	91	>95:5
7	**1a**	*p*-MeOPh	OEt	**3c**	AgOAc	rt	2	82	90:10
8	**1a**	Ph	O-*i*-Bu	**3d**	AgOAc	rt	2	88	87:13
9	**1a**	Ph	O-*i*-Bu	**3d**	AgOAc	−78 °C	4	90	>95:5
10	**1a**	Ph	NH_2	**3e**	AgOAc	rt	3	73	72:28
11	**1a**	Ph	NH_2	**3e**	AgOAc	−78 °C	8	72	81:19
12	**1b**	Ph	OEt	**3f**	AgOAc	rt	2	96	92:8
13	**1b**	Ph	OEt	**3f**	AgOAc	−78 °C	4	95	>95:5
14	**1b**	3-Py	OEt	**3g**	AgOAc	rt	2	98	95:5
15	**1c**	Ph	OEt	**3h**	AgOAc	rt	2	78	>95:5
16	**1d**	Ph	OEt	**3i**	LiBr	rt	2	65	>95:5
17	**1d**	Ph	OEt	**3i**	AgOAc	rt	2	88	>95:5
18	**1d**	3-Py	OEt	**3j**	AgOAc	rt	2	76	>95:5
19	**1e**	Ph	OEt	**3k**	AgOAc	rt	2	94	>95:5
20	**1e**	3-Py	OEt	**3l**	AgOAc	rt	2	98	>95:5
21	**1e**	C_6H_{11}	OEt	**3m**	AgOAc	rt	6	96	85:15

Table 2. Pyrrolidines 6 from α,β-Unsaturated Ester 4

entry	metal salt	temp	time (h)	yield (%)	6:6′
1	LiBr	rt	2	57	75:25
2	AgOAc	rt	2	77	85:15
3	LiBr	−78 °C	4	55	90:10
4	AgOAc	−78 °C	4	87	>95:5

Scheme 2

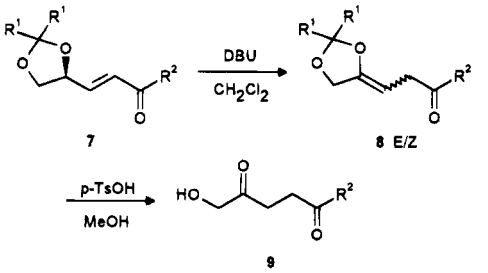


Moreover, the AgOAc/DBU system also gave higher chemical yields than LiBr/DBU. In the latter case, comparable chemical yields could only be attained by using an excess of the imine component, necessitating additional chromatographic separation. Considerable improvement of the diastereoselectivity and the chemical yield could also be attained in the reported ester series[6] (see Table 2) if the AgOAc/DBU method was applied to the cycloaddition of azomethine ylides derived from **5** and the chiral α,β-unsaturated ester **4**. As a result, it became possible to perform this reaction in excellent yield to afford a single diastereomer **6** (Scheme 2).

In further experiments, we varied the substituents in the imine component **2**. When carboxylic amides of amino acids (R^2 = NH_2) were used in metallodipole formation, the reaction was found to be slower than it was in the glycine ester series (R^2 = OEt). Only modest diastereoselectivity (dr = 81:19) was found even at −78 °C (see Table 1, entries 10 and 11). A plausible explanation is the decreased CH acidity of the amide **2** (R^2 = NH_2) as compared with that of the ester **2** (R^2 = OEt) which may result in a slower deprotonation process.

It is known that imines of aliphatic aldehydes are poor azomethine ylide precursors in the presence of lithium bromide.[3] Remarkably, the AgOAc/DBU system also allowed us to extend the cycloaddition reaction of **1** to

Scheme 3



aliphatic imines **2** (R^1 = cyclohexyl; see Table 1, entry 21). The rate of the reaction was slower, but no products of a competitive Michael reaction were observed. This corresponds with the results observed in the cycloaddition of azomethine ylides to methyl acrylate.[3b]

The influence of the chiral controller R* on the diastereoselectivity was investigated by using different enone compounds **1**. The highest stereoselectivities could be achieved with the bulky dibenzylamino substituent in the γ-position (**1d** and **1e**) or by using the enone **1c** with the γ-benzyloxy group and the unprotected terminal hydroxyl function (compare entries 2, 12, 15, 17, and 19 in Table 1).

In the course of our investigations of cycloaddition reactions of enones **1**, we sometimes observed unknown products during longer reaction times. These products were formed in the absence of both the azomethine **2** and the metal salt. Thus, stirring of the enone **1a** in the presence of DBU at room temperature for 4 days gave a complete conversion to two new products (detected by TLC). Further experiments revealed that all enones of acetal structure **1a,b** as well as the corresponding ester **4** undergo this reaction in the presence of a base such as DBU.[9] The resulting stereoisomers could be separated by column chromatography and analyzed as *E*- and *Z*-enol acetals **8** (see Scheme 3). Acidic removal of the acetal moiety afforded the known[10] 5-hydroxy-1,4-dicarbonyl compounds **9**, confirming the correctness of the structure **8** (Table 3). As a mechanism for this unusual

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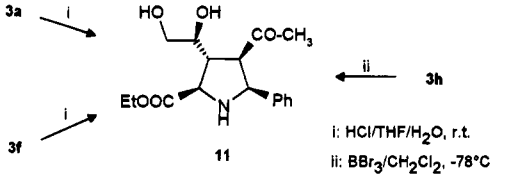
(10) (a) Stetter, H.; Mohrmann, K.-H.; Schlenker, W. *Chem. Ber.* **1981**, *114*, 581. (b) Lüond, R.; Walker, J.; Neier, R. *J. Org. Chem.* **1992**, *57*, 5005.

