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Stereospecific Synthesis of Pyrrolidines with Varied Configurations via 1,3-Dipolar Cycloadditions to Sugar-Derived Enones

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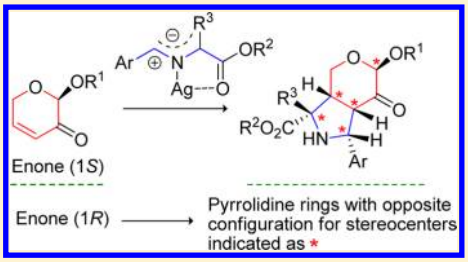
Supporting Information

ABSTRACT: Enantiomerically pure pyrrolidines have been obtained by 1,3-dipolar cycloaddition of stabilized azomethine ylides and sugar enones (dihydropyranones) derived from pentoses. Thus, the *S*-enone (menthyl 3,4-dideoxy-(1*S*)-pent-3-enopyranosid-2-ulose) was prepared from D-xylose, while the *R* analogue was obtained from L-arabinose. The dipoles were generated in situ from α-arylimino esters of common amino acids (glycine, alanine, or phenylalanine) and aromatic aldehydes (benzaldehyde, 3-formylpyridine and 4-methoxybenzaldehyde). Under optimized conditions, the cycloaddition reactions were highly diastereo- and regioselective to yield, in most of the cases, a very major adduct of the 16 theoretically possible. The diastereoselectivity relies on the strict stereocontrol exerted by the stereogenic center of the pyranone. Thus, the (*S*)-enone, derived from D-xylose, gave tetrasubstituted pyrrolidines having a defined stereochemistry for the four stereocenters of the ring, while they had the opposite configuration when starting from the (*R*)-dihydropyranone. Furthermore, some *endo*-cycloadducts underwent isomerization of the carbons vicinal to the nitrogen atom to afford pyrrolidines with a rather unusual stereochemistry for the direct dipolar cycloadditions.



INTRODUCTION

The 1,3-dipolar cycloaddition reaction of azomethine ylides with alkenes is a powerful and reliable strategy for the regio- and stereocontrolled synthesis of substituted pyrrolidines.[1−4] The pyrrolidine framework is found within a variety of natural products,[5] as well as a component of many biologically active molecules and pharmaceuticals.[6] In order to achieve stereoselective transformations, the versatile pyrrolidine scaffold has been employed as a chiral auxiliary,[7] as a chiral ligand,[8] or as an organocatalyst.[9]

Among the numerous strategies for the stereoselective synthesis of pyrrolidines, the cycloaddition-based reactions are attractive because of their ability to induce stereoselectivity in a highly efficient process, which involves the construction of multiple bonds in a single step.[2−4,10] Varied molecules have been used as stereodifferentiating auxiliaries in such cycloadditions, and carbohydrates have shown to be particularly competent for these purposes.[11] On the other hand, enantiomerically pure carbohydrate derivatives have also been used as chiral dipolarophiles in 1,3-dipolar cycloadditions with achiral dipoles. The pioneering work of Wee[12] exploited the reaction of carbohydrate-derived dipolarophiles with non-stabilized azomethine ylides. However, the use of carbohydrate enones in 1,3-dipolar cycloadditions are scarce,[13,14] compared with their use as dienophiles in Diels−Alder reactions. For example, we have reported the highly diastereoselective cycloaddition of sugar enones with varied dienes to afford enantiomerically pure carbocycles.[15] Therefore, we decided to explore the use of sugar enones (3-enopyranosid-2-uloses) as the π-deficient counterparts in 1,3-dipolar cycloadditions with azomethine ylides. This way, we succeeded in the synthesis of tetrasubstituted pyrrolidine derivatives, obtained under the strict stereocontrol exerted by the configuration of the stereocenter of the starting sugar-derived dihydropyranone.

RESULTS AND DISCUSSION

We have described a straightforward preparation of enantiomerically pure sugar enones (3-enopyranosid-2-uloses or 2-alkoxy-dihydropyran-3-ones) by the $SnCl_4$-promoted glycosylation of 2,3,4,6-tetra-*O*-acetylglycal derivatives of hexoses.[16] However, this procedure applied to glycals derived from pentoses afforded the corresponding dihydropyranones with enantiomeric excesses (ee) lower than 90%.[15a] To overcome this difficulty, the glycosylation was performed using chiral 2-octanol to obtain the syrupy mixture of diasteroisomers, which required a rather tedious separation by column chromatography. Alternatively, an enantiospecific synthesis of dihydropyranones from common pentoses was developed.[17] In this case, the several steps required for the generation of the α,β-unsaturated system lowered the overall yield, compared with the "one-pot" glycosylation of the glycal, which is obtained from a pentose in a very good overall yield. Therefore, we studied the glycosylation of the xylal derivative **1** using (−)-menthol as chiral alcohol (Scheme 1). The dihydropyranone **2** (configuration 1*S*) was obtained as a crystalline product. As an additional advantage, the conditions for the glycosylation were optimized using indium(III) chloride as

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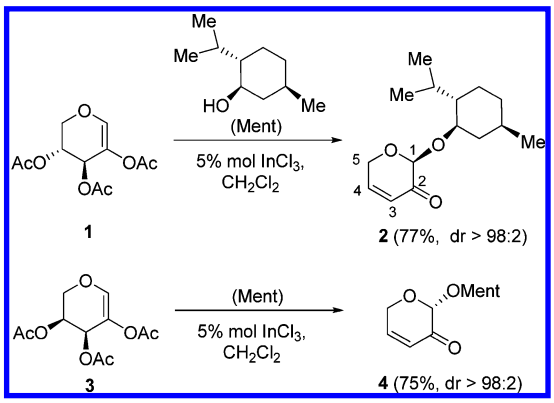
Scheme 1. Synthesis of Sugar Enones 2 and 4



Lewis acid catalyst, instead of the hygroscopic and moisture sensitive $SnCl_4$, previously employed.[15] The concentration of the indium catalyst was lowered as much as to 5 mol %, and the yield of the enone **2**, for several large-scale preparations, was higher than 80%. The slight contamination with the diastereoisomer **4** (dr >10:1) was practically eliminated after two successive recrystallizations (dr >98:2). The use of the $InCl_3$ to promote the Ferrier rearrangement of a glucal derivative to afford 2,3-unsaturated glycosides has been reported.[18]

The $InCl_3$-catalyzed reactions between the L-arabino derivative **3** and (−)-menthol afforded the (1*R*)-pent-3-enopyranosid-2-ulose **4**, having opposite configuration for the anomeric center with respect to that of **2**. This reaction seems to follow the mechanism proposed for the $SnCl_4$-promoted Ferrier rearrangement of **1** or **3**.[15a] Thus, the elimination of the 3-acetoxy group, assisted by the Lewis acid, gives a resonance-stabilized carbocation which is attacked by the alcohol from the face of the glycal opposite to that containing the acetoxy group at C-4. The resulting 2-enopyranoside intermediate undergoes a second allylic rearrangement to give **2** or **4**.

The diastereomeric purity of enones **2** and **4** was readily established on the basis of the NMR spectra, which showed characteristic chemical shifts for the signals of H-1 (4.99 and 4.81 ppm, respectively) and C-1 (94.8 and 99.7 ppm, respectively). The signal of the CH−O of the menthyl group in **2** and **4** was also clearly differentiated.

The enones **2** and **4** were evaluated as dipolarophiles in the 1,3-dipolar cycloadditions with azomethine ylides. One of the most simple and reliable procedures for the formation of azomethine ylides consists in the preparation of α-aryliminio esters (**5Aa−5Cc**) starting from common amino acids (Scheme 2).[19] The reaction of **5Aa−5Cc** with a base such as tertiary amine, in the presence of metal cations, leads to the in situ formation of stabilized *N*-metalated azomethine ylides (**6Aa−6Cc**) as reactive species for the cycloadditions.[1−4]

In order to optimize the reaction conditions, we studied the addition of the imino ester **5Aa** to the enone **2**. The reactions were conducted at room temperature, and compound **2** showed to be an excellent dipolarophile, as cycloadducts were formed under varied conditions (Table 1). From the theoretically possible 16 diastereoisomeric adducts only three have been isolated. As described later, they have been identified as *endo*-**7**, *exo*-**8**, and **9** (the C-4a epimer of **7**). The data collected in Table 1 show that the overall yield and the composition of the diastereomeric mixtures was highly affected upon changes in catalyst and catalyst load, solvent, and concentration of the base (DBU).

Several metal cations such as Li(I),[20] Cu(I)[10e,21] and Cu(II),[22] Ag(I),[10b,19,23] etc. have been employed to promote these reactions, mainly as complexes for enantioselective procedures. Therefore, in the first instance, we evaluated the effect of the cation employed as catalyst (Table 1, entries 1−6). Under identical conditions, silver acetate gave higher overall yield and higher diastereoselectivity, in comparison with the other salts employed, and it was selected for the following experiments. The advantage of using triphenylphosphine to facilitate the dissolution of the Ag^+ catalyst has been described.[24] However, the addition of triphenylphosphine in the Ag^+-catalyzed reaction of **2** with **5Aa** led to a lower yield and loss of the selectivity (Table 1, entry 7).

A lowering in the concentration of AgOAc led to longer times for completion of the reaction (Table 1, entries 8 and 9) and poorer yields and diastereoselectivities, compared to those of entry 6. However, under the same reaction conditions, a longer reaction time has practically no effect on the product distribution (Table 1, entries 10−12), which suggested that compounds **7** and **8** are quite stable and they do not interconvert when the concentration of the base remains low (0.1 molar equiv). In contrast, an increase in the concentration of DBU (to 1 molar equiv) resulted in a lower yield and loss of selectivity (Table 1, entry 13), and in addition to **7** and **8**, a third diastereoisomer **9** was isolated and identified as the C-4a epimer of **7**. In contrast to the *all-cis* substitution pattern for the pyrrolidine ring of **7**, the ethyl ester group at C-4a of **9** is *anti* to the other substituents of such a ring. An increased formation of **9** was observed when, maintaining the concentration of DBU (1 molar equiv), the catalyst load was lowered to 0.1 molar equiv (Table 1, entry 14). Adduct **9** was the major product if the last reaction was conducted for a longer time (Table 1, entry 15).

Scheme 2. Synthesis of Carbohydrate-Derived Pyrrolidines 7−37

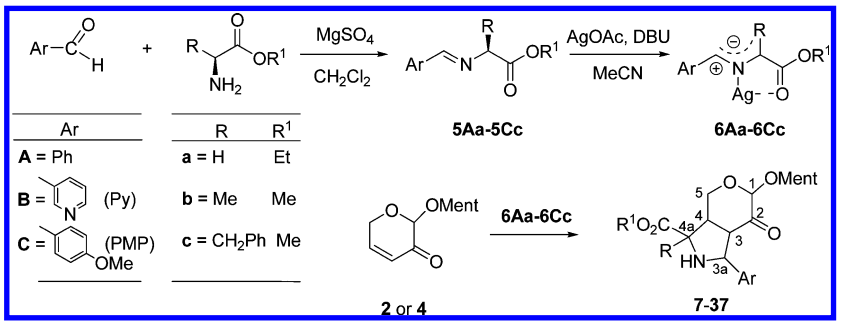


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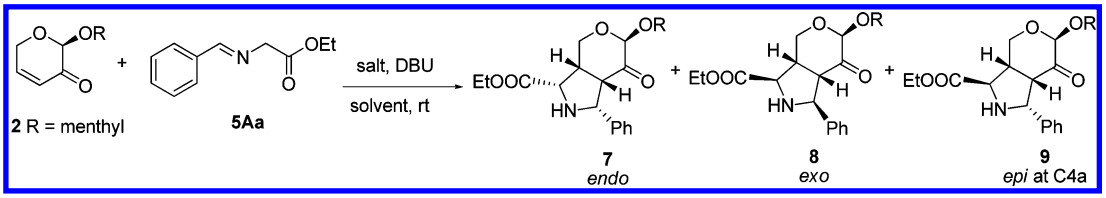
Table 1. Reaction Conditions Employed for the Synthesis of Pyrrolidines 7−9

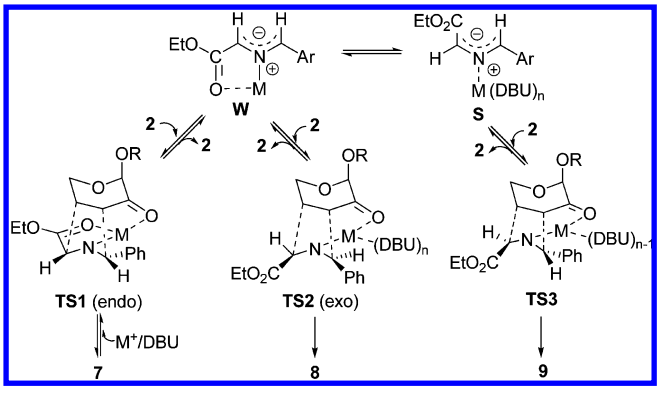


entry[a]	catalyst (molar equiv)	DBU (molar equiv)	solvent[b]	time[c] (h)	yield[d] (%)	ratio 7:8:9[e]
1	LiBr (0.3)	0.1	MeCN	A	36	40:39:21
2	CuI (0.3)	0.1	MeCN	A	45	83:17:0
3	$CaCl_2$(0.3)	0.1	MeCN	A	35	16:48:36
4	$CuSO_4$ (0.3)	0.1	MeCN	A	33	31:50:19
5	$CeCl_3{\cdot}7H_2O$ (0.3)	0.1	MeCN	A	51	34:26:40
6	AgOAc (0.3)	0.1	MeCN	A	83	78:22:0
7	AgOAc (0.3), Ph_3P (0.6)	0.1	MeCN	A	60	50:50:0
8	AgOAc (0.1)	0.1	MeCN	A	68	50:50:0
9	AgOAc (0.05)	0.1	MeCN	16	61	60:40:0
10	AgOAc (0.3)	0.1	MeCN	1	[f]	80:20:0
11	AgOAc (0.3)	0.1	MeCN	3	[f]	80:20:0
12	AgOAc (0.3)	0.1	MeCN	16	[f]	80:20:0
13	AgOAc (0.3)	1.0	MeCN	A	58	54:34:12
14	AgOAc (0.1)	1.0	MeCN	A	52	18:44:38
15	AgOAc (0.1)	1.0	MeCN	16	46	0:14:86
16	AgOAc (0.3)	0.1	hexane	A	60	40:50:10
17	AgOAc (0.3)	0.1	toluene	A	48	60:30:10
18	AgOAc (0.3)	0.1	Et_2O	A	60	60:40:0
19	AgOAc (0.3)	0.1	THF	A	58	70:30:0
20	AgOAc (0.3)	0.1	Me_2CO	A	53	67:33:0
21	AgOAc (0.3)	0.1	EtOAc	A	52	84:16:0
22	AgOAc (0.3)	0.1	H_2O	A	47	62:38:0

[a]The reactions were conducted at room temperature. [b]Except for entry 22, anhydrous solvents were used. [c]A = The reaction time was 15−30 min. [d]Overall yields after isolation of the products by column chromatography. [e]Relative ratio of isolated products. [f]The ratio of products was estimated from the ^1H and ^{13}C NMR spectra of the crude mixture.

The fact that in Ag^+/acetonitrile cycloadditions the formation of **9** increased in the presence of a higher concentration of DBU suggested that the base could promote the epimerization of **7** by enolization of the ester carboxylate at C-4a. However, this hypothesis was ruled out as **7** did not isomerize on treatment with DBU (1 molar equiv) in acetonitrile. Therefore, the formation of **9** was attributed to the isomerization of the ylide. Pyrrolidines like **7** and **8**, that bear a *cis* relationship for the substituent at C-3a and C-4a, result from the cycloaddition of the W-shaped dipole (**6Aa−6Cc**) to the dipolarophile **2**, while the *trans* product involves an S-shaped ylide (Scheme 3).[3] A mixture of stereoisomers may be formed as result of the isomerization of the ylide.[20,25] The W or S conformations of the ylide can be stabilized by metalation.[26] The stability of the ylide and, hence, the stereoselectivity of the cycloaddition reactions depend on the metal salt employed.[27] The Ag^+ cation in acetonitrile seems to stabilize, at low concentration of DBU, the W arrangement to give, via the *endo* (TS1) or exo (TS2) transition states, the respective adducts **7** and **8** (Table 1, entries 6−12). A higher concentration of DBU could contribute to the stabilization of the metal through chelation, with formation of the S ylide, the precursor of **9** (Table 1, entry 13). In line with this behavior, a lowering in the catalyst load (Table 1, entry 14) at the same concentration of DBU should shift the conformational equilibrium to the S ylide, increasing the formation of **9**, which became more important at a longer reaction time (Table 1, entry 15); the absence of *endo*-**7** suggested its isomerization under these reaction conditions.

