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Synthesis of Pyrrolizidine Derivatives by 1,3-Dipolar Cycloaddition Reactions of Chiral Five-Membered Cyclic Azomethine Ylides

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The 1,3-dipolar cycloaddition reactions of chiral five-membered cyclic azomethine ylides, generated in situ from ethyl glyoxylate and protected (3*S*,4*S*)-dihydroxypyrrolidines **3** and **6** have been studied. The facial selectivity of the cycloaddition reaction is governed by the steric effect of the substituent on the pyrrolidine ring next to the azomethine ylide functionality, leading in all cases to an exclusive *Si* face approach of the dipolarophile. The *exo*/*endo* selectivity depends on the dipolarophile and on the size of the other substituent on the pyrrolidine ring.

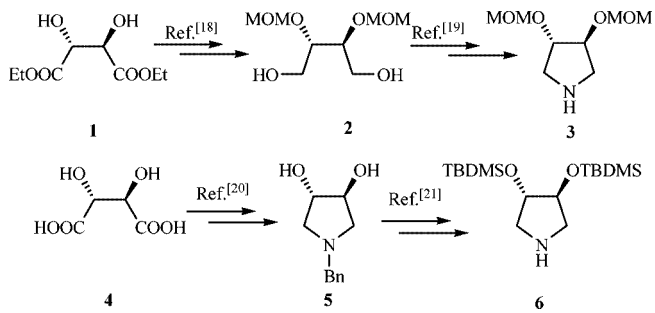
Introduction

The cycloaddition of azomethine ylides to alkenes is an important way to synthesize heterocycles containing pyrrolidine substructures with high stereoselectivity.[1] The stereoselectivity of these cycloaddition reactions is greatly enhanced if the azomethine ylide functionality is part of an N-heterocycle, thus providing a rather rigid ring template that results in a better diastereofacial approach between dipole and dipolarophile. Cyclic azomethine ylides, in which the central nitrogen atom is part of a pyrrolidine ring, are of particular importance, since they can be directly transformed into pyrrolizidine rings through a cycloaddition reaction with alkenes in a highly stereoselective way. In fact, pyrrolizidines are among the most popular targets of azomethine ylide cycloaddition reactions.[2] Their skeleton (1-azabicyclo[3.3.0]octane) is found in many biologically interesting natural products.[3] Some of them, especially those that have hydroxy groups with a stereochemistry analogous to that of monosaccharides, as well as several other synthetic analogues, show important biological activities as glycoprotein-processing glycosidase inhibitors and have potential as chemotherapeutic agents.[4]

Several methods have been developed for the generation of pyrrolidine-based cyclic azomethine ylides. Among them, of particular importance are the base-induced deprotonation of *N*-{(phenylthio)methyl]proline esters followed by phenylthiolate anion abstraction[5] and the decarboxylation of immonium betaines obtained from carbonyl compounds and proline derivatives.[6] Other very interesting routes to azomethine ylide generation are the desilylation of *N*-[(trimethylsilyl)methyl]pyrrolidinium salts[7] and the base-induced deprotonation of [(trifluoromethyl)thio]amidinium salts[8] or *N*-methylpyrrolidine *N*-oxides.[9] Grigg and co-workers proposed another approach in which azomethine ylides were generated in situ by condensation of bifunctional carbonyl compounds and secondary amines.[10] As part of a project directed towards the synthesis of aza heterocycles from sugar derivatives,[11] it was found that 1,3-dipolar cycloaddition reactions of chiral cyclic azomethine ylides could be an attractive alternative route to the synthesis of chiral polyhydroxy analogues. In this paper we present our results on this subject.

Results and Discussion

The above-mentioned approach of Grigg and co-workers was adopted by using ethyl glyoxylate and the protected chiral dihydroxypyrrolidine derivatives **3** and **6** as azomethine ylide precursors. Standard methods, starting from diethyl tartrate or L-tartaric acid, were used for the synthesis of the protected 3,4-dihydroxypyrrolidines **3** and **6** (Scheme 1).



Scheme 1.

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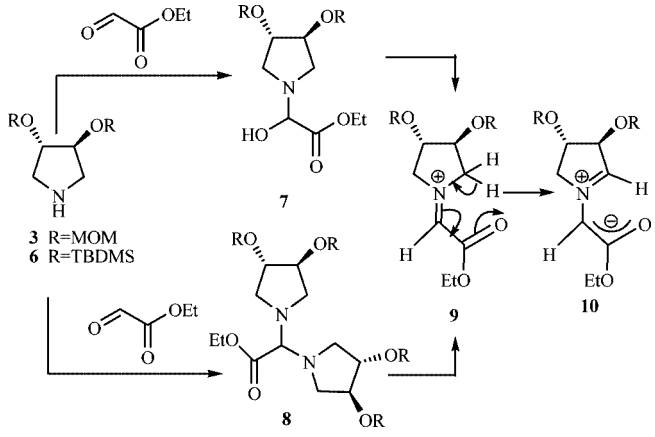
According to the protocol of Grigg and co-workers, the ester-stabilized azomethine ylides **10** (R = TBDMS, MOM) were formed in situ from ethyl glyoxylate and the corresponding (3*S*,4*S*)-dihydroxypyrrolidine derivatives **3** or **6** (Scheme 2). There are two variations of the method, either using equimolar amounts of the reactants or an excess of the secondary amine. In both cases it seems probable that an iminium ion intermediate **9** is formed, either through the nonisolable carbinol amine **7** or through the diaminal derivative **8**. According to the proposed mechanistic scheme, the iminium intermediate is further transformed into the desired ylide by deprotonation, either by a 1,5-proton shift or by an external base.[10] It has been assumed[10c,10d] that the *anti* stereochemistry of the resulting ylide is the predominant one and this form will be considered throughout this paper.