Table 3. Products 8 and 9 Derived from DBU-Catalyzed Isomerization

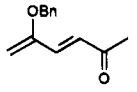
entry	7	R^1	R^2	8 (E:Z ratio)	9
1	**1a**	Me	Me	**8a** (80:20)	**9a**
2	**1b**	$(CH_2)_5$	Me	**8b** (81:19)	**9a**
3	**4**	Me	OMe	**8c** (73:27)	**9b**

Scheme 4



deconjugation process, a base-catalyzed γ-deprotonation–protonation sequence via a dienolate anion[11] is postulated.[12]

In contrast, if the enone **1c** was treated with DBU, the dienone **10** and benzyl alcohol were isolated from the reaction mixture. The formation of **10** can be rationalized



10

by an elimination of water via an E1cB process.[13]

The structural assignments for the pyrrolidine compounds **3** and **3′** were based on X-ray analyses[7] of the major isomer **3a** and **3i**. All compounds were characterized by ^1H and ^{13}C NMR spectroscopy. Proton-decoupling and $^1H-^{13}C$ correlation experiments helped to assign the signals, and NOE difference measurements allowed for the evaluation of the substitution pattern of the pyrrolidine ring. The examination of the NMR spectra (^{13}C and ^1H shifts, H–H coupling constants) supported an identical relative stereochemistry of the ring carbon atoms of all major isomers **3** (see the Experimental Section). Hence, in all compounds **3**, the relative orientation of the substituents at C2/C3 and C3/C4 is *anti* and at C4/C5 is *syn*. This stereochemical outcome is caused by the regiospecific *endo* cycloaddition of the W-shaped dipole[14] to the *E*-configured dipolarophile already observed in the ester series.[6]

The absolute configuration of products **3** derived from amino enones **1d** and **1e** can be assumed to be identical to that of **3i** (for X-ray analysis, see ref 7). X-ray analysis of compound **3a** revealed an *anti* orientation of the substituents at C3 and at the stereocenter C1′ of the chiral controller R*. In the alkoxy-substituted series of products derived from **1a–c**, the absolute configuration was determined by removal of the O protective groups of one compound from each series (Scheme 4). Acidic acetal cleavage of **3a** and **3f** as well as debenzylation of **3h** furnished the identical diol **11** characterized on the basis of NMR spectroscopic and optical rotation measure-

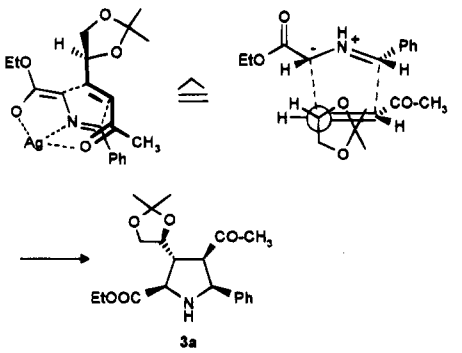
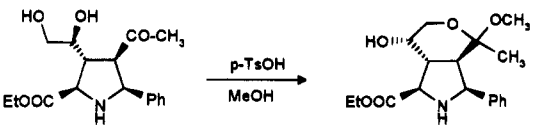


Figure 1. Model of the transition state for the formation of pyrrolidine **3a**.

Scheme 5



ments. If the acetal cleavage is conducted with *p*-toluenesulfonic acid in methanol, an interesting byproduct can be isolated. On the basis of NMR spectroscopic data (e.g. acetal C at 99.0 ppm), we concluded that the byproduct was the inner acetal **12** (see Scheme 5). An alternative five-membered acetal is less probable due to higher ring strain of the two *trans*-fused five-membered rings. The noteworthy fact that only one diastereomer of **12** appeared was certainly caused by the fixed configurations of the reacting functional groups.

On the basis of the structural assignments of **3**, the preferred stereochemical mode of attack at the diastereotopic faces of the enone system could be determined. As mentioned above, *anti* selectivity was observed in the alkoxy series. This result is in agreement with Cinquini's findings in the ester series and comparable with nitrile oxide[15a] and nitrone[15b] cycloadditions to related olefins bearing an oxygen-substituted allylic stereocenter. It can be explained by Houk's inside alkoxy effect.[16,17] As illustrated in Figure 1, the transition state for the formation of the major diastereomer **3a** involves attack of the ylide with the olefin orientated away from the most bulky alkyl moiety. The alkoxy substituent occupies the stereoelectronically favored inside position and the small H atom the crowded outside region. If the olefin were attacked from the other side, only the less stable transition structures would be possible because of unfavorable steric interactions.

Unlike the analysis of product **3a**, X-ray analysis of compound **3i** revealed *syn* orientation of the substituents at C3 and C1′. For explaining this stereochemical outcome of the cycloaddition of azomethine ylides to the amino-substituted enones **1d** and **1e**, Houk's model is

(11) Patai, S., Rapoport, Z., Eds. *The Chemistry of Enones*; Wiley Interscience: Chichester, U.K., 1989.

(12) For a related deconjugation process of unsaturated esters in Grignard reactions, see: Ibuka, T.; Taga, T.; Habashita, H.; Nakai, K.; Tamamura, H.; Fujii, N. *J. Org. Chem.* **1993**, *58*, 1207.

(13) As already observed at γ,δ-diacetoxy-substituted α,β-unsaturated aldehydes derived from sugars: Roman, E.; Serrano, J. A.; Cuellar, M. E., Marfil, A.; Galbis, J. A. *J. Carbohydr. Chem.* **1992**, *11*, 1.

(14) (a) Tsuge, O.; Kanemasa, S. *Adv. Heterocycl. Chem.* **1989**, *45*, 231. (b) Tsuge, O.; Kanemasa, S.; Yoshioka, M. *J. Org. Chem.* **1988**, *53*, 1384.

(15) (a) Jäger, V.; Müller, I.; Schohe, R.; Frey, M.; Ehrler, R.; Häfele, B.; Schröter, D. *Lect. Heterocycl. Chem.* **1985**, *8*, 79. (b) Annunziata, R.; Benaglia, M.; Cinquini, M.; Raimondi, L. *Tetrahedron* **1993**, *38*, 8629.

