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Acetals of γ-oxo-α,β-unsaturated esters in nitrone cycloadditions. Regio- and stereochemical implications

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Abstract—Several acetals of γ-oxo-α,β-unsaturated esters have been prepared, mainly from enantiopure C_2-symmetric diols, and their 1,3-dipolar cycloaddition to 2,3,4,5-tetrahydropyridine 1-oxide has been studied. All the reactions showed complete regioselectivity and a high preference for the *endo* approach of the reactants in the transition state. The enantiopure acetals derived from (*cis*,*cis*)-spiro[4.4]nonane-1,6-diol gave the highest diastereofacial selectivity.

1. Introduction

Since the general concept of the 1,3-dipole was introduced by Huisgen in 1963,[1] these reactive species have received much attention, both from synthetic and mechanistic points of view. 1,3-Dipolar cycloaddition to multiple bonds constitutes one of the most useful and versatile reactions for the construction of five-membered heterocyclic systems with different degrees of unsaturation. The regio- and stereocontrol of the cycloaddition reaction are major concerns to achieve a good synthetic performance of the process. Asymmetric versions of these cycloadditions are a subject of current interest in the field of synthetic organic chemistry. Nevertheless, the development of the asymmetric 1,3-dipolar cycloadditions[2] is far behind the advances reached in the closely related Diels–Alder process and the reported enantioselectivities are usually low to moderate.

During the last years we have been studying different aspects of the reaction between nitrones and olefins. Our interest in this chemistry stems from the exploitation of isoxazolidines as valuable intermediates in the synthesis of target molecules, mainly alkaloids. As part of our investigations, a series of γ-oxy- and γ-oxo-α,β-unsaturated carboxylic acid derivatives were tested as dipolarophiles towards cyclic nitrones.[3] The γ-oxy derivatives showed complete regioselectivity with remarkable *endo* or *exo* diastereoselectivity, depending on the (*E*) or (*Z*) geometry of the starting olefin, respectively. In contrast, the γ-oxo derivatives showed good, but not complete, regioselectivities and poor *endo*/*exo* selectivities. We also studied the reaction of nitrones with *p*-benzoquinone monoacetals,[4] some of which were enantiopure substrates containing a dioxolane moiety derived from a C_2-symmetric diol. As a complement to these former studies, we decided to investigate the effect in the regio- and stereochemical outcome of the cycloaddition produced by the incorporation of an acetal function into open-chain γ-oxo-α,β-unsaturated esters. It was foreseen that masking of the ketone as a dioxolane would result in complete regioselectivity and favor the *endo*-ester diastereoselectivity. The use of homochiral C_2-symmetric diols as chiral auxiliaries in the formation of the acetal could provide a means for inducing diastereofacial discrimination on the olefin. The results of these studies are presented herein.

2. Results and discussion

Examples dealing with the use of acetals derived from γ-oxo-α,β-unsaturated esters (or closely related molecules) as dipolarophiles are scarce. Most of the reported studies refer to cyclic pseudoesters of the type **1** (Fig. 1), which have been reacted with nitrile oxides,[5] diazo compounds,[5b,5d,5e,6] nitrones,[5b,5d,5e,7] azides[8] and azomethine ylides,[5b,5e,7,8b,9] giving rise in many cases to mixtures of cycloadducts.[5d,5e,5g,5i,6a] To the best of our

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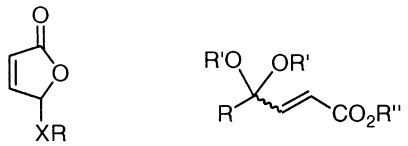


1 2

X=O, R=Me, Et, (*R*)-menthyl
X=S, R=Et, Ph

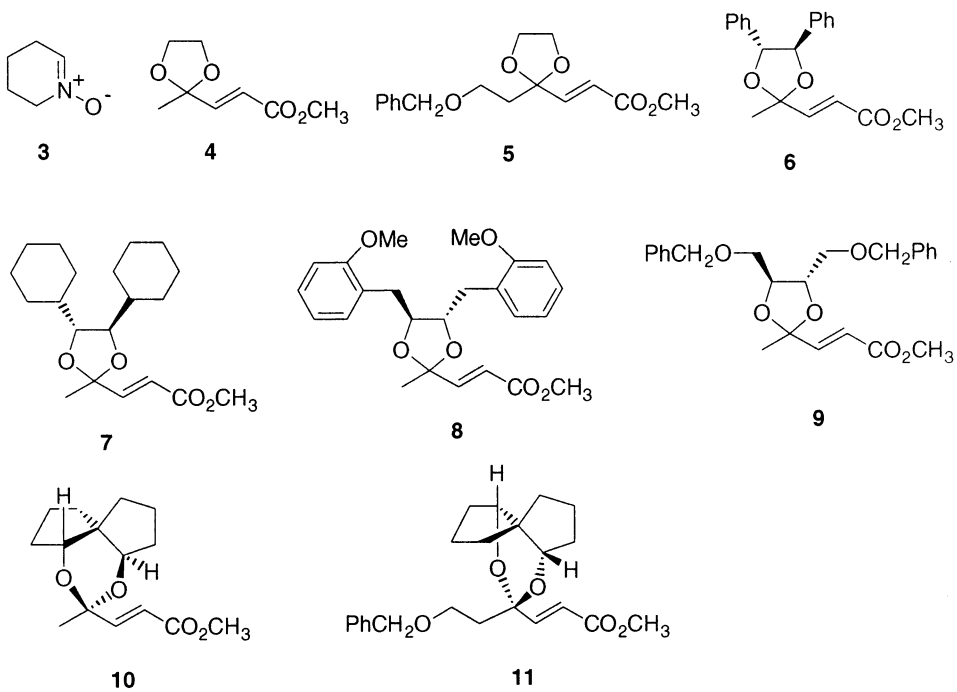
Figure 1.

knowledge, only five published works deal with the use of (*E*) or (*Z*) open-chain acetals of the type **2** in dipolar cycloaddition processes in combination with nitrile oxides[5f,5g,5i] and diazo compounds[6a,10] and, except for one case, the reactions are not regioselective. With these precedents, we undertook the study of the 1,3-dipolar cycloaddition of nitrones to γ-oxo-α,β-unsaturated esters, in terms of regiochemistry, *endo*/*exo* stereoselectivity and asymmetric induction.

The configurationally stable cyclic nitrone **3** (Fig. 2) was selected for this study. The ethylene glycol acetals **4** and **5** were investigated initially, for reasons of simplicity, accessibility and because the cycloaddition of **3** to their corresponding γ-oxoesters had been previously investigated.[3c] In order to study the asymmetric induction, we prepared the chiral dioxolanes **6**–**11**, all derived from C_2-symmetric 1,2-diols. This kind of chiral auxiliary avoids the formation of a new stereocenter at the acetal carbon atom, reducing the number of possible competitive transition states.

Acetal **4** was prepared as previously reported.[10] The rest of acetals **5**–**11** were synthesized from methyl (*E*)-4-oxo-2-pentenoate or methyl (*E*)-6-benzyloxy-4-oxo-2-hexenoate[3c] and the appropriate diol by a standard methodology. Thus, heating a benzene solution of the carbonyl compound and the diol in the presence of a catalytic amount of *p*-toluenesulfonic acid in a Dean–Stark azeotropic separator furnished the corresponding dioxolanes in ca. 90% yield, except for **7** (74%) and **11** (59%). All the acetals were completely characterized by their spectral data and gave correct elemental analyses. The value of the coupling constant between the olefinic protons evidences that the (*E*) configuration of the double bond was retained in all the cases examined.

The reaction of acetal **4** with an excess of nitrone **3** was performed in methylene chloride at room temperature and followed by TLC analysis, which revealed the consumption of the dipolarophile after 2 days. From this reaction, we isolated only two products, **12** (*exo*) and **13** (*endo*), in 9 and 75% yield, respectively (Fig. 3). In both cycloadducts the perhydroisoxazolo[2,3-*a*]pyridine system exists preferentially in the *trans* ring fusion as indicated by the large $\Delta\delta$ value between the two protons attached at C(7).[11] The connectivity of **12** was established through an HMBC experiment, that showed a correlation between H(3a) and the carbon atom of the carboxyl group, and the (*trans*) relationship between the C(3) and C(3a) protons was deduced from the value of $J_{3,3a}=10.2$ Hz.[3a,12] The chemical shifts of C(2) and C(3) of the major adduct **13** are very similar to those of **12**, proving that both isomers present identical regiochemistry, while the value of $J_{3,3a}=8.4$ Hz in **13** is in agreement with a *cis* relative geometry of C(3) and C(3a) protons.[3a,12]



3 4 5 6 7 8 9 10 11

Figure 2.

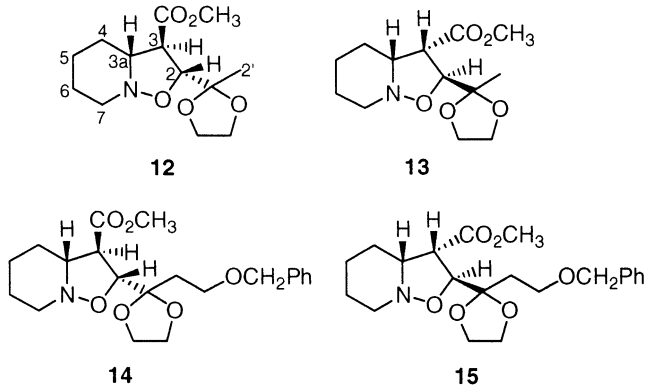


Figure 3.