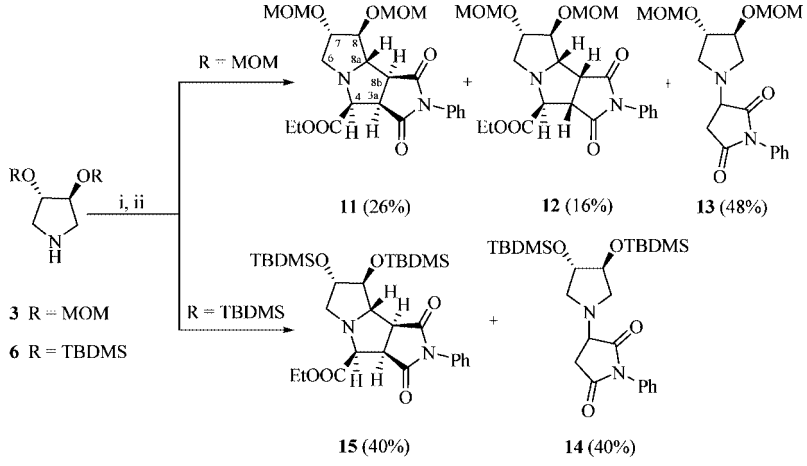
Scheme 2.

Preliminary experiments carried out by heating equimolar amounts of ethyl glyoxylate, pyrrolidine **3** and *N*-phenylmaleimide in boiling dry acetonitrile resulted in the formation of a complex mixture from which the diastereomeric cycloadducts **11** and **12** were isolated in a ratio of about 1.5:1, but in a disappointedly low yield (8%). The main reaction product was the Michael adduct **13**, isolated in moderate yield (30%), plus other unidentified byproducts (Scheme 3). The yield of the cycloaddition step was improved by using an excess of pyrrolidine **3** (2 equiv.) and ethyl glyoxylate in dry dichloromethane solution in the presence of anhydrous magnesium sulfate at room temp. The intermediate diaminal **8** (R = MOM) was not stable and attempts to isolate it resulted in its decomposition. However, after briefly heating the crude diaminal **8** and *N*-phenylmaleimide in dry acetonitrile (ca. 2 h), a mixture of cycloadducts **11** and **12** was obtained in the same ratio (ca. 1.5:1) and in a total yield of 42%. In addition, the Michael adduct **13** was also isolated in a yield of 48%.

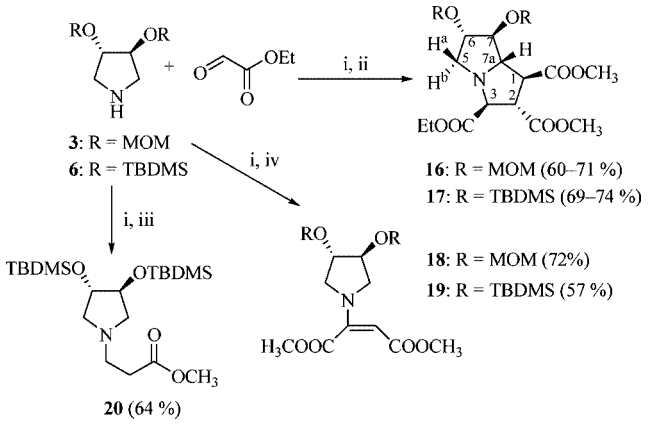
The reaction course showed a better diastereoselectivity when azomethine ylide **10** (R = TBDMS) was employed, although the yield of the cycloaddition reaction was not improved. Thus, briefly heating of the crude diaminal **8** (R = TBDMS), obtained by using an excess of the pyrrolidine **6**, ethyl glyoxylate and *N*-phenylmaleimide in acetonitrile solution resulted in the exclusive formation the cycloadduct **15** in a yield of ca. 40%. The Michael adduct **14** was also obtained as a mixture of two diastereomers (in an undetermined ratio) in a yield of 40%, possibly as a result of the presence of an undetermined quantity of unreacted pyrrolidine in the crude diaminal.

Analogous reactions were also studied using dimethyl maleate and dimethyl fumarate as dipolarophiles. These reactions were also carried out by refluxing the corresponding crude aminals and dipolarophiles in acetonitrile solution (Scheme 4). Note that the yields of the cycloaddition reactions with dimethyl maleate and fumarate were fairly good (ca. 70%) compared with those obtained with maleimide, while no Michael adducts were isolated. On the other hand, these cycloaddition reactions proceeded with high stereoselectivity and only one stereoisomer was isolated.

Both dipolarophiles gave the same cycloadduct **16** or **17**, respectively, with the carboxylate groups of the reacting dipolarophile in *trans* positions, indicating that when methyl maleate is used, isomerization to the more stable fumarate takes place, possibly prior to the cycloaddition step. Note



Scheme 3. Reagents and conditions: (i) ethyl glyoxylate, CH_2Cl_2, $MgSO_4$, room temp., overnight; (ii) *N*-phenylmaleimide, CH_3CN, reflux.



Scheme 4. Reagents and conditions: (i) CH_2Cl_2, $MgSO_4$, room temp., overnight; (ii) dimethyl maleate or dimethyl fumarate, CH_3CN, reflux, 12–18 h; (iii) methyl acrylate, CH_3CN, reflux, 3 h; (iv) dimethyl acetylenedicarboxylate, CH_3CN, reflux.

that analogous isomerization reactions, attributed to the catalytic action of either secondary amines[12–14] or aminals,[15] have also been reported. In our case both options are possible, since besides the crude aminal, undetermined quantities of unreacted pyrrolidines **3** or **6** may be present in the crude reaction mixture. This assumption is further supported by the fact that when dimethyl maleate was used as the dipolarophiles, dimethyl fumarate was isolated as a byproduct. Analogous isomerization reactions have also been reported in the cycloaddition reactions of other 1,3-dipoles with maleate esters as dipolarophiles.[16]

Structural elucidation of the cycloadducts was based on their spectroscopic data, while the structure of compound **12** was unambiguously determined by X-ray crystal structure analysis. An ORTEP drawing of compound **12** is given in Figure 1. Proton assignments were based on double-resonance experiments and selected chemical shifts and coupling constants are given in Table 1. The low values (J = 3.0 and 2.6 Hz) observed for the coupling constants of the proton 8-H of compound **12** (see Table 1) with its neighbouring protons 7-H and 8a-H and also the low value of the coupling constant between 3a-H and 4-H (J = 2.3 Hz) support their mutual *trans* arrangement. All these observations are in accordance with the X-ray crystal structure analysis.