(16) (a) Houk, K. N.; Wu, Y.-D.; Duh, H.-Y.; Moses, S. R. *J. Am. Chem. Soc.* **1986**, *108*, 2754. (b) Houk, K. N.; Moses, S. R.; Wu, Y.-D.; Rondan, N. G.; Jäger, V.; Schohe, R.; Fronczek, F. *J. Am. Chem. Soc.* **1984**, *106*, 3880.

(17) Modified models for similar reactions were proposed by Mulzer and Reetz: (a) Mulzer, J.; Kappert, M.; Huttner, G.; Jibril, I. *Tetrahedron Lett.* **1985**, *26*, 1631. (b) Reetz, M. T.; Kayser, F.; Harms, K. *Tetrahedron Lett.* **1992**, *33*, 3453.

(18) Röhrig, D. Dissertation, University Marburg, Marburg, Germany. 1991.

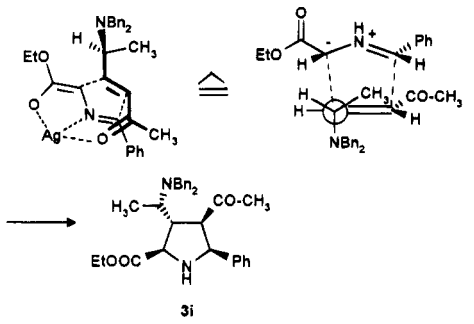


Figure 2. Model of the transition state for the formation of pyrrolidine **3i**.

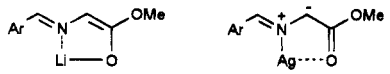


Figure 3. Formation of metallodipoles from an imine and a metal salt.

again useful. The bulky dibenzylamino group is situated in an *anti* position with respect to the incoming dipole, while the alkyl moiety (CH_3) occupies the inside position and again the small H atom adopts the crowded outside region (Figure 2). The same diastereoselection is observed in Diels–Alder reactions of dibenzylamino substituted enones[18] and may also be explained by using this model.

The application of this model to the reactions of γ-amino enones **1d** and **1e** reveals that the extent of diastereoselectivity depends on the relative size of the allylic substituents which therefore prefer specific positions. Hence, the higher diastereomeric ratio observed with enone **1d**, as compared with that of **1e**, can be explained by the higher difference in size between the dibenzylamino group on one side and the methyl group or the benzyl substituent on the other side.

As outlined above, the nature of the metal salt, i.e. the effectiveness of the complexation of both reactants, is of great importance to both the yield and the extent of diastereoselectivity. Although a comparative investigation of the suitability of silver acetate and lithium bromide in the presence of triethylamine for the generation of metallodipoles is known,[19] the reason for better catalytic activity and higher chemical yields achieved with silver acetate still remains unclear. It is possible that the nature of chelation with the azomethine ylide exerts an influence on selectivity. If mesomeric structures of the metallodipole are considered, the lithium as a hard cation should mainly interact with the carbonyl oxygen atom, whereas the soft silver cation would prefer interaction with the nitrogen (see Figure 3). In the latter case, the dipole character of the N-metallated azomethine ylide is more pronounced, thus certainly favoring the cycloaddition reaction.

It is known for the ester series that *Z*-configured alkenes do not give clean reactions with metallodipoles generated from imines in the presence of LiBr and DBU.[6] Accordingly, our attempts with *Z*-enones in the presence of AgOAc and DBU were unsuccessful and yielded only complex mixtures. One explanation for this observation might be found in the concept of 1,3-allylic strain.[20] The preferred transition state of the *E*-isomer (see Figure 1) is not favorable for the *Z*-isomer because of repulsive forces between the allylic substituents and the *Z*-orientated acetyl group. Hence, other transition states are preferred and lead to low stereoselectivity.

Experimental Section

All solvents and reagents were purchased from commercial sources and used as received, unless otherwise stated. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl prior to use. The reactions and the purity of compounds were monitored by TLC performed on precoated silica gel plates with a fluorescence indicator (Merck 60 F_{254}). Column chromatography was carried out on Merck Kieselgel 60 (0.040–0.063). NMR samples were recorded in $CDCl_3$. The chemical shifts are given in δ values relative to residual proton or carbon resonances of $CDCl_3$ (7.26 or 77.0, respectively). Optical rotations were measured using a 2 mL cell. $[\alpha]$ values are given in 10^{-1} deg cm^2 g^{-1}.

Synthesis of Enones 1. The enones were prepared by Wittig reaction according to literature procedures (**1a**,[21] **1b,c**,[8] and **1d,e**[18]) from the corresponding chiral aldehydes[22] and acetylmethylene triphenylphosphorane. The enoate **4** was purchased from Merck Co.

Preparation of Imines (2 or 5). Imines from aromatic[14b] and aliphatic[3b] aldehydes and glycine esters were prepared according to literature procedures.

Benzylidene Glycine Amide. A mixture of glycine amide (2.2 g, 20 mmol), benzaldehyde (2.1 g, 20 mmol), and triethylamine (2.0 g, 20 mmol) in 10 mL of benzene/20 mL of methanol was heated to reflux for 8 h, concentrated, and washed with 5 mL of ether (to remove unreacted benzaldehyde). The remaining solid was dissolved in CH_2Cl_2, washed with water, dried with $MgSO_4$, and evaporated until crystallization began. The white solid was collected (2.0 g, 62%): mp 140 °C; ^{1}H NMR δ 8.30 (1H, t, J = 1.3 Hz), 7.70–7.85 (2H, m), 7.40–7.25 (3H, m), 6.90 and 6.00 (1H, b), 4.26 (2H, d, J = 1.3 Hz).