Under the same conditions the reaction between nitrone **3** and acetal **5** gave adducts **14** (*exo*) and **15** (*endo*), isolated in 8 and 77% yield, respectively. The structural and stereochemical assignment of these new compounds was based on their NMR data, according to the same criteria used above. The preferred ring fusion conformation showed by both compounds in solution was again (*trans*).

From these experiments, we concluded that the cycloaddition is completely regioselective (the electrophilic β-carbonylic end of the dipolarophile binds to the nucleophilic oxygen atom of the nitrone), the chemical yields of the cycloadducts are very high and the *endo*-ester approach of the educts in the transition state is clearly preferred, with *endo*/*exo* stereoselectivity of ca. 9:1.

Next, in the search for a diastereofacially selective process, the reactions between nitrone **3** and the dioxolanes **6**–**10** bearing the chiral auxiliaries were performed (Fig. 4). The reaction of **3** with **6** at room temperature was completed in 2 days and furnished two inseparable ca. 3:2 (or 2:3) mixtures of both *exo* adducts, **16a** and **16b**, and both *endo* adducts, **17a** and **17b**, in 8 and 77% yield, respectively. The regiochemistry of all these products was confirmed by HMBC experiments and, although for **17a** and **17b** the coupling constant $J_{3,3a}$ was not measurable, the upfield shifted signals of C(3) is in agreement with their *endo* stereochemistry.[3a] It is clear that the chirality of the dioxolane ring in **6** does not induce any asymmetry in the generation of the new stereocenters.

The reaction between nitrone **3** and acetal **7** was much slower. After 15 days at room temperature, we isolated two approximately 1:1 mixtures of both *exo*, **18a** and **18b**, and *endo* adducts, **19a** and **19b**, in 12 and 63% yield, respectively. The incorporation of tertiary carbon atoms at the dioxolane substituents, which increases the steric demand of the substrate, diminishes the reaction rate, but does not improve the diastereofacial selectivity of the cycloaddition and, more surprisingly, the *endo*/*exo* selectivity is somewhat lower.

Acetals **8** and **9** were chosen in the hope that good diastereofacial differentiation could be attained if the aromatic ring tethered to the dioxolane was able to establish a π-stacking interaction with one of the olefin faces. Molecular models of both substrates show an appropriate geometry for this interaction, which in **8** could be further enhanced by the favorable electronic effect of the *o*-MeO substituents.

From the cycloaddition of nitrone **3** to **8** we could isolate two fractions. The minor and less polar one contained a 2:1 (or 1:2) mixture of the *exo* adducts **20a** and **20b** (11% yield) and the major fraction was formed by equimolar amounts of the *endo* adducts **21a** and **21b** (82% yield). The *exo* or *endo* stereochemistry was inferred from the $J_{3,3a}$ values. Very similar results were obtained with the benzyloxymethyl substituted acetal **9**.

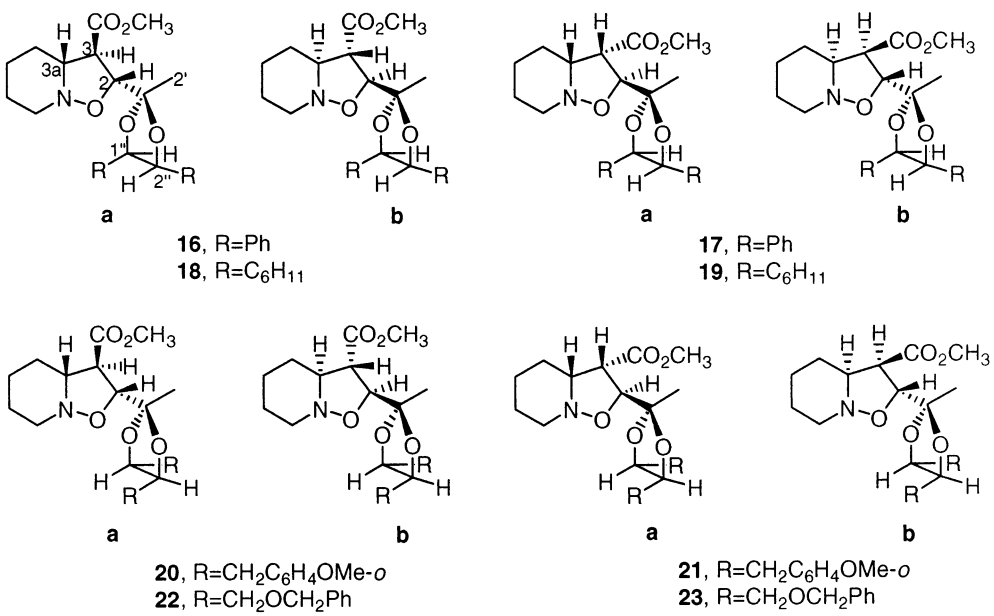


Figure 4.

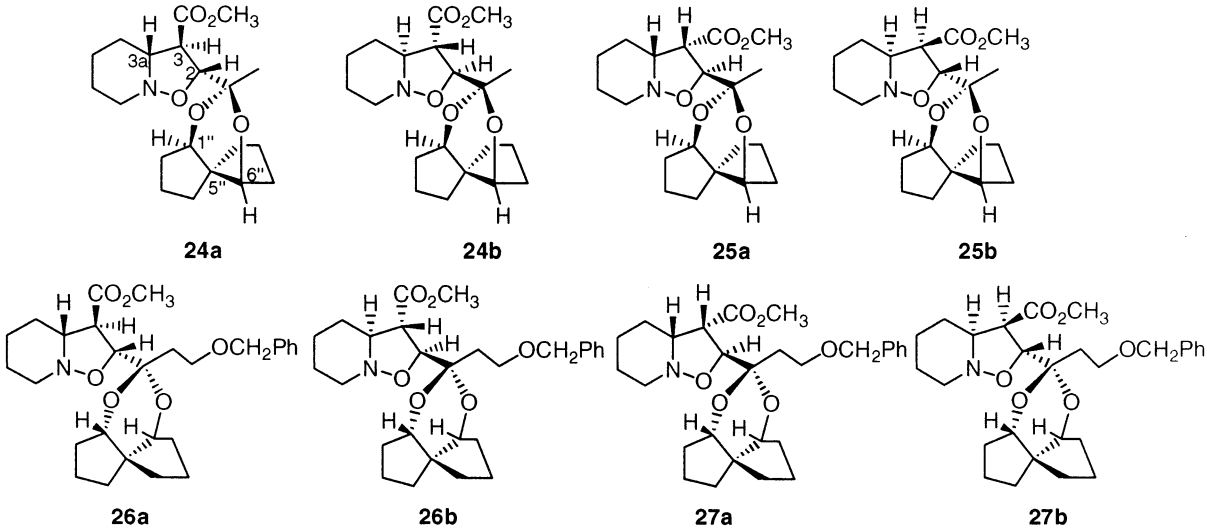


Figure 5.

Again, we obtained an inseparable 2:1 (or 1:2) mixture of the *exo* cycloadducts **22a** and **22b** (10% yield) and a 1:1 mixture of the *endo* isomers **23a** and **23b** (82% yield). Hence, the use of dioxolanes **8** and **9** has resulted in some diastereofacial differentiation in the formation of the cycloadducts derived from an *exo* transition state, but none in the formation of the major *endo* adducts. Steric effects may be invoked to explain this observation, considering that in the former approach the bulky dioxolane moiety lays in the proximity of the nitrone residue.

The unsatisfactory results so far obtained, prompted us to try a more sterically demanding auxiliary. Keeping in mind the advantages of using a C_2-symmetric diol, we selected the rigid and highly crowded (*cis*,*cis*)-spiro[4.4]nonane-1,6-diol,[13] which has been used as a chiral auxiliary in an asymmetric Diels–Alder reaction.[14] Thus, the new acetal **10** was synthesized and its cycloaddition to nitrone **3** was examined. This reaction was very slow and, after 15 days at room temperature, some unreacted olefin still remained. As in the precedent experiments, two fractions containing cycloadducts were obtained. The less polar was a 10:1 (or 1:10) mixture of the *exo* products **24a** and **24b** (9% yield) and the second eluted contained a 4:1 (or 1:4) mixture of **25a** and **25b** (68% yield) (Fig. 5). Therefore, in this case the diastereofacial discrimination of the double bond was significant, ranging from high for the *exo* isomers to moderate for the major *endo* adducts.

This promising finding, led us to prepare acetal **11**, which should furnish isoxazolidines which would be highly valuable to our synthetic interests. The reaction between **3** and **11** was also slow and afforded a 10:1 (or 1:10) mixture of the *exo* cycloadducts **26a** and **26b** (11% yield) and a 7:1 (or 1:7) mixture of the *endo* products **27a** and **27b** (57% yield). Repeated flash chromatography of these mixtures provided a pure sample of the major *exo* diastereoisomer and a 43% yield of the major *endo* diastereoisomer, whose relative configurations could not be established on the basis of its spectroscopic properties and will have to be determined by chemical correlation after further synthetic elaboration.