Scheme 3. Formation of Adducts 7−9 in the Presence of Ag^+ and DBU



Therefore, compound **7** was treated with DBU/Ag^+ as in entry 13 (Table 1). The gradual conversion of **7** into **8** was observed, and after 16 h, isomer **8** was practically the only product obtained. However, this adduct remained unchanged when subjected to the same treatment. Similarly, adduct **9** was also quite stable and did not isomerize under the reaction conditions employed. In an additional experiment, the concentration of Ag^+ was lowered to 0.1 molar equiv and compound **7** was increasingly converted into **8**, but the formation of **9** remained low during the process. All these results seem to indicate that *endo*-**7** is formed under kinetic

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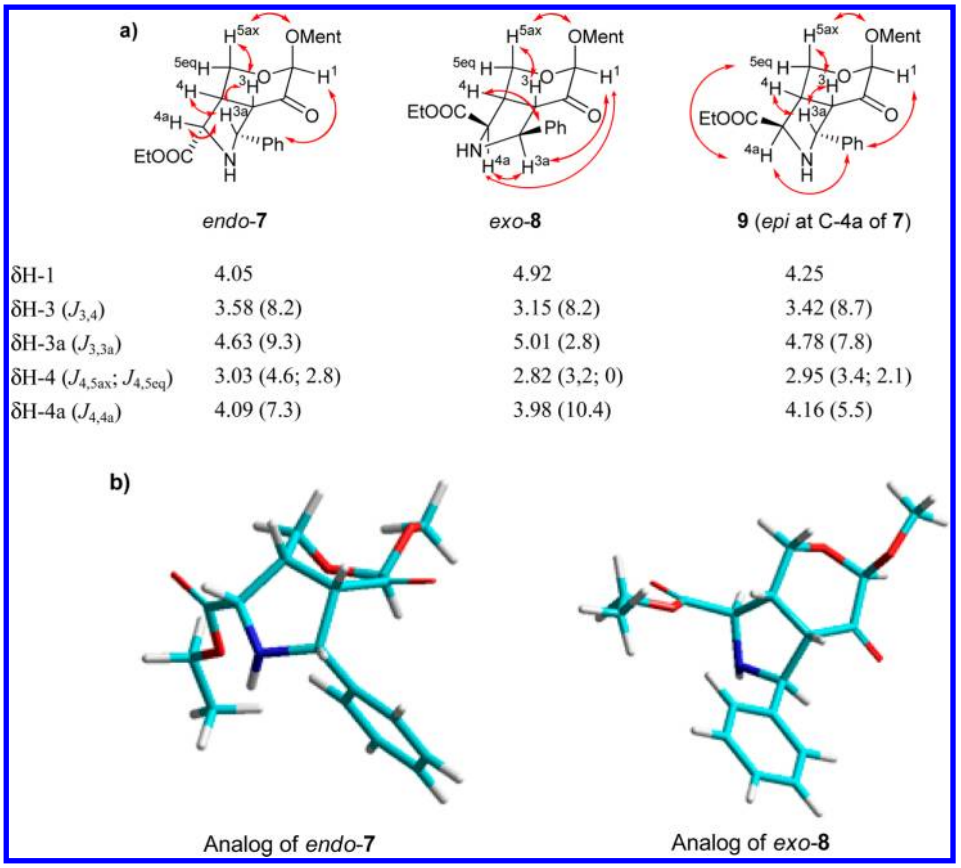

Figure 1. (a) Stereochemical assignment of isomers *endo*-**7**, *exo*-**8**, and **9**, according to NOE correlations and selected NMR data (δ in ppm, J in Hz). (b) Calculated low energy conformations for simplified model compounds analogues of *endo*-**7** and *exo*-**8**.

control and isomerized to the thermodynamic product *exo*-**8** in the presence of Ag^+ and a relatively high concentration of DBU (1 molar equiv). As depicted in Scheme 3, the isomerization seems to take place through the W ylide, which is released from **7**. The approach of this ylide to the enone **2**, via the TS2, leads to **8**. The adduct **9** is accumulated under reaction conditions that favor the equilibrium between the W and S arrangements of the ylide.

The formation of **9** observed for catalysts like Ca^{2+}, Cu^{2+}, or Ce^{3+} (Table 1, entries 3−5) could be attributed to a less effective stabilization of the W ylide by these cations, shifting slightly the conformational equilibrium to the S ylide, the precursor of **9**, through the TS3. The stereochemical course of the reaction is highly sensitive to the ligand employed for chelation of the metal.[10a] For example, according to the chelating agent, Cu^+ ylides can lead to an *exo*-adduct[10e] or to a cycloadduct with the same relative stereochemistry as pyrrolidine **9**.[28] In the case of Ag^+, the compact TS1, which involves chelation of the oxygen atom of the electron-withdrawing group of the dipolarophile,[10d] leads to the *endo*-adduct as major product. Similar *endo*-selectivity has been reported for Ag^+-catalyzed reactions of azomethine ylides with α-enones.[10a,b,14]

The reaction solvent plays also an important role in dipolar cycloadditions, as they contribute to stabilize polar species.[25a] The reaction of **2** with azomethine ylides was successfully conducted with a variety of anhydrous organic solvents of different polarity and even in water (Table 1, entry 22). The W arrangement of the ylide seems to be stabilized in more polar, oxygen-containing solvents[25a] (Table 1, entries 18−21), while in hexane or toluene a low proportion of **9** was obtained, probably via the S ylide.

According to the results in Table 1, the optimal experimental conditions to carry out the cycloaddition reactions are those of entry 6 (0.30 molar equiv of AgOAc, 0.10 equiv of DBU in MeCN at room temperature). Under these conditions, a higher selectivity in favor of *endo*-**7** was observed (dr **7**:**8** = 77:23), while the isomer **9** was a very minor product. However, compound **9** was isolated in 34% yield when the cycloaddition was conducted in the presence of a larger concentration of DBU and for a longer time (16 h).

The absolute configuration of the stereocenters of adducts **7**−**9** were assigned using ^{1}H NMR data (coupling constants (J) and chemicals shift values) and NOE experiments (Figure 1). A central issue for all these reactions is the remarkable facial diastereoselectivity, which was also observed for Diels−Alder cycloadditions and other additions to the double bond of **2**.[15,29] The stereocontrol was attributed to the axially oriented anomeric menthoxy substituent (anomeric effect), which induced the approach of the dipole from the less hindered α face of the pyranone ring. The fact that some protons of the menthoxy group showed NOE contacts with just one of the methylene protons at C-5, allowed us to identify as H-5ax the one involved in such a correlation (Figure 1a). Then, the configuration of the new stereocenter at C-3, of both **7** and **8**, was established on the basis of the NOE contact between H-3 and H-5ax. Furthermore, H-3 showed an intense NOE with H-4, as expected for vicinal *syn*-disposed protons and, in addition, the small coupling constants for $J_{4,5ax}$ (4.6 Hz for **7**, 3.2 Hz for **8**) and $J_{4,5eq}$ (2.8 Hz for **7**, 0 Hz for **8**) are indicative that the C-

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Table 2. Pyrrolidines Obtained by Dipolar Cycloaddition of Dihydropyranones 2 and 4 with Imines 5Aa−5Cc

Entry	Imine	Sugar enone (pyranone)	
		2 R = menthyl	4 R = menthyl
1	5Aa	7 (64%)[a]; 8 (19%); 9 (traces)	24 (43%); 25 (11%)
2	5Ab	10 (90%)	26 (68%)
3	5Ac	11 (63%)	27 (77%)
4	5Ba	12 (62%); 13 (10%)	28 (59%); 29 (11%)
5	5Bb	14 (88%)	30 (53%); 31 (14%)
6	5Bc	15 (89%)	32 (73%)
7	5Ca	16 (6%); 17 R^1 = COOEt, R^2 = H (14%); 18 R^1 = H, R^2 = COOEt (4%); 19 (40%)	33 (68%); 34 (12%)
8	5Cb	20 (45%); 21 (21%)	35 (60%); 36 (11%)
9	5Cc	22 (29%); 23 (5%)	37 (43%)

[a]Yield of the isolated product after column chromatography.

4−H-4 bond bisects the angle formed by the vicinal methylene group at C-5 and confirmed the configuration of C-4.

Another significant feature in the reaction of **2** with azomethine ylides is the complete level of regioselectivity, as the only isolated regioisomers result from the bonding of the most nucleophilic carbon of the dipole to the most electrophilic center of the enone system. Thus, the NOESY spectra of **7**−**9** exhibited NOE contacts between the aromatic protons with H-

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3 and H-3a, indicating the location of the phenyl group on C-3a. In agreement with this result, H-4a showed the expected NOE contacts with H-4 and with the protons of ethyl group of the ester. The configuration of C-3a and C-4a of pyrrolidines *endo*-**7** and *exo*-**8** was established by means of diagnostic NOE contacts. Thus, in compound **7**, H-3a showed cross peaks with H-3, H-4, and H-4a, in agreement with the all *cis* disposition for the protons of the pyrrolidine ring (*endo* configuration). In contrast, in the isomer **8** the NOE contacts between H-1−H-3a, H-1−H-4a, H-3a−H-4a and the observed cross peak between H-4 and the aromatic protons indicated that we were dealing with the *exo*-adduct.

Comparison of the ^{1}H NMR spectra of *endo*-**7** and *exo*-**8** showed two significant differences regarding the chemical shifts of the signals of H-1 and H-3 and the values of $J_{3,3a}$. The H-1 signal in *endo*-**7** (4.05 ppm) is strongly shifted upfield, with respect to the same signal in *exo*-**8** (4.92 ppm), to a rather unusual region of the spectra for an anomeric proton. In contrast, the resonance of H-3 (3.58 ppm) in *endo*-**7** is deshielded compared to that of *exo*-**8** (3.15 ppm). These effects can be attributed to the relative orientation of the phenyl group attached to C-3a. The phenyl and ethyl ester groups are *syn* oriented, although in opposite faces, in the pyrrolidine ring of **7** and **8**. Therefore, from the conformational point of view, this ring for **7** is expected to populate the E_0 region of the pseudorotational cycle (with the N atom, numbered as 0, below the plane defined by the contiguous carbon atoms C-3a, C-3, C-4, and C-4a), while the pyrrolidine ring of **8** should prefer the opposite ^0E region. In the respective conformations, the bulky substituents on C-3a and C-4a for **7** and **8** are quasiequatorially oriented.

A preliminary theoretical calculation, using the semiempirical AM1 method, was performed for the analogue of *endo*-**7**, in which the menthyl group has been replaced by methyl to facilitate the calculation (Figure 1b). The minimum energy conformation for **7** shows a parallel disposition of the aromatic ring with respect to H-1. Then, this proton is expected to be shielded due to the anisotropy of the aryl group. In the adduct *exo*-**8** the orientation of the aromatic ring respect to H-1 is not adequate for anisotropy shielding. Hence, the H-1 signal appears in a δ value typical of anomeric protons of pyranosyd-2-uloses.[15,29] However, in *exo*-**8** H-3 is located in the shielding zone of the aromatic ring, and this proton signal is shifted upfield compared with that of **7**. The effect of the anisotropy of the phenyl group on the chemical shift has been extensively used to determine the absolute configuration of chiral alcohols via Mosher esters.[30] On the other hand, the larger $J_{3,3a}$ value (9.3 Hz) for **7**, compared with that of **8** (2.8 Hz) should be the result of the respective ^0E and E_0 conformations adopted by the pyrrolidine ring. Each J value matches with the dihedral angle H-3−C-3−C-3a−H-3a measured from the low-energy conformation depicted in Figure 1b, which is close to 5° in the former (H-3 and H-3a are nearly eclipsed) and 105° in the latter.

The structure of the third diastereoisomer **9**, isolated in some cases, was determined on the basis of the NOE contacts observed between the aromatic protons with H-1, H-3a, and H-4a. Other diagnostic cross peaks were also detected between H-3a with H-3 and H-4, as well as H-4a−H-5eq and H-3−H-5ax. Furthermore, adduct **9** showed chemical shifts values for H-1 (4.25 ppm) and H-3 (3.42 ppm) similar to those of *endo*-**7**, confirming the configuration of C-3a. However, the $J_{3,3a}$ value (7.8 Hz) in **9** was somewhat smaller than the one measured for **7** (9.3 Hz). This could be explained because of the conformational instability caused by the 1,3-*anti* disposition for the substituents at C-3a and C-4a of the pyrrolidine, which determines that one or the other should be quasiaxially oriented in either the ^0E or E_0 forms.

To evaluate the scope of the 1,3-dipolar cycloaddition, a representative set of α-imino esters of glycine (**5Aa−5Ca**), alanine (**5Ab−5Cb**), and phenylalanine (**5Ac−5Cc**) were prepared (Scheme 2) using aromatic aldehydes with varied electronic properties, such as benzaldehyde (**5Aa−5Ac**), 3-formylpyridine (**5Ba−5Bc**), and 4-anisaldehyde (**5Ca−5Cc**). Reaction of the imino esters with the enone **2**, under the optimized conditions, led to cycloadducts in good to excellent yields (Table 2). However, a different *endo*-selectivity was observed for reactions performed on imino esters derived from benzaldehyde (Table 2, entries 1−3). While the stereoselectivity remained modest for the glycine derivative **5Aa**, the *endo* adducts **10** and **11** were almost exclusively formed for the alanine (**5Ab**) and phenylalanine (**5Ac**) derivatives, respectively. This result suggests that the replacement of a hydrogen atom by a bulkier Me or $PhCH_2$ substituent at the α-position of the imine destabilizes the competing *exo* transition state. An example has been found in the literature[14] that shows a similar effect when a hydrogen atom at the carbon vicinal to the ester of the imine was replaced by a bulkier group.

Dipole precursors **5Ba−5Bc** have also been prepared and used for the cycloadditions (Table 2, entries 4−6). They possess a 3-pyridyl substituent as the electron-withdrawing aromatic group. The reactivity and selectivity shown by pyridylimines were very similar to those of phenylimines. Thus, the increased *endo*-selectivity for the alanine (**5Bb**) and phenylalanine (**5Bc**) derivatives led to adducts **14** and **15** in excellent yields, while the glycine imine (**5Ba**) afforded **12** (62%) accompanied by the *exo*-**13** (10%).

Next, we explored the effect on the course of the dipolar cycloaddition of the replacement of the phenyl or 3-pyridyl substituent of the α-imino esters by the electron-donating *p*-methoxyphenyl (PMP) group (Table 2, entry 7). Thus, the glycine imine (**5Ca**) was allowed to react with enone **2** under standard conditions. The crude ^{1}H NMR spectrum of the reaction mixture showed two main products, which were later characterized as *endo*-**16** and *exo*-**17** (ratio 5:1). Column chromatography of this mixture led first to *exo*-**17**, in a yield (14%) that was in agreement with the proportion estimated by NMR. Surprisingly, the isomer *endo*-**16** was recovered from the column in a very low yield (6%), and two other compounds, not detected in the original mixture neither by TLC nor by NMR, were obtained.