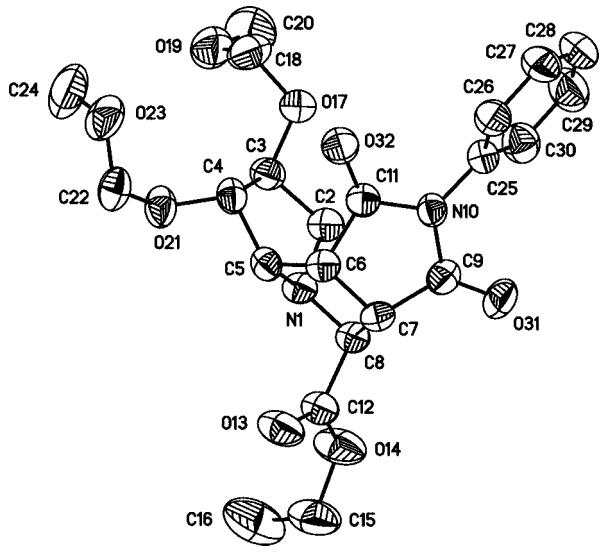


Figure 1. ORTEP drawing of **12** (thermal ellipsoids drawn at the 30% probability level; hydrogen atoms have been omitted for clarity).

As regards compounds **11** and **15**, there is a close similarity in both the chemical shifts and the corresponding coupling constants, indicating that both adducts have analogous structures. Thus, the small coupling constants of the 8a-H with 8-H and 8b-H are consistent with a mutual *trans* arrangement. On the other hand, the high value of the coupling constant between 3a-H and 4-H (J = 8.4 and 8.9 Hz, respectively) supports their *cis* arrangement. These observations are further supported by NOE experiments carried out on compound **15**. Interactions with diagnostic values supporting the proposed structure **15** are illustrated in Figure 2. The significant mutual NOE enhancement observed between 6-H^a and 8a-H, as well as between 6-H^b and 4-H, shows that they are in close proximity on the same side of the plane, as shown in molecular models of structure **15**. Furthermore, the large mutual NOE enhancement between 4-H and 3a-H confirms their *cis* arrangement.

Table 1. Selected chemical shifts [ppm] and coupling constants of compounds **11**, **12**, **15** and **17**.

Compound **11**	Compound **12**	Compound **15**	Compound **17**
8-H: 4.17–4.32 (m)[a]	8-H: 4.23 (dd, $J_{8,8a}$ = 3.0, $J_{7,8}$ = 2.6 Hz)	8-H: 4.17–4.32 (m)[b]	7-H: 4.08 (br. s)
8a-H: 3.86 (dd, $J_{8,8a}$ = 4.8, $J_{8a,8b}$ = 3.2 Hz)	8a-H: 3.99 (dd, $J_{8,8a}$ = 3.0, $J_{8a,8b}$ = 9.2 Hz)	8a-H: 3.87 (dd, $J_{8,8a}$ = 2.3, $J_{8a,8b}$ = 4.2 Hz)	7a-H: 3.56 (d, $J_{1,7a}$ = 11.3 Hz)
8b-H: 3.73 (dd, $J_{8a,8b}$ = 3.2, $J_{3a,8b}$ = 9.0 Hz)	8b-H: 3.80 (t, $J_{8a,8b}$ = $J_{8b,3a}$ = 9.2 Hz)	8b-H: 3.66 (dd, $J_{8a,8b}$ = 4.2, $J_{3a,8b}$ = 8.0 Hz)	1-H: 3.46 (dd, $J_{1,7a}$ = 11.3, $J_{1,2}$ = 9.7 Hz)
3a-H: 3.85 (dd, $J_{3a,8b}$ = 9.0, $J_{3a,4}$ = 8.4 Hz)	3a-H: 3.87 (dd, $J_{3a,8b}$ = 9.2, $J_{3a,4}$ = 2.3 Hz)	3a-H: 3.84 (t, $J_{3a,\ 8b}$ = $J_{3a,4}$ = 8.9 Hz)	2-H: 3.67 (m)[c]
4-H: 4.17–4.32 (m)[a]	4-H: 4.29 (d, $J_{3a,4}$ = 2.3 Hz)	4-H: 4.35 (d, $J_{3a,4}$ = 8.9 Hz)	3-H: 4.0 (d, $J_{2,3}$ = 10.7 Hz)
6-H^a: 3.50 (dd, $J_{6(a),7}$ = 6.1, $J_{6(a),6(b)}$ = 12.9 Hz)	6-H^a: 3.46 (dd, $J_{6(a),7}$ = 4.6, $J_{6(a),6(b)}$ = 11.2 Hz)	6-H^a: 3.52 (dd, $J_{6(a),7}$ = 3.3, $J_{6(a),6(b)}$ = 12.1 Hz)	5-H^a: 3.21 (dd, $J_{5(a),6}$ = 2.5, $J_{5(a),5(b)}$ = 12.7 Hz)
6-H^b: 2.90 (dd, $J_{6(a),7}$ = 2.9, $J_{6(a),6(b)}$ = 12.9 Hz)	6-H^b: 2.84 (dd, $J_{6(a),7}$ = 5.6, $J_{6(a),6(b)}$ = 11.2 Hz)	6-H^b: 2.76 (d, $J_{6(a),6(b)}$ = 12.1 Hz)	5-H^b: 2.65 (d, $J_{5(a),5(b)}$ = 12.7 Hz)

[a] Overlapped with 7-H, 8-H and OCH_2. [b] Overlapped with OCH_2. [c] Overlapped with OCH_3.