3. Conclusion

In conclusion, we have explored the regio- and stereochemical outcome of the cycloaddition between a configurationally stable nitrone and several acetals of γ-oxo-α,β-unsaturated esters, including various enantiopure derivatives of chiral C_2-symmetric diols. These cycloadditions were high yielding and showed complete regioselectivity, giving isoxazolidines with the oxygen atom attached to the β-carbonyl position exclusively. In all of the cases examined, the cycloadducts derived from *endo*-ester transition states predominate. The best diastereofacial discrimination of double bond was obtained using the (*cis*,*cis*)-spiro[4.4]nonane-1,6-diol as a chiral auxiliary. The cycloaddition of the enantiopure acetal derived from the (+)-(1*S*,5*S*,6*S*) enantiomer of this diol and methyl (*E*)-6-benzyloxy-4-oxo-2-hexenoate furnished a major *endo* diastereoisomer, isolable in enantiopure form by chromatography, in 43% yield, useful for our plans on the field of alkaloids synthesis.

4. Experimental

Methyl (*E*)-4-oxo-2-pentenoate is commercial. The following compounds were prepared according to previously described methods: nitrone **3**,[15] (*R*,*R*)-hydrobenzoin,[16] (*R*,*R*)-dicyclohexylethyleneglycol,[17] (2*S*,3*S*)-1,4-bis(2-methoxyphenyl)-2,3-butanediol,[18] (2*S*,3*S*)-1,4-bis(benzyloxy)-2,3-butanediol,[19] (1*R*,5*R*,6*R*)- and (1*S*,5*S*,6*S*)-spiro[4.4]nonane-1,6-diol,[13] methyl (*E*)-6-benzyloxy-4-oxo-2-hexenoate[3c] and acetal **4**.[10] Reaction mixtures were stirred magnetically. The organic extracts were dried over anhydrous sodium sulfate. Reaction solutions were concentrated using a rotary evaporator at 15–20 Torr. Flash column chromatography was performed using Merck silica gel (230–400 mesh). Infrared spectra were recorded on a Nicolet

5 ZDX spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-250-WB instrument at 250 and 62.5 MHz, respectively, in $CDCl_3$ solutions unless otherwise indicated. Mass spectra were performed on a Hewlett–Packard 5985B instrument at 70 eV; only peaks with higher intensity than 20% are reported, unless they belong to molecular ions or to significant fragments.

4.1. Methyl (*E*)-6-benzyloxy-4,4-ethylenedioxy-2-hexenoate, 5

A solution of methyl (*E*)-6-benzyloxy-4-oxo-2-hexenoate (800 mg, 3.23 mmol), ethylene glycol (600 mg, 9.68 mmol) and *p*-toluenesulfonic acid (28 mg, 0.15 mmol) in benzene (80 mL) was heated under reflux in a reaction flask equipped with a Dean–Stark azeotropic separator for 4 h. The reaction mixture was washed with saturated aqueous $NaHCO_3$ (50 mL) and water (50 mL). Flash chromatography of the crude material (960 mg) using hexane/ethyl acetate (1:1) as eluent afforded **5** as a colorless oil (850 mg, 2.91 mmol, 90%); ^{1}H NMR: δ 7.35–7.20 (m, 5H), 6.74 (d, $J_{3,2}=15.7$ Hz, 1H, H-3), 6.05 (d, $J_{2,3}=15.7$ Hz, 1H, H-2), 4.45 (s, 2H), 3.95–3.80 (m, 4H), 3.71 (s, 3H, OCH_3), 3.56 (t, $J_{6,5}=7.0$, 2H, 2H-6), 2.09 (t, $J_{5,6}=7.0$, 2H, 2H-5); ^{13}C NMR: δ 166.5 (C-1), 146.2 (C-3), 138.2/128.3/127.6/127.5 (Ph), 121.1 (C-2), 107.1 (C-4), 73.0 (CH_2Ph), 65.3 (C-6), 64.8 (OCH_2CH_2O), 51.7 (OCH_3), 37.9 (C-5). Anal. calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.90; H, 6.95%.

4.2. Methyl (*E*)-4,4-[(1*R*,2*R*)-1,2-diphenylethylenedioxy]-2-pentenoate, 6

A solution of methyl (*E*)-4-oxo-2-pentenoate (1.00 g, 7.81 mmol), (*R*,*R*)-hydrobenzoin (1.84 g, 8.59 mmol) and *p*-toluenesulfonic acid (67 mg, 0.39 mmol) in benzene (80 mL) was heated under reflux in a reaction flask equipped with a Dean–Stark azeotropic separator for 4 h. The reaction mixture was washed with saturated aqueous $NaHCO_3$ (60 mL) and water (60 mL). Flash chromatography of the crude material (2.53 g) using hexane/ether (2:1) as eluent afforded **6** as a colorless oil (2.32 g, 7.16 mmol, 92%); IR (film): 3035, 2989, 2950, 2920, 2890, 1728, 1305, 1280, 1170, 1037 cm^{-1}; ^{1}H NMR: δ 7.40–7.15 (m, 10H), 7.13 (d, $J_{3,2}=16.3$ Hz, 1H, H-3), 6.32 (d, $J_{2,3}=16.3$ Hz, 1H, H-2), 4.80 (d, $J=8.0$ Hz, 1H, H-1′/H-2′), 4.70 (d, $J=8.0$ Hz, 1H, H-1′/H-2′), 3.78 (s, 3H, OCH_3), 1.76 (s, 3H, 3H-5); ^{13}C NMR: δ 166.9 (C-1), 147.6 (C-3), 136.0/135.5/128.5/126.0 (Ph), 120.2 (C-2), 107.2 (C-4), 85.8/85.6 (C-1′/C-2′), 51.8 (OCH_3), 25.9 (C-5). Anal. calcd for $C_{20}H_{20}O_4$: C, 74.06; H, 6.21. Found: C, 74.02; H, 6.23%. $[\alpha]_D^{20}=+37.0$ (*c* 3.3, ethanol).

4.3. Methyl (*E*)-4,4-[(1*R*,2*R*)-1,2-dicyclohexylethylenedioxy]-2-pentenoate, 7

A solution of methyl (*E*)-4-oxo-2-pentenoate (100 mg, 0.78 mmol), (*R*,*R*)-1,2-dicyclohexyl-1,2-ethanediol (200 mg, 0.88 mmol) and *p*-toluenesulfonic acid (7.5 mg, 0.04 mmol) in benzene (10 mL) was heated under reflux in a reaction flask equipped with a Dean–Stark azeotropic separator for 8 h. The reaction mixture was washed with saturated aqueous $NaHCO_3$ (6 mL) and water (6 mL). Flash chromatography of the crude material (270 mg) using hexane/ethyl acetate (50:1) as eluent afforded **7** as a colorless oil (195 mg, 0.68 mmol, 74%); IR (film): 2931, 2853, 1728, 1658, 1447, 1307, 1278, 1222, 1025 cm^{-1}; ^{1}H NMR: δ 6.82 (d, $J_{3,2}=15.7$ Hz, 1H, H-3), 6.02 (d, $J_{2,3}=15.7$ Hz, 1H, H-2), 3.72 (s, 3H, OCH_3), 3.65–3.50 (m, 2H, H-1′, H-2′), 1.90–0.90 (m, 22H), 1.40 (s, 3H, 3H-5); ^{13}C NMR: δ 167.0 (C-1), 149.5 (C-3), 119.4 (C-2), 105.8 (C-4), 83.7/83.4 (C-1′/C-2′), 51.6 (OCH_3), 41.0, 40.7, 31.1, 30.4, 29.6, 28.7, 27.2, 26.4, 26.0 (C-5); MS (*m*/*z*): 336 (M$^+$, 1), 321 (53), 253 (20), 251 (40), 191 (33), 165 (64), 129 (60), 125 (23), 112 (56), 109 (100), 95 (85). Anal. calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 71.26; H, 9.81%. $[\alpha]_D^{20}=-17.0$ (*c* 4.0, ethanol).

4.4. Methyl (*E*)-4,4-[(2*S*,3*S*)-1,4-bis(2-methoxyphenyl)-2,3-butylenedioxy]-2-pentenoate, 8

A solution of methyl (*E*)-4-oxo-2-pentenoate (190 mg, 1.48 mmol), (*S*,*S*)-1,4-bis(2-methoxyphenyl)-2,3-butanediol (500 mg, 1.65 mmol) and *p*-toluenesulfonic acid (14 mg, 0.07 mmol) in benzene (20 mL) was heated under reflux in a reaction flask equipped with a Dean–Stark azeotropic separator for 8 h. The reaction mixture was washed with saturated aqueous $NaHCO_3$ (10 mL) and water (10 mL). Flash chromatography of the crude material (679 mg) using hexane/ethyl acetate (7:1) as eluent afforded **8** as a colorless oil (564 mg, 1.36 mmol, 92%); IR (film): 3000, 2938, 2839, 1728, 1645, 1609, 1510, 1433, 1300, 1250, 1173, 1039 cm^{-1}; ^{1}H NMR (400 MHz): δ 7.08–6.98 (m, 2H, 2Ar), 6.85–6.75 (m, 3H, 2Ar, H-3), 6.03 (d, $J_{2,3}=15.7$ Hz, 1H, H-2), 3.95–3.79 (m, 2H, H-2′, H-3′), 3.76 (s, 6H, 2×OCH_3), 3.71 (s, 3H, OCH_3), 2.80–2.65 (m, 2H, H-1′/H-4′), 2.59 (dd, $J=14.0$ Hz, $J'=4.7$ Hz, 1H, H-1′/H-4′), 2.49 (dd, $J=14.0$ Hz, $J'=4.7$ Hz, 1H, H-1′/H-4′), 1.43 (s, 3H, 3H-5); ^{13}C NMR (100 MHz): δ 166.8 (C-1), 158.3 (Ar), 148.5 (C-3), 130.3/130.2/129.1/129.0 (Ar), 119.9 (C-2), 113.8/113.7 (Ar), 106.1 (C-4), 81.8/81.4 (C-2′/C-3′), 55.2/51.7 (2×OCH_3), 38.3/37.7 (C-1′/C-4′), 25.7 (C-5); MS (*m*/*z*): 412 (M$^+$, 5), 327 (1), 163 (95), 135 (20), 121 (100). Anal. calcd for $C_{24}H_{28}O_6$: C, 69.89; H, 6.84. Found: C, 69.82; H, 6.86%. $[\alpha]_D^{20}=+6.4$ (*c* 3.75, ethanol).