A detailed analysis of the NMR spectra of the minor component isolated from the column indicated that compound **18** was the epimer at C-3a of *endo*-**16**. Examination of the ^{1}H NMR spectrum of the major product (40% yield) showed the absence of the signals of H-3a and those corresponding to the aromatic protons. Instead, a methylene group at C-3 was detected, with one of the protons exhibiting a long-range coupling ($J \approx 1$ Hz) with H-5eq (the correlation was also observed in the 2D-COSY spectrum), indicating the W disposition of these two hydrogen atoms in a six-membered ring. On the basis of this evidence, and taking into account the molecular weight determined by HRMS, the structure of the compound was assigned as the aminoacetal **19**. In agreement with this structure, the NOESY spectrum of **19** exhibited the expected NOE contacts between H-3ax−H-5ax, H-3eq−H-4a,

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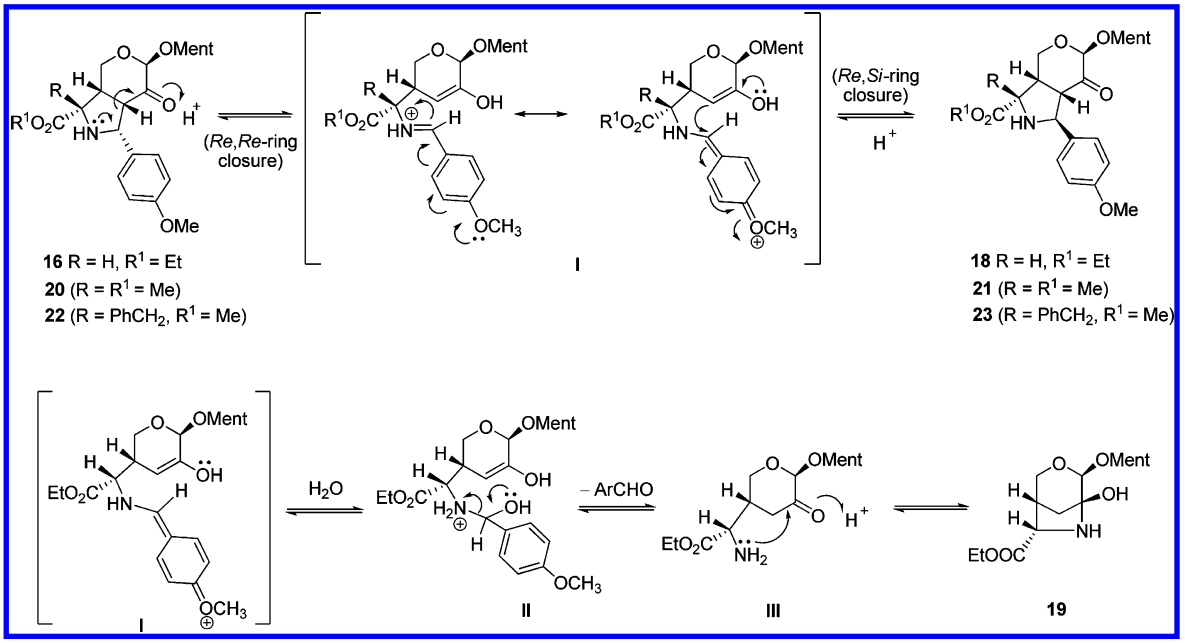
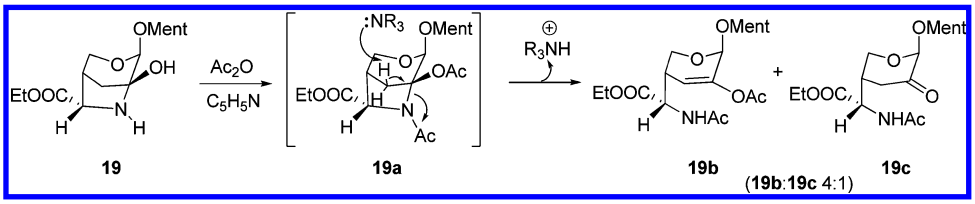
Scheme 4. Mechanism Proposed for the Acid-Promoted Isomerization



Scheme 5. Acetylation Reaction of Aminal 19



the methylene of the ethyl ester with H-4 and H-5eq, and H-1 and H-5ax with protons of the menthyl group.

The fact that **18** and **19** were absent in the crude reaction mixture suggested, and it was later confirmed, that they were formed due to the acidity provided by the silica gel during the purification. Therefore, the mechanism proposed for the epimerization of **16** into **18**, depicted in Scheme 4, consists of the acid-catalyzed retro-Mannich reaction, which leads to an iminium cation (**I**) stabilized by resonance due to electron donation by the *p*-methoxyphenyl group. Ring closure by Mannich-type attack of the α-face (*Re*) of the enol function either to the *Re* or *Si* face of the PMP benzylic carbon leads, respectively, back to **16** or to the isomer **18**. Alternatively, hydration of **I** by the water contained in the silica gel and *O* → *N* proton transfer leads to the intermediate **II**, which undergoes the releasing of anisaldehyde to produce **III**. The nucleophilic attack of the amine of **III** to the carbonyl gives the aminoacetal **19**.

Interestingly, when compound **19** was subjected to acetylation with a 1:1 mixture of pyridine–Ac_2O, instead of the expected *N*- and *O*-diacetyl derivative **19a**, an inseparable mixture of the enol acetate **19b** and the ketone **19c** (ratio **19b**:**19c** 4:1) was obtained (Scheme 5). This result suggests that the cyclic aminal **19** becomes unstable upon *N*-acetylation and undergoes elimination of H-3 with concomitant ring-opening through a β-elimination process to afford **19b**. The formation of a small amount of **19c** may be ascribed to hydrolysis of the enol ester of **19b** during column chromatography.

The pyrrolidine ring-opening mechanism shown in Scheme 4, which explains the conversion of **16** into **18**, justifies also the formation of **21** and **23** as byproducts of the reaction of the enone **2** with the *p*-methoxyphenyl imines **5Cb** and **5Cc**, respectively. Similar to **18**, compounds **21** and **23** could not be detected in the original reaction mixtures (TLC and NMR). However, after column chromatography, the isomeric products **21** and **23**, respectively, together with the *endo*-adducts **20** and **22** were isolated. The structure of compounds **20**–**24** was assigned, as already described for analogous pyrrolidine derivatives, using extensive NMR experiments. Thus, the structure of **21** was unambiguously established, mainly on the basis of the NOESY spectrum, as the epimer of *endo*-**20** at the benzylic position (C-3a). Diagnostic NOE contacts were detected between H-1 with H-3a, H-4 with aromatic protons and with Me_{Ala}, H-5ax with H-3 and with H-Ment, and H-5eq with Me_{Ala}. A similar analysis led to the determination of the structure of **22** as the *endo*-adduct and the minor product **23** as the epimer at C-3a of **22**. Compounds **21** and **23** may be formed according to the mechanism proposed in Scheme 4. In these cases, the intermediate cation **I** (R = Me or R = $PhCH_2$), formed respectively from **20** or **22**, may undergo ring closure returning back to **20** or **22** or to produce the epimers **21** or **23**, depending on the face (*Re* or *Si*, respectively) of the benzylic carbon of PMP attacked by the enol.

In order to verify if other pyrrolidine derivatives are susceptible to the acid-promoted isomerization, the crude mixture of the reaction of **2** with imine **5Aa** was treated with a suspension of SiO_2 in toluene. The isomer *epi*-**7** was slowly formed at room temperature. Sarotti et al.[14] have observed a

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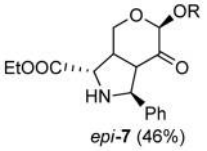
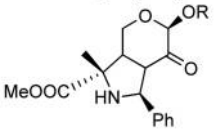
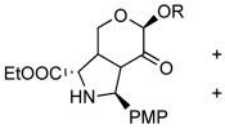
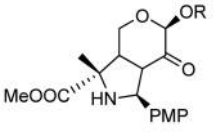
Table 3. Treatment of the Crude Mixture of the Cycloaddition Reaction with SiO_2−Toluene at 80 °C for 2 h

Entry	Crude mixture of reaction of 2 with imine	Pyrrolidine derivatives
1	5Aa	 + *endo*-**7** (9%) + *exo*-**8** (14%) *epi*-**7** (46%)
2	5Ab	 + *endo*-**10** (43%) *epi*-**10** (30%)
3	5Ba or 5Bb	No epimeric products are formed
4	5Ca	 + *exo*-**17** (20%) + **19** (8%) **18** (30%)
5	5Cb	 **21** (56%)

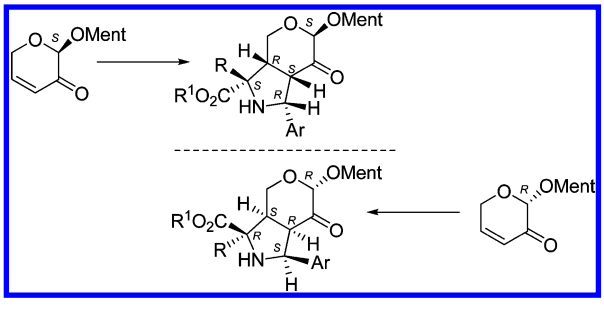
similar low isomerization rate, and they found that conversion was more efficient at higher temperatures, particularly under microwave irradiation. Therefore, the crude mixture of reaction of **2** with **5Aa** was treated with SiO_2 in toluene at 80 °C. The progress of the reaction was followed by ^{13}C NMR, which showed increasing formation of *epi*-**7** ($\delta_{C\text{-}1}$ = 95.3 ppm), while the proportion of *endo*-**7** ($\delta_{C\text{-}1}$ = 96.6 ppm) in the mixture was decreasing. The relative proportion of *exo*-**8** ($\delta_{C\text{-}1}$ = 95.7 ppm) remained practically unchanged. After 2 h of heating at 80 °C, *epi*-**7** was isolated in 46% yield (Table 3). According to these results, *epi*-**7** seems to be formed by isomerization of *endo*-**7**. This fact was experimentally verified since treatment of pure *endo*-**7** with hot SiO_2−toluene led to *epi*-**7** as the main product. It should be highlighted that by adjusting the conditions of the dipolar cycloaddition of **2** with **5Aa**, or via isomerization, the four stereoisomers at C-3a and C-4a (**7**, **8**, **9** and *epi*-**7**) have been obtained in moderate to good yields.

In order to synthesize pyrrolidines with a stereochemistry that is not achieved by the direct dipolar cycloaddition, the crude mixture of reaction of **2** with **5Ab**, **5Ba**, **5Bb**, **5Ca**, and **5Cb** was subjected to treatment with a suspension of SiO_2 in toluene at 80 °C for 2 h. As depicted in Table 3, in most of the cases, the C-3a epimers of the respective *endo*-adducts were the major products isolated, confirming the SiO_2-promoted isomerization. However, the crude mixtures of pyrrolidines prepared from pyridylimines **5Ba** or **5Bb** remained unchanged upon the SiO_2 treatment. These results further support the mechanism proposed (Scheme 4), as the isomerization does not take place when the aromatic substituent vicinal to the amine function of the pyrrolidine ring is an electron-withdrawing group, which should destabilize the iminium cation **I**, preventing the cleavage of the C-3−C-3a bond.

The cycloaddition protocol described for the dihydropyranone **2** was applied, under identical reaction conditions, to the enone **4** having opposite configuration for the stereogenic center. As this center controls the stereochemical output of the reaction with azomethine ylides, we were able to install the four stereocenters of the resulting pyrrolidine rings in a predictable way. Thus, the 1,3-dipolar cycloaddition of the same metalloazomethine ylides (**6Aa**−**6Cc**) to dipolarophile **4** afforded tetrasubstituted pyrrolidine rings with the four stereocenters having opposite configuration with respect to those of the pyrrolidines obtained from **2** (Table 2), as illustrated in Scheme 6 for *endo*-adducts.

The configurations of compounds **24**−**37** were readily established by comparison of their NMR spectra with those of the pyrrolidines derived from **2** and also on the basis of the NOESY contacts. It is worth mentioning that the PMP derivative *endo*-**33** seems to be more stable than the

Scheme 6. Pyrrolidine Rings (*Endo* Isomers) Showed Opposite Configuration for the Four Stereocenters, According to the Starting Enone 2 or 4



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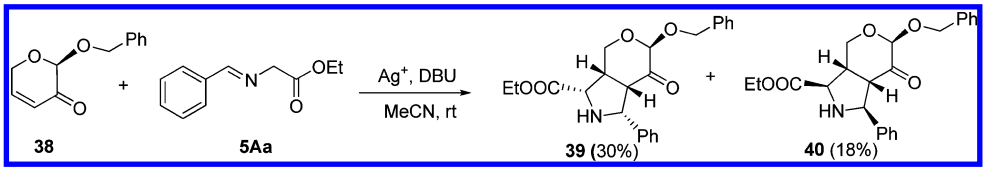
Scheme 7. Pyrrolidines Obtained from Enone 38



diastereomeric analogue *endo*-**16** as, in contrast to this, it could be isolated by column chromatography in good yield (68%). In addition, Table 2 shows that the yields and dr of cycloadducts obtained from **2** or **4** are quite different, suggesting that the menthyl moiety influences the stereochemical course of the respective cycloadditions acting as a chiral auxiliary. As a further confirmation, the cycloaddition was conducted under the usual conditions with the dihydropyranone **38** (Scheme 7), which possesses a benzoyloxy group as an achiral counterpart of the menthyl moiety of **2**. Thus, the reaction of **38** with **5Aa** was, as observed in previous cycloadditions, highly diastereofacial selective due to the influence of the stereocenter of the dihydropyranone. However, a higher proportion of the *exo* adduct (dr *endo*/*exo* 62.5:37.5) was formed in comparison with those observed for the analogous reaction applied to **2** (dr 77:23) or **4** (dr 80:20). All these results indicate that the anomeric substituent of the dyhydropyranone influences the yield and stereochemistry of the resulting cycloadducts.

CONCLUSIONS

The 1,3-dipolar cycloaddition of azomethine ylides, derived from common amino acids (glycine, alanine and phenylalanine), with sugar enones afforded enantiomerically pure tetrasubstituted pyrrolidines. Crystalline dihydropyranones, having the *S* or *R* configuration for the anomeric center, were readily prepared from D-xylose or L-arabinose via de $InCl_3$-promoted glycosylation with L-menthol followed by a double-Ferrier rearrangement. The dipolar cycloadditions were highly diastereo- and regioselective reactions, which led in many cases to a very major pyrrolidine, from the 16 theoretically possible. In particular, the strict stereocontrol exerted by the stereocenter of the sugar dipolarophile allowed generation during the cycloadditions of four asymmetric carbons of the pyrrolidine ring with a configuration that depend on the starting (*R*) or (*S*)-dihydropyranone. Thus, pairs of diastereomeric pyrrolidines with inverse configurations for the four stereocenters of the ring were successfully obtained. This is a relevant result as pyrrolidines have been used as chiral auxiliaries[7] and as organocatalysts.[9,14]

In addition, depending on the substitution pattern, the *endo* cycloadducts are prone to isomerize to afford pyrrolidines with relative stereochemistries that are not accessible via the direct 1,3-dipolar cycloaddition. The adducts that contain a *p*-methoxyphenyl group at C-3a of the pyrrolidine showed a particular tendency to the acid-promoted isomerization or even to the degradation with elimination of *p*-methoxybenzaldehyde to give a cyclic aminal.

As continuation of the present studies, we are currently performing chemical modifications of the cycloadducts, such as removal of the menthyl group and degradation of the sugar-derived dihydropyranone ring, to obtain polysubstituted pyrrolidines and D- or L-prolines with different patterns of substitution.

EXPERIMENTAL SECTION

Synthesis of Sugar Enones (Dihydropyranones) 2 and 4. Glycal derivatives (2,3,4-tri-*O*-acetyl-1,5-anhydropent-1-enitols) **1** and **3** were prepared from D-xylose or L-arabinose, respectively, by the procedure previously described.[15a] To a solution of each glycal (4.50 g, 17.4 mmol) and (1*R*,2*S*,5*R*)-(−)-menthol (2.72 g, 17.4 mmol) in anhydrous CH_2Cl_2 (130 mL) was added $InCl_3$ (192 mg, 0.87 mmol). The solution was stirred at room temperature (rt) overnight, when TLC (hexane/EtOAc, 7:3) showed a higher moving spot and complete disappearance of the starting glycal. The organic solution was washed with satd aq $NaHCO_3$, water, and brine. Solvent evaporation afforded a residue that was purified by column chromatography (hexane/EtOAc, 40:1) to afford menthyl 3,4-dideoxy-(1*S*)-pent-3-enopyranosid-2-ulose (**2**) or menthyl 3,4-dideoxy-(1*R*)-pent-3-enopyranosid-2-ulose (**4**).

Compound 2: white solid (3.80 g, 87%), purified after two successive recrystallizations from ethanol/water (3.36 g, 77%); mp = 54 °C; $[\alpha]_D^{25}$ −200.8 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.04 (ddd, 1H, $J_{3,4}$ = 10.5, $J_{4,5}$ = 1.9, $J_{4,5'}$ = 3.8 Hz, H-4), 6.13 (br dt, 1H, $J_{3,4}$ = 10.5 Hz, H-3), 4.99 (s, 1H, H-1), 4.58 (br dt, 1H, $J_{5,5'}$ = 19.2 Hz, H-5), 4.27 (ddd, 1H, $J_{3,5'}$ = 1.9, $J_{4,5'}$ = 3.8, $J_{5,5'}$ = 19.2 Hz, H-5′), 3.56 (ddd, 1H, *J* = 4.1, *J* = 10.7 Hz, H-1 menthyl), 2.24−2.12 (m, 2H, H menthyl), 1.65 (d, 2H, H menthyl), 1.41−1.26 (m, 2H, H menthyl), 1.00−0.75 (m, 12H, H menthyl); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 189.3 (C-2), 148.0 (C-4), 125.0 (C-3), 94.8 (C-1), 77.4 (C-1 menthyl), 60.0 (C-5), 48.0, 40.2, 34.5, 31.6, 25.4, 23.1, 22.3, 21.2, 15.6 (C-menthyl); HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{24}NaO_3$ 275.1618, found 275.1627.