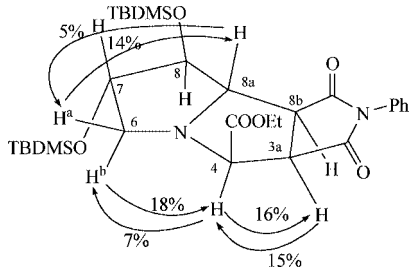
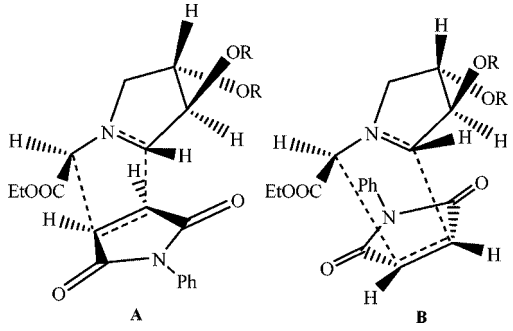


Figure 2. Observed NOEs for compound **15** demonstrating the *exo* approach of the dipolarophile to the *Si* face of the azomethine ylide.

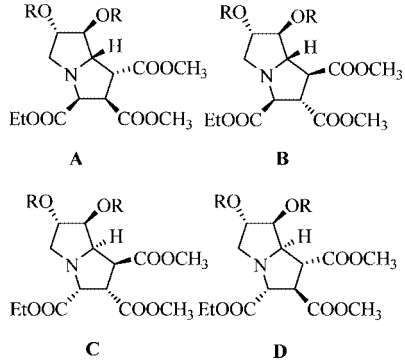
Taking into account the C_2 symmetry of the pyrrolidine ring, there are four possible diastereomeric cycloadducts for the *anti* form of the reacting azomethine ylides arising from the *face* and the *exo*/*endo* approaches of the dipole and dipolarophile. Molecular models indicate that steric hindrance of the C-3 substituent in the *anti* azomethine ylide makes more accessible its *Si* face (TSs **A** and **B** in Scheme 5). Moreover the *exo*/*endo* discrimination of the *Si* face should be the result of the size of the C-7 substituent in the azomethine ylide. The exclusive formation of cycloadduct **15** as a result of the bulky *tert*-butyldimethylsilyl group at C-7 and the preferable formation of cycloadduct **11** from the *exo* approach support this assumption. On the other hand, the concave structure of compound **12**, as illustrated in the ORTEP drawing of Figure 1, demonstrates the *endo* approach of the maleimide to the *Si* face of the *anti* ylide, possibly as a result of favourable secondary orbital interactions.



Scheme 5.

The proposed structure of compound **17** was mainly based on ^{1}H NMR spectroscopic data. Proton assignment was confirmed by decoupling experiments, and some selected chemical shifts are given in Table 1.

There are four possible isomers **A**–**D** for compounds **16** and **17** arising from the *anti* ylides (Scheme 6). Taking into account the fact that the *Re* face of the *anti* ylide is stereochemically congested by the C-7 substituent (structures **C** and **D**), it is expected that as in the cycloaddition reactions with *N*-phenylmaleimide, the *Si* face of the azomethine ylide is more accessible than the *Re* face, leading to structures **A** and **B**. The preference for the *Si* face is evidenced by the *trans* disposition of 7-H and 7a-H, whose signals appear with an almost zero coupling constant ($J_{7,7a} \approx$ 0 Hz). This is further supported by the significant mutual enhancement observed between 5-H^b and 3-H (13% enhancement of 3-H upon saturation of 5-H^b and 6% of 5-H^b upon saturation of 3-H) in NOE measurements carried out on compound **17**. Furthermore, the mutual enhancement observed between 7-H and 1-H (10% upon saturation of 1-H and 8% upon saturation of 7-H) indicate their close proximity as represented in structure **B** (Figure 3).



Scheme 6.

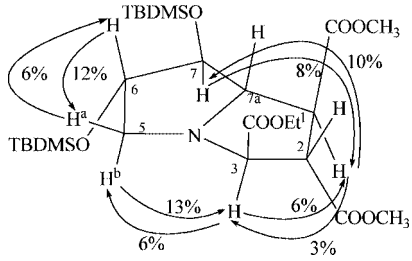


Figure 3. Observed NOEs for compound **17**.

Although the relatively large coupling constants observed between 7a-H and 1-H (J = 11.3 Hz), 1-H and 2-H (J = 9.7 Hz) and 2-H and 3-H (J = 10.7 Hz) are not typical for protons in a *trans* disposition, we have to mention that analogously large coupling constants have also been observed between *trans* hydrogen atoms in cyclopentane derivatives bearing an electron-deficient substituent, especially when they adopt quasi-axial positions with dihedral angles approaching 180°.[16,17] The flexibility of cyclopentane derivatives seems to permit all 1-H, 2-H and 3-H atoms to adopt quasi-axial conformations and the corresponding dihedral angles to be synchronously close to 180°.