Synthesis of Pyrrolidines (3 or 6). Imine **2** (0.5 mmol) was dissolved in dry THF (4 mL), and silver acetate (12 mg, 0.075 mmol) or LiBr (65 mg, 0.75 mmol) was added. The mixture was stirred for 10 min at the given temperature (see Table 1). Enone **1** or ester **4** (0.5 mmol) and DBU (91 mg, 0.6 mmol) were added, and the mixture was stirred until no starting material could be detected by TLC (2–8 h, see Table 1). Ether (15 mL) was added, the solution was extracted with saturated NH_4Cl solution, and the aqueous solution was reextracted with ether. The combined organic layers were washed with water (2 × 10 mL), dried ($MgSO_4$), and concentrated under reduced pressure.

Ethyl (2*R*,3*R*,4*R*,5*S*)-4-acetyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-5-phenylpyrrolidine-2-carboxylate (3a): ^{13}C NMR δ 209.3, 172.1, 137.6, 128.4, 127.6, 126.2, 108.9, 76.2, 68.0, 65.5, 62.7, 61.2, 58.3, 50.3, 31.2, 26.3, 25.0, 14.0; ^{1}H NMR δ 7.20–7.35 (5H, m), 4.50 (1H, d, J = 7.6 Hz), 4.24 (2H, q, J = 7.1 Hz), 4.22–4.30 (1H, m), 4.04 (1H, J = 6.5, 8.5 Hz), 3.66 (1H, d, J = 6.7 Hz), 3.57 (1H, J = 6.5, 8.5 Hz), 3.49 (1H, dd, J = 3.5, 7.6 Hz), 2.76 (1H, dt, J = 3.5, 6.5 Hz), 1.47 (3H, s), 1.39, 1.31 (3H, s), 1.27 (3H, t, J = 7.1 Hz); $[\alpha]^{20}_{546}$ −23.0 (c = 1.0, CH_2Cl_2). Anal. Calcd for $C_{20}H_{27}NO_5$ (361.43): C, 66.46; H, 7.53; N, 3.88. Found: C, 66.36; H, 7.38; N, 3.95.

Ethyl (2*S*,3*S*,4*S*,5*R*)-4-acetyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-5-phenylpyrrolidine-2-carboxylate (3a′, minor): ^{13}C NMR δ 208.8, 173.0, 138.0, 128.9, 127.8, 126.7, 109.2, 76.9, 67.0, 65.7, 62.8, 61.2, 60.3, 48.6, 31.1, 26.4, 25.0, 14.1.

Ethyl (2*R*,3*R*,4*R*,5*S*)-4-acetyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-5-(pyridin-3-yl)pyrrolidine-2-carboxylate (3b): ^{13}C NMR δ 208.9, 172.0, 149.2, 148.7, 134.2, 133.8,

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123.4, 109.1, 76.1, 68.0, 62.8, 62.7, 61.4, 57.8, 50.4, 31.6, 26.4, 25.0, 14.1; ^{1}H NMR δ 8.50 (1H, s), 8.45 (1H, d, J = 4.6 Hz), 7.57 (1H, d, J = 7.9 Hz), 7.20 (1H, dd, J = 8.1, 4.7 Hz), 4.52 (1H, d, J = 7.7 Hz), 4.23 (2H, q, J = 7.1 Hz), 4.20–4.30 (1H, m), 4.04 (1H, J = 6.6, 8.5 Hz), 3.69 (1H, d, J = 7.0 Hz), 3.57 (1H, J = 6.6, 8.5 Hz), 3.55 (1H, dd, J = 3.1, 7.7 Hz), 2.77 (1H, dt, J = 3.1, 7.0 Hz), 1.61 (3H, s), 1.39 (3H, s), 1.31 (3H, s), 1.27 (3H, t, J = 7.2 Hz); $[\alpha]^{20}_{546}$ −28.0 (c = 1.0, CH_2Cl_2). Anal. Calcd for $C_{19}H_{26}N_2O_5$ (362.42): C, 62.96; H, 7.23; N, 7.73. Found: C, 62.66; H, 7.08; N, 7.79.

Ethyl (2*R*,3*R*,4*R*,5*S*)-4-acetyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-5-(*p*-methoxyphenyl)pyrrolidine-2-carboxylate (3c): ^{13}C NMR δ 209.5, 172.2, 158.9, 129.5, 127.7, 113.7, 108.9, 76.1, 67.9, 64.9, 62.5, 61.1, 54.9, 58.2, 50.1, 31.3, 26.3, 24.9 13.9; ^{1}H NMR δ 7.18–7.38 (4H, m), 4.54 (1H, d, J = 7.7 Hz), 4.30 (2H, q, J = 7.1 Hz), 4.28–4.35 (1H, m), 4.11 (1H, J = 6.4, 8.5 Hz), 3.79 (3H, s), 3.71 (1H, d, J = 7.0 Hz), 3.63 (1H, J = 6.4, 8.5 Hz), 3.52 (1H, dd, J = 3.6, 7.7 Hz), 2.83 (1H, dt, J = 3.7, 6.2 Hz), 1.58 (3H, s), 1.43 (3H, s), 1.34 (3H, s), 1.25 (3H, t, J = 7.1 Hz), $[\alpha]^{20}_{546}$ −21.0 (c = 1.0, CH_2Cl_2). Anal. Calcd for $C_{21}H_{29}NO_6$ (391.46): C, 64.43; H, 7.47; N, 3.58. Found: C, 64.26; H, 7.18; N, 3.85.

Isobutyl (2*R*,3*R*,4*R*,5*S*)-4-acetyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-5-phenylpyrrolidine-2-carboxylate (3d): ^{13}C NMR δ 209.8, 172.6, 138.0, 128.9, 128.1, 127.0, 109.5, 76.6, 71.7, 68.4, 66.0, 63.2, 58.8, 50.8, 31.7, 28.1, 26.8, 25.4, 19.4; ^{1}H NMR δ 7.16–7.28 (5H, m), 4.50 (1H, d, J = 7.6 Hz), 4.20–4.30 (1H, m), 4.03 (1H, J = 6.5, 8.4 Hz), 3.96 (2H, d, J = 6.6 Hz), 3.67 (1H, d, J = 6.6 Hz), 3.58 (1H, J = 6.5, 8.4 Hz), 3.48 (1H, dd, J = 3.3, 7.6 Hz), 2.77 (1H, dt, J = 3.4, 6.3 Hz), 1.78 (3H, s), 1.38 (3H, s), 1.30 (3H, s), 1.89–2.02 (1H, m), 0.91 (6H, d, J = 6.7 Hz); $[\alpha]^{20}_{546}$ −29.5 (c = 1.0, CH_2Cl_2). Anal. Calcd for $C_{22}H_{31}NO_5$ (389.49): C, 67.84; H, 8.02; N, 3.59. Found: C, 67.48; H, 7.84; N, 3.43.