Compound 4: white solid (3.71 g, 85%), purified after two successive recrystallizations from ethanol/water (3.27 g, 75%); mp = 75 °C; $[\alpha]_D^{25}$ +121.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.96 (ddd, 1H, $J_{3,4}$ = 10.5, $J_{4,5}$ = 1.9, $J_{4,5'}$ = 3.8 Hz, H-4), 6.05 (br dt, 1H, $J_{3,4}$ = 10.5 Hz, H-3), 4.84 (s, 1H, H-1), 4.55 (br dt, 1H, $J_{5,5'}$ = 19.1 Hz, H-5), 4.20 (ddd, 1H, $J_{5,5'}$ = 19.1 Hz, H-5′), 3.38 (ddd, 1H, *J* = 4.1, *J* = 10.7, H-1 menthyl), 2.14−2.03 (m, 2H, H menthyl), 1.62−1.54 (d, 2H, H menthyl), 1.35 (m, 1H, H menthyl), 1.18 (m, 1H, H menthyl), 1.05−0.65 (m, 12H, H menthyl); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 188.7 (C-2), 148.0 (C-4), 125.0 (C-3), 99.7 (C-1), 82.3 (C-1 menthyl), 60.0 (C-5), 48.6, 42.9, 34.3, 31.8, 25.4, 23.4, 22.4, 21.0, 16.2 (C-menthyl); HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{24}NaO_3$ 275.1618, found 275.1626.

General Procedures for the Synthesis of α-Imino esters. The α-imino esters were prepared by a slight modification of the reported procedures.[19,24] A suspension of the methyl ester hydrochloride derivative of the amino acid (glycine, alanine or phenylalanine, 1.10 mol) and anhydrous magnesium sulfate (2.00 mol) in anhydrous CH_2Cl_2 and Et_3N (1.10 mol) was stirred at rt for 1 h, and the corresponding aldehyde (benzaldehyde, 3-formylpyridine or *p*-methoxybenzaldehyde, 1.00 mol) was added. The mixture was stirred at rt overnight, and then $MgSO_4$ was filtered off. The organic solution was washed with satd aq $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated to afford the α-imino esters (**5Aa**−**5Cc**). The NMR spectra of the crude imino esters showed that the compounds were pure enough to be used for the cycloaddition reaction without further purification.

General Procedure for the [3 + 2] Cycloaddition Reactions. The corresponding sugar enone **2** or **4** (1.00 mmol) and the α-imino ester **5Aa**−**5Cc** (1.50 mmol) were dissolved in the anhydrous solvent (Table 1) to afford a final concentration of imino ester 0.5 M. In the absence of light, the salt and DBU were added. The mixture was stirred at rt, until TLC showed complete disappearance of the starting

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enone. The reaction was diluted with CH_2Cl_2 and filtered through Celite. Evaporation of the solvent afforded a residue which was subjected to column chromatography with the solvent specified in each individual case.

Synthesis of Pyrrolidine Derivatives 7−23 from Pyranone 2. *Synthesis of Pyrrolidine Derivatives 7−9 from Imino Ester 5Aa.* The general procedure described above was followed starting from **2** (0.10 g, 0.40 mmol) and the imino ester derived from glycine (**5Aa**, 0.115 g, 0.60 mmol) dissolved in anhydrous MeCN (1.2 mL). After addition of AgOAc (20 mg, 0.12 mmol) and DBU (6 μL, 0.04 mmol) the mixture, which immediately changed the color to a dark brown, was stirred at rt for 15 min and then processed as indicated above. The residue showed by TLC (hexane/EtOAc, 7:3) spots corresponding to **8** (R_f 0.67), **9** (R_f 0.45), and **7** (R_f 0.22). Under these conditions, only compounds **7** and **8** could be isolated by column chromatography (hexane/EtOAc, 92.5:7.5 → 85:15), while adduct **9** was a very minor component.

Compound 7: white solid, recrystallized from ethanol/water (113 mg, 64%); mp = 149 °C; $[\alpha]_D^{25}$ −121.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39−7.23 (5H, H-aromatic), 4.63 (d, 1H, $J_{3,3a}$ = 9.3 Hz, H-3a), 4.31 (m, 2H, OCH_2CH_3), 4.09 (d, 1H, $J_{4,4a}$ = 7.3 Hz, H-4a), 4.06 (dd, 1H, $J_{4,5ax}$ = 4.6, $J_{5ax,5eq}$ = 12.6 Hz, H-5ax), 4.05 (s, 1H, H-1), 3.77 (dd, 1H, $J_{4,5eq}$ = 2.8, $J_{5ax,5eq}$ = 12.6 Hz, H-5eq), 3.58 (dd, 1H, $J_{3,3a}$ = 9.3, $J_{3,4}$ = 8.2 Hz, H-3), 3.28 (ddd, 1H, *J* = 4.1, *J* = 10.7, H-1 menthyl), 3.03 (m, 1H, $J_{3,4}$ = 8.2, $J_{4,4a}$ = 7.3, $J_{4,5ax=}$ 4.6, $J_{4,5eq}$ = 2.8 Hz, H-4), 2.12 (m, 1H, H menthyl), 1.61−1.53 (m, 3H, H menthyl), 1.34 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3), 1.26−1.18 (m, 2H, H menthyl), 0.92−0.63 (m, 12H, H menthyl); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 203.7 (C-2), 171.2 (OCOEt), 138.1−126.7 (C-aromatic), 96.6 (C-1), 76.4 (C-1 menthyl), 64.3 (C-3a), 64.1 (C-4a), 61.5 (OCH_2CH_3), 60.6 (C-5), 55.3 (C-3), 47.5 (C-menthyl), 44.6 (C-4), 39.4, 34.4, 31.5, 25.3, 23.0, 22.3, 21.1, 15.4 (C-menthyl), 14.4 (OCH_2CH_3); HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{38}NO_5$ 444.2744, found 444.2749.

Compound 8: white solid, recrystallized from ethanol (34 mg, 19%), mp = 88 °C; $[\alpha]_D^{25}$ −128.0 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.47−7.25 (5H, H-aromatic), 5.01 (d, 1H, $J_{3,3a}$ = 2.8 Hz, H-3a), 4.92 (s, 1H, H-1), 4.36 (dd, 1H, $J_{4,5ax}$ = 3.2, $J_{5,5eq}$ = 12.5 Hz, H-5ax), 4.26 (m, 2H, OCH_2CH_3), 3.98 (d, 1H, $J_{4,4a}$ = 10.4 Hz, H-4a), 3.90 (d, 1H, $J_{5ax,5eq}$ = 12.5 Hz, H-5eq), 3.54 (ddd, 1H, *J* = 4.1, *J* = 10.7 Hz, H-1 menthyl), 3.15 (dd, 1H, $J_{3,3a}$ = 2.8, $J_{3,4}$ = 8.2 Hz, H-3), 2.82 (ddd, 1H, $J_{3,4}$ = 8.2, $J_{4,4a}$ = 10.4, $J_{4,5ax}$ = 3.2 Hz, H-4), 2.21 (m, 1H, H menthyl), 2.08 (d, 1H, H menthyl), 1.65 (d, 2H, H menthyl), 1.39−1.25 (m, 2H, H menthyl), 1.31 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3), 0.98−0.72 (m, 12H, H menthyl); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 201.4 (C-2), 172.9 (OCOEt), 143.4−126.6 (C-aromatic), 95.7 (C-1), 77.0 (C-1 menthyl), 61.5 (OCH_2CH_3), 60.9 (C-4a), 60.3 (C-3a), 57.6 (C-5), 56.3 (C-3), 47.9 (C-menthyl), 44.3 (C-4), 40.0, 34.4, 31.5, 25.4, 22.9, 22.3, 21.2, 15.4 (C-menthyl), 14.4 (OCH_2CH_3); HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{38}NO_5$ 444.2744, found 444.2744.

Synthesis of Adduct 9. The cycloaddition reaction between **2** (0.10 g, 0.40 mmol) and **5Aa** (0.115 g, 0.60 mmol) was repeated using AgOAc (3 mg, 0.02 mmol) and DBU (60 μL, 0.40 mmol). The mixture was stirred at rt overnight. After the same workup and column chromatography (hexane/EtOAc, 19:1), the following products were obtained: **7** (10 mg, 6%) and **9** (60 mg, 34%).

Compound 9: white solid, recrystallized from hexane; mp = 145 °C; $[\alpha]_D^{25}$ −80.3 (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37−7.20 (5H, H-aromatic), 4.78 (d, 1H, $J_{3,3a}$ = 7.8 Hz, H-3a), 4.25 (m, 4H, H-1, 5ax, OCH_2CH_3), 4.16 (d, 1H, $J_{4,4a}$ = 5.5 Hz, H-4a), 3.90 (d, 1H, $J_{4,5eq}$ = 2.1, $J_{5,5eq}$ = 12.2 Hz, H-5eq), 3.42 (t, 1H, $J_{3,3a}$ = 7.8, $J_{3,4}$ = 8.7 Hz, H-3), 3.36 (ddd, 1H, *J* = 4.1, *J* = 10.7 Hz, H-1 menthyl), 2.95 (dddd, 1H, $J_{3,4}$ = 8.7, $J_{4,4a}$ = 5.5, $J_{4,5ax}$ = 3.4, $J_{4,5eq=}$ 2.1 Hz, H-4), 2.18 (m, 1H, H menthyl), 1.73 (d, 1H, H menthyl), 1.60 (d, 2H, H menthyl), 1.31 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3), 1.25 (m, 2H, H menthyl), 0.96−0.72 (m, 12H, H menthyl); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 202.8 (C-2), 174.5 (OCOEt), 139.8−126.9 (C-aromatic), 96.6 (C-1), 77.0 (C-1 menthyl), 65.3 (C-3a), 63.1 (C-4a), 61.9 (C-5), 61.5 (OCH_2CH_3), 53.4 (C-3), 47.6 (C-menthyl), 45.5 (C-4), 39.7, 34.4, 31.5, 25.4, 22.9, 22.2, 21.1, 15.4 (C-menthyl), 14.4 (OCH_2CH_3); HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{38}NO_5$ 444.2744, found 444.2731.

Synthesis of Pyrrolidine Derivative 10 from Imino Ester 5Ab. According to the general procedure starting from enone **2** and imino ester **5Ab** (0.115 g, 0.60 mmol) at rt for 20 min. The reaction mixture showed by TLC (hexane/EtOAc, 4:1) a main spot (R_f 0.17). After column chromatography (hexane/EtOAc, 95:5 → 92.5:7.5), the adduct **10** was isolated.

Compound 10: syrup (160 mg, 90%); $[\alpha]_D^{25}$ −60.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40−7.23 (5H, H-aromatic), 4.73 (d, 1H, $J_{3,3a}$ = 8.2 Hz, H-3a), 4.18 (dd, 1H, $J_{4,5ax}$ = 4.5, $J_{5ax,5eq}$ = 12.8 Hz, H-5ax), 4.09 (s, 1H, H-1), 3.81 (s, 3H, OCH_3), 3.75 (dd, 1H, $J_{4,5eq}$= 2.9, $J_{5ax,5eq}$ = 12.8 Hz, H-5eq), 3.68 (dd, 1H, $J_{3,3a}$ = 8.2, $J_{3,4}$ = 7.7 Hz, H-3), 3.29 (ddd, 1H, *J* = 4.1, *J* = 10.7 Hz, H-1 menthyl), 2.74 (ddd, 1H, $J_{3,4}$ = 7.7, $J_{4,5ax}$ = 4.5, $J_{4,5eq}$ = 2.9 Hz, H-4), 2.13 (m, 1H, H menthyl), 1.62−1.54 (m, 6H, H menthyl, CH_3), 1.27−1.19 (m, 2H, H menthyl), 0.92−0.70 (m, 12H, H menthyl); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 202.1 (C-2), 174.3 (OCOMe), 137.9−126.7 (C-aromatic), 96.5 (C-1), 76.7 (C-1 menthyl), 68.4 (C-4a), 62.3 (C-3a), 59.9 (C-5), 53.8 (C-3), 53.0 (C-4), 52.7 (OCH_3), 47.6, 39.5, 34.3, 31.5 (C-menthyl), 25.5, 25.4 (C-menthyl, CH_3), 22.9, 22.2, 21.1, 15.4 (C-menthyl); HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{38}NO_5$ 444.2744, found 444.2762.

Synthesis of Pyrrolidine Derivative 11 from Imino Ester 5Ac. The general procedure starting from **2** (0.10 g, 0.40 mmol) and imino ester **5Ac** (0.16 g, 0.60 mmol) at rt for 30 min afforded crude compound **11** (R_f 0.49, hexane/EtOAc, 4:1), which was purified by column chromatography (hexane/EtOAc, 20:1).

Compound 11: white solid, recrystallized from methanol (131 mg, 63%); mp = 117 °C; $[\alpha]_D^{25}$ −120.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.48−7.14 (10H, H-aromatic), 4.73 (d, 1H, $J_{3,3a}$ = 9.0 Hz, H-3a), 4.15 (dd, 1H, $J_{4,5ax}$ = 5.1, $J_{5ax,5eq}$ = 12.5 Hz, H-5ax), 4.00 (s, 1H, H-1), 3.83 (dd, 1H, $J_{4,5eq}$ = 4.5, $J_{5ax,5eq}$ = 12.5 Hz, H-5eq), 3.74 (s, 3H, OCH_3), 3.70 (dd, 1H, $J_{3,3a}$ = 9.0, $J_{3,4}$ = 8.0 Hz, H-3), 3.25 (ddd, 1H, *J* = 4.1, *J* = 10.7 Hz, H-1 menthyl), 3.21, 2.98 (2d, 2H, *J* = 13.5 Hz, CH_2Ph), 2.87 (m, 1H, $J_{3,4}$ = 8.0, $J_{4,5ax}$ = 5.1, $J_{4,5eq}$ = 4.5 Hz, H-4), 2.78 (br s, 1H, N*H*), 2.15 (m, 1H, H menthyl), 1.61−1.45 (m, 3H, H menthyl), 1.26−1.16 (m, 2H, H menthyl), 0.90−0.68 (m, 12H, H menthyl); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 202.5 (C-2), 173.4 (OCOMe), 139.3−127.2 (C-aromatic), 97.0 (C-1), 76.8 (C-1 menthyl), 72.6 (C-4a), 61.5 (C-3a), 61.3 (C-5), 54.0 (C-3), 52.4 (OCH_3), 50.8 (C-4), 47.5(C-menthyl), 43.1 (CH_2Ph), 39.5, 34.4, 31.5, 25.4, 23.0, 22.2, 21.1, 15.5 (C-menthyl); HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{32}H_{41}NNaO_5$ 542.2877, found 542.2886.

Synthesis of Pyrrolidine Derivatives 12 and 13 from Imino Ester 5Ba. According to the general procedure starting from **2** (0.10 g, 0.40 mmol) and imino ester **5Ba** (0.115 g, 0.60 mmol) at rt for 15 min. The reaction mixture showed by TLC (EtOAc) two main spots corresponding to **13** (R_f 0.61) and **12** (R_f 0.20). The mixture was separated by column chromatography (hexane/EtOAc, 1:1 → 3:7).