4.5. Methyl (*E*)-4,4-[(2*S*,3*S*)-1,4-bis(benzyloxy)-2,3-butylenedioxy]-2-pentenoate, 9

A solution of methyl (*E*)-4-oxo-2-pentenoate (213 mg, 1.66 mmol), (*S*,*S*)-1,4-bis(benzyloxy)-2,3-butanediol (500 mg, 1.65 mmol) and *p*-toluenesulfonic acid (40 mg, 0.2 mmol, added slowly in four fractions) in benzene (25 mL) was heated under reflux in a reaction flask equipped with a Dean–Stark azeotropic separator for 25 h. The reaction mixture was washed with saturated aqueous $NaHCO_3$ (15 mL) and water (15 mL). Flash chromatography of the crude material (750 mg) using hexane/ethyl acetate (10:1 to 7:1) as eluent afforded **9** as a colorless oil (626 mg, 1.52 mmol, 93%); IR (film):

3029, 2931, 2868, 1728, 1665, 1602, 1447, 1370, 1307, 1278, 1208, 1103 cm^{-1}; ^1H NMR: δ 7.35–7.20 (m, 10H), 6.85 (d, $J_{3,2}=16.0$ Hz, 1H, H-3), 6.11 (d, $J_{2,3}=16.0$ Hz, 1H, H-2), 4.56 (s, 2H, CH_2Ph), 4.52 (s, 2H, CH_2Ph), 4.07 (dt, $J=8.0$ Hz, $J'=4.4$ Hz, 1H, H-2′/H-3′), 3.98 (dt, $J=8.0$ Hz, $J'=4.4$ Hz, 1H, H-2′/H-3′), 3.72 (s, 3H, OCH_3), 3.67–3.48 (m, 4H, 2×CH_2O), 1.50 (s, 3H, 3H-5); ^{13}C NMR: δ 166.6 (C-1), 147.8 (C-3), 137.7/128.3/128.0/127.6 (Ph), 120.4 (C-2), 107.3 (C-4), 78.1/77.9 (C-2′/C-3′), 73.4 (2×CH_2Ph), 70.3/69.8 (2×CH_2O), 51.6 (OCH_3), 25.5 (C-5); MS (m/z): 397 (M^+−15, 1), 321 (2), 215 (10), 91 (100). Anal. calcd for $C_{24}H_{28}O_6$: C, 69.89; H, 6.84. Found: C, 69.75; H, 6.61%. $[\alpha]_D^{20}=+3.8$ (c 6.0, ethanol).

4.6. Methyl (*E*)-4,4-[(1*R*,5*R*,6*R*)-spiro[4.4]nonylene-1,6-dioxy]-2-pentenoate, 10

A solution of methyl (*E*)-4-oxo-2-pentenoate (500 mg, 3.91 mmol), (1*R*,5*R*,6*R*)-spiro[4.4]nonane-1,6-diol (609 mg, 3.91 mmol) and *p*-toluenesulfonic acid (34 mg, 0.2 mmol) in benzene (60 mL) was heated under reflux in a reaction flask equipped with a Dean–Stark azeotropic separator for 7 h. The reaction mixture was washed with saturated aqueous $NaHCO_3$ (60 mL) and water (60 mL). Flash chromatography of the crude material (1.25 g) using hexane/ethyl acetate (5:1) as eluent afforded **10** as a colorless oil (905 mg, 3.40 mmol, 87%); IR (film): 2953, 2903, 2887, 1729, 1661, 1438, 1369, 1300, 1280, 1220, 1153, 1057, 1012 cm^{-1}; ^1H NMR: δ 6.69 (d, $J_{3,2}=15.7$ Hz, 1H, H-3), 6.04 (d, $J_{2,3}=15.7$ Hz, 1H, H-2), 3.81 (d, $J=5.1$, 1H, H-1′/H-6′), 3.69 (s, 3H, OCH_3), 3.56 (d, $J=5.5$, 1H, H-1′/H-6′), 1.90–1.20 (m, 12H), 1.32 (s, 3H, 3H-5); ^{13}C NMR: δ 166.9 (C-1), 147.9 (C-3), 120.5 (C-2), 97.4 (C-4), 79.6/78.9 (C-1′/C-6′), 57.1 (C-5′), 51.4 (OCH_3), 36.8/36.3/32.0/31.7/24.0/23.9 (C-2′/C-3′/C-4′/C-7′/C-8′/C-9′), 23.9 (C-5); MS (m/z): 267 (M^++1, 10), 251 (4), 235 (1), 121 (100), 120 (57), 94 (50), 79 (35), 43 (30). Anal. calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.74; H, 8.43%. $[\alpha]_D^{20}=+21.6$ (c 2.5, ethanol).

4.7. Methyl (*E*)-6-benzyloxy-4,4-[(1*S*,5*S*,6*S*)-spiro[4.4]nonylene-1,6-dioxy]-2-hexenoate, 11

A solution of methyl (*E*)-6-benzyloxy-4-oxo-2-hexenoate (300 mg, 1.21 mmol), (1*S*,5*S*,6*S*)-spiro[4.4]nonane-1,6-diol (198 mg, 1.27 mmol) and *p*-toluenesulfonic acid (8 mg, 0.05 mmol) in benzene (15 mL) was heated under reflux in a reaction flask equipped with a Dean–Stark azeotropic separator for 2 h. The reaction mixture was diluted with ethyl acetate (20 mL) washed with saturated aqueous $NaHCO_3$ (20 mL) and water (10 mL). Flash chromatography of the crude material using hexane/ethyl acetate (5:1) as eluent afforded **11** as a colorless oil (232 mg, 0.58 mmol, 59%) and recovered ketone (58 mg, 0.23 mmol); IR (film): 2952, 2860, 1728, 1660, 1440, 1293, 1152, 1103 cm^{-1}; ^1H NMR: δ 7.34–7.21 (m, 5H), 6.72 (d, $J_{3,2}=15.7$ Hz, 1H, H-3), 6.07 (d, $J_{2,3}=15.7$ Hz, 1H, H-2), 4.45 (s, 2H), 3.82 (br d, $J=4.4$, 1H, H-1′/H-6′), 3.72 (s, 3H, OCH_3), 3.60 (br d, $J=3.7$, 1H, H-1′/H-6′), 3.50 (t, $J_{6,5}=7.3$ Hz, 2H, 2H-6), 2.10 (dt, $J_{5,5}=13.9$ Hz, $J_{5,6}=7.3$ Hz, 1H, H-5), 2.01 (dt, $J_{5,5}=13.9$ Hz, $J_{5,6}=7.3$ Hz, 1H, H-5), 1.83–1.20 (m, 12H); ^{13}C NMR: δ 166.8 (C-1), 147.2 (C-3), 138.3/128.2/127.5/127.4 (Ph), 121.2 (C-2), 97.9 (C-4), 79.2/79.1 (C-1′/C-6′), 72.9 (CH_2Ph), 65.6 (C-6), 57.0 (C-5′), 51.5 (OCH_3), 37.1/36.9/36.4/32.1/31.7/24.0/23.9 (C-2′/C-3′/C-4′/C-7′/C-8′/C-9′); MS (m/z): 251 (2), 121 (100), 91 (40). Anal. calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.94; H, 8.17%. $[\alpha]_D^{20}=-28.8$ (c 2.5, ethanol).