(2*R*,3*R*,4*R*,5*S*)-4-Acetyl-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-5-phenylpyrrolidine-2-carboxylic acid amide (3e): ^{13}C NMR δ 208.9, 176.6, 138.3, 128.5, 128.0, 126.9, 109.0, 76.7, 67.8, 64.4, 62.5, 57.1, 49.1, 31.4, 26.4, 24.9; ^{1}H NMR δ 7.18–7.45 (5H, m), 4.59 (1H, d, J = 7.7 Hz), 4.30 (1H, q, J = 6.2 Hz), 4.03, 3.61 (1H, J = 6.6, 8.5 Hz), 3.51 (1H, d, J = 6.4 Hz), 3.39 (1H, dd, J = 2.7, 7.7 Hz), 2.69 (1H, dt, J = 2.8, 6.1 Hz), 2.40 (2H, b, J = 6.7 Hz), 1.38 (3H, s), 1.37 (3H, s), 1.29 (3H, s); $[\alpha]^{20}_{546}$ −20.0 (c = 1.0, CH_2Cl_2). Anal. Calcd for $C_{18}H_{24}N_2O_4$ (332.40): C, 65.04; H, 7.28; N, 8.43. Found: C, 64.88; H, 7.44; N, 8.52.

Ethyl (2*R*,3*R*,4*R*,5*S*)-4-acetyl-3-[(1*S*)-1,2-*O*-cyclohexylideneethyl]-5-phenylpyrrolidine-2-carboxylate (3f): ^{13}C NMR δ 209.5, 172.1, 137.5, 128.5, 126.6, 127.7, 109.5, 76.0, 67.7, 65.6, 62.8, 61.2, 58.5, 50.5, 36.1, 34.5, 31.4, 25.0, 23.9, 23.7, 14.1; ^{1}H NMR δ 7.20–7.35 (5H, m), 4.57 (1H, d, J = 7.5 Hz), 4.30 (2H, q, J = 7.2 Hz), 4.25–4.33 (1H, m), 4.09 (1H, J = 6.4, 8.4 Hz), 3.74 (1H, d, J = 6.7 Hz), 3.62 (1H, J = 6.4, 8.4 Hz), 3.57 (1H, dd, J = 3.4, 7.6 Hz), 2.78 (1H, dt, J = 3.4, 6.4 Hz), 1.54 (3H, s), 1.35–1.65 (10H, m), 1.32 (3H, t, J = 7.2 Hz); $[\alpha]^{20}_{546}$ −20.0 (c = 1.0, CH_2Cl_2); MS (CI) m/z (relative intensity) 402 (M^+, 100), 401 (20), 400 (16), 304 (24), 286 (17), 191 (13), 107 (17). Anal. Calcd for $C_{23}H_{31}NO_5$ (401.50): C, 68.80; H, 7.78; N, 3.49. Found: C, 68.77; H, 7.71; N, 3.61.

Ethyl (2*R*,3*R*,4*R*,5*S*)-4-acetyl-3-[(1*S*)-1,2-*O*-cyclohexylideneethyl]-5-(pyridin-3-yl)pyrrolidine-2-carboxylate (3g): ^{13}C NMR δ 208.8, 171.9, 149.0, 148.5, 134.2, 133.8, 123.4, 109.6, 75.8, 67.6, 62.8, 62.7, 61.4, 57.9, 50.6, 36.1, 34.5, 31.6, 24.9, 23.8, 23.6, 14.1; ^{1}H NMR δ 8.55 (1H, s), 8.50 (1H, d, J = 3.9 Hz), 7.62 (1H, d, J = 8.0 Hz), 7.25 (1H, dd, J = 7.8, 4.8 Hz), 4.57 (1H, d, J = 7.6 Hz), 4.27–4.35 (1H, m), 4.27 (2H, q, J = 7.1 Hz), 4.09 (1H, J = 6.3, 8.4 Hz), 3.77 (1H, d, J = 7.0 Hz), 3.62 (1H, J = 6.3, 8.4 Hz), 3.63 (1H, dd, J = 4.1, 6.9 Hz), 2.80 (1H, dt, J = 4.0, 6.6 Hz), 1.67 (3H, s), 1.35–1.65 (10H, m), 1.31 (3H, t, J = 7.1 Hz); $[\alpha]^{20}_{546}$ −26 (c = 1.0, CH_2Cl_2). Anal. Calcd for $C_{22}H_{30}N_2O_5$ (402.49): C, 65.65; H, 7.51; N, 6.96. Found: C, 65.39; H, 7.57; N, 6.78.