Compound 12: white solid, recrystallized from ethanol/water (110 mg, 62%); mp = 147 °C dec; $[\alpha]_D^{25}$ −119.0 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.61 (d, 1H, *J* = 1.8 Hz, H-2′Py), 8.48 (dd, 1H, *J* = 1.3, 4.7 Hz, H-6′Py), 7.71 (dt, 1H, *J* = 1.5, 7.9 Hz, H-4′Py), 7.24 (dd, 1H, *J* = 4.7, 7.9 Hz, H-5′Py), 4.47 (d, 1H, $J_{3,3a}$ = 7.7 Hz, H-3a), 4.26 (m, 2H, OCH_2CH_3), 4.23 (s, 1H, H-1), 4.22 (dd, 1H, $J_{4,5ax}$ = 4.2, $J_{5ax,5eq}$ = 12.7 Hz, H-5ax), 4.04 (d, 1H, $J_{4,4a}$ = 8.3 Hz, H-4a), 3.86 (d, 1H, $J_{4,5eq}$= 2.0, $J_{5ax,5eq}$ = 12.7 Hz, H-5eq), 3.53 (dd, 1H, $J_{3,3a}$ = 7.7, $J_{3,4}$ = 7.8 Hz, H-3), 3.34 (ddd, 1H, *J* = 4.1, *J* = 10.7, H-1 menthyl), 3.08 (dddd, 1H, $J_{3,4}$ = 7.8, $J_{4,4a}$ = 8.3, $J_{4,5ax}$ = 4.2, $J_{4,5eq}$ = 2.0 Hz, H-4), 2.85 (br s, 1H, N*H*), 2.15 (m, 1H, H menthyl), 1.73 (m, 1H, H menthyl), 1.62−1.55 (m, 2H, H menthyl), 1.31 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3), 1.26−1.19 (m, 2H, H menthyl), 0.92−0.70 (m, 12H, H menthyl); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 201.9 (C-2), 171.7 (OCOEt), 148.7−123.1 (C-aromatic), 96.2 (C-1), 76.7 (C-1 menthyl), 62.3 (C-4a), 62.1 (C-3a), 61.7 (OCH_2CH_3), 58.9 (C-5), 52.7 (C-3), 47.7 (C-menthyl), 44.7 (C-4), 39.6, 34.2, 31.4, 25.4, 22.9, 22.2, 21.1, 15.4 (C-menthyl), 14.3 (OCH_2CH_3); HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{36}N_2NaO_5$ 467.2516, found 467.2522.

Compound 13: syrup (18 mg, 10%); $[\alpha]_D^{25}$ −107.5 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.63 (d, 1H, *J* = 2.0 Hz, H-2′Py), 8.47 (dd, 1H, *J* = 1.6, 4.8 Hz, H-6′Py), 7.86 (dt, 1H, *J* = 1.8, 7.9 Hz, H-4′Py), 7.24 (dd, 1H, *J* = 4.8, 7.9 Hz, H-5′Py), 5.06 (d, 1H, $J_{3,3a}$ = 2.4

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Hz, H-3a), 4.91 (s, 1H, H-1), 4.38 (dd, 1H, $J_{4,5ax}$ = 3.0, $J_{5ax,5eq}$ = 12.5 Hz, H-5ax), 4.25 (m, 2H, OCH_2CH$_3$), 3.96 (d, 1H, $J_{4,4a}$ = 10.5 Hz, H-4a), 3.88 (d, 1H, $J_{5ax,5eq}$ = 12.5 Hz, H-5eq), 3.53 (ddd, 1H, J = 4.1, J = 10.7, H-1 menthyl), 3.13 (dd, 1H, $J_{3,3a}$ = 2.4, $J_{3,4}$ = 8.1 Hz, H-3), 2.79 (m, 1H, $J_{3,4}$ = 8.1, $J_{4,4a}$ = 10.5, $J_{4,5ax}$ = 3.0 Hz, H-4), 2.44 (br s, 1H, N*H*), 2.20 (m, 1H, H menthyl), 2.07 (m, 1H, H menthyl), 1.67−1.61 (m, 2H, H menthyl), 1.36−1.21 (m, 2H, H menthyl), 1.31 (t, 3H, J = 7.1 Hz, OCH$_2$CH_3), 0.94−0.75 (m, 12H, H menthyl); ^{13}C NMR (CDCl$_3$, 125.7 MHz) δ 201.0 (C-2), 173.0 (OCOEt), 148.6−123.4 (C-aromatic), 95.7 (C-1), 77.2 (C-1 menthyl), 61.5 (OCH_2CH$_3$), 60.6 (C-4a), 57.5 (C-3a), 57.3 (C-5), 56.1 (C-3), 47.9 (C-menthyl), 44.3 (C-4), 40.0, 34.3, 31.6, 25.5, 22.9, 22.3, 21.2, 15.4 (C-menthyl), 14.4 (OCH_2CH$_3$); HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{25}H_{37}N_2O_5$ 445.2697, found 445.2717.

Synthesis of Pyrrolidine Derivative ***14*** *from Imino Ester* ***5Bb***. According to the general procedure, starting from **2** (0.10 g, 0.40 mmol) and imino ester **5Bb** (0.115 g, 0.60 mmol) at rt for 15 min. The product (R_f 0.15, EtOAc) was purified by column chromatography (EtOAc/hexane 1.5:1).

Compound ***14:*** syrup (156 mg, 88%); $[\alpha]_D^{25}$ −108.0 (c 1.0, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 500 MHz) δ 8.58 (br s, 1H, Hz, H-2′Py), 8.45 (dd, 1H, J = 1.3, 4.8 Hz, H-6′Py), 7.75 (br d, 1H, J = 7.9 Hz, H-4′Py), 7.24 (dd, 1H, J = 4.8, 7.9 Hz, H-5′Py), 4.47 (d, 1H, $J_{3,3a}$ = 6.5 Hz, H-3a), 4.32 (dd, 1H, $J_{4,5ax}$ = 3.9, $J_{5ax,5eq}$ = 12.7 Hz, H-5ax), 4.28 (s, 1H, H-1), 3.85 (dd, 1H, $J_{4,5eq}$= 1.9, $J_{5ax,5eq}$ = 12.7 Hz, H-5eq), 3.74 (s, 3H, OCH_3), 3.57 (dd, 1H, $J_{3,3a}$ = 6.5, $J_{3,4}$ = 7.3 Hz, H-3), 3.35 (ddd, 1H, J = 4.1, J = 10.7 Hz, H-1 menthyl), 2.68 (ddd, 1H, $J_{3,4}$ = 7.3, $J_{4,5ax}$ = 3.9, $J_{4,5eq}$ = 1.9 Hz, H-4), 2.17 (m, 1H, H menthyl), 2.00 (s, 1H, H menthyl), 1.77 (m, 1H, H menthyl), 1.61−1.55 (m, 2H, H menthyl) 1.50 (s, 3H, CH_3), 1.24−1.20 (m, 1H, H menthyl), 0.92−0.72 (m, 12H, H menthyl); ^{13}C NMR (CDCl$_3$, 125.7 MHz) δ 200.5 (C-2), 174.9 (OCOMe), 148.3−123.0 (C-aromatic), 96.0 (C-1), 76.7 (C-1 menthyl), 66.4 (C-4a), 60.4 (C-3a), 58.0 (C-5), 53.8 (C-4), 52.9 (OCH_3), 52.3 (C-3), 47.7, 39.7, 34.3, 31.4 (C-menthyl), 26.4 (CH_3), 25.5, 22.9, 22.1, 21.1, 15.4 (C-menthyl); HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{25}H_{37}N_2O_5$ 445.2697, found 445.2702.

Synthesis of Pyrrolidine Derivative ***15*** *from Imino Ester* ***5Bc***. According to the general procedure, starting from **2** (0.10 g, 0.40 mmol) and imino ester **5Bc** (0.16 g, 0.60 mmol) at rt for 1 h. The product of R_f 0.35 (hexane/EtOAc, 1:1) was purified by column chromatography (hexane/EtOAc, 85:15).

Compound ***15:*** syrup (185 mg, 89%); $[\alpha]_D^{25}$ −75.7 (c 1.0, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 500 MHz) δ 8.63−7.21 (9H, H-aromatic), 4.34 (d, 1H, $J_{3,3a}$ = 7.2 Hz, H-3a) 4.33 (dd, 1H, $J_{4,5ax}$ = 4.2, $J_{5ax,5eq}$ = 12.6 Hz, H-5ax), 4.26 (s, 1H, H-1), 3.96 (dd, 1H, $J_{4,5eq}$= 2.8, $J_{5ax,5eq}$ = 12.6 Hz, H-5eq), 3.71 (s, 3H, OCH_3), 3.60 (t, 1H, $J_{3,3a}$ = $J_{3,4}$ = 7.2 Hz, H-3), 3.36 (ddd, 1H, J = 4.1, J = 10.7, H-1 menthyl), 3.23, 2.97 (2d, 2H, J = 13.5 Hz, CH_2Ph), 2.87 (m, 1H, $J_{3,4}$ = 7.2, $J_{4,5ax}$ = 4.2, $J_{4,5eq}$ = 2.8 Hz, H-4), 2.20 (m, 1H, H menthyl), 1.74 (d, 1H, H menthyl), 1.64−1.58 (m, 2H, H-menthyl), 1.25−1.21 (m, 2H, H menthyl), 0.92−0.75 (m, 12H, H menthyl); ^{13}C NMR (CDCl$_3$, 125.7 MHz) δ 201.0 (C-2), 173.7 (OCOMe), 148.7−123.0 (C-aromatic), 96.3 (C-1), 76.8 (C-1 menthyl), 70.8 (C-4a), 59.9 (C-3a), 58.8 (C-5), 52.7 (OCH_3), 52.1 (C-3), 51.5 (C-4), 47.7 (C-menthyl), 43.6 (CH_2Ph), 39.7, 34.3, 31.5, 25.5, 22.9, 22.2, 21.2, 15.5 (C-menthyl); HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{31}H_{41}N_2O_5$ 521.3010, found 521.3001.

Synthesis of Pyrrolidine Derivatives ***16−19*** *from Imino Ester* ***5Ca***. The general procedure was followed starting from **2** (0.10 g, 0.40 mmol) and imino ester **5Ca** (0.13 g, 0.60 mmol) at rt for 15 min. Monitoring by TLC (hexane/EtOAc, 7:3) showed two main spots corresponding to compounds **17** (R_f 0.55) and **16** (R_f 0.24). However, after column chromatography (hexane/EtOAc, 19:1 → 4:1) of the crude mixture, two new compounds were isolated. One of them (compound **19**, R_f 0.10) turned out to be the major product.

Compound ***16:*** white solid recrystallized from ethanol/water (11 mg, 6%); $[\alpha]_D^{25}$ −54.9 (c 1.0, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.29, 6.86 (2d, 2H each, J = 8.8 Hz, H-aromatic), 4.60 (d, 1H, $J_{3,3a}$ = 9.4 Hz, H-3a), 4.31 (q, 2H, OCH_2CH$_3$), 4.08 (s, 1H, H-1), 4.07 (d, 1H, $J_{4,4a}$ = 6.8 Hz, H-4a), 4.04 (dd, 1H, $J_{4,5ax}$ = 4.7, $J_{5ax,5eq}$ = 12.7 Hz, H-5ax), 3.78 (s, 3H, OCH_3), 3.75 (dd, 1H, $J_{4,5eq}$ = 3.0, $J_{5ax,5eq}$ = 12.7 Hz, H-5eq), 3.52 (dd, 1H, $J_{3,3a}$ = 9.4, $J_{3,4}$ = 8.4 Hz, H-3), 3.29 (ddd, 1H, J = 4.1, J = 10.7, H-1 menthyl), 3.01 (m, 1H, $J_{3,4}$ = 8.4, $J_{4,4a}$ = 6.8, $J_{4,5ax}$ = 4.7, $J_{4,5eq}$ = 3.0 Hz, H-4), 2.12 (m, 1H, H menthyl), 1.61−1.56 (m, 2H, H menthyl), 1.34 (t, 3H, J = 7.1 Hz, OCH$_2$CH_3), 1.30−1.20 (m, 3H, H menthyl), 0.89−0.68 (m, 12H, H menthyl); ^{13}C NMR (CDCl$_3$, 125.7 MHz) δ 204.2 (C-2), 171.2 (OCOEt), 159.0−113.9 (C-aromatic), 96.6 (C-1), 76.4 (C-1 menthyl), 64.2 (C-4a), 63.9 (C-3a), 61.5 (OCH_2CH$_3$), 60.8 (C-5), 55.5 (C-3), 55.3 (OCH_3), 47.5 (C-menthyl), 44.4 (C-4), 39.5, 34.4, 31.5, 25.3, 22.9, 22.3, 21.1, 15.4 (C-menthyl), 14.4 (OCH_2CH$_3$); HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{27}H_{39}NNaO_6$ 496.2670, found 496.2650.

Compound ***17:*** white solid, recrystallized from ethanol/water (26 mg, 14%); mp = 107 °C; $[\alpha]_D^{25}$ −88.5 (c 1.0, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.40, 6.86 (2d, 2H each, J = 8.8 Hz, H-aromatic), 4.92 (s, 1H, H-1), 4.90 (d, 1H, $J_{3,3a}$ = 3.2 Hz, H-3a), 4.36 (dd, 1H, $J_{4,5ax}$ = 3.3, $J_{5ax,5eq}$ = 12.4 Hz, H-5ax), 4.26 (m, 2H, OCH_2CH$_3$), 3.94 (d, 1H, $J_{4,4a}$ = 10.2 Hz, H-4a), 3.89 (d, 1H, $J_{5ax,5eq}$ = 12.4 Hz, H-5eq), 3.79 (s, 3H, OCH_3), 3.53 (ddd, 1H, J = 4.1, J = 10.7, H-1 menthyl), 3.09 (dd, 1H, $J_{3,3a}$ = 3.2, $J_{3,4}$ = 8.4 Hz, H-3), 2.78 (m, 1H, $J_{3,4}$ = 8.4, $J_{4,4a}$ = 10.2, $J_{4,5ax}$ = 3.3 Hz, H-4), 2.22 (m, 1H, H menthyl), 2.09 (m, 1H, H menthyl), 1.69−1.62 (m, 2H, H menthyl), 1.36 (m, 1H, H menthyl), 1.32 (t, 3H, J = 7.1 Hz, OCH$_2$CH_3), 1.27 (m, 1H, H menthyl), 0.98−0.75 (m, 12H, H menthyl); ^{13}C NMR (CDCl$_3$, 125.7 MHz) δ 201.9 (C-2), 173.2 (OCOEt), 158.9−114.0 (C-aromatic), 95.7 (C-1), 77.0 (C-1 menthyl), 61.4 (OCH_2CH$_3$), 61.2 (C-4a), 60.2 (C-3a), 58.0 (C-5), 56.7 (C-3), 55.4 (OCH_3), 47.9 (C-menthyl), 44.6 (C-4), 40.0, 34.4, 31.6, 25.5, 23.0, 22.3, 21.2, 15.4 (C-menthyl), 14.4 (OCH_2CH$_3$); HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{27}H_{40}NO_6$ 474.2850, found 474.2830.

Compound ***18:*** syrup (4 mg, 4%); R_f 0.52; $[\alpha]_D^{25}$ −91.7 (c 1.1, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.34, 6.86 (2d, 2H each, J = 8.8 Hz, H-aromatic), 5.26 (br s, 1H, $J_{3,3a}$ < 1 Hz, H-3a), 4.75 (s, 1H, H-1), 4.36 (dd, 1H, $J_{4,5ax}$ = 2.9, $J_{5ax,5eq}$ = 12.5 Hz, H-5ax), 4.17 (q, 2H, OCH_2CH$_3$), 4.01 (d, 1H, $J_{4,4a}$ = 7.9 Hz, H-4a), 3.97 (d, 1H, $J_{5ax,5eq}$ = 12.5 Hz, H-5eq), 3.79 (s, 3H, OCH_3), 3.48 (ddd, 1H, J = 4.1, J = 10.7, H-1 menthyl), 2.99 (m, 1H, $J_{3,4}$ = 9.0, $J_{4,4a}$ = 7.9, $J_{4,5ax}$ = 2.9 Hz, H-4), 2.97 (dd, 1H, $J_{3,3a}$ < 1, $J_{3,4}$ = 9.0 Hz, H-3), 2.20 (m, 1H, H menthyl), 2.07 (m, 1H, H menthyl), 1.67−1.62 (m, 2H, H menthyl), 1.32−1.25 (m, 2H, H menthyl), 1.28 (t, 3H, J = 7.1 Hz, OCH$_2$CH_3), 0.92−0.76 (m, 12H, H menthyl); ^{13}C NMR (CDCl$_3$, 125.7 MHz) δ 200.7 (C-2), 174.6 (OCOEt), 158.7−113.9 (C-aromatic), 95.3 (C-1), 76.8 (C-1 menthyl), 61.8 (C-4a), 61.7 (OCH_2CH$_3$), 59.8 (C-3a), 56.3 (C-5), 55.5 (OCH_3), 55.1 (C-3), 48.0 (C-menthyl), 43.0 (C-4), 40.0, 34.4, 31.6, 25.4, 22.9, 22.3, 21.2, 15.4 (C-menthyl), 14.4 (OCH_2CH$_3$); HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{27}H_{40}NO_6$ 474.2850, found 474.2848.

