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One step preparation and 1,3-dipolar cycloadditions of (*S*)-5-hydroxymethyl-1-pyrroline *N*-oxide

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Abstract: The cyclic nitrone **1b** has been prepared in enantiomerically pure form by direct oxidation of L-(+)-prolinol with dimethyldioxirane. A complete diastereoface differentiation has been observed in the 1,3-dipolar cycloaddition reaction of this nitrone to several 1,2-disubstituted electron deficient olefins. © 1997 Elsevier Science Ltd

The 1,3-dipolar cycloaddition reaction of nitrones to olefins is an effective procedure for the preparation of chiral isoxazolidines, which are useful intermediates for the synthesis of nitrogen containing natural products.[1] Since the preparation of enantiomerically pure compounds is a major goal for synthetic organic chemists, the availability of enantiopure nitrones becomes very convenient. Although five membered cyclic nitrones have been frequently employed as precursors of pyrrolizidine alkaloids, only a few examples of enantiopure nitrones of this kind have been previously reported,[2] and in most of them the preparation of the target nitrone from enantiopure precursors of the chiral pool involves multistep procedures. As a consequence, the subsequent 1,3-dipolar cycloadditions render the desired adducts in low overall yields.

The transformation of symmetric pyrrolidines into nitrones has been successfully performed using several oxidation reagents, such as H_2O_2/cat. SeO_2,[2b,3] 2-(phenylsulfonyl)-3-phenyloxaziridine,[2c] and H_2O_2–urea complex/metal catalyst,[4] and although the yields are only moderate the brevity of these methods make them competitive in relation to other more elaborated procedures. Unfortunately, the oxidation of methyl prolinate leads regioselectively to the more stable achiral ketonitrone.[3]

We recently described a six step sequence for the conversion of L-(+)-ethyl pyroglutamate into nitrone **1a**,[2g] a monosubstituted pyrroline *N*-oxide that can be a valuable intermediate for the synthesis of 2,5-disubstituted pyrrolidines. The need for a shorter more convenient method that gave access to an aldonitrone of type **1** led us to investigate the direct oxidation of L-(+)-prolinol. A very recently published and closely related work on the oxidation of azasugars to cyclic nitrones[5] moves us to disclose our findings in this area.

Using Murahashi's methodology (H_2O_2/cat. SeO_2), we performed the oxidation of L-(+)-prolinol and the resulting nitrones were treated with an excess of *N*-phenylmaleimide, **4**. We obtained a complex mixture of four different cycloaddition products, derived from nitrones **1b**, **2** and **3** (Scheme 1). The formation of nitrone **3** can be explained by the decarboxylative oxidation of proline,[6] generated from prolinol in the reaction medium. The structure of the cycloadducts **5–8** was elucidated on the basis of spectroscopic analyses. The ^{13}C NMR spectra of compounds **5** (8%) and **6** (8%), derived from nitrone **1b**, show absorptions for two methinic carbon atoms (SEFT) adjacent to the nitrogen atom (δ 69.0/69.3 for **5** and δ 67.8/68.0 for **6**). On the contrary, in cycloadduct **7** (8%), derived from nitrone **2**, the α-nitrogen positions are occupied by tetrasubstituted (δ 79.8) and methylenic (δ 55.6) carbon atoms and in cycloadduct **8** (20%), derived from nitrone **3**, by methinic (δ 70.8) and methylenic (δ 55.8) carbon atoms. Compound **8** has been already reported,[7] but its spectroscopic data have not been described yet.