As regards compound **16**, although a complete proton assignment was not possible since the 2-H/7a-H and 1-H/5-H^a signals appear as multiplets, the coupling constant between 2-H and 3-H ($J_{2,3}$ = 9.9 Hz), which is closely related to that of cycloadduct **17**, is indicative of a similar configuration at C-2 and C-3. On this basis we tentatively assigned the same stereochemical structure to both adducts. The exclusive formation of compounds with structure **B** from an *endo* approach of the 2-COOCH$_3$ group can be attributed to the prevalence of secondary orbital interactions in connection with a better stereochemical accommodation of substituents at C-2 and C-3 as revealed by inspection of molecular models.

Attempts to carry out cycloaddition reactions using dimethyl acetylenedicarboxylate and methyl acrylate failed, and only the Michael adducts **18**, **19** and **20** were obtained in fairly good yields, but no cycloaddition products.

Conclusions

In summary, several cycloaddition reactions of azomethine ylides, generated from chiral 3,4-dihydroxypyrrolidine derivatives and ethyl glyoxylate, have been studied. Both hydroxy groups were transformed into the corresponding methoxymethoxy (MOMO) or *tert*-butyldimethylsilyloxy (TBDMSO) groups in order to control the stereochemical course of the cycloaddition reactions. Complete discrimination in favour of the *Si* face was observed between approach on the *Re* and *Si* faces of the azomethine ylide as a result of the substituent on the pyrrolidine ring next to the azomethine ylide functionality. In addition, the *exo*/*endo* selectivity depends on the size of the other substituent on the pyrrolidine ring and also on the nature of the dipolarophile. While moderate yields were obtained using *N*-phenylmaleimide, with which the undesired Michael byproducts predominate, cycloaddition reactions with dimethyl fumarate and maleate occurred with fairly good yields and excellent diastereoselectivity.

Experimental Section

General: All reagents are commercially available and were used without further purification. Solvents were dried according to standard methods. Reaction progress was monitored by thin-layer chromatography on silica gel TLC plates (Merck) visualised by heat-staining with anisaldehyde in ethanol/sulfuric acid/acetic acid. Column chromatography was performed with silica gel 60 (Merck, 0.063–0.2 mm). Optical rotations were measured at room temperature with a Krüss P3000 polarimeter. Melting points were determined with a Kofler hot-stage microscope and are uncorrected. IR spectra were recorded with a Perkin-Elmer 297 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, with a Bruker 300 AM spectrometer with tetramethylsilane as internal standard. Mass spectra were measured under electron impact conditions at 70 eV with a VG TS-250 spectrometer. Microanalyses were performed with a Perkin-Elmer 2400 II elemental analyzer. High-resolution mass spectra were obtained with an IONSPEC FTMS spectrometer [matrix-assisted laser desorption ionization (MALDI)] with 2,5-dihydroxybenzoic acid (DHB) as the matrix.

Starting Materials

(2*S*,3*S*)-2,3-Bis(methoxymethoxy)-1,4-butanediol (2): This compound was prepared in 90% combined yield from diethyl L-tartrate according to the procedure described by Gras and co-workers.[18]

(3*S*,4*S*)-3,4-Bis(methoxymethoxy)pyrrolidine (3): This compound was prepared as described previously in three steps from compound **2** in 80% combined yield.[19]

(3*S*,4*S*)-1-Benzyl-3,4-pyrrolidinediol (5): This compound was prepared as described previously[20] in three steps and 60% combined yield from L-tartaric acid; m.p. 99.2–100.1 °C (ref.[19] 100 °C). ^{1}H NMR ($CDCl_3$): δ = 2.46 (dd, *J* = 3.5, 10.4 Hz, 2 H), 2.94 (dd, *J* = 5.6, 10.4 Hz, 2 H), 3.12 (br. s, 2 H), 3.58 (d, *J* = 12.6 Hz, 1 H), 4.06 (dd, *J* = 3.5, 5.6 Hz, 2 H), 7.35 (m, 5 H) ppm.

(3*S*,4*S*)-3,4-Bis{[*tert*-butyl(dimethyl)silyl]oxy}pyrrolidine (6): This compound was prepared from compound **5** as described previously in two steps and in 80% combined yield.[21]

General Procedure for the Formation of Diaminals 8: Pyrrolidines **3** or **6** (2 mmol) and ethyl glyoxylate (1 mmol), dissolved in dry dichloromethane (5 mL), and anhydrous $MgSO_4$ (1.3 mmol) were stirred at room temp. under argon for 24 h. The mixture was filtered and the resulting filtrate concentrated under reduced pressure to afford the crude diaminals **8** (R = MOM or TBDMS) which were used without purification in the next step.

Cycloaddition Reactions

Reaction of Diaminal 8 (R = MOM) and *N*-Phenylmaleimide: *N*-Phenylmaleimide (100 mg, 0.58 mmol), diaminal **8** (R = MOM), obtained from pyrrolidine **3** (0.3 g, 1.57 mmol), ethyl glyoxylate hydrate (0.095 g, 0.785 mmol) and anhydrous $MgSO_4$ (0.252 g, 2.1 mmol), were refluxed in dry acetonitrile solution (10 mL) under argon for 4 h. The solvent was removed under reduced pressure and the residue dissolved in dichloromethane, washed with water and dried (Na_2SO_4). The residue was purified by flash chromatography using EtOAc/hexane (1:1) as eluent to afford the products. Compound **11** was eluted first as an oily material (0.09 g, 26%), followed by compound **12** (0.055 g, 16%) obtained as a white crystalline material, m.p. 125–127 °C. Finally, compound **13** (0.138 g, 48%) was eluted as an oily mixture of the two possible diastereomers.