Compound ***19:*** syrup (57 mg, 40%); $[\alpha]_D^{25}$ −142.8 (c 0.9, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 500 MHz) δ 4.63 (s, 1H, H-1), 4.24 (m, 2H, OCH_2CH$_3$), 4.06 (d, 1H, $J_{4,4a}$ = 5.2 Hz, H-4a), 3.75 (d, 1H, $J_{5ax,5eq}$ = 11.3 Hz, H-5ax), 3.54 (dt, 1H, $J_{3eq,5eq}$ ∼ $J_{4,5eq}$ ∼ 1.0, $J_{5ax,5eq}$ = 11.3 Hz, H-5eq), 3.48 (ddd, 1H, J = 4.1, J = 10.7, H-1 menthyl), 2.56 (br m, 1H, H-4), 2.40 (d, 1H, $J_{3ax,3eq}$ = 10.9 Hz, H-3ax), 2.26 (m, 1H, H menthyl), 2.09 (m, 1H, H menthyl), 1.94 (br dd, 1H, $J_{3ax,3eq}$ = 10.9, $J_{3eq,4}$ = 3.5, $J_{3eq,5eq}$ ∼ 1 Hz, H-3eq), 1.65−1.60 (m, 2H, H menthyl), 1.29 (t, 3H, J = 7.1 Hz, OCH$_2$CH_3), 0.92−0.74 (m, 12H, H menthyl); ^{13}C NMR (CDCl$_3$, 125.7 MHz) δ 172.2 (OCOEt), 98.9 (C-1), 75.2 (C-1 menthyl), 63.9 (C-5), 61.4 (OCH_2CH$_3$), 59.5 (C-4a), 47.8 (C-menthyl), 40.5 (C-4), 39.7 (C-menthyl), 37.8 (C-3), 34.6, 31.6, 25.5, 23.0, 22.4, 21.2, 15.4 (C-menthyl), 14.4 (OCH_2CH$_3$); HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{19}H_{34}NO_5$ 356.2431, found 356.2438.

Synthesis of Pyrrolidine Derivatives ***20*** *and* ***21*** *from Imino Ester* ***5Cb***. According to the general procedure, starting from **2** (0.10 g, 0.40 mmol) and imino ester **5Cb** (0.13 g, 0.60 mmol) at rt for 1 h. The residue showed by TLC (hexane/EtOAc, 4:1) spots corresponding to **20** (R_f 0.10) and **21** (R_f 0.35). The mixture was purified by column chromatography (hexane/EtOAc, 9:1).

Compound ***20:*** syrup (85 mg, 45%); $[\alpha]_D^{25}$ −80.9 (c 1.1, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.29, 6.86 (2d, 2H each, J = 8.5 Hz, H-aromatic), 4.67 (d, 1H, $J_{3,3a}$ = 8.6 Hz, H-3a), 4.12 (dd, 1H, $J_{4,5ax}$ = 4.8, $J_{5ax,5eq}$ = 12.7 Hz, H-5ax), 4.04 (s, 1H, H-1), 3.81, 3.78 (2s, 3H each, 2

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OCH_3), 3.71 (dd, 1H, $J_{4,5eq}$= 3.2, $J_{5ax,5eq}$ = 12.7 Hz, H-5eq), 3.60 (dd, 1H, $J_{3,3a}$ = 8.6, $J_{3,4}$ = 7.8 Hz, H-3), 3.28 (ddd, 1H, J = 4.1, J = 10.7 Hz, H-1 menthyl), 2.68 (m, 1H, $J_{3,4}$ = 7.8, $J_{4,5ax}$ = 4.8, $J_{4,5eq}$ = 3.2 Hz, H-4), 2.13 (m, 1H, H menthyl), 1.62−1.56 (m, 3H, H menthyl), 1.51 (s, 3H, CH_3), 1.26−1.18 (m, 2H, H menthyl), 0.92−0.69 (m, 12H, H menthyl); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 203.0 (C-2), 174.6 (OCOMe), 158.9−113.8 (C-aromatic), 96.6 (C-1), 76.6 (C-1 menthyl), 68.6 (C-4a), 62.0 (C-3a), 60.7 (C-5), 55.3, 52.7 (2 OCH_3), 54.4 (C-3), 52.1 (C-4), 47.6, 39.6, 34.4, 31.5 (C-menthyl), 25.6 (CH_3), 25.4, 23.0, 22.2, 21.1, 15.4 (C-menthyl); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{27}H_{40}NO_6$ 474.2850, found 474.2863.

Compound ***21****:* syrup (40 mg, 21%); $[\alpha]_D^{25}$ −88.1 (c 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41, 6.86 (2d, 2H each, J = 8.6 Hz, H-aromatic), 5.20 (d, 1H, $J_{3,3a}$ = 3.1 Hz, H-3a), 4.74 (s, 1H, H-1), 4.33 (dd, 1H, $J_{4,5ax}$ = 4.1, $J_{5ax,5eq}$ = 12.7 Hz, H-5ax), 3.86 (d, 1H, $J_{5ax,5eq}$ = 12.7 Hz, H-5eq), 3.79, 3.64 (2s, 3H each, 2 OCH_3), 3.48 (ddd, 1H, J = 4.1, J = 10.1 Hz, H-1 menthyl), 2.96 (dd, 1H, $J_{3,3a}$ = 3.1, $J_{3,4}$ = 9.3 Hz, H-3), 2.51 (dd, 1H, $J_{3,4}$ = 9.3, $J_{4,5ax}$ = 4.1 Hz, H-4), 2.18 (m, 1H, H menthyl), 2.08 (m, 1H, H menthyl), 1.65−1.60 (m, 2H, H menthyl), 1.54 (s, 3H, CH_3), 1.36−1.21 (m, 2H, H menthyl), 0.93−0.75 (m, 12H, H menthyl); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 200.5 (C-2), 176.8 (OCOMe), 158.7−113.9 (C-aromatic), 95.1 (C-1), 76.9 (C-1 menthyl), 66.7 (C-4a), 59.9 (C-3a), 55.5 (× 2), 55.4 (C-3, C-5, OCH_3), 52.3 (OCH_3), 50.0 (C-4), 48.0, 40.0, 34.4, 31.6, 25.4 (C-menthyl), 25.2 (CH_3), 23.0, 22.3, 21.2, 15.5 (C-menthyl); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{27}H_{40}NO_6$ 474.2850, found 474.2845.

Synthesis of Pyrrolidine Derivatives ***22*** *and* ***23*** *from Imino Ester* ***5Cc****.* According to the general procedure starting from **2** (0.10 g, 0.40 mmol) and imino ester **5Cc** (0.18 g, 0.60 mmol) at rt for 1 h. The reaction mixture showed by TLC (hexane/EtOAc, 4:1) spots corresponding to **22** (R_f 0.38) and **23** (R_f 0.44). The products were separated by column chromatography (hexane/EtOAc, 20:1).

Compound ***22****:* syrup (64 mg, 29%); $[\alpha]_D^{25}$ −69.5 (c 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38−6.84 (9H, H-aromatic), 4.75 (d, 1H, $J_{3,3a}$ = 9.3 Hz, H-3a), 4.13 (dd, 1H, $J_{4,5ax}$ = 5.2, $J_{5ax,5eq}$ = 12.5 Hz, H-5ax), 4.00 (s, 1H, H-1), 3.81 (dd, 1H, $J_{4,5eq}$ = 4.9, $J_{5ax,5eq}$ = 12.5 Hz, H-5eq), 3.78, 3.73 (2s, 3H each, 2 OCH_3), 3.66 (dd, 1H, $J_{3,3a}$ = 9.3, $J_{3,4}$ = 8.2 Hz, H-3), 3.26 (ddd, 1H, J = 4.1, J = 10.7 Hz, H-1 menthyl), 3.21, 2.97 (2d, 2H, J = 13.5 Hz, CH_2Ph), 2.86 (m, 1H, $J_{3,4}$ = 8.2, $J_{4,5ax}$ = 5.2, $J_{4,5eq}$ = 4.9 Hz, H-4), 2.14 (m, 1H, H menthyl), 1.61−1.56 (m, 2H, H menthyl), 1.50 (m, 1H, H-menthyl), 1.28−1.20 (m, 2H, H-menthyl), 0.86−0.69 (m, 12H, H menthyl); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 202.8 (C-2), 173.3 (OCOMe), 159.0−113.8 (C-aromatic), 97.1 (C-1), 76.8 (C-1 menthyl), 72.8 (C-4a), 61.7 (C-5), 61.0 (C-3a), 55.3 (OCH_3), 54.1 (C-3), 52.3 (OCH_3), 50.4 (C-4), 47.5 (C-menthyl), 43.0 (CH_2Ph), 39.5, 34.4, 31.5, 25.3, 23.0, 22.2, 21.1, 15.5 (C-menthyl); HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{33}H_{43}NNaO_6$ 572.2983, found 572.2991.

Compound ***23****:* syrup (11 mg 5%); $[\alpha]_D^{25}$ −105.5 (c 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.35−6.82 (9H, H-aromatic), 5.14 (d, 1H, $J_{3,3a}$ = 3.4 Hz, H-3a), 4.76 (s, 1H, H-1), 4.37 (dd, 1H, $J_{4,5ax}$ = 4.1, $J_{5ax,5eq}$ = 12.7 Hz, H-5ax), 4.05 (dd, 1H, $J_{5ax,5eq}$ = 12.7 Hz, H-5eq), 3.79, 3.63 (2s, 3H each, 2 OCH_3), 3.48 (m, 2H, CHPh, H-1 menthyl), 2.91 (dd, 1H, $J_{3,3a}$ = 3.4, $J_{3,4}$ = 9.4 Hz, H-3), 2.89 (d, 1H, J = 13.5 Hz, CHPh), 2.64 (m, 1H, $J_{3,4}$ = 9.4, $J_{4,5ax}$ = 4.1 Hz, H-4), 2.20 (m, 1H, H menthyl), 2.07 (m, 1H, H menthyl), 1.67−1.60 (m, 3H, NH, H-menthyl), 1.33 (m, 1H, H-menthyl), 1.24 (m, 1H, H menthyl), 0.92−0.78 (m, 12H, H menthyl); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 200.6 (C-2), 175.6 (OCOMe), 158.6−113.8 (C-aromatic), 95.2 (C-1), 76.9 (C-1 menthyl), 70.6 (C-4a), 59.2 (C-3a), 55.7 (C-5), 55.5 (OCH_3), 55.2 (C-3), 52.2 (OCH_3), 48.3 (C-4), 48.0 (C-menthyl), 43.8 (CH_2Ph), 40.0, 34.4, 31.6, 25.5, 23.0, 22.3, 21.2, 15.5 (C-menthyl); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{33}H_{44}NO_6$ 550.3163, found 550.3140.

Isomerization of Pyrrolidines with SiO_2*−Toluene.* The general procedure for the cycloaddition reaction was followed starting from **2** (50 mg, 0.20 mmol) and the corresponding α-imino ester. After the usual workup and filtration through Celite, the solvent was evaporated, the residue was dissolved in toluene (5 mL), and SiO_2 (200 mg) was added. The mixture was heated at 80 °C for 2 h. The SiO_2 was removed by filtration, and the solution was concentrated and chromatographed on silica gel. The results are shown in Table 3. The new compounds have been isolated and characterized as follows.

*Compound epi-****7****:* white solid, recrystallized from ethanol/water (41 mg, 46%); mp = 82 °C; R_f 0.61, hexane/EtOAc, 7:3; $[\alpha]_D^{25}$ −97.3 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.43−7.23 (5H, H-aromatic), 5.33 (br s, 1H, H-3a), 4.76 (s, 1H, H-1), 4.34 (dd, 1H, $J_{4,5ax}$ = 3.0, $J_{5ax,5eq}$ = 12.5 Hz, H-5ax), 4.18 (m, 2H, OCH_2CH_3), 4.03 (d, 1H, $J_{4,4a}$ = 8.0 Hz, H-4a), 3.98 (d, 1H, $J_{5ax,5eq}$ = 12.5 Hz, H-5eq), 3.48 (ddd, 1H, J = 4.1, J = 10.7, H-1 menthyl), 3.00 (m, 2H, H-3, H-4), 2.19 (m, 1H, H menthyl), 2.08 (m, 1H, H menthyl), 1.66−1.61 (m, 2H, H menthyl), 1.29 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 1.32−1.25 (m, 2H, H menthyl), 0.93−0.65 (m, 12H, H menthyl); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 200.5 (C-2), 174.6 (OCOEt), 144.9−126.3 (C-aromatic), 95.3 (C-1), 76.8 (C-1 menthyl), 61.8 (C-4a), 61.7 (OCH_2CH_3), 60.2 (C-3a), 56.2 (C-5), 55.1, 43.0 (C-3, C-4), 48.0 (C-menthyl), 40.0, 34.4, 31.6, 25.4, 22.9, 22.3, 21.2, 15.4 (C-menthyl), 14.2 (OCH_2CH_3); HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{26}H_{37}NNaO_5$ 466.2564, found 466.2559.

*Compound epi-****10****:* syrup (26 mg, 30%); R_f 0.63, hexane/EtOAc, 7:3; $[\alpha]_D^{25}$ −74.9 (c 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.52−7.20 (5H, H-aromatic), 5.27 (d, 1H, $J_{3,3a}$ = 3.0 Hz, H-3a), 4.75 (s, 1H, H-1), 4.34 (dd, 1H, $J_{4,5ax}$ = 4.1, $J_{5ax,5eq}$ = 12.7 Hz, H-5ax), 3.87 (d, 1H, $J_{5ax,5eq}$ = 12.7 Hz, H-5eq), 3.65 (s, 3H, OCH_3), 3.48 (ddd, 1H, J = 4.1, J = 10.1 Hz, H-1 menthyl), 2.99 (dd, 1H, $J_{3,3a}$ = 3.0, $J_{3,4}$ = 9.3 Hz, H-3), 2.52 (dd, 1H, $J_{3,4}$ = 9.3, $J_{4,5ax}$ = 4.1, $J_{4,5eq}$ = 0 Hz, H-4), 2.18 (m, 1H, H menthyl), 2.08 (m, 1H, H menthyl), 1.66−1.61 (m, 2H, H menthyl), 1.56 (s, 3H, CH_3), 1.36−1.20 (m, 2H, H menthyl), 0.92−0.76 (m, 12H, H menthyl); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 200.3 (C-2), 176.8 (OCOMe), 146.0−126.5 (C-aromatic), 95.1 (C-1), 76.9 (C-1 menthyl), 66.8 (C-4a), 60.2 (C-3a), 55.5, 55.4 (C-3, C-5), 52.3 (OCH_3), 49.9 (C-4), 48.0, 40.0, 34.4, 31.6, 25.4 (C- menthyl), 25.2 (CH_3), 23.0, 22.3, 21.2, 15.5 (C-menthyl); HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{26}H_{37}NNaO_5$ 466.2564, found 466.2576.

*Isomerization of endo-****7*** *to epi-****7*** *with* SiO_2*−Toluene.* Compound *epi*-**7** was obtained upon treatment of pure *endo*-**7** (50 mg, 1.13 mmol) with SiO_2 (100 mg) in toluene (2 mL). The suspension was heated at 80 °C for 2 h, filtered, and concentrated. Column chromatography (hexane/EtOAc, 12:1) of the resulting syrup gave *epi*-**7** (20 mg, 40%), and starting *endo*-**7** (9 mg) was also recovered.

Synthesis of Pyrrolidine Derivatives 24−37 from Dihydropyranone 4. The dipolar cycloaddition reactions of azomethine ylides (**6Aa−6Cc**) to the pyranone **4** have been conducted using the general procedures and the particular methodologies applied for the preparation of the analogous adducts from **2**. The following pyrrolidines derived from the sugar pyranone **4** have been obtained.

Synthesis of Pyrrolidine Derivatives ***24*** *and* ***25*** *from Imino Ester* ***5Aa****. Compound* ***24****:* white crystals obtained upon slow evaporation of MeCN; mp = 139 °C; R_f 0.18, 76 mg, 43%; $[\alpha]_D^{25}$ +32.4 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36−7.20 (5H, H-aromatic), 4.62 (d, 1H, $J_{3,3a}$ = 9.3 Hz, H-3a), 4.30 (m, 2H, OCH_2CH_3), 4.08 (dd, 1H, $J_{4,5ax}$ = 4.7, $J_{5ax,5eq}$ = 12.8 Hz, H-5ax), 4.06 (d, 1H, $J_{4,4a}$ = 6.9 Hz, H-4a), 3.94 (s, 1H, H-1), 3.76 (dd, 1H, $J_{4,5eq}$ = 2.9, $J_{5ax,5eq}$ = 12.8 Hz, H-5eq), 3.56 (dd, 1H, $J_{3,3a}$ = 9.3, $J_{3,4}$ = 8.4 Hz, H-3), 3.08 (ddd, 1H, J = 4.1, J = 10.7 Hz H-1 menthyl), 3.00 (m, 1H, $J_{3,4}$ = 8.4, $J_{4,4a}$ = 6.9, $J_{4,5ax}$ = 4.7, $J_{4,5eq}$ = 2.9 Hz, H-4), 1.95−1.88 (m, 2H, H menthyl), 1.59−1.51 (m, 2H, H menthyl), 1.34 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 1.30−1.40 (m, 2H, H menthyl), 0.86−0.45 (m, 12H, H menthyl); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 202.8 (C-2), 171.3 (OCOEt), 138.1−126.7 (C-aromatic), 101.2 (C-1), 81.0 (C-1 menthyl), 64.1 (× 2) (C-3a, 4a), 61.5 (OCH_2CH_3), 60.2 (C-5), 55.0 (C-3), 48.7 (C-menthyl), 44.7 (C-4), 42.9, 34.3, 31.8, 25.0, 23.2, 22.3, 21.1, 16.0 (C-menthyl), 14.4 (OCH_2CH_3); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{26}H_{38}NO_5$ 444.2744, found 444.2763.