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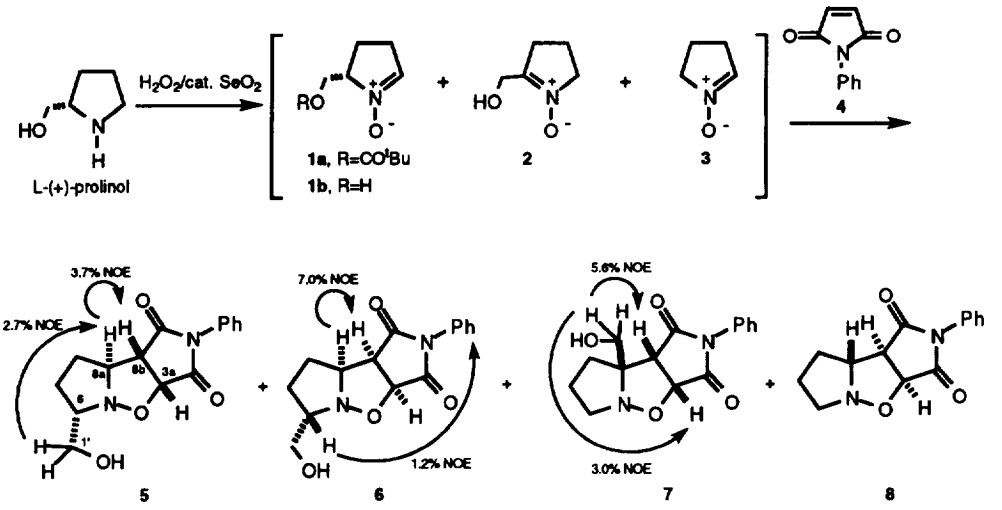

Scheme 1.

In compounds **5** and **6** the value of the coupling constant between H_{8a} and H_{8b} is diagnostic for the *endo/exo* stereochemistry. A small value of $J_{8a,8b}$ is in agreement with a *trans* relationship between these two protons, while larger values correspond to a *cis* geometry.[8] The $J_{8a,8b}$ values experimentally measured were 1.3 Hz for **5** and 9.1 Hz for **6**. The stereochemical assignment was confirmed by NOE experiments. With these experiments we were also able to determine the *syn/anti* geometry of the succinimide moiety in relation to the hydroxymethyl group and, consequently, we could establish the diastereofacial selectivity of the process. In compound **6**, presaturation of H_{8a} induces 7.0% enhancement of the signal corresponding to H_{8b} (*endo*) and irradiation of H_6 induces 1.2% enhancement of the aromatic proton signal (*anti*). For its isomer **5**, irradiation of H_{8a} causes only 3.7% NOE on H_{8b} and irradiation of $H_{1'}$ induces 2.7% NOE on H_{8a} (*anti*). The stereochemistry of adduct **7** was established as *endo* in a similar way. In this compound, presaturation of $H_{1'}$ at δ 3.64 causes NOE on both H_{3a} (3.0%) and H_{8b} (5.6%).

The need to employ a more selective oxidation reagent became obvious. Dimethyldioxirane (DMD) has been used to prepare nitrones from secondary amines lacking other oxidisable functional groups.[9] After several trials under different conditions, we found that L-(+)-prolinol can be chemoselectively oxidised with a slight excess of DMD in acetone at low temperature. In this way, an inseparable *ca* 1:1 mixture of nitrones **1b** and **2** is obtained in an estimated yield around 50%. We also discovered that the achiral nitrone **2** decomposes on heating in toluene at reflux, meanwhile the desired chiral nitrone **1b** remains stable. Flash chromatography over silica gel allows the isolation of **1b** in 32% yield. One can therefore in that way obtain the pure nitrone **1b** in a single step starting from L-prolinol.

The results of the cycloaddition of nitrone **1b** to several 1,2-disubstituted electron deficient dipolarophiles, **4** and **9–13**, (Figure 1) are summarised in Table 1.

Very recently, Saito *et al.* described that the cycloaddition of a chiral five membered cyclic nitrone to several electron deficient olefins was completely stereoselective. In this work a three- or fourfold excess of dipolarophile in a quite concentrated benzene solution was always used, the reaction mixtures were heated at 70°C for 4 to 24 h, and the yields were in the range 60–89%.[2h]

When we performed the cycloaddition between nitrone **1b** and maleimide **4** under similar conditions (entry 1), we obtained a 2/1 mixture of the *exo*, **5**, and *endo*, **6**, cycloadducts in a 64% overall yield. The two diastereoisomers were separated by flash chromatography, the minor adduct **6** was subjected again to the reaction conditions, and its evolution was followed by ^1H NMR analysis. A slow isomerization of **6** to **5** was observed, that could be accelarated by the addition of a catalytic amount of silica gel to