Compound 11: $[\alpha]_D$ = –18 (*c* = 0.33, $CHCl_3$). IR(film): $\tilde{\nu}$ = 1720, 1700 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.29 (t, *J* = 7.2 Hz, 3 H), 2.90 (dd, *J* = 2.9, 12.9 Hz, 1 H), 3.38 (s, 3 H), 3.45 (s, 3 H), 3.50 (dd, *J* = 6.1, 12.9 Hz, 1 H), 3.73 (dd, *J* = 3.2, 9.0 Hz, 1 H), 3.85 (dd, *J* = 8.4, 9.0 Hz, 1 H), 3.86 (dd, *J* = 4.8, 3.2 Hz, 1 H), 4.17–4.32 (m, 5 H), 4.65 (d, *J* = 6.8 Hz, 1 H), 4.71 (d, *J* = 6.8 Hz, 1 H), 4.76 (d, *J* = 6.9 Hz, 1 H), 4.79 (d, *J* = 6.9 Hz, 1 H), 7.29–7.47 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.0, 48.2, 49.1, 55.7, 55.8, 57.3, 61.6, 68.9, 72.8, 83.7, 87.1, 96.1, 96.2, 126.5, 128.6, 129.1, 131.8, 170.1, 174.7, 175.9 ppm. HRMS: calcd. for $C_{22}H_{28}N_2O_8$ $[MH]^+$ 449.1918; found 449.1928.

Compound 12: $[\alpha]_D \approx 0$ (*c* = 0.12, $CHCl_3$). IR(film): $\tilde{\nu}$ = 1720, 1700 cm^{-1} cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 1.33 (t, *J* = 7.2 Hz, 3 H), 2.84 (dd, *J* = 5.6, 11.2 Hz, 1 H), 3.27 (s, 3 H), 3.40 (s, 3 H), 3.46 (dd, *J* = 4.6, 11.2 Hz, 1 H), 3.80 (t, *J* = 9.2 Hz, 1 H), 3.87 (dd, *J* = 2.3, 9.2 Hz, 1 H), 3.99 (dd, *J* = 3.0, 9.2 Hz, 1 H), 4.23 (dd, *J* = 2.6, 3.0 Hz, 1 H), 4.24–4.26 (m, 3 H), 4.29 (d, *J* = 2.3 Hz, 1 H), 4.46 (d, *J* = 6.7 Hz, 1 H), 4.56 (d, *J* = 6.7 Hz, 1 H), 4.72 (d, *J* = 6.7 Hz, 1 H), 4.78 (d, *J* = 6.7 Hz, 1 H), 7.28–7,50 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.2, 47.9, 50.5, 55.7, 55.8, 57.3, 61.7, 68.6, 72.4, 81.7, 84.9, 95.5, 96.4, 126.2, 128.7, 129.1, 134.5, 171.1, 175.9, 177.0 ppm. MS (EI): *m*/*z* (%) = 448 (12), 375 (100). HRMS: calcd. for $C_{22}H_{28}N_2O_8Na$ $[MNa]^+$ 471.1738; found 471.1737.

Compound 13: IR (film): $\tilde{\nu}$ = 1710, 1700 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ = 2.8–2.95 (m, 2 H), 3.0–3.2 (m, 3 H), 3.40 (s, 6 H), 3.24–3.52 (m, 1 H), 3.74–3.85 (m, 1 H), 4.12–4.22 (m, 2 H), 4.65–4.75 (m, 4 H), 7.22–7.40 (m, 2 H), 7.40–7.55 (m, 3 H) ppm. $C_{18}H_{24}N_2O_6$ (364.16): calcd. C 59.33, H 6.64, N 7.69; found C 59.11, H 6.38, N 7.81.

Reaction of Diaminal 8 (R = TBDMS) and *N*-Phenylmaleimide: The crude diaminal **8** (R = TBDMS), obtained by mixing pyrrolidine **6** (0.400 g, 1,21 mmol), ethyl glyoxylate hydrate (0.072 g, 0.6 mmol) and $MgSO_4$ (0.039 g, 0.3 mmol), was refluxed with *N*-phenylmale-

imide (0.208 g, 1.2 mmol) in dry acetonitrile (5 mL) under argon for 14 h. The solvent was removed under reduced pressure and the residue dissolved in dichloromethane, washed with water and dried (Na_2SO_4). The residue was purified by flash chromatography (EtOAc/hexane, 1:6) to give compound **15** (0.141 g, 40%) as an oil and the Michael adduct **14** as an oily mixture of inseparable diastereomers (0.121 g, 40%).

Compound 14: IR (film): $\tilde{\nu}$ = 1700 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.07 (s, 6 H), 0.08 (s, 6 H), 0.89 (s, 18 H), 2.72 (d, J = 8.8 Hz, 1 H), 2.85–2.90 (m, 2 H), 2.97–3.07 (m, 1 H), 3.10–3.15 (m, 1 H), 3.82–3.89 (m, 2 H), 4.09–4.12 (t, J = 3.9 Hz, 2 H), 7.28–7.5 (m, 5 H) ppm. MS (EI): *m*/*z* (%) = 504 (10), 447 (83), 330 (14), 302 (30), 241 (15), 173 (14), 147 (56), 133 (21), 115 (10), 101 (19), 73 (97), 57 (100). $C_{26}H_{44}N_2O_4Si_2$ (504.81): calcd. C 61.86, H 8.79, N 5.55; found C 61.69, H 8.90, N 5.34.

Compound 15: $[\alpha]_D \approx 0$ (c = 0.15, $CHCl_3$). IR (film): $\tilde{\nu}$ = 1720, 1700 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.09 (s, 3 H), 0.11 (s, 3 H), 0.14 (s, 3 H), 0.15 (s, 3 H), 0.90 (s, 18 H), 1.26 (t, J = 7.0 Hz, 3 H), 2.76 (d, J = 12.1 Hz, 1 H), 3.52 (dd, J = 3.3, 12.1 Hz, 1 H), 3.66 (dd, J = 4.2, 8.0 Hz, 1 H), 3.84 (t, J = 8.9 Hz, 1 H), 3.87 (dd, J = 4.2, 2.3 Hz, 1 H), 4.02 (br. s, 1 H), 4.17–4.32 (m, 3 H), 4.35 (d, J = 8.9 Hz, 1 H), 7.29–7.45 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$): δ = –4.8, –4.6, 14.2, 17.9, 18.0, 25.8, 48.8, 50.8, 61.4, 62.1, 71.6, 75.7, 80.1, 84.5, 126.5, 128.5, 129.1, 132.0, 171.1, 175.0, 176.4 ppm. HRMS: calcd. for $C_{30}H_{48}N_2O_6Si_2Na$ 611.2943; found 611.2951.