Compound ***25****:* syrup; R_f 0.60, 19 mg, 11%; $[\alpha]_D^{25}$ +70.1 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.46−7.22 (5H, H-aromatic), 5.01 (d, 1H, $J_{3,3a}$ = 2.5 Hz, H-3a), 4.82 (s, 1H, H-1), 4.44 (dd, 1H, $J_{4,5ax}$ = 3.3, $J_{5ax,5eq}$ = 12.4 Hz, H-5ax), 4.27 (q, 2H, J = 7.1 Hz, OCH_2CH_3), 3.93 (d, 1H, $J_{4,4a}$ = 10.5 Hz, H-4a), 3.92 (d, 1H, $J_{5ax,5eq}$ = 12.4 Hz, H-5eq), 3.42 (ddd, 1H, J = 4.1, J = 10.7, H-1 menthyl), 3.15 (dd, 1H, $J_{3,3a}$

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= 2.5, $J_{3,4}$ = 8.2 Hz, H-3), 2.78 (m, 1H, $J_{3,4}$ = 8.2, $J_{4,4a}$ = 10.5, $J_{4,5ax}$ = 3.3 Hz, H-4), 2.17 (m, 1H, H menthyl), 2.04 (m, 1H, H menthyl), 1.67−1.59 (m, 2H, H menthyl), 1.40 (m, 1H, H menthyl), 1.32 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 1.29−1.25(m, 1H, H menthyl), 0.94−0.73 (m, 12H, H menthyl); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 200.7 (C-2), 173.3 (OCOEt), 144.0−126.5 (C-aromatic), 100.8 (C-1), 82.5 (C-1 menthyl), 61.4 (OCH_2CH_3), 61.0 (C-4a), 60.1 (C-3a), 57.5 (C-5), 56.3 (C-3), 48.6 (C-menthyl), 44.6 (C-4), 43.1, 34.3, 31.8, 25.5, 23.3, 22.3, 21.1, 16.2 (C-menthyl), 14.4 (OCH_2CH_3); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{26}H_{38}NO_5$ 444.2744, found 444.2756.

*Synthesis of Pyrrolidine Derivative **26** from Imino Ester **5Ab**. Compound **26**:* white crystals obtained upon slow evaporation of MeCN; mp = 116 °C; R_f 0.17, 120 mg, 68%; $[\alpha]_D^{25}$ +36.5 (c 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37−7.20 (5H, H-aromatic), 4.66 (d, 1H, $J_{3,3a}$ = 8.4 Hz, H-3a), 4.16 (dd, 1H, $J_{4,5ax}$ = 4.6, $J_{5ax,5eq}$ = 12.8 Hz, H-5ax), 3.93 (s, 1H, H-1), 3.81 (s, 3H, OCH_3), 3.72 (dd, 1H, $J_{4,5eq}$ = 2.9, $J_{5ax,5eq}$ = 12.8 Hz, H-5eq), 3.63 (dd, 1H, $J_{3,3a}$ = 8.4, $J_{3,4}$ = 7.7 Hz, H-3), 3.09 (ddd, 1H, J = 4.1, J = 10.7 Hz, H-1 menthyl), 2.66 (ddd, 1H, $J_{3,4}$ = 7.7, $J_{4,5ax}$ = 4.6, $J_{4,5eq}$ = 2.9 Hz, H-4), 1.96−1.86 (m, 2H, H menthyl), 1.60−1.49 (m, 5H, H menthyl, CH_3), 1.34−1.13 (m, 2H, H menthyl), 0.88−0.48 (m, 12H, H menthyl); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 201.8 (C-2), 174.5 (OCOMe), 138.4−126.7 (C-aromatic), 101.1 (C-1), 81.0 (C-1 menthyl), 68.5 (C-4a), 62.2 (C-3a), 60.0 (C-5), 54.1 (C-3), 52.7 (OCH_3), 52.4 (C-4), 48.6, 42.9, 34.2, 31.7 (C-menthyl), 25.6 (CH_3), 25.0, 23.2, 22.2, 21.1, 16.1 (C-menthyl); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{26}H_{38}NO_5$ 444.2744, found 444.2755.

*Synthesis of Pyrrolidine Derivative **27** from Imino Ester **5Ac**. Compound **27**:* syrup; R_f 0.56, 160 mg, 77%; $[\alpha]_D^{25}$ +15.4 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.44−7.16 (5H, H-aromatic), 4.73 (d, 1H, $J_{3,3a}$ = 9.1 Hz, H-3a), 4.17 (dd, 1H, $J_{4,5ax}$ = 5.1, $J_{5ax,5eq}$ = 12.6 Hz, H-5ax), 3.90 (s, 1H, H-1), 3.82 (dd, 1H, $J_{4,5eq}$ = 4.4, $J_{5ax,5eq}$ = 12.6 Hz, H-5eq), 3.74 (s, 3H, OCH_3), 3.69 (dd, 1H, $J_{3,3a}$ = 9.1, $J_{3,4}$ = 7.9 Hz, H-3), 3.22, 2.97 (2d, 2H, J = 13.5 Hz, CH_2Ph), 3.07 (ddd, 1H, J = 4.1, J = 10.7 Hz, H-1 menthyl), 2.85 (ddd, 1H, $J_{3,4}$ = 7.9, $J_{4,5ax}$ = 5.1, $J_{4,5eq}$ = 4.4 Hz, H-4), 1.96−1.86 (m, 2H, H menthyl), 1.59−1.52 (m, 2H, H menthyl), 1.28−1.16 (m, 2H, H menthyl), 0.90−0.46 (m, 12H, H menthyl); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 201.7 (C-2), 173.3 (OCOMe), 139.3−127.1 (C-aromatic), 101.2 (C-1), 80.9 (C-1 menthyl), 72.7 (C-4a), 61.3 (C-3a), 60.9 (C-5), 53.7 (C-3), 52.3 (OCH_3), 50.6 (C-4), 48.5 (C-menthyl), 42.9, 42.8 (CH_2Ph, C-menthyl), 34.2, 31.7, 25.0, 23.1, 22.2, 21.0, 16.0 (C-menthyl); HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{32}H_{41}NNaO_5$ 542.2877, found 542.2877.

*Synthesis of Pyrrolidine Derivatives **28** and **29** from Imino Ester **5Ba**. Compound **28**:* white solid, recrystallized from ethanol/water; mp = 75 °C; R_f 0.18, 105 mg, 59%; $[\alpha]_D^{25}$ +30.3 (c 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.60 (d, 1H, J = 2.2 Hz, H-2′Py), 8.49 (dd, 1H, J = 1.5, 4.8 Hz, H-6′Py), 7.74 (m, 1H, H-4′Py), 7.26 (dd, 1H, J = 4.8, 7.9 Hz, H-5′Py), 4.46 (d, 1H, $J_{3,3a}$ = 7.5 Hz, H-3a), 4.30 (dd, 1H, $J_{4,5ax}$ = 4.3, $J_{5ax,5eq}$ = 12.4 Hz, H-5ax), 4.26 (m, 2H, OCH_2CH_3), 4.16 (s, 1H, H-1), 4.04 (d, 1H, $J_{4,4a}$ = 8.3 Hz, H-4a), 3.87 (d, 1H, $J_{4,5eq}$= 2.4, $J_{5ax,5eq}$ = 12.4 Hz, H-5eq), 3.53 (t, 1H, $J_{3,3a}$ = $J_{3,4}$ = 7.5 Hz, H-3), 3.19 (ddd, 1H, J = 4.1, J = 10.7, H-1 menthyl), 3.08 (m, 1H, $J_{3,4}$ = 7.5, $J_{4,4a}$ = 8.3, $J_{4,5ax}$ = 4.3, $J_{4,5eq}$ = 2.4 Hz, H-4), 2.70 (br s, 1H, N*H*), 2.01 (m, 1H, H menthyl), 1.92 (m, 1H, H menthyl), 1.62−1.53 (m, 2H, H menthyl), 1.32 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 1.27−1.14 (m, 2H, H menthyl), 0.97−0.53 (m, 12H, H menthyl); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 200.8 (C-2), 171.8 (OCOEt), 148.6−123.2 (C-aromatic), 101.1 (C-1), 81.7 (C-1 menthyl), 62.1 (C-4a), 61.9 (C-3a), 61.8 (OCH_2CH_3), 58.6 (C-5), 52.2 (C-3), 48.7 (C-menthyl), 45.1 (C-4), 42.9, 34.3, 31.8, 25.4, 23.2, 22.3, 21.0, 16.1 (C-menthyl), 14.3 (OCH_2CH_3); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{25}H_{37}N_2O_5$ 445.2697, found 445.2677

*Compound **29**:* syrup; R_f 0.62, 20 mg, 11%; $[\alpha]_D^{25}$ +38.5 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.65 (d, 1H, J = 2.0 Hz, H-2′Py), 8.48 (dd, 1H, J = 1.3, 4.8 Hz, H-6′Py), 7.89 (dt, 1H, J = 1.7, 7.9 Hz, H-4′Py), 7.27 (dd, 1H, J = 4.8, 7.9 Hz, H-5′Py), 5.08 (d, 1H, $J_{3,3a}$ = 1.9 Hz, H-3a), 4.83 (s, 1H, H-1), 4.45 (dd, 1H, $J_{4,5ax}$ = 3.3, $J_{5ax,5eq}$ = 12.4 Hz, H-5ax), 4.25 (m, 2H, OCH_2CH_3), 3.95 (d, 1H, $J_{4,4a}$ = 10.6 Hz, H-4a), 3.90 (d, 1H, $J_{5ax,5eq}$ = 12.4 Hz, H-5eq), 3.42 (ddd, 1H, J = 4.1, J = 10.7, H-1 menthyl), 3.15 (dd, 1H, $J_{3,3a}$ = 1.9, $J_{3,4}$ = 8.0 Hz, H-3), 2.78 (m, 1H, $J_{3,4}$ = 8.0, $J_{4,4a}$ = 10.6, $J_{4,5ax}$ = 3.3 Hz, H-4), 2.59 (br s, 1H, N*H*), 2.16 (m, 1H, H menthyl), 2.02 (m, 1H, H menthyl), 1.67−1.59 (m, 2H, H menthyl), 1.40 (m, 1H, H menthyl), 1.32 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 1.24 (m, 1H, H menthyl), 0.92−0.73 (m, 12H, H menthyl); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 200.1 (C-2), 173.1 (OCOEt), 148.5−123.5 (C-aromatic), 100.8 (C-1), 82.7 (C-1 menthyl), 61.5 (OCH_2CH_3), 60.6 (C-4a), 57.3 (C-3a), 57.2 (C-5), 55.9 (C-3), 48.6 (C-menthyl), 44.5 (C-4), 43.1, 34.3, 31.8, 25.6, 23.3, 22.3, 21.1, 16.2 (C-menthyl), 14.4 (OCH_2CH_3); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{25}H_{37}N_2O_5$ 445.2697, found 445.2696.

*Synthesis of Pyrrolidine Derivatives **30** and **31** from Imino Ester **5Bb**. Compound **30**:* syrup; R_f 0.18, 95 mg, 53%; $[\alpha]_D^{25}$ +27.4 (c 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.59 (d, 1H, J = 1.3 Hz, H-2′Py), 8.48 (dd, 1H, J = 1.3, 4.8 Hz, H-6′Py), 7.77 (dt, 1H, J = 1.4, 7.9 Hz, H-4′Py), 7.27 (dd, 1H, J = 4.8, 7.9 Hz, H-5′Py), 4.48 (d, 1H, $J_{3,3a}$ = 6.4 Hz, H-3a), 4.39 (dd, 1H, $J_{4,5ax}$ = 4.0, $J_{5ax,5eq}$ = 12.6 Hz, H-5ax), 4.22 (s, 1H, H-1), 3.86 (dd, 1H, $J_{4,5eq}$= 2.0, $J_{5ax,5eq}$ = 12.6 Hz, H-5eq), 3.77 (s, 3H, OCH_3), 3.59 (dd, 1H, $J_{3,3a}$ = 6.4, $J_{3,4}$ = 7.4 Hz, H-3), 3.22 (ddd, 1H, J = 4.1, J = 10.7 Hz, H-1 menthyl), 2.68 (ddd, 1H, $J_{3,4}$ = 7.4, $J_{4,5ax}$ = 4.0, $J_{4,5eq}$ = 2.0 Hz, H-4), 2.03 (m, 1H, H menthyl), 1.90 (m, 1H, H menthyl), 1.62−1.55 (m, 2H, H menthyl), 1.52 (s, 3H, CH_3), 1.34 (m, 1H, H menthyl), 1.18 (m, 1H, H menthyl), 0.92−0.57 (m, 12H, H menthyl); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 199.7 (C-2), 175.0 (OCOMe), 148.5−123.1 (C-aromatic), 101.0 (C-1), 81.8 (C-1 menthyl), 66.5 (C-4a), 60.3 (C-3a), 58.0 (C-5), 54.0 (C-4), 53.0 (OCH_3), 52.2 (C-3), 48.7, 43.0, 34.3, 31.8 (C-menthyl), 26.5 (CH_3), 25.3, 23.2, 22.3, 21.0, 16.1 (C-menthyl); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{25}H_{37}N_2O_5$ 445.2697, found 445.2689.

*Compound **31**:* syrup; R_f 0.38, 25 mg, 14%; $[\alpha]_D^{25}$ +27.3 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.85 (d, 1H, J = 2.0 Hz, H-2′Py), 8.49 (dd, 1H, J = 1.6, 4.8 Hz, H-6′Py), 8.00 (dt, 1H, J = 1.8, 7.9 Hz, H-4′Py), 7.24 (dd, 1H, J = 4.8, 7.9 Hz, H-5′Py), 4.73 (s, 1H, H-1), 4.60 (d, 1H, $J_{3,3a}$ = 9.4 Hz, H-3a), 4.21 (dd, 1H, $J_{4,5ax}$ = 6.9, $J_{5ax,5eq}$ = 10.7 Hz, H-5ax), 3.80 (s, 3H, OCH_3), 3.74 (dd, 1H, $J_{4,5eq}$= 10.6, $J_{5ax,5eq}$ = 10.7 Hz, H-5eq), 3.37 (ddd, 1H, J = 4.1, J = 10.7 Hz, H-1 menthyl), 3.26 (dd, 1H, $J_{3,3a}$ = 9.4, $J_{3,4}$ = 14.4 Hz, H-3), 2.68 (ddd, 1H, $J_{3,4}$ = 14.4, $J_{4,5ax}$ = 6.9, $J_{4,5eq}$ = 10.6 Hz, H-4), 2.23 (m, 1H, H menthyl), 2.13 (m, 1H, H menthyl), 1.65−1.61 (m, 2H, H menthyl), 1.56 (s, 3H, CH_3), 1.39 (m, 1H, H menthyl), 1.28 (m, 1H, H menthyl), 0.92−0.72 (m, 12H, H menthyl); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 201.7 (C-2), 175.2 (OCOMe), 149.4−123.4 (C-aromatic), 100.3 (C-1), 82.7 (C-1 menthyl), 65.6 (C-4a), 62.9 (C-5), 57.7 (C-3a), 57.5 (C-3), 52.5 (OCH_3), 51.4 (C-4), 48.7, 43.0, 34.3, 31.9 (C-menthyl), 25.6 (CH_3), 25.3, 23.3, 22.4, 21.1, 16.2 (C-menthyl); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{25}H_{37}N_2O_5$ 445.2697, found 445.2679.