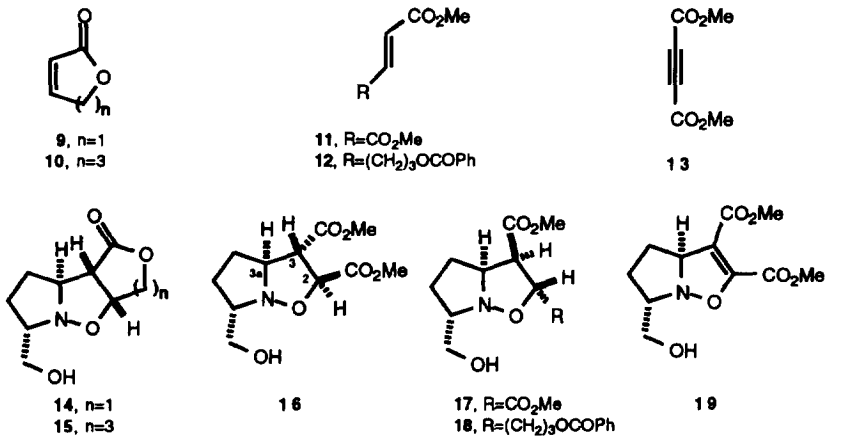

Figure 1.

Table 1. Cycloadditions of enantiopure nitrone **1b** to 1,2-disubstituted electron deficient olefins **4** and **9–13**

entry	Olefin (eq)	Conditions	*exo-anti* (%)	*endo-anti* (%)
1	**4** (3.0)	Toluene, 70 °C, 4 h	**5** (43)	**6** (21)
2	**4** (1.2)	AcOEt, rt, 2 d	**5** (35)	**6** (32)
3	**9** (2.1)	Toluene, 110 °C, 18 h	**14** (45)	
4	**10** (2.1)	Toluene, 110 °C, 26 h	**15** (45)	
5	**11** (1.2)	$CHCl_3$, 61 °C, 3 h	**16** (33)	**17** (33)
6	**12** (0.9)	$CHCl_3$, 61 °C, 5 d		**18** (45)
7	**13** (3.1)	AcOEt, rt, 16 h	**19** (40)	

the solution. Then, the cycloaddition was repeated under milder conditions to ensure kinetic control (entry 2) and a *ca* 1/1 mixture of **5** and **6** was obtained in a similar overall yield.

For the other dipolarophiles, **9–13**, the reaction conditions were modified according to their activity. All the cycloadditions afforded the expected regioselectivity consistent with the FMO predictions.[1] The stereochemical assignment of adducts **14**, **15** and **18** was based on NOE experiments as above. The stereochemistry of adducts **16** and **17**, derived from dimethyl fumarate, was deduced by comparison with closely related compounds prepared in our laboratories.[10] For those compounds we have observed that the absorptions of C_2 and C_3 in the ^{13}C NMR spectrun of the *exo* isomer are downfield shifted in relation to the corresponding *endo* isomer. Finally, the stereochemistry of compound **19** was elucidated by analogy with the closely related adduct derived from nitrone **1a** and dimethyl acetylenedicarboxylate, **13**.[2g] The *endo*/*exo* selectivity was dependent on the olefin as it was previously observed in related cycloadditions of nitrone **3**.[7,11] Nevertheless, in the reactions between **1b** and lactones **9** and **10**, the formation of *endo* adducts was not detected, in contrast to the results obtained in the cycloaddition of nitrone **3** to these lactones.[8] In all the cases a complete diastereofacial differentiation was observed, resulting of the approach of the olefin to the less hindered *anti* face of the nitrone in the transition state.

The stereochemical integrity of the original chiral center in the products was established through ^1H NMR analysis of the *exo-anti* cycloadduct **5**, derived from *N*-phenylmaleimide, in the presence of (-)-Eu(tfc)$_3$. For the racemic cycloadduct, prepared from racemic prolinol, the chiral shift reagent caused splitting of the signals corresponding to H_{3a} (δ 4.95, d, J=7.5 Hz) and H_{8b} (δ 3.66, dd, J=7.5 and 1.3 Hz). For the cycloadduct prepared from L-(+)-prolinol a single set of signals was always observed.

In summary, we have developed a straightforward methodology to prepare synthetically valuable

intermediates derived from an enantiopure five membered cyclic nitrone. The simplicity and brevity of the method make it advantageous in comparison to other approaches.