4.8. Cycloaddition of nitrone 3 to acetal 4

To a solution of **3** (prepared from 405 mg, 4.01 mmol, of *N*-hydroxypiperidine and 2.61 g, 12.0 mmol, of yellow HgO) in methylene chloride (25 mL), a solution (460 mg, 2.67 mmol) of acetal **4** (460 mg, 2.67 mmol) in the same solvent (2 mL) was added and the mixture was stirred at rt for 2 days. Flash chromatography of the crude material (910 mg) using hexane/ethyl acetate (2:1) as eluent afforded methyl (2*RS*,3*RS*,3a*RS*)-2-(1,1-ethylenedioxy)ethylhexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-3-carboxylate, *exo*-adduct **12**, as a solid (65 mg, 0.24 mmol, 9%) and its (2*RS*,3*RS*,3a*SR*) isomer, *endo*-adduct **13**, as a colorless oil (542 mg, 2.00 mmol, 75%). Compound **12**: mp 46–47°C (ethyl acetate/pentane); IR (KBr): 2944, 2811, 1740, 1441, 1281, 1251, 1198, 1167, 1049, 1012 cm^{-1}; ^1H NMR: δ 4.24 (d, $J_{2,3}=7.3$ Hz, 1H, H-2), 4.05–3.90 (m, 4H, OCH_2CH_2O), 3.70 (s, 3H, OCH_3), 3.37 (m, 1H, H-7eq), 3.04 (dd, $J_{3,3a}=10.2$ Hz, $J_{3,2}=7.3$ Hz, 1H, H-3), 2.45–2.30 (m, 2H, H-7ax, H-3a), 1.95 (m, 1H, H-4eq), 1.80–1.10 (m, 5H, H-5eq, H-6eq, H-6ax, H-5ax, H-4ax), 1.32 (s, 3H, 3H-2′); ^{13}C NMR: δ 171.9 (C=O), 109.6 (C-1′), 81.3 (C-2), 70.9 (C-3a), 65.5 and 65.0 (OCH_2CH_2O), 55.5 (C-7), 54.0 (C-3), 52.1 (OCH_3), 28.3 (C-4), 24.3 (C-6), 23.1 (C-5), 20.4 (C-2′); MS (m/z): 271 (M^+, 4), 240 (1), 184 (3), 100 (10), 99 (13), 87 (100), 43 (29). Anal. calcd for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.43; H, 7.88; N, 5.14%. Compound **13**: IR (KBr): 2986, 2939, 2839, 1734, 1441, 1281, 1205, 1049, 1008 cm^{-1}; ^1H NMR: δ 4.44 (d, $J_{2,3}=5.1$ Hz, 1H, H-2), 4.05–3.85 (m, 4H, OCH_2CH_2O), 3.68 (s, 3H, OCH_3), 3.48 (br d, $J=9.1$ Hz, 1H, H-7eq), 3.13 (dd, $J_{3,3a}=8.4$ Hz, $J_{3,2}=5.1$ Hz, 1H, H-3), 2.45–2.30 (m, 2H, H-7ax, H-3a), 1.90 (m, 1H, H-4eq), 1.75–1.15 (m, 5H, 2H-5, 2H-6, H-4ax), 1.30 (s, 3H, 3H-2′); ^{13}C NMR: δ 171.8 (C=O), 108.2 (C-1′), 81.6 (C-2), 69.1 (C-3a), 65.3/65.1 (OCH_2CH_2O), 55.4 (C-7), 52.0/51.7 (C-3/OCH_3), 26.5 (C-4), 24.1 (C-6), 23.3 (C-5), 20.8 (C-2′); MS (m/z): 271 (M^+, 5), 256 (1), 240 (1), 184 (1), 87 (100), 43 (36). Anal. calcd for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.55; H, 7.73; N, 5.19%.

4.9. Cycloaddition of nitrone 3 to acetal 5

To a solution of **3** (prepared from 291 mg, 2.88 mmol, of *N*-hydroxypiperidine and 1.87 g, 8.63 mmol, of yellow HgO) in methylene chloride (25 mL), a solution of acetal **5** (560 mg, 1.92 mmol) in the same solvent (2 mL) was added and the mixture was stirred at rt for 3 days. Flash chromatography of the crude material (890 mg) using hexane/ethyl acetate (3:1) as eluent afforded

methyl (2*RS*,3*RS*,3a*RS*)-2-(3-benzyloxy-1,1-ethylenedioxy)propylhexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-3-carboxylate, *exo*-adduct **14**, as a solid (60 mg, 0.15 mmol, 8%) and its (2*RS*,3*RS*,3a*SR*) isomer, *endo*-adduct **15**, as a colorless oil (580 mg, 1.48 mmol, 77%). Compound **14**: mp 47–48°C (ethyl acetate/pentane); IR (KBr): 3029, 2946, 1741, 1441, 1263, 1203, 1166, 1098, 1052 cm^{-1}; ^1H NMR: δ 7.35–7.25 (m, 5H, Ph), 4.46 (s, 2H, CH_2Ph), 4.29 (d, $J_{2,3}=6.9$ Hz, 1H, H-2), 4.05–3.80 (m, 4H, OCH_2CH_2O), 3.68 (s, 3H, OCH_3), 3.60–3.50 (m 2H, 2H-3′), 3.35 (br d, $J=8.8$ Hz, 1H, H-7eq), 3.08 (dd, $J_{3,3a}=10.3$ Hz, $J_{3,2}=6.9$ Hz, 1H, H-3), 2.45–2.30 (m, 2H, H-7ax, H-3a), 2.21 (ddd, $J=14.3$ Hz, $J'=8.4$ Hz, $J''=6.2$ Hz, 1H, H-2′), 2.08–1.90 (m, 2H, H-2′, H-4eq), 1.80–1.50 (m, 3H, H-5eq, H-6eq, H-6ax), 1.42 (dddd, $J_{4ax,4eq}\approx J_{4ax,5ax}\approx J_{4ax,3a}\approx 11.3$ Hz, $J_{4ax,5eq}\approx 3.3$ Hz, 1H, H-4ax), 1.15 (m, 1H, H-5ax); ^{13}C NMR: δ 172.6 (C=O), 138.4/128.6/128.0/127.6 (Ph), 110.3 (C-1′), 80.9 (C-2), 73.0 (*C*H_2Ph), 70.9 (C-3a), 65.9/65.5/65.2 (O*C*H_2*C*H_2O/C-3′), 55.3 (C-7), 53.7 (C-3), 52.0 (OCH_3), 33.1 (C-2′), 28.0 (C-4), 24.0 (C-6), 22.8 (C-5). Anal. calcd for $C_{21}H_{29}NO_6$: C, 64.43; H, 7.47; N, 3.58. Found: C, 64.46; H, 7.50; N, 3.68%. Compound **15**: IR (KBr): 3029, 2945, 1740, 1441, 1262, 1203, 1167, 1098, 1052 cm^{-1}; ^1H NMR: δ 7.30–7.15 (m, 5H, Ph), 4.47 (d, $J_{2,3}=5.1$ Hz, 1H, H-2), 4.43 (s, 2H, CH_2Ph), 4.00–3.80 (m, 4H, OCH_2CH_2O), 3.64 (s, 3H, OCH_3), 3.60–3.50 (m 2H, 2H-3′), 3.45 (br d, $J=9.1$ Hz, 1H, H-7eq), 3.15 (dd, $J_{3,3a}=8.0$ Hz, $J_{3,2}=5.1$ Hz, 1H, H-3), 2.45–2.30 (m, 2H, H-7ax, H-3a), 2.09 (ddd, $J=14.3$ Hz, $J'=8.1$ Hz, $J''=6.2$ Hz, 1H, H-2′), 2.00–1.80 (m, 2H, H-2′, H-4eq), 1.75–1.50 (m, 3H, H-5eq, H-6eq, H-6ax), 1.25–1.10 (m, 2H, H-4ax, H-5ax); ^{13}C NMR: δ 171.8 (C=O), 138.3/128.3/127.7/127.5 (Ph), 108.9 (C-1′), 81.2 (C-2), 73.1 (*C*H_2Ph), 69.2 (C-3a), 65.9/65.6/65.3 (O*C*H_2-*C*H_2O/C-3′), 55.5 (C-7), 52.0/51.8 (C-3/OCH_3), 34.4 (C-2′), 26.6 (C-4), 24.2 (C-6), 23.4 (C-5); MS (*m*/*z*): 392 (M^++1, 2), 207 (45), 99 (37), 91 (100), 84 (30). Anal. calcd for $C_{21}H_{29}NO_6$: C, 64.43; H, 7.47; N, 3.58. Found: C, 64.45; H, 7.53; N, 3.67%.