Ethyl (2*R*,3*R*,4*R*,5*S*)-4-acetyl-3-[(1*S*)-1-(benzyloxy)-2-hydroxyethyl]-5-phenylpyrrolidine-2-carboxylate (3h): ^{13}C NMR δ 209.9, 172.6, 138.3, 138.0, 128.4, 128.2, 127.9, 127.8, 127.7, 126.9, 78.0, 72.6, 65.5, 62.5, 62.2, 61.2, 57.8, 48.9, 31.2, 14.1; ^{1}H NMR δ 7.15–7.40 (10H, m), 4.70, 4.59 (2H, J = 11.6 Hz), 4.44 (1H, d, J = 8.6 Hz), 4.22 (2H, q, J = 7.1 Hz), 3.76 (1H, d, J = 8.4 Hz), 3.71–3.76 (1H, m), 3.67 (1H, dd, J = 6.2, 8.6 Hz), 3.60–3.63 (2H, m), 2.93 (1H, dt, J = 4.1, 8.4 Hz), 2.85 (2H, b), 1.26 (3H, t, J = 7.1 Hz); $[\alpha]^{20}_{546}$ −36.0 (c = 1.0, CH_2Cl_2); MS (CI) m/z (relative intensity) 412 (M^+, 100), 411 (21), 368 (20), 232 (31), 230 (26), 192 (20), 191 (33), 117 (22). Anal. Calcd for $C_{24}H_{29}NO_5$ (411.50): C, 70.05; H, 7.10; N, 3.40. Found: C, 70.09; H, 7.41; N, 3.48.

Ethyl (2*R*,3*R*,4*R*,5*S*)-4-acetyl-3-[(1*S*)-1-(dibenzylamino)ethyl]-5-phenylpyrrolidine-2-carboxylate (3i): ^{13}C NMR δ 209.2, 173.4, 139.5, 138.2, 128.5, 128.3, 128.2, 127.6, 126.8, 126.6, 65.2, 63.4, 61.4, 61.0, 55.0, 53.4, 49.8, 30.9, 13.8, 10.8; ^{1}H NMR δ 7.20–7.45 (15H, m), 4.24 (1H, d, J = 7.0 Hz), 4.23 (1H, d, J = 5.1 Hz), 4.00–4.15 (2H, m), 3.90, 3.35 (2H, J = 13.7 Hz), 3.05 (1H, dt, J = 2.4, 3.8 Hz), 2.97 (1H, dd, J = 3.0, 7.5 Hz), 2.60–2.72 (1H, m), 1.53 (3H, s), 1.16 (3H, t, J = 7.6 Hz), 1.12 (3H, d, J = 6.6 Hz); $[\alpha]^{20}_{546}$ −49.5 (c = 1.0, CH_2Cl_2). Anal. Calcd for $C_{31}H_{36}N_2O_3$ (484.64): C, 76.83; H, 7.49; N, 5.78. Found: C, 76.63; H, 7.45; N, 5.92.

Ethyl (2*R*,3*R*,4*R*,5*S*)-4-acetyl-3-[(1*S*)-1-(dibenzylamino)ethyl]-5-(pyridin-3-yl)pyrrolidine-2-carboxylate (3j): ^{13}C NMR δ 207.9, 172.7, 148.5, 148.1, 134.0, 139.1, 134.2, 128.2, 127.8, 126.5, 122.9, 63.3, 62.0, 60.7, 60.5, 54.9, 53.0, 49.1, 30.6, 13.5, 10.3; ^{1}H NMR δ 8.44 (1H, s), 8.42 (1H, d, J = 4.9 Hz), 7.60 (1H, d, J = 8.0 Hz), 7.15–7.40 (10H, m), 7.17–7.22 (1H, m), 4.21 (1H, d, J = 5.2 Hz), 4.20 (1H, d, J = 6.8 Hz), 4.02–4.16 (2H, m), 3.80, 3.36 (2H, J = 13.7 Hz), 3.07 (1H, dt, J = 4.1, 6.8 Hz), 2.98 (1H, dd, J = 4.1, 6.7 Hz), 2.64 (1H, q, J = 6.5 Hz), 1.58 (3H, s), 1.14 (3H, t, J = 7.1 Hz), 1.09 (3H, d, J = 6.6 Hz); $[\alpha]^{20}_{546}$ −46.5 (c = 1.0, CH_2Cl_2). Anal. Calcd for $C_{30}H_{35}N_3O_3$ (485.63): C, 74.20; H, 7.26; N, 8.65. Found: C, 74.63; H, 6.95; N, 8.31.

Ethyl (2*R*,3*R*,4*R*,5*S*)-4-acetyl-3-[(1*S*)-1-(dibenzylamino)-2-phenylethyl]-5-phenylpyrrolidine-2-carboxylate (3k): ^{13}C NMR δ 209.4, 173.7, 140.7, 139.4, 137.8, 129.0, 128.6, 128.6, 128.3, 128.2, 127.5, 126.9, 126.4, 126.1, 65.4, 62.8, 61.1, 61.0, 60.7, 53.8, 49.6, 34.6, 31.1, 13.9; ^{1}H NMR δ 6.95–7.35 (20H, m), 4.47 (1H, d, J = 4.8 Hz), 4.07–4.17 (2H, m), 3.93 (1H, d, J = 6.1 Hz), 3.92, 3.50 (2H, J = 13.7 Hz), 3.32 (2H, J = 4.8, 13.8 Hz), 3.19 (1H, dt, J = 4.6, 7.2 Hz), 3.00–3.10 (1H, m), 2.70 (1H, dd, J = 3.9, 7.2 Hz), 2.60 (2H, J = 4.8, 13.8 Hz), 1.21 (3H, t, J = 7.2 Hz), 1.16 (3H, s); $[\alpha]^{20}_{546}$ +8.0 (c = 1.0, CH_2Cl_2). Anal. Calcd for $C_{37}H_{40}N_2O_3$ (560.73): C, 79.25; H, 7.19; N, 5.00. Found: C, 79.50; H, 7.19; N, 5.04.