Experimental section

Reaction solutions were concentrated using a rotary evaporator at 15–20 Torr. Flash chromatographies were performed on silica gel (230–400 mesh). Infrared spectra were recorded on a Nicolet 5 ZDX spectrophotometer. ^{1}H NMR and ^{13}C NMR (62.5 MHz) spectra were recorded on Bruker AC-250-WB or AM-400-WB instruments from deuterated chloroform solutions. Mass spectra were performed on a Hewlett–Packard 5985B instrument at 70 eV.

Oxidation of L-prolinol with H_2O_2/cat. SeO_2 and cycloaddition of the nitrones to N*-phenylmaleimide, 4*

To a stirred solution of 400 mg (3.9 mmol) of L-prolinol in acetone (40 mL) at 0°C, 11 mg (0.10 mmol) of SeO_2 were added. Then, 1.4 mL (12 mmol) of 30% H_2O_2 were added dropwise and the mixture was stirred at 0°C for 30 min and at room temperature for 2.5 h. Removal of the solvent and flash chromatography of the reaction crude using AcOEt/MeOH 4/1 gave a mixture of nitrones that was treated with 685 mg (3.96 mmol) of *N*-phenylmaleimide, **4**, in AcOEt for 2 d at room temperature. Removal of the solvent, followed by flash chromatography of the crude product using hexane/AcOEt 2/1 as eluent afforded the following fractions: 335 mg (49%) of *N*-phenylmaleimide, **4**, 207 mg (20%) of (3a*RS*,8a*SR*,8b*SR*)-hexahydro-2-phenyl-2*H*-pyrrolo[1,2-*b*]pyrrolo[3,4-*d*]isoxazole-1,3-dione, **8**, 83 mg (7%) of (3a*R*,6*S*,8a*S*,8b*S*)-hexahydro-6-hydroxymethyl-2-phenyl-2*H*-pyrrolo[1,2-*b*]pyrrolo[3,4-*d*]isoxazole-1,3-dione, **5**, 89 mg (8%) of (3a*RS*,8a*RS*,8b*SR*)-hexahydro-8a-hydroxymethyl-2-phenyl-2*H*-pyrrolo[1,2-*b*]pyrrolo[3,4-*d*]-isoxazole-1,3-dione, **7**, and 91 mg (8%) of (3a*S*,6*S*,8a*S*,8b*R*)-hexahydro-6-hydroxymethyl-2-phenyl-2*H*-pyrrolo[1,2-*b*]pyrrolo[3,4-*d*]isoxazole-1,3-dione, **6**. **5**: mp 154–155 °C (AcOEt/hexane); IR (KBr) 3487, 3430, 3065, 2931, 2875, 1785, 1715, 1470, 1391, 1194 cm^{-1}; ^{1}H NMR (400 MHz) δ 7.46 (t, J=7.5 Hz, 2H: 2H$_{m\text{-Ph}}$), 7.39 (t, J=7.5 Hz, 1H: H$_{p\text{-Ph}}$), 7.29 (d, J=7.5 Hz, 2H: 2H$_{o\text{-Ph}}$), 4.95 (d, $J_{3a,8b}$=7.5 Hz, 1H: H$_{3a}$), 3.90 (br dd, $^{cis}J_{8a,8} \approx {}^{trans}J_{8a,8} \approx$ 8.2 Hz, 1H: H$_{8a}$), 3.74 (m, 1H: H$_6$), 3.66 (dd, $J_{8b,3a}$=7.5 Hz, $J_{8b,8a}$=1.3 Hz, 1H: H$_{8b}$), 3.59 (ddd, $J_{1',1'}$=11.5 Hz, $J_{1',OH}$=8.6 Hz, $J_{1',6}$=4.6 Hz, 1H: H$_{1'}$), 3.34 (ddd, $J_{1',1'}$=11.5 Hz, $J_{1',6}$=8.0 Hz, $J_{1',OH}$=3.3 Hz, 1H: H$_{1'}$), 2.20 (m, 2H: H$_7$, H$_8$), 