4.10. Cycloaddition of nitrone 3 to acetal 6

To a solution of **3** (prepared from 327 mg, 3.24 mmol, of *N*-hydroxypiperidine and 2.103 g, 9.71 mmol, of yellow HgO) in methylene chloride (30 mL), a solution of acetal **6** (700 mg, 2.16 mmol) in the same solvent (2 mL) was added and the mixture was stirred at rt for 2 days. Flash chromatography of the crude material (910 mg) using hexane/ethyl acetate (4:1) as eluent afforded a ca. 3:2 (or 2:3) mixture of methyl (2*R*,3*R*,3a*R*)-2-[1,1-[(1*R*,2*R*)-1,2-diphenylethylenedioxy]ethyl]hexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-3-carboxylate, *exo*-adduct **16a**, and its (2*S*,3*S*,3a*S*) diastereoisomer, *exo*-adduct **16b**, as a colorless oil (71 mg, 0.17 mmol, 8%) and a ca. 3:2 (or 2:3) mixture of the *endo*-isomers (2*R*,3*R*,3a*S*), **17a**, and (2*S*,3*S*,3a*R*), **17b**, as a colorless oil (706 mg, 1.67 mmol, 77%). Compounds **16a**+**16b**: IR (film): 3063, 2941, 1739, 1443, 1206, 1166, 1046, 1020 cm^{-1}; ^1H NMR: δ (major isomer) 7.35–7.05 (m, 10H, 2×Ph), 4.81 (d, $J=8.8$ Hz, 1H, H-1″/H-2″), 4.65 (d, $J=8.8$ Hz, 1H, H-1″/H-2″), 4.53 (d, $J_{2,3}=6.9$ Hz, 1H, H-2), 3.68 (s, 3H, OCH_3), 3.44 (m, 1H, H-7eq), 3.23 (dd, $J_{3,3a}=9.9$ Hz, $J_{3,2}=6.9$ Hz, 1H, H-3), 2.58–2.45 (m, 2H, H-7ax, H-3a), 2.00 (m, 1H, H-4eq), 1.85–1.52 (m, 3H, H-5eq, H-6eq, H-6ax), 1.43 (m, 1H, H-4ax), 1.20 (m, 1H, H-5ax), 1.61 (s, 3H, 3H-2′); (minor isomer) 7.35–7.05 (m, 10H, 2×Ph), 4.83 (d, $J=8.8$ Hz, 1H, H-1″/H-2″), 4.71 (d, $J=8.8$ Hz, 1H, H-1″/H-2″), 4.56 (d, $J_{2,3}=6.9$ Hz, 1H, H-2), 3.68 (s, 3H, OCH_3), 3.44 (m, 1H, H-7eq), 3.26 (dd, $J_{3,3a}=9.9$ Hz, $J_{3,2}=6.9$ Hz, 1H, H-3), 2.58–2.45 (m, 2H, H-7ax, H-3a), 2.00 (m, 1H, H-4eq), 1.85–1.52 (m, 3H, H-5eq, H-6eq, H-6ax), 1.43 (m, 1H, H-4ax), 1.20 (m, 1H, H-5ax), 1.58 (s, 3H, 3H-2′); ^{13}C NMR: δ (M: major isomer; m: minor isomer) 172.3 (C=O M), 172.0 (C=O m), 136.6/136.4/136.3/136.1/128.3/128.2/128.1/127.2/127.1/127.0/126.8/126.7 (Ph), 110.4 (C-1′ M), 110.1 (C-1′ m), 86.7/85.8/85.7 (C-1″, C-2″), 82.3 (C-2 m), 82.0 (C-2 M), 71.1 (C-3a M), 70.8 (C-3a m), 55.5 (C-7 M), 55.2 (C-7 m), 54.5 (C-3 M), 54.3 (C-3 m), 52.1 (OCH_3), 28.5 (C-4 m), 28.4 (C-4 M), 24.5 (C-6 m), 24.4 (C-6 M), 23.2 (C-5), 22.2 (C-2′ m), 21.5 (C-2′ M); MS (*m*/*z*): 423 (M^+, 2), 239 (52), 197 (100), 179 (66), 112 (26), 100 (26), 43 (84). Anal. calcd for $C_{25}H_{29}NO_5$: C, 70.90; H, 6.90; N, 3.31. Found: C, 70.97; H, 7.02; N, 3.32%. Compounds **17a**+**17b**: IR (film): 3060, 2941, 1740, 1378, 1261, 1205, 1174, 1049, 1020 cm^{-1}; ^1H NMR: δ (major isomer) 7.30–7.05 (m, 10H, 2×Ph), 4.87 (d, $J=8.8$ Hz, 1H, H-1″/H-2″), 4.72–4.63 (m, 2H, H-1″/H-2″, H-2), 3.69 (s, 3H, OCH_3), 3.54 (m, 1H, H-7eq), 3.35 (m, 1H, H-3), 2.60–2.35 (m, 2H, H-7ax, H-3a), 1.90 (m, 1H, H-4eq), 1.80–1.60 (m, 3H, H-5eq, H-6eq, H-6ax), 1.40–1.20 (m, 2H, H-4ax, H-5ax), 1.57 (s, 3H, H-2′); (minor isomer) 7.35–7.05 (m, 10H, 2×Ph), 4.80 (d, $J=8.8$ Hz, 1H, H-1″/H-2″), 4.72 (m, 2H, H-1″/H-2″, H-2), 3.70 (s, 3H, OCH_3), 3.54 (m, 1H, H-7eq), 3.35 (m, 1H, H-3), 2.60–2.35 (m, 2H, H-7ax, H-3a), 1.90 (m, 1H, H-4eq), 1.80–1.55 (m, 3H, H-5eq, H-6eq, H-6ax), 1.35–1.10 (m, 2H, H-4ax, H-5ax), 1.60 (s, 3H, 3H-2′); ^{13}C NMR: δ (M: major isomer; m: minor isomer) 171.9 (C=O M), 171.8 (C=O m), 136.6/136.2/135.9/135.8/128.4/128.3/128.2/127.0/126.9/126.5 (Ph), 109.0 (C-1′ M), 108.9 (C-1′ m), 86.8/86.3/85.6/85.3 (C-1″/C-2″), 82.9 (C-2 m), 82.4 (C-2 M), 69.4 (C-3a), 55.6 (C-7 M), 55.4 (C-7 m), 52.5 (C-3 M), 52.2 (C-3 m), 51.8 (OCH_3), 26.6 (C-4), 24.3 (C-6), 23.4 (C-5), 22.6 (C-2′ m), 22.4 (C-2′ M); MS (*m*/*z*): 423 (M^+, 3), 239 (43), 197 (91), 179 (63), 112 (70), 97 (25), 43 (100). Anal. calcd for $C_{25}H_{29}NO_5$: C, 70.90; H, 6.90; N, 3.31. Found: C, 70.94; H, 7.01; N, 3.23%.

4.11. Cycloaddition of nitrone 3 to acetal 7

To a solution of **3** (prepared from 108 mg, 1.10 mmol, of *N*-hydroxypiperidine and 710 mg, 3.27 mmol, of yellow HgO) in methylene chloride (8 mL), a solution of acetal **7** (245 mg, 0.73 mmol) in the same solvent (4 mL) was added and the mixture was stirred at rt for 15 days. Flash chromatography of the crude material (320 mg) using hexane/ethyl acetate (from 10:1 to 4:1) as eluent afforded a ca. 1:1 mixture of methyl

(2*R*,3*R*,3a*R*)-2-[1,1-[(1*R*,2*R*)-1,2-dicyclohexylethylenedioxy] ethyl]hexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-3-carboxylate, *exo*-adduct **18a**, and its (2*S*,3*S*,3a*S*) diastereoisomer, *exo*-adduct **18b**, as a colorless oil (37 mg, 0.08 mmol, 12%) and a ca. 1:1 mixture of the *endo*-isomers (2*R*,3*R*,3a*S*), **19a**, and (2*S*,3*S*,3a*R*), **19b**, as a colorless oil (201 mg, 0.46 mmol, 63%). Compounds **18a**+**18b**: IR (film): 2924, 2853, 1743, 1447, 1384, 1166, 1011 cm^{-1}; ^1H NMR: δ 4.25 (d, $J_{2,3}=7.3$ Hz, 1H, H-2), 4.16 (d, $J_{2,3}=7.3$ Hz, 1H, H-2), 3.70 (s, 6H, 2×OCH_3), 3.70–3.50 (m, 4H, 2H-1″, 2H-2″), 3.41 (m, 2H, 2H-7eq), 3.01 (m, 2H, 2H-3), 2.46–2.31 (m, 4H, 2H-7ax, 2H-3a), 1.89–0.98 (m, 56H), 1.35 (s, 3H, 3H-2′), 1.32 (s, 3H, 3H-2′); ^{13}C NMR: δ 172.3 and 172.0 (C=O), 109.3 and 109.2 (C-1′), 83.9/83.2/82.53/82.47/82.2 (C-1″/C-2″/C-2), 71.2 and 70.6 (C-3a), 55.3 (C-7), 54.6 (C-3), 51.9 (OCH_3), 40.9, 40.6, 40.3, 30.6–21.0 (26 signals). Compounds **19a**+**19b**: IR (film): 2924, 2853, 1743, 1447, 1384, 1166, 1011 cm^{-1}; ^1H NMR: δ 4.38 (d, $J_{2,3}=5.1$ Hz, 1H, H-2), 4.35 (d, $J_{2,3}=5.1$ Hz, 1H, H-2), 3.75–3.42 (m, 6H, 2H-1″, 2H-2″, 2H-7eq), 3.66 (s, 6H, 2×OCH_3), 3.14 (dd, $J_{3,3a}=8.0$ Hz, $J_{3,2}=5.1$ Hz, 1H, H-3), 3.12 (dd, $J_{3,3a}=8.0$ Hz, $J_{3,2}=5.1$ Hz, 1H, H-3), 2.45–2.30 (m, 4H, 2H-7ax, 2H-3a), 1.90–0.96 (m, 56H), 1.28 (s, 3H, 3H-2′), 1.27 (s, 3H, 3H-2′); ^{13}C NMR: δ 172.1 and 172.0 (C=O), 107.8 and 107.6 (C-1′), 84.3/83.8/83.0/82.7/82.2 (C-1″/C-2″/C-2), 69.3 and 69.2 (C-3a), 55.5 and 55.4 (C-7), 52.4/52.1/51.6 (C-3/OCH_3), 41.2, 40.8, 40.7, 40.6, 30.5–20.9 (26 signals); MS (*m*/*z*): 436 (M^++1, 1), 251 (24), 191 (26), 109 (100), 95 (72), 83 (27), 81 (32), 67 (34), 55 (50), 43 (25), 41 (28). Anal. calcd for $C_{25}H_{41}NO_5$: C, 68.93; H, 9.49; N, 3.22. Found: C, 68.98; H, 9.29; N, 3.05%.