Ethyl (2*R*,3*R*,4*R*,5*S*)-4-acetyl-3-[(1*S*)-1-(dibenzylamino)-2-phenylethyl]-5-(pyridin-3-yl)pyrrolidine-2-carboxylate (3l): ^{13}C NMR δ 208.8, 173.6, 149.0, 148.6, 133.8, 140.6, 139.1, 134.0, 128.9, 128.8, 128.7, 128.3, 127.0, 126.3, 123.4, 62.6, 62.5, 61.2, 60.7, 60.5, 53.9, 49.9, 34.6, 31.3, 13.9; ^{1}H NMR δ 8.47 (1H, s), 8.21 (1H, s), 7.52 (1H, d, J = 7.9 Hz), 7.20–7.45 (15H, m), 7.20 (1H, d, J = 7.9 Hz), 4.61 (1H, d, J = 4.6 Hz), 4.22 (2H, q, J = 7.2 Hz), 4.21 (1H, d, J = 5.2 Hz), 4.03, 3.57 (2H, J = 13.7 Hz), 3.43 (2H, J = 4.0, 14.0 Hz), 3.18 (1H, dt, J = 4.6, 7.2 Hz), 3.00–3.10 (1H, m), 2.70 (2H, J = 4.0, 14.0 Hz), 2.69 (1H, dd, J = 3.9, 7.2 Hz), 1.21 (3H, t, J = 7.2 Hz), 1.16 (3H, s); $[\alpha]^{20}_{546}$ −29.5 (c = 1.0, CH_2Cl_2). Anal. Calcd for $C_{36}H_{39}N_3O_3$ (561.72): C, 76.98; H, 7.00; N, 7.48. Found: C, 76.98; H, 6.86; N, 7.19.

Ethyl (2*R*,3*R*,4*R*,5*S*)-4-acetyl-3-[(1*S*)-1-(dibenzylamino)-2-phenylethyl]-5-cyclohexylpyrrolidine-2-carboxylate (3m): ^{13}C NMR δ 211.3, 173.4, 140.7, 139.4, 129.0, 128.6, 128.2, 127.9, 126.8, 126.1, 68.4, 62.3, 61.0, 61.0, 57.3, 53.9, 51.2, 38.1, 35.0, 31.7, 31.2, 26.0, 25.5, 13.8; ^{1}H NMR δ 6.99–7.29 (15H, m), 4.59 (1H, d, J = 4.2 Hz), 4.00–4.17 (2H, m), 3.94 (2H, J = 13.7 Hz), 3.71 (1H, d, J = 4.1 Hz), 3.46 (2H, J = 13.7 Hz), 3.28 (2H, J = 4.8, 13.8 Hz), 3.06–3.12 (1H, m), 2.69–2.82 (2H, m), 2.59 (2H, J = 4.8, 13.8 Hz), 2.15–2.22 (1H, m), 1.78 (3H, s), 1.07 (3H, t, J = 7.1 Hz), 0.55–1.65 (10H, m); $[\alpha]^{20}_{546}$ −4.5 (c = 1.0, CH_2Cl_2). Anal. Calcd for $C_{37}H_{46}N_2O_3$ (566.78): C, 78.41; H, 8.18; N, 4.94. Found: C, 78.32; H, 8.22; N, 4.92.

Diethyl (2*R*,3*R*,4*R*,5*S*)-3-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-5-phenylpyrrolidine-2,4-dicarboxylate (6): ^{13}C NMR δ 172.9, 172.2, 138.1, 128.0, 127.3, 126.5, 109.0, 75.9, 67.8, 65.4, 62.9, 61.2, 60.2, 51.4, 50.9, 26.3, 24.9, 14.1, 13.4; ^{1}H NMR δ 7.20–7.31 (5H, m), 4.53 (1H, d, J = 7.5 Hz), 4.36, 4.24 (2H, q, J = 7.1 Hz), 4.15–4.21 (1H, m), 4.09 (1H, J = 6.5, 8.4 Hz),

3.79 (1H, d, J = 7.1 Hz), 3.60 (1H, J = 6.5, 8.4 Hz), 3.36 (1H, dd, J = 3.8, 7.5 Hz), 2.80 (1H, dt, J = 4.4, 7.8 Hz), 1.45, 1.36 (3H, s), 1.31, 0.75 (3H, t, J = 7.1 Hz); $[\alpha]^{20}_{546}$ −37.0 (c = 1.0, CH_2Cl_2).

Preparation of β,γ-Unsaturated Carbonyl Compounds (8). To a solution of enone **1** or ester **4** (0.5 mmol) in CH_2Cl_2 (4 mL) was added DBU (91 mg, 0.6 mmol). The solution was stirred at room temperature until TLC showed completion of the reaction. Saturated NH_4Cl solution was added, and the mixture was extracted several times with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The products were separated by column chromatography (hexane/ethyl acetate, 8:2).

5,6-*O*-Isopropylidenehex-4-en-2-one (8a, major): 72%; colorless oil; ^{13}C NMR δ 207.5, 151.1, 112.0, 85.8, 66.2, 40.5, 29.3, 25.2; ^{1}H NMR δ 4.42−4.43 (2H, m), 4.31 (1H, tt, J = 7.1, 1.5 Hz), 3.14 (2H, d, J = 7.1 Hz), 2.09 (3H, s), 1.38 (6H, s). **8a** (minor): 18%; colorless oil; ^{13}C NMR δ 206.6, 152.6, 111.8, 86.9, 64.9, 41.8, 29.2, 25.2; ^{1}H NMR δ 4.83 (1H, tt, J = 7.9, 2.2 Hz), 4.46−4.47 (2H, m), 2.88 (2H, d, J = 7.9 Hz), 2.12 (3H, s), 1.41 (6H, s).

5,6-*O*-Cyclohexylidenehex-4-en-2-one (8b, major): 74%; colorless oil; ^{13}C NMR δ 207.3, 150.9, 112.4, 85.6, 65.7, 40.4, 29.0, 34.5, 24.7, 23.5; ^{1}H NMR δ 4.40−4.41 (2H, m), 4.29 (1H, tt, J = 7.1, 1.5 Hz), 3.15 (2H, d, J = 7.1 Hz), 2.09 (3H, s), 1.35−1.63 (10H, m).