2.03 (dd, $J_{OH,1'}$=8.6 Hz, $J_{OH,1'}$=3.3 Hz, 1H: OH), 1.84 (dddd, $J_{8,8}$=13.0 Hz, $^{trans}J_{8,8a} \approx {}^{cis}J_{8,7} \approx {}^{trans}J_{8,7} \approx$ 9.5 Hz, 1H: H$_8$), 1.55 (m, 1H: H$_7$); ^{13}C NMR δ 174.5/173.8 (C$_1$/C$_3$), 131.2/129.2/128.9/126.3 (Ph), 75.4 (C$_{3a}$), 69.3 (C$_{8a}$), 69.0 (C$_6$), 64.1 (C$_{1'}$), 53.3 (C$_{8b}$), 30.2 (C$_8$), 27.0 (C$_7$); MS *m/z* 288 (M$^+$, 8), 257 (100), 82 (30); $[\alpha]_D$=−62.7 (*c* 0.75, CHCl$_3$). Anal. Calcd for C$_{15}$H$_{16}$N$_2$O$_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.44; H, 5.60; N, 9.66. **6**: mp 138–139°C (AcOEt/hexane); IR (KBr) 3479, 3071, 2959, 2889, 1778, 1707, 1595, 1497, 1419, 1391, 1194 cm^{-1}; ^{1}H NMR (250 MHz) δ 7.45 (m, 3H: 2H$_{m\text{-Ph}}$, H$_{p\text{-Ph}}$), 7.26 (d, J=7.0 Hz, 2H: 2H$_{o\text{-Ph}}$), 5.04 (d, $J_{3a,8b}$=8.0 Hz, 1H: H$_{3a}$), 4.09 (ddd, $J_{8a,8b}$=9.1 Hz, $^{cis}J_{8a,8} \approx {}^{trans}J_{8a,8} \approx$ 6.4 Hz, 1H: H$_{8a}$), 3.90 (dd, $J_{8b,8a} \approx J_{8b,3a} \approx$ 8.7 Hz, 1H: H$_{8b}$), 3.71 (br d, $J_{1',1'}$=11.0 Hz, 1H: H$_{1'}$), 3.44 (br d, $J_{1',1'}$=11.0 Hz, 1H: H$_{1'}$), 3.31 (m, 1H: H$_6$), 2.39 (br, 1H: OH), 2.10 (m, 3H: 2H$_8$, H$_7$), 1.68 (m, 1H: H$_7$); ^{13}C NMR δ 173.5/172.8 (C$_1$/C$_3$), 131.1/129.3/129.0/125.9 (Ph), 78.8 (C$_{3a}$), 68.0/67.8 (C$_6$/C$_{8a}$), 64.0 (C$_{1'}$), 51.9 (C$_{8b}$), 25.6 (C$_8$), 23.8 (C$_7$); MS *m/z* 288 (M$^+$, 7), 257 (97), 173 (73), 84 (100), 41 (36); $[\alpha]_D$=−99.0 (*c* 1.00, CHCl$_3$). Anal. Calcd for C$_{15}$H$_{16}$N$_2$O$_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.50; H, 5.62; N, 9.71. **7**: mp 168–169°C (AcOEt/hexane); IR (KBr) 3339, 3005, 2959, 2924, 2875, 1785, 1715, 1497, 1391, 1194 cm^{-1}; ^{1}H NMR (250 MHz) δ 7.51–7.24 (m, 5H: Ph), 4.98 (d, $J_{3a,8b}$=8.0 Hz, 1H: H$_{3a}$), 3.93 (d, $J_{8b,3a}$=8.0 Hz, 1H: H$_{8b}$), 3.64 (dd, $J_{1',1'}$=11.5 Hz, $J_{1',OH}$=8.0 Hz, 1H: H$_{1'}$), 3.51 (dd, $J_{1',1'}$=11.5 Hz, $J_{1',OH}$=5.0 Hz, 1H: H$_{1'}$), 3.23 (m, 2H: 2H$_6$), 2.31 (dd, $J_{OH,1'}$=8.0 Hz, $J_{OH,1'}$=5.0 Hz, 1H: OH), 2.27–1.70 (m, 4H: 2H$_7$, 2H$_8$); ^{13}C NMR δ 173.9/172.5 (C$_1$/C$_3$), 131.1/129.3/129.0/126.0 (Ph), 79.8 (C$_{8a}$), 78.6 (C$_{3a}$), 66.4 (C$_{1'}$), 55.6 (C$_6$), 54.1 (C$_{8b}$), 27.1(C$_8$), 23.0 (C$_7$); MS *m/z* 288 (M$^+$, 4), 257 (100), 177 (44), 110 (30). Anal. Calcd for C$_{15}$H$_{16}$N$_2$O$_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.37;