4.12. Cycloaddition of nitrone 3 to acetal 8

To a solution of **3** (prepared from 178 mg, 1.80 mmol, of *N*-hydroxypiperidine and 1.18 g, 5.45 mmol, of yellow HgO) in methylene chloride (8 mL), a solution of acetal **8** (500 mg, 1.22 mmol) in the same solvent (6 mL) was added and the mixture was stirred at rt for 15 days. Flash chromatography of the crude material (750 mg) using hexane/ethyl acetate (5:1) as eluent afforded a ca. 2:1 (or 1:2) mixture of methyl (2*R*,3*R*,3a*R*)-2-[1,1-[(2*S*,3*S*)-1,4-bis(2-methoxyphenyl)-2,3-butylenedioxy]-ethyl]hexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-3-carboxylate, *exo*-adduct **20a**, and its (2*S*,3*S*,3a*S*) diastereoisomer, *exo*-adduct **20b**, as a colorless oil (70 mg, 0.13 mmol, 11%) and a ca. 1:1 mixture of the *endo*-isomers (2*R*,3*R*,3a*S*), **21a**, and (2*S*,3*S*,3a*R*), **21b**, as a colorless oil (505 mg, 0.98 mmol, 82%). Compounds **20a**+**20b**: IR (film): 2932, 2858, 1738, 1616, 1515, 1453, 1250, 1175, 1033 cm^{-1}; ^1H NMR: δ 7.10–6.95 (m, 8H, 8Ar), 6.85–6.75 (m, 8H, 8Ar), 4.26 (d, $J_{2,3}=7.3$ Hz, 2H, 2H-2), 4.04–3.22 (m, 6H, 2H-2″, 2H-3″, 2H-7eq), 3.75 (s, 12H, 4×OCH_3), 3.65 (s, 3H, $COOCH_3$, major isomer), 3.60 (s, 3H, $COOCH_3$, minor isomer), 3.06 (dd, $J_{3,3a}=10.2$ Hz, $J_{3,2}=7.3$ Hz, 1H, H-3), 2.90–2.30 (m, 12H), 1.98 (m, 2H, 2H-4eq), 1.76–1.11 (m, 10H), 1.30 (s, 3H, 3H-2′), 1.26 (s, 3H, 3H-2′); ^{13}C NMR: δ 172.2 (C=O), 158.1 (Ar), 130.2–113.5 (Ar), 109.5 and 109.4 (C-1′), 82.7/81.8/81.6/81.3/81.1 (C-2″/C-3″/C-2), 70.9 and 70.8 (C-3a), 55.4/55.1/54.3 (C-7/C-3/OCH_3), 51.9 ($COOCH_3$), 38.2/38.0/37.4 (CH_2Ar), 31.8–21.3 (eight signals); MS (*m*/*z*): 327 (17), 267 (16), 193 (15), 159 (17), 121 (100). Anal. calcd for $C_{29}H_{37}NO_7$: C, 68.08; H, 7.29; N, 2.74. Found: C, 68.06; H, 7.48; N, 2.96%. Compounds **21a**+**21b**: IR (film): 3001, 2945, 2839, 1743, 1609, 1581, 1518, 1440, 1250, 1173, 1039 cm^{-1}; ^1H NMR: δ 7.05–6.95 (m, 8H, 8Ar), 6.80–6.75 (m, 8H, 8Ar), 4.45 (d, $J_{2,3}=5.1$ Hz, 2H, 2H-2), 4.05–3.75 (m, 4H, 2H-2″, 2H-3″), 3.76 (s, 12H, 4×OCH_3), 3.65 (s, 6H, 2×$COOCH_3$), 3.50 (m, 2H, 2H-7eq), 3.15 (dd, $J_{3,3a}=8.7$ Hz, $J_{3,2}=5.1$ Hz, 1H, H-3), 3.04 (dd, $J_{3,3a}=8.7$ Hz, $J_{3,2}=5.1$ Hz, 1H, H-3), 2.80–2.30 (m, 12H), 1.87 (m, 2H, 2H-4eq), 1.80–1.20 (m, 10H), 1.28 (s, 3H, 3H-2′), 1.26 (s, 3H, 3H-2′); ^{13}C NMR: δ 172.2 (C=O), 158.3 (Ar), 130.5–113.7 (Ar), 107.9 (C-1′), 83.0/82.6/82.0/81.4/81.1/81.0 (C-2″/C-3″/C-2), 69.3 and 69.2 (C-3a), 55.5, 55.4, 55.1, 52.2, 52.0, 51.7 (C-7/C-3/OCH_3/$COOCH_3$), 38.4, 37.8, 29.6, 26.6, 24.3, 23.5, 22.8, 22.0 (C-4/C-5/C-6/C-2′); MS (*m*/*z*): 412 (1), 327 (4), 163 (58), 121 (100). Anal. calcd for $C_{29}H_{37}NO_7$: C, 68.08; H, 7.29; N, 2.74. Found: C, 68.09; H, 7.31; N, 2.77%.

4.13. Cycloaddition of nitrone 3 to acetal 9

To a solution of **3** (prepared from 180 mg, 1.78 mmol, of *N*-hydroxypiperidine and 1.17 g, 5.4 mmol, of yellow HgO) in methylene chloride (10 mL), a solution of acetal **9** (500 mg, 1.21 mmol) in the same solvent (5 mL) was added and the mixture was stirred at rt for 15 days. An additional quantity of nitrone **3** (prepared from 118 mg, 1.17 mmol, of *N*-hydroxypiperidine) was added and the mixture was stirred at rt for 2 days. Flash chromatography of the crude material (805 mg) using hexane/ethyl acetate (7:1 to 2:1) as eluent afforded a ca. 2:1 (or 1:2) mixture of methyl (2*R*,3*R*,3a*R*)-2-[1,1-[(2*S*,3*S*)-1,4-dibenzyloxy-2,3-butylenedioxy]ethyl]hexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-3-carboxylate, *exo*-adduct **22a**, and its (2*S*,3*S*,3a*S*) diastereoisomer, *exo*-adduct **22b**, as a colorless oil (62 mg, 0.12 mmol, 10%) and a ca. 1:1 mixture of the *endo*-isomers (2*R*,3*R*,3a*S*), **23a**, and (2*S*,3*S*,3a*R*), **23b**, as a colorless oil (505 mg, 0.98 mmol, 82%). Compounds **22a**+**22b**: IR (film): 2931, 2860, 1743, 1447, 1377, 1278, 1208, 1173, 1089, 1018 cm^{-1}; ^1H NMR: δ (M: major isomer; m: minor isomer) 7.29 (m, 10H, 10Ph), 4.54 (s, 4H, 2×CH_2Ph), 4.36 (d, $J_{2,3}=7.3$ Hz, H-2 m) and 4.26 (d, $J_{2,3}=7.3$ Hz, H-2 M) (1H), 4.12 (s, 2H, H-2″, H-3″), 3.70–3.45 (m, 7H, OCH_3, 2×OCH_2), 3.36 (br d, $J=8.0$ Hz, 1H, H-7eq), 3.18 (dd, $J_{3,3a}=10.2$ Hz, $J_{3,2}=7.3$ Hz, H-3 M) and 3.09 (dd, $J_{3,3a}=10.2$ Hz, $J_{3,2}=7.3$ Hz, H-3 m) (1H), 2.50–2.30 (m, 2H, H-7ax, H-3a), 1.95 (m, 1H, H-4eq), 1.73–1.12 (m, 5H), 1.40 (s) and 1.18 (s) (3H, 3H-2′); ^{13}C NMR: δ (M: major isomer; m: minor isomer) 172.1 and 171.9 (C=O), 138.0 (Ph), 130.8–127.5 (Ph), 110.7 (C-1′), 82.2 (C-2 m), 81.7 (C-2 M), 79.2/78.1/78.0 (C-2″/C-3″), 73.5/73.3 (CH_2Ph), 71.1/70.8/70.5/70.4/70.2 (CH_2O/C-3a), 55.4, (C-7 M), 55.3 (C-7 m), 54.1 (C-3 m), 53.9 (C-3

M), 52.0 (OCH_3), 29.6 (C-4 M), 28.3 (C-4 m), 24.8 (C-6), 23.7 (C-5), 21.8 (C-2′ m), 21.6 (C-2′ M); MS (m/z): 327 (6), 237 (1), 181 (6), 91 (100). Anal. calcd for $C_{29}H_{37}NO_7$: C, 68.08; H, 7.29; N, 2.74. Found: C, 68.01; H, 7.29; N, 2.93. Compounds **23a**+**23b**: IR (film): 2931, 2860, 1743, 1447, 1377, 1257, 1201, 1089, 1018 cm^{-1}; ^1H NMR: δ 7.28 (m, 10H, 10Ph), 4.55 (br s, 4H, 2×CH_2Ph), 4.46 (d, $J_{2,3}=5.1$ Hz, 1H, H-2), 4.20–4.00 (m 2H, H-2″, H-3″), 3.70–3.50 (m, 7H, OCH_3, 2×OCH_2), 3.50–3.40 (m, 1H, H-7eq), 3.29 (dd, $J_{3,3a}=8.0$ Hz, $J_{3,2}=5.1$ Hz) and 3.20 (dd, $J_{3,3a}=8.0$ Hz, $J_{3,2}=5.1$ Hz) (1H, H-3), 2.45–2.25 (m, 2H, H-7ax, H-3a), 1.90–1.25 (m, 6H, 2H-4, 2H-5, 2H-6), 1.42 (s) and 1.39 (s) (3H, 3H-2′); ^{13}C NMR: δ 171.9 (C=O), 138.0/137.9 (Ph), 128.0/127.0 (Ph), 109.3 and 109.2 (C-1′), 82.7 and 82.1 (C-2), 79.1/78.5/78.2/77.7 (C-2″/C-3″), 73.4 (*C*H_2Ph), 70.4/70.3/70.2/69.9/69.3/69.1 (*C*H_2O/C-3a), 55.5 and 55.3 (C-7), 52.4/52.1/51.8/51.7 (C-3/OCH_3), 26.6, 24.2, 23.5, 22.8, 22.3; MS (m/z): 327 (2), 181 (5), 91 (100). Anal. calcd for $C_{29}H_{37}NO_7$: C, 68.08; H, 7.29; N, 2.74. Found: C, 68.20; H, 7.15; N, 2.62%.