Ethyl 4,5-*O*-isopropylidenepent-3-enoate (8c, major): 64%; colorless oil; ^{13}C NMR δ 172.3, 150.8, 111.8, 85.8, 66.1, 60.3, 30.8, 25.1, 14.1; ^{1}H NMR δ 4.41 (2H, d, J = 1.4 Hz), 4.31 (1H, tt, J = 7.0, 1.4 Hz), 4.06 (2H, q, J = 7.1 Hz), 3.05 (2H, d, J = 7.0 Hz), 1.37 (6H, s), 1.18 (3H, t, J = 7.1 Hz). **8c** (minor): 24%; colorless oil; ^{13}C NMR δ 171.7, 152.3, 111.5, 86.9, 64.7, 60.5, 32.3, 24.9, 14.0; ^{1}H NMR δ 4.77 (1H, tt, J = 7.0, 1.4 Hz), 4.47 (2H, d, J = 1.4 Hz), 4.06 (2H, q, J = 7.1 Hz), 2.76 (2H, d, J = 7.9 Hz), 1.37 (6H, s), 1.18 (3H, t, J = 7.1 Hz).

Preparation of the 5-Hydroxy-1,4-dicarbonyl Compounds (9). p-Toluenesulfonic acid (10 mg) was added to a solution of the corresponding compound **8** (0.25 mmol) in CH_3OH (2 mL). After the solution was stirred at rt for 2 h, CH_2Cl_2 (25 mL) was added, and the mixture was washed with an aqueous $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The products were purified by column chromatography (hexane/ethyl acetate, 7:3). (Note: it was detected by TLC that compounds **9** were already formed to some extent after storing enol ethers **8** even in the refrigerator).

1-Hydroxyhexane-2,5-dione (9a): ^{13}C NMR δ 208.7, 207.0, 68.0, 36.7, 31.6, 29.5; ^{1}H NMR δ 4.26 (2H, s), 3.61 (2H, t, J = 6.4 Hz), 2.56 (2H, t, J = 6.4 Hz), 2.13 (3H, s); NMR data identical to literature data.[10a]

Methyl 5-hydroxy-4-oxopentanoate (9b): ^{13}C NMR δ 208.2, 172.7, 68.0, 51.8, 32.6, 27.3; ^{1}H NMR δ 4.25 (2H, s), 3.61 (3H, s), 3.16 (1H, bs), 2.61 (4H, s); NMR data identical to literature data.[10b]

Ethyl (2*R*,3*R*,4*R*,5*S*)-4-Acetyl-3-[(1*S*)-1,2-dihydroxyethyl]-5-phenylpyrrolidine-2-carboxylate (11). (a) From 3a or 3f. The pyrrolidine **3a** or **3f** (0.25 mmol) was dissolved in a mixture of THF (3 mL) and water (0.5 mL), treated with hydrochloric acid (37%, 0.3 mL), and stirred at rt for 1 h. The solution was basified with aqueous NH_3 solution and concentrated until THF was evaporated. The residue was extracted with CH_2Cl_2, and the organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The remaining oil was purified by column chromatography ($CHCl_3/CH_3OH$, 9:1) to afford **11** (from **3a**: 65 mg, 81%. From **3f**: 59 mg, 73%).

(b) From 3h. Compound **3h** (102 mg, 0.25 mmol) was dissolved in CH_2Cl_2 (1 mL) and cooled to −78 °C under argon. A solution of boron tribromide (200 mg, 0.8 mmol) in CH_2Cl_2 (0.5 mL) was slowly added, and the mixture was stirred for an additional 2 h. To decompose the excess of boron tribromide, 200 mg of ethanol was added at −78 °C. The reaction mixture was separated by column chromatography ($CHCl_3/CH_3OH$, 9:1) to afford **11** (32 mg, 40%): mp 101 °C; ^{1}H NMR δ 7.18−7.39 (5H, m), 4.49 (1H, d, J = 7.9 Hz), 4.22 (2H, q, J = 7.1 Hz), 3.76 (1H, d, J = 7.5 Hz), 3.72−3.82 (1H, m), 3.57−3.64 (2H, m), 3.42 (1H, dd, J = 3.6, 7.7 Hz), 2.72−2.81 (1H, m), 2.50 (3H, b), 1.51 (3H, s), 1.25 (3H, t, J = 7.1 Hz); $[\alpha]^{20}_{546}$ −47.3 (c = 1.0, CH_2Cl_2). Anal. Calcd for $C_{17}H_{23}NO_5$ (321.37): C, 63.54; H, 7.21; N, 4.96. Found: C, 63.17; H, 7.59; N, 4.86.

Ethyl (1*R*,3*S*,3a*R*,7*S*,7a*R*)-7-Hydroxy-4-methoxy-4-methyl-3-phenyloctahydropyrano[3,4-*c*]pyrrole-1-carboxylate (12). The pyrrolidine **3f** (0.25 mmol, 100 mg) was dissolved in CH_3OH (4 mL), treated with p-toluenesulfonic acid (100 mg), and stirred at rt for 2 h. CH_2Cl_2 (25 mL) was added, and the mixture was washed with an aqueous $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The products were separated by column chromatography ($CHCl_3/CH_3OH$, 9:1) to afford **11** (12 mg, 15%) and **12** (55 mg, 66%): ^{13}C NMR δ 174.2, 143.7, 128.0, 127.4, 126.7, 99.0, 65.3, 65.1, 62.3, 61.2, 58.9, 50.4, 47.8, 42.3, 21.3, 14.3; ^{1}H NMR δ 7.11−7.21 (5H, m), 4.44 (1H, d, J = 7.3 Hz), 4.22 (2H, m), 4.01 (1H, d, J = 1.5 Hz), 3.88 (1H, d, J = 10.0 Hz), 3.51 (2H, d, J = 1.5 Hz), 2.60−2.77 (1H, m), 2.65 (2H, b), 2.58 (3H, s), 2.48−2.56 (1H, m), 1.27 (3H, s), 1.26 (3H, t, J = 7.2 Hz); $[\alpha]^{20}_{546}$ −39.4 (c = 1.0, CH_2Cl_2); MS (CI) m/z (relative intensity) 336 (M^+, 100), 334 (11), 305 (14), 304 (66), 302 (11), 262 (51).

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