H, 5.49; N, 9.63. **8:** mp 129–131°C (AcOEt/pentane); IR (film) 2966, 1785, 1722, 1497, 1384, 1194 cm^{-1}; ^1H NMR (250 MHz) δ 7.38 (m, 5H: Ph), 4.90 (d, $J_{3a,8b}$=7.3 Hz, 1H: H_{3a}), 3.83 (dd, $^{cis}J_{8a,8} \approx {}^{trans}J_{8a,8} \approx$ 8.2 Hz, 1H: H_{8a}), 3.66 (d, $J_{8b,3a}$=7.3 Hz, 1H: H_{8b}), 3.55 (ddd, $J_{6,6}$=14.3 Hz, $J_{6,7}$=7.3 Hz, $J'_{6,7}$=3.1 Hz, 1H: H_6), 3.00 (ddd, $J_{6,6}$=14.3 Hz, $^{cis}J_{6,7} \approx {}^{trans}J_{6,7} \approx$ 8.4 Hz, 1H: H_6), 2.14 (m, 2H), 1.77 (m, 2H); ^{13}C NMR δ 174.7/174.3 (C_1/C_3), 131.4/129.1/128.8/126.3 (Ph), 75.8 (C_{3a}), 70.8 (C_{8a}), 55.8 (C_6), 54.2 (C_{8b}), 30.0 (C_8), 24.3 (C_7); MS *m/z* 258 (M^+, 54), 173 (72), 85 (100), 55 (55).

(S)-5-Hydroxymethyl-1-pyrroline N*-oxide, **1b***

To a stirred solution of 500 mg (4.94 mmol) of L-prolinol in acetone (15 mL) at −78°C, 64 mL (10.9 mmol) of 0.17 M solution of DMD in acetone were added. The mixture was stirred at −78°C for 30 min and the solvent evaporated under vacuum. The oily residue was dissolved in 20 mL of toluene and heated at the reflux temperature for 6 h. Evaporation of the solvent and purification by flash chromatography (AcOEt/MeOH 5/1) yielded 182 mg (32%) of (*S*)-5-hydroxymethyl-1-pyrroline *N*-oxide, **1b**: ^1H NMR (250 MHz) δ 6.91 (d, $J_{2,3}$=1.5 Hz, 1H: H_2), 4.05 (m, 1H: H_5), 4.00 (dd, $J_{1',1'}$=12.1 Hz, $J_{1',5}$=2.6 Hz, 1H: $H_{1'}$), 3.78 (dd, $J_{1',1'}$=12.1 Hz, $J_{1',5}$=7.1 Hz, 1H: $H_{1'}$), 2.66 (m, 2H: $2H_3$), 2.30 (m, 1H: H_4), 1.93 (m, 1H: H_4); ^{13}C NMR δ 136.7 (C_2), 72.8 ($C_{1'}$), 62.1 (C_5), 27.0 (C_3), 21.0 (C_4); $[\alpha]_D$=+83 (*c* 2.65, $CHCl_3$).

For the cycloadditions to **9–13**, the chromatography solvent of the fractions containing **1b** was exchanged by the reaction solvent, through evaporation under vacuum avoiding dryness. A 32% yield of **1b** was always considered.

*Cycloaddition of nitrone **1b** to* N*-phenylmaleimide, **4***

98 mg (0.85 mmol) of nitrone **1b** were treated with 442 mg (2.55 mmol) of *N*-phenylmaleimide, **4**, in 1 mL of toluene at 70°C for 4 h. Solvent evaporation, followed by flash chromatography of the reaction crude using hexane/AcOEt 2/1 as eluent afforded the following fractions: 304 mg (69%) of *N*-phenylmaleimide, **4**, 108 mg (43%) of **5** and 53 mg (21%) of **6**.

The same reaction was performed with 55 mg (0.48 mmol) of nitrone **1b** and 102 mg (0.59 mmol) of *N*-phenylmaleimide, **4**, in 15 mL of AcOEt for 2 d at room temperature. After purification of the crude product, 29 mg (28%) of *N*-phenylmaleimide, **4**, 48 mg (35%) of **5** and 44 mg (32%) of **6** were obtained.