Reaction of Diaminal 8 (R = MOM) and Dimethyl Maleate: The crude diaminal **8** (R = MOM) was obtained in a similar way by reaction of pyrrolidine **3** (0.478 g, 2.50 mmol), ethyl glyoxylate hydrate (0.075 g, 0.625 mmol) and $MgSO_4$ (0.2 g, 1.7 mmol) at room temp. under argon in a dry dichloromethane solution (2.5 mL) with stirring for 24 h. This crude product and dimethyl maleate (0.180 g, 1.25 mmol) were refluxed under argon in dry acetonitrile (10 mL) for 12 h. The solvent was evaporated under vacuum and the residue was taken up in dichloromethane, washed with water and dried (Na_2SO_4). The residue was purified by chromatography on a silica gel column eluting with hexane/EtOAc (3:1). A fast-moving band, consisting mainly of dimethyl fumarate, was eluted first (0.10 g), followed by the product **16** as an oil (0.157 g, 60%).

Compound 16: $[\alpha]_D$ = –15.30 (c = 0.73, $CHCl_3$). IR (film): $\tilde{\nu}$ = 1730, 1720 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.20 (t, J = 7.2 Hz, 3 H), 2.96 (d, J = 13.0 Hz, 1 H), 3.24–3.37 (m, 2 H), 3.29 (s, 3 H), 3.32 (s, 3 H), 3.60–3.71 (s, 2 H), 3.65 (s, 3 H), 3.67 (m, 3 H), 3.86 (d, J = 9.9 Hz, 1 H), 4.12–4.19 (m, 4 H), 4.54–4.69 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.1, 50.4, 50.7, 52.2, 52.4, 55.5, 55.7, 57.8, 61.3, 70.6, 72.8, 82.6, 83.7, 95.5, 95.7, 170.8, 171.6, 171.7 ppm. HRMS: calcd. for $C_{18}H_{29}NO_{10}$ $[MH]^+$ 420.1864; found 420.1868.

Reaction of Diaminal 8 (R = MOM) and Dimethyl Fumarate: The crude diaminal **8** (R = MOM) was obtained from pyrrolidine **3** (0.2 g, 1.05 mmol), ethyl glyoxylate (0.063 g, 0.525 mmol) and $MgSO_4$ (0.168 g, 1.4 mmol) according to the same procedure as described above. This crude product was refluxed with dimethyl fumarate (0.151 g, 1.048 mmol) under argon in dry acetonitrile (5 mL) for 18 h. Workup as above gave unreacted dimethyl fumarate (0.08 g) and compound **16** (0.151 g) in 71% yield. Spectral data are identical with compound **16** obtained in the previous experiment.

Reaction of Diaminal 8 (R = TBDMS) and Dimethyl Maleate: The crude diaminal **8** (R = TBDMS), obtained in a similar way from pyrrolidine **6** (0.4 g, 1.21 mmol), ethyl glyoxylate hydrate (0.072 g, 0.6 mmol) and $MgSO_4$ (0.072 g, 0.6 mmol), was refluxed with dimethyl maleate (0.173 g, 1.2 mmol) under argon in dry acetonitrile (10 mL) for 20 h. The solvent was evaporated under vacuum and the residue taken up in dichloromethane, washed with water and dried (Na_2SO_4). The residue was purified by chromatography on a silica gel column eluting with hexane/EtOAc (4:1) to give dimethyl fumarate (0.07 g) and compound **17** as an oil (0.235 g, 69%).

Compound 17: $[\alpha]_D$ = +16.69 (c = 0.78, $CHCl_3$). IR (film): $\tilde{\nu}$ = 1730 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.01(s, 3 H), 0.03 (s, 3 H), 0.08 (s, 3 H), 0.09 (s, 3 H), 0.81 (s, 9 H), 0.89 (s, 9 H), 1.25 (t, J = 7.2 Hz, 3 H), 2.65 (d, J = 12.7 Hz, 1 H), 3.21 (dd, J = 2.5, 12.7 Hz, 1 H), 3.46 (dd, J = 9.7, 11.3 Hz, 1 H), 3.56 (d, J = 11.3 Hz, 1 H), 3.64 (s, 3 H), 3.67 (m, 1 H), 3.71 (s, 3 H), 3.97 (br. s, 1 H), 4.01 (d, J = 10.7 Hz, 1 H), 4.08 (br. s, 1 H), 4.19 (q, J = 7.2 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = –5.0, –4.9, 14.2, 17.8, 25.6, 49.8, 50.2, 52.7, 59.8, 61.1, 65.7, 71.0, 75.8, 80.6, 81.3, 171.2, 171.9, 172.1 ppm. HRMS: calcd. for $C_{26}H_{49}NO_8Si_2$ $[MH]^+$ 560.3075; found 560.3059.

Reaction of Diaminal 8 (R = TBDMS) and Dimethyl Fumarate: According to the same procedure and workup as above and using the same quantities of crude diaminal **8** (R = TBDMS) and dimethyl fumarate, compound **17** was obtained (0.251 g, 74%) with identical spectroscopic data.