4.14. Cycloaddition of nitrone 3 to acetal 10

To a solution of **3** (prepared from 370 mg, 3.66 mmol, of *N*-hydroxypiperidine and 2.38 g, 11.0 mmol, of yellow HgO) in methylene chloride (30 mL), a solution of acetal **10** (650 mg, 2.44 mmol) in the same solvent (2 mL) was added and the mixture was stirred at rt for 10 days. Flash chromatography of the crude material (1.05 g) using hexane/ethyl acetate (4:1) as eluent afforded starting acetal **10** (180 mg, 0.7 mmol), a ca. 10:1 (or 1:10) mixture of methyl (2*R*,3*R*,3a*R*)-2-[1,1-[(1*R*,5*R*,6*R*) - spiro[4.4]nonylene - 1,6 - dioxy]ethyl]hexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-3-carboxylate, *exo*-adduct **24a**, and its (2*S*,3*S*,3a*S*) diastereoisomer, *exo*-adduct **24b**, as a colorless oil (57 mg, (0.16 mmol, 9%) and a ca. 4:1 or (1:4) mixture of the *endo*-isomers (2*R*,3*R*,3a*S*), **25a**, and (2*S*,3*S*,3a*R*), **25b**, as a colorless oil (439 mg, 1.20 mmol, 68%). Compounds **24a**+**24b**: IR (film): 2945, 2860, 1740, 1439, 1380, 1278, 1196, 1156, 1058, 1019 cm^{-1}; ^1H NMR: δ (major isomer) 4.45 (d, $J_{2,3}=8.0$ Hz, 1H, H-2), 3.87 (d, $J=4.7$ Hz, 1H, H-1″/H-6″), 3.79 (d, $J=5.2$ Hz, 1H, H-1″/H-6″), 3.68 (s, 3H, OCH_3), 3.40 (m, 1H, H-7eq), 2.98 (dd, $J_{3,3a}=10.2$ Hz, $J_{3,2}=7.3$ Hz, 1H, H-3), 2.46–2.32 (m, 2H, H-7ax, H-3a), 2.00–1.10 (m, 18H), 1.30 (s, 3H, H-2′); observable signals of the minor isomer: δ 4.48 (d, $J_{2,3}\approx 8.0$ Hz, 1H, H-2), 3.69 (s, 3H, OCH_3); ^{13}C NMR: δ 172.2 (C=O), 100.9 (C-1′), 78.5/78.3/78.2 (C-2/C-1″/C-6″), 70.7 (C-3a), 56.3 (C-5″), 55.4 (C-7), 54.7 (C-3), 51.8 (OCH_3), 37.0, 32.4, 32.0, 28.3, 24.4, 23.8, 23.7, 23.1, 17.8 (C-2′); MS (m/z): 366 (M^++1, 9), 365 (M^+, 1), 121 (100), 79 (22), 43 (25). Anal. calcd for $C_{20}H_{31}NO_5$: C, 65.73; H, 8.55; N, 3.83. Found: C, 65.90; H, 8.63; N, 3.68%. Compounds **25a**+**25b**: IR (film): 2945, 1742, 1440, 1378, 1251, 1204, 1154, 1058, 1023 cm^{-1}; ^1H NMR (major isomer): δ 4.57 (d, $J_{2,3}=5.5$ Hz, 1H, H-2), 3.99 (d, $J=5.1$ Hz, 1H, H-1″/H-6″), 3.80 (d, $J=5.8$ Hz, 1H, H-1″/H-6″), 3.68 (s, 3H, OCH_3), 3.51 (m, 1H, H-7eq), 3.16 (dd, $J_{3,3a}=8.4$ Hz, $J_{3,2}=5.5$ Hz, 1H, H-3), 2.45–2.30 (m, 2H, H-7ax, H-3a), 2.00–1.10 (m, 18H), 1.24 (s, 3H, 3H-2′); observable signals of the minor isomer: δ 4.61 (d, $J_{2,3}=5.5$ Hz, 1H, H-2), 3.13 (dd, $J_{3,3a}=8.4$ Hz, $J_{3,2}=5.5$ Hz, 1H, H-3); ^{13}C NMR: δ 172.1 (C=O), 99.3 (C-1′), 79.7/79.0/78.3 (C-2/C-1″/C-6″), 69.2 (C-3a), 56.2 (C-5″), 55.5 (C-7), 52.3/51.6 (C-3/OCH_3), 37.1, 37.0, 32.3, 32.2, 26.6, 24.3, 23.7, 23.5, 18.8 (C-2′); MS (m/z): 366 (M^++1, 4), 121 (100), 43 (21). Anal. calcd for $C_{20}H_{31}NO_5$: C, 65.73; H, 8.55; N, 3.83. Found: C, 65.86; H, 8.71; N, 3.83%.

4.15. Cycloaddition of nitrone 3 to acetal 11

To a solution of **3** (prepared from 189 mg, 1.87 mmol, of *N*-hydroxypiperidine and 1.21 g, 5.61 mmol, of yellow HgO) in methylene chloride (15 mL), a solution of acetal **11** (501 mg,1.25 mmol) in the same solvent (2 mL) was added and the mixture was stirred at rt for 20 days. Flash chromatography of the crude material using hexane/ethyl acetate (4:1) as eluent afforded starting acetal **11** (243 mg, 0.60 mmol), a ca. 10:1 (or 1:10) mixture of methyl (2*R*,3*R*,3a*R*)-2-[3-benzyloxy-[1,1-(1*S*,5*S*,6*S*) - spiro[4.4]nonylene - 1,6 - dioxy]propyl]hexahydro-2*H*-isoxazolo[2,3-*a*]pyridine-3-carboxylate, *exo*-adduct **26a**, and its (2*S*,3*S*,3a*S*) diastereoisomer, *exo*-adduct **26b**, as a colorless oil (36 mg, 0.07 mmol, 11%) and a ca. 7:1 or (1:7) mixture of the *endo*-isomers (2*R*,3*R*,3a*S*), **27a**, and (2*S*,3*S*,3a*R*), **27b**, as a colorless oil (186 mg, 0.37 mmol, 57%), a second chromatography of these mixtures furnished a pure sample of the *exo* major adduct and the pure *endo* major diastereoisomer (140 mg, 0.28 mmol, 43%). Compounds **26a**+**26b**: IR (film): 2945, 2860, 1743, 1440, 1363, 1278, 1201, 1152, 1018 cm^{-1}; ^1H NMR (major isomer): δ 7.30–7.10 (m, 5H, 5Ph), 4.50–4.35 (m, 3H, H-2, CH_2Ph), 3.89 (d, $J=5.5$ Hz, 1H, H-1″/H-6″), 3.74 (d, $J=5.5$ Hz, 1H, H-1″/H-6″), 3.70–3.50 (m, 5H, 2H-3′, OCH_3), 3.24 (m, 1H, H-7eq), 2.99 (dd, $J_{3,3a}=10.2$ Hz, $J_{3,2}=7.3$ Hz, 1H, H-3), 2.40–1.10 (m, 22H); ^{13}C NMR: δ 172.4 (C=O), 138.8/128.2/127.7/127.3 (Ph), 100.4 (C-1′), 78.9/78.5/78.1 (C-2/C-1″/C-6″), 72.8 (*C*H_2Ph), 70.6 (C-3a), 66.3 (C-3′), 55.6/55.2/54.5 (C-3/C-7/C-5″), 51.9 (OCH_3), 37.6, 37.2, 33.5, 32.7, 32.3, 28.4, 24.4, 23.9, 23.6, 23.1; MS (m/z): 301 (3), 167 (4), 121 (100), 91 (44). Major isolated *exo* adduct $[\alpha]_D^{20}=-27.4$ (c 3.8, ethanol). Compounds **27a**+**27b**: IR (film): 2945, 2860, 1743, 1440, 1363, 1257, 1201, 1152, 1103, 1068, 1025 cm^{-1}; ^1H NMR (major isolated isomer): δ 7.25–7.15 (m, 5H, 5Ph), 4.65 (d, $J_{2,3}=5.1$ Hz, 1H, H-2), 4.46 (s, 2H, CH_2Ph), 4.14 (d, $J=5.1$ Hz, 1H, H-1″/H-6″), 3.77 (d, $J=4.4$ Hz, 1H, H-1″/H-6″), 3.70–3.55 (m, 5H, 2H-3′, OCH_3), 3.49 (m, 1H, H-7eq), 3.24 (dd, $J_{3,3a}=8.4$ Hz, $J_{3,2}=5.1$ Hz, 1H, H-3), 2.40–2.25 (m, 2H, H-7ax, H-3a), 2.15–1.12 (m, 20H); observable signals of the minor isomer: δ 4.62 (d, $J_{2,3}=5.1$ Hz, 1H, H-2), 3.92 (d, $J=5.1$ Hz, 1H, H-1″/H-6″); ^{13}C NMR: δ 172.1 (C=O), 138.5/128.3/127.7/127.4 (Ph), 99.0 (C-1′), 79.8/79.1/78.9 (C-2/C-1″/C-6″), 72.9 (*C*H_2Ph), 69.2 (C-3a), 65.8 (C-3′), 55.6/52.0/51.6 (C-3/C-7/C-5″/OCH_3), 37.7, 37.1, 34.5, 32.8, 32.2, 29.6, 26.5, 24.3, 23.8, 23.5; MS (m/z): 301 (3), 167 (4), 121 (100), 91 (44). Anal. calcd for $C_{28}H_{39}NO_6$: C, 69.25; H, 8.09; N, 2.88. Found: C, 69.47; H, 8.22; N, 2.82%. Major isolated *endo* adduct: $[\alpha]_D^{20}=+6.0$ (c 4.0, ethanol).

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