*Synthesis of Pyrrolidine Derivative **32** from Imino Ester **5Bc**. Compound **32**:* syrup; R_f 0.30, 152 mg, 73%; $[\alpha]_D^{25}$ +14.8 (c 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.61−7.23 (9H, H-aromatic), 4.39 (dd, 1H, $J_{4,5ax}$ = 4.3, $J_{5ax,5eq}$ = 12.5 Hz, H-5ax), 4.33 (d, 1H, $J_{3,3a}$ = 7.0 Hz, H-3a), 4.17 (s, 1H, H-1), 3.95 (dd, 1H, $J_{4,5eq}$ = 2.9, $J_{5ax,5eq}$ = 12.5 Hz, H-5eq), 3.71 (s, 3H, OCH_3), 3.60 (dd, 1H, $J_{3,3a}$ = 7.0, $J_{3,4}$ = 7.4 Hz, H-3), 3.22, 2.96 (2d, 2H, J = 13.5 Hz, CH_2Ph), 3.21 (ddd, 1H, J = 4.1, J = 10.7, H-1 menthyl), 2.86 (m, 1H, $J_{3,4}$ = 7.4, $J_{4,5ax}$ = 4.3, $J_{4,5eq}$ = 2.9 Hz, H-4), 2.04 (m, 1H, H menthyl), 1.90 (m, 1H, H menthyl), 1.63−1.54 (m, 2H, H-menthyl), 1.33 (m, 1H, H menthyl), 1.18 (m, 1H, H menthyl), 0.90−0.56 (m, 12H, H menthyl); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 200.0 (C-2), 173.8 (OCOMe), 148.7−123.1 (C-aromatic), 101.1 (C-1), 81.7 (C-1 menthyl), 70.8 (C-4a), 59.8 (C-3a), 58.7 (C-5), 52.7 (OCH_3), 51.8 (C-3), 51.6 (C-4), 48.6 (C-menthyl), 43.6 (CH_2Ph), 43.0, 34.3, 31.8, 25.3, 23.3, 22.3, 21.0, 16.1 (C-menthyl); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{31}H_{41}N_2O_5$ 521.3010, found 521.2992.

*Synthesis of Pyrrolidine Derivatives **33** and **34** from Imino Ester **5Ca**. Compound **33**:* white solid, recrystallized from hexane; mp = 145 °C; R_f 0.16, 130 mg, 68%; $[\alpha]_D^{25}$ +37.4 (c 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.28, 6.86 (2d, 2H each, J = 8.8 Hz, H-aromatic), 4.60 (d, 1H, $J_{3,3a}$ = 9.5 Hz, H-3a), 4.31 (m, 2H, OCH_2CH_3), 4.09−4.03 (m, 2H, H-4a, H-5ax), 3.96 (s, 1H, H-1),

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3.77 (s, 3H, OCH_3), 3.75 (dd, 1H, $J_{4,5eq}$= 3.1, $J_{5ax,5eq}$ = 12.8 Hz, H-5eq), 3.52 (dd, 1H, $J_{3,3a}$ = 9.5, $J_{3,4}$ = 8.3 Hz, H-3), 3.11 (ddd, 1H, J = 4.1, J = 10.7, H-1 menthyl), 3.00 (m, 1H, $J_{3,4}$ = 8.3, $J_{4,4a}$ = 6.9, $J_{4,5ax}$ = 4.8, $J_{4,5eq}$ = 3.1 Hz, H-4), 1.98−1.90 (m, 2H, H menthyl), 1.61−1.52 (m, 3H, H menthyl), 1.34 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 1.19 (m, 1H, H menthyl), 0.95−0.50 (m, 12H, H menthyl); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 203.2 (C-2), 171.3 (OCOEt), 159.0−113.9 (C-aromatic), 101.2 (C-1), 81.0 (C-1 menthyl), 64.3 (C-4a), 63.7 (C-3a), 61.5 (OCH_2CH_3), 60.4 (C-5), 55.3 (OCH_3), 55.2 (C-3), 48.7 (C-menthyl), 44.6 (C-4), 42.9, 34.3, 31.8, 25.0, 23.2, 22.3, 21.1, 16.0 (C-menthyl), 14.4 (OCH_2CH_3); HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{27}H_{40}NO_6$ 474.2850, found 474.2831.

Compound ***34****:* syrup; R_f 0.52, 22 mg, 12%; $[\alpha]_D^{25}$ +48.2 (c 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.39, 6.86 (2d, 2H each, J = 8.8 Hz, H-aromatic), 4.91 (d, 1H, $J_{3,3a}$ = 2.9 Hz, H-3a), 4.81 (s, 1H, H-1), 4.42 (dd, 1H, $J_{4,5ax}$ = 3.3, $J_{5ax,5eq}$ = 12.4 Hz, H-5ax), 4.26 (m, 2H, OCH_2CH_3), 3.91 (d, 1H, $J_{4,4a}$ = 10.3 Hz, H-4a), 3.90 (d, 1H, $J_{5ax,5eq}$ = 12.4 Hz, H-5eq), 3.78 (s, 3H, OCH_3), 3.41 (ddd, 1H, J = 4.1, J = 10.7, H-1 menthyl), 3.10 (dd, 1H, $J_{3,3a}$ = 2.9, $J_{3,4}$ = 8.3 Hz, H-3), 2.76 (m, 1H, $J_{3,4}$ = 8.3, $J_{4,4a}$ = 10.3, $J_{4,5ax}$ = 3.3 Hz, H-4), 2.16 (m, 1H, H menthyl), 2.05 (m, 1H, H menthyl), 1.66−1.59 (m, 2H, H menthyl), 1.40 (m, 1H, H menthyl), 1.32 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 1.23 (m, 1H, H menthyl), 0.95−0.72 (m, 12H, H menthyl); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 200.9 (C-2), 173.3 (OCOEt), 158.9−114.0 (C-aromatic), 100.7 (C-1), 82.5 (C-1 menthyl), 61.4 (OCH_2CH_3), 61.2 (C-4a), 60.0 (C-3a), 57.6 (C-5), 56.3 (C-3), 55.4 (OCH_3), 48.7 (C-menthyl), 44.7 (C-4), 43.1, 34.3, 31.8, 25.5, 23.3, 22.3, 21.1, 16.2 (C-menthyl), 14.4 (OCH_2CH_3); HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{27}H_{40}NO_6$ 474.2850, found 474.2859.

Synthesis of Pyrrolidine Derivatives ***35*** *and* ***36*** *from Imino Ester* ***5Cb****. Compound* ***35****:* syrup; R_f 0.13, 114 mg, 60%; $[\alpha]_D^{25}$ +29.3 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.26, 6.86 (2d, 2H each, J = 8.8 Hz, H-aromatic), 4.65 (d, 1H, $J_{3,3a}$ = 8.7 Hz, H-3a), 4.12 (dd, 1H, $J_{4,5ax}$ = 4.8, $J_{5ax,5eq}$ = 12.8 Hz, H-5ax), 3.91 (s, 1H, H-1), 3.80, 3.75 (2s, 3H each, 2 OCH_3), 3.68 (dd, 1H, $J_{4,5eq}$= 3.1, $J_{5ax,5eq}$ = 12.8 Hz, H-5eq), 3.58 (dd, 1H, $J_{3,3a}$ = 8.7, $J_{3,4}$ = 7.9 Hz, H-3), 3.09 (ddd, 1H, J = 4.1, J = 10.7 Hz, H-1 menthyl), 2.64 (m, 1H, $J_{3,4}$ = 7.9, $J_{4,5ax}$ = 4.8, $J_{4,5eq}$ = 3.1 Hz, H-4), 1.95−1.86 (m, 2H, H menthyl), 1.59−1.51 (m, 2H, H menthyl), 1.48 (s, 3H, CH_3), 1.29 (m, 1H, H menthyl), 1.16 (m, 1H, H menthyl), 0.86−0.47 (m, 12H, H menthyl); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 202.3 (C-2), 174.5 (OCOMe), 158.8−113.7 (C-aromatic), 101.1 (C-1), 80.9 (C-1 menthyl), 68.7 (C-4a), 61.8 (C-3a), 60.4 (C-5), 55.2 (OCH_3), 54.3 (C-3), 52.7 (OCH_3), 51.9 (C-4), 48.6, 42.9, 34.2, 31.7 (C-menthyl), 25.4 (CH_3), 25.0, 23.1, 22.2, 21.0, 15.9 (C-menthyl); HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{27}H_{40}NO_6$ 474.2850, found 474.2833.

Compound ***36****:* syrup; R_f 0.41, 20 mg, 11%; $[\alpha]_D^{25}$ +20.1 (c 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41, 6.86 (2d, 2H each, J = 8.8 Hz, H-aromatic), 5.18 (d, 1H, $J_{3,3a}$ = 3.0 Hz, H-3a), 4.64 (s, 1H, H-1), 4.41 (dd, 1H, $J_{4,5ax}$ = 4.1, $J_{5ax,5eq}$ = 12.7 Hz, H-5ax), 3.86 (d, 1H, $J_{5ax,5eq}$ = 12.7 Hz, H-5eq), 3.79, 3.64 (2s, 3H each, 2 OCH_3), 3.36 (ddd, 1H, J = 4.1, J = 10.1 Hz, H-1 menthyl), 2.98 (dd, 1H, $J_{3,3a}$ = 3.0, $J_{3,4}$ = 9.4 Hz, H-3), 2.50 (dd, 1H, $J_{3,4}$ = 9.4, $J_{4,5ax}$ = 4.1, $J_{4,5eq}$ = 0 Hz, H-4), 2.14 (m, 1H, H menthyl), 2.02 (m, 1H, H menthyl), 1.65−1.59 (m, 2H, H menthyl), 1.53 (s, 3H, CH_3), 1.43−1.33 (m, 2H, H menthyl), 0.91−0.70 (m, 12H, H menthyl); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 199.5 (C-2), 176.7 (OCOMe), 158.7−114.0 (C-aromatic), 100.4 (C-1), 82.6 (C-1 menthyl), 66.8 (C-4a), 60.0 (C-3a), 55.5 (× 2) (C-5, OCH_3), 55.2 (C-3), 52.3 (OCH_3), 50.2 (C-4), 48.7, 43.1, 34.3, 31.8, 25.4 (C-menthyl), 25.1 (CH_3), 23.2, 22.3, 21.1, 16.1 (C-menthyl); HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{27}H_{40}NO_6$ 474.2850, found 474.2835.

Synthesis of Pyrrolidine Derivative ***37*** *from Imino Ester* ***5Cc****. Compound* ***37****:* white crystals obtained upon slow evaporation of MeCN; mp = 158 °C; R_f 0.42, 95 mg, 43%; $[\alpha]_D^{25}$ +43.4 (c 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37−6.84 (9H, H-aromatic), 4.75 (d, 1H, $J_{3,3a}$ = 9.4 Hz, H-3a), 4.16 (dd, 1H, $J_{4,5ax}$ = 5.3, $J_{5ax,5eq}$ = 12.6 Hz, H-5ax), 3.91 (s, 1H, H-1), 3.80 (dd, 1H, $J_{4,5eq}$ = 4.8, $J_{5ax,5eq}$ = 12.6 Hz, H-5eq), 3.77, 3.75 (2s, 3H each, 2 OCH_3), 3.65 (dd, 1H, $J_{3,3a}$ = 9.4, $J_{3,4}$ = 7.9 Hz, H-3), 3.21, 2.97 (2d, 2H, J = 13.5 Hz, CH_2Ph), 3.08 (ddd, 1H, J = 4.1, J = 10.7 Hz, H-1 menthyl), 2.85 (m, 1H, $J_{3,4}$ = 7.9, $J_{4,5ax}$ = 5.3, $J_{4,5eq}$ = 4.8 Hz, H-4), 1.98−1.88 (m, 2H, H menthyl), 1.60−1.52 (m, 2H, H menthyl), 1.30 (m, 1H, H-menthyl), 1.20 (m, 1H, H-menthyl), 0.90−0.48 (m, 12H, H menthyl); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 202.1 (C-2), 173.3 (OCOMe), 159.0−113.7 (C-aromatic), 101.4 (C-1), 81.0 (C-1 menthyl), 72.9 (C-4a), 61.3 (C-5), 60.9 (C-3a), 55.3 (OCH_3), 53.9 (C-3), 52.3 (OCH_3), 50.3 (C-4), 48.8 (C-menthyl), 42.9, 42.8 (CH_2Ph, C-menthyl), 34.3, 31.8, 25.1, 23.2, 22.3, 21.1, 16.0 (C-menthyl); HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{33}H_{44}NO_6$ 550.3163, found 550.3153.

Synthesis of Pyrrolidine Derivatives ***39*** *and* ***40*** *from Dihydropyranone* ***38****.* The general procedure for the dipolar cycloaddition was followed starting from enone **38** (0.082 g, 0.40 mmol) and the imino ester derived from glycine (**5Aa**, 0.115 g, 0.60 mmol), which were dissolved in anhydrous MeCN (1.2 mL). After addition of AgOAc (20 mg, 0.12 mmol) and DBU (6 μL, 0.04 mmol), the mixture was stirred at rt for 15 min. The reaction mixture showed by TLC (hexane/EtOAc, 7:3) spots corresponding to **40** (R_f 0.46) and **39** (R_f 0.10), which were separated by column chromatography (hexane/EtOAc, 93:7).

*Compound endo-****39****:* syrup (58 mg, 30%); $[\alpha]_D^{25}$ −44.1 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35−7.20 (10H, H-aromatic), 4.62, 4.41 (2d, 2H, J = 11.8 Hz, CH_2Ph), 4.59 (d, 1H, $J_{3,3a}$ = 9.3 Hz, H-3a), 4.31 (m, 2H, OCH_2CH_3), 4.08 (d, 1H, $J_{4,4a}$ = 7.2 Hz, H-4a), 4.07 (dd, 1H, $J_{4,5ax}$ = 4.6, $J_{5ax,5eq}$ = 12.8 Hz, H-5ax), 4.04 (s, 1H, H-1), 3.82 (dd, 1H, $J_{4,5eq}$ = 2.4, $J_{5ax,5eq}$ = 12.8 Hz, H-5eq), 3.58 (dd, 1H, $J_{3,3a}$ = 9.3, $J_{3,4}$ = 8.0 Hz, H-3), 3.03 (m, 1H, $J_{3,4}$ = 8.0, $J_{4,4a}$ = 7.3, $J_{4,5ax}$= 4.6, $J_{4,5eq}$ = 2.4 Hz, H-4), 1.35 (t, 3H, J = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 202.9 (C-2), 171.2 (OCOEt), 137.7−126.6 (C-aromatic), 98.5 (C-1), 69.8 (CH_2Ph), 64.4 (C-3a), 64.0 (C-4a), 61.6 (OCH_2CH_3), 60.3 (C-5), 55.0 (C-3), 44.5 (C-4), 14.4 (OCH_2CH_3); HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{23}H_{25}NNaO_5$ 418.1625, found 418.1624.

*Compound exo-****40****:* syrup (34 mg, 18%); $[\alpha]_D^{25}$ −66.5 (c 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.44−7.20 (10H, H-aromatic), 5.00 (d, 1H, $J_{3,3a}$ = 2.6 Hz, H-3a), 4.85 (s, 1H, H-1), 4.80, 4.61 (2d, 2H, J = 11.6 Hz, CH_2Ph), 4.36 (dd, 1H, $J_{4,5ax}$ = 3.3, $J_{5,5eq}$ = 12.4 Hz, H-5ax), 4.27 (m, 2H, OCH_2CH_3), 3.96 (br d, 2H, J = 10.8 Hz, H-4a, H-5eq), 3.18 (dd, 1H, $J_{3,3a}$ = 2.6, $J_{3,4}$ = 8.2 Hz, H-3), 2.81 (ddd, 1H, $J_{3,4}$ = 8.2, $J_{4,4a}$ ∼ 10.0, $J_{4,5ax}$ = 3.3 Hz, H-4), 1.32 (t, 3H, J = 7.1 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 200.9 (C-2), 173.1 (OCOEt), 143.7−126.5 (C-aromatic), 98.1 (C-1), 70.0 (CH_2Ph), 61.4 (OCH_2CH_3), 60.9 (C-4a), 60.0 (C-3a), 57.6 (C-5), 56.4 (C-3), 44.6 (C-4), 14.4 (OCH_2CH_3); HRMS (ESI) m/z [M + Na]+ calcd for $C_{23}H_{25}NNaO_5$ 418.1625, found 418.1626.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Details on general experimental methods; copies of ^{1}H and ^{13}C NMR and NOESY spectra for compounds **2**, **4**, **7**, ***epi*-7**, **8**−**10**, ***epi*-10**, **11**−**37**, **39**, and **40**. A table with relevant ^{1}H NMR data for configurational assignments is also included. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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