Reaction of Diaminal 8 (R = MOM) and Dimethyl Acetylenedicarboxylate: The crude diaminal **8** (R = MOM), obtained in a similar way from pyrrolidine **3** (0.478 g, 2.50 mmol), ethyl glyoxylate (0.075 g, 0.625 mmol) and $MgSO_4$ (0.2 g, 1.7 mmol), and dimethyl acetylenedicarboxylate (DMAD) (0.178 g, 1.25 mmol) were refluxed in dry acetonitrile solution (10 mL) under argon for 6 h. Workup as above and chromatography on silica with hexane/EtOAc (2:1) as eluent gave the Michael adduct **18** as an oil (0.299 g, 72%).

Dimethyl 2-[(3*S*,4*S*)-3,4-Bis(methoxymethoxy)pyrrolidinyl]-2-butenedioate (18): $[\alpha]_D$ = +5 (c = 2.58, $CHCl_3$). IR (film): $\tilde{\nu}$ = 1730 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 3.3 (m, 2 H), 3.35 (s, 6 H), 3.55 (m, 2 H), 3.65 (s, 3 H), 3.95 (s, 3 H), 4.25 (br. s, 2 H), 4.55 (s, 1 H), 4.65 (d, J = 6.4 Hz, 2 H), 4.7 (d, J = 6.4 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 50.7, 52.0, 52.9, 55.7, 78.5, 84.6, 95.9, 152.2, 165.7, 168.0 ppm. $C_{14}H_{23}NO_8$ (347.34): calcd. C 50.44, H 6.95, N 4.20; found C 50.31, H 6.62, N 4.24.

Reaction of Diaminal 8 (R = TBDMS) and Dimethyl Acetylenedicarboxylate: The crude diaminal **8** (R = TBDMS), obtained in a similar way from pyrrolidine **6** (0.4 g 1.21 mmol), ethyl glyoxylate hydrate (0.072 g, 0.6 mmol) and $MgSO_4$ (0.039 g, 3.25 mmol), was refluxed with dimethyl acetylenedicarboxylate (0.17 g, 1.2 mmol) in dry acetonitrile (5 mL) for 3 h. After the same workup as above, the crude reaction mixture was purified by chromatography on silica gel with hexane/EtOAc (10:1) as eluent to give compound **19** as an oil (0.271 g, 57%).

Dimethyl (*E*)-2-{(3*S*,4*S*)-3,4-Bis[(*tert*-butyldimethylsilyl)oxy]pyrrolidinyl}-2-butenedioate (19): IR (film): $\tilde{\nu}$ = 1740, 1695 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.05 (s, 6 H), 0.06 (s, 6 H), 0.85 (s, 18 H), 3.05 (br. s, 2 H), 3.47 (br. s 2 H), 3.63 (s, 3 H) 3.92 (s, 3 H), 4.04 (br. s, 2 H), 4.50 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = –4.9, –4.8, 17.9 25.6, 50.7, 52.8, 54.2, 75.9, 83.8, 152.7, 165.9, 168.2 ppm. $C_{22}H_{43}NO_6Si_2$ (473.75): calcd. C 55.78, H 9.15, N 2.96; found: C 55.42, H 9.22, N 3.21.

Reaction of Diaminal 8 (R = TBDMS) and Methyl Acrylate: According to the same procedure and workup as above and using the same quantities of crude diaminal **8** (R = TBDMS) and methyl acrylate (0.103 g, 1.2 mmol), compound **20** was obtained as an oil (0.162 g, 64% yield).

Methyl 3-{(3*S*,4*S*)-3,4-Bis[(*tert*-butyldimethylsilyl)oxy]pyrrolidinyl}-propanoate (20): ^1H NMR ($CDCl_3$): δ = 0.02 (s, 6 H), 0.03 (s, 6 H),

0.85 (s, 18 H), 2.41–2.49 (m, 4 H), 2.61–2.69 (m, 1 H), 2.76–2.86 (m, 3 H), 3.64 (s, 3 H), 4.04–4.07 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = –4.7, –4.6, 18.0, 25.4, 33.3, 51.5, 51.8, 60.7, 79.5, 172.7 ppm. $C_{20}H_{43}NO_4Si_2$ (420.47): calcd. C 57.50, H 10.38, N 3.35; found C 57.22, H 10.20, N 3.52.

X-ray Structure Analysis of Compound 12: X-ray diffraction measurements were performed with a KM-4 four-circle diffractometer with graphite-monochromated Cu-K_a radiation at room temperature. The structure was solved by direct methods using SHELXS-97[22] and refined by the full-matrix least-squares method using SHELXL-97.[23] An ORTEP drawing of the molecule is shown in Figure 1. Details of the crystal data and structure refinement are given in Table 2. CCDC-272464 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table 2. Crystal data and structure refinement details for compound **12**.

Empirical formula	$C_{22}H_{28}N_2O_8$
Formula mass	448.86
Wavelength λ [Å]	1.54178
Crystal dimensions [mm]	0.60 × 0.07 × 0.05
Space group	$P2_1$
Unit cell dimensions	
a [Å]	11.429(5)
b [Å]	6.413(3)
c [Å]	15.493(7)
β [°]	101.17(4)
Volume [Å^3]	1114.0(9)
Z	2
Density [Mg m^{-3}]	1.337
Absorption coefficient [mm^{-1}]	0.857
2θ range for data collection [°]	2.91–65.1
Index ranges	$13 \le h \le 13$, $0 \le k \le 7$, $0 \le l \le 18$
Reflections collected/unique	2085/1970
Reflections with $I > 2\sigma(I)$	1357
Data/restraints/parameters	1970/1/270
Goodness of fit on F^2	1.004
Final R indices [$I > 2\sigma(I)$]	$R(F)$ = 0.0591, $wR(F^2)$ = 0.1359
R indices (all data)	$R(F)$ = 0.1077, $wR(F^2)$ = 0.1472
Extinction coefficient	0.0106(16)

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