*Cycloaddition of nitrone **1b** to 2(5*H*)-furanone, **9***

Nitrone **1b**, prepared from 250 mg (2.47 mmol) of L-prolinol, was treated with 138 mg (1.64 mmol) of 2(5*H*)-furanone, **9**, in 10 mL of toluene at 110°C for 18 h. Solvent removal and flash chromatography using AcOEt as eluent afforded 100 mg (72%) of the starting lactone **9** and 71 mg (45%) of (3a*R*,6*S*,8a*S*,8b*S*)-hexahydro-6-hydroxymethylfuro[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-1(3*H*)-one, **14**: mp 66–67°C (AcOEt/pentane); IR (film) 3402, 2945, 2875, 1771, 1173, 1040 cm^{-1}; ^1H NMR (400 MHz) δ 4.92 (ddd, $J_{3a,\ 8b}$=6.4 Hz, $^{cis}J_{3a,3}$=3.7 Hz, $^{trans}J_{3a,3}$=1.8 Hz, 1H: H_{3a}), 4.40 (m, 2H: $2H_3$), 3.98 (ddd, $^{cis}J_{8a,8} \approx {}^{trans}J_{8a,8} \approx$ 7.3 Hz, $J_{8a,8b} \approx$ 1.2 Hz, 1H: H_{8a}), 3.64 (dd, $J_{1',1'}$=11.0 Hz, $J_{1',6}$=3.9 Hz, 1H: $H_{1'}$), 3.44 (dd, $J_{1',1'}$=11.0 Hz, $J_{1',6}$=6.7 Hz, 1H: $H_{1'}$), 3.34 (dddd, $J_{6,1'} \approx {}^{cis}J_{6,7} \approx {}^{trans}J_{6,7} \approx$ 7.3 Hz, $J_{6,1'}$=3.9 Hz, 1H: H_6), 3.25 (dd, $J_{8b,3a}$=6.4 Hz, $J_{8b,8a}$=1.8 Hz, 1H: H_{8b}), 2.35 (br, 1H: OH), 2.22 (dddd, $J_{8,8} \approx$ 11.3 Hz, $J_{8,8a} \approx {}^{cis}J_{8,7} \approx$ 7.3 Hz, $^{trans}J_{8,7} \approx$ 3.3 Hz, 1H: H_8), 1.98 (dddd, $J_{7,7} \approx$ 12.2 Hz, $J_{7,6} \approx J_{7,8} \approx$ 8.0 Hz, $J_{7,8} \approx$ 3.3 Hz, 1H: H_7), 1.77 (dddd, $J_{8,8} \approx$ 12.8 Hz, $^{cis}J_{8,7} \approx {}^{trans}J_{8,7} \approx J_{8,8a} \approx$ 8.2 Hz, 1H: H_8), 1.57 (dddd, $J_{7,7} \approx$ 12.8 Hz, $^{cis}J_{7,8} \approx {}^{trans}J_{7,8} \approx J_{7,6} \approx$ 8.2 Hz, 1H: H_7); ^{13}C NMR δ 176.2 (C_1), 76.3 (C_{3a}), 71.4 (C_3), 68.8/67.6 (C_6/C_{8a}), 63.8 ($C_{1'}$), 54.8 (C_{8b}), 30.2 (C_8), 25.9 (C_7); MS *m/z* 199 (M^+, 4), 168 (100); $[\alpha]_D$=−26.0 (*c* 0.50, $CHCl_3$). Anal. Calcd for $C_9H_{13}NO_4$: C, 54.26; H, 6.58; N, 7.03. Found: C, 54.22; H, 6.49; N, 6.89.

*Cycloaddition of nitrone **1b** to 6,7-dihydro-2(5*H*)-oxepinone, **10***

Nitrone **1b**, prepared from 230 mg (2.27 mmol) of L-prolinol, was treated with 176 mg (1.57 mmol) of 6,7-dihydro-2(5*H*)-oxepinone, **10**, in 10 mL of toluene at 110°C for 26 h. After solvent removal

and purification by flash chromatography using AcOEt as eluent, 109 mg (62%) of starting **10** and 75 mg (45%) of (5a*S*,8*S*,10a*S*,10b*S*)-8-hydroxymethyloctahydrooxepino[3,4-*d*]pyrrolo[1,2-*b*]isoxazol-1(3*H*)-one, **15**, were obtained. **15**: mp 161–162°C (AcOEt/hexane); IR (film) 3311, 2959, 2924, 2882, 1708, 1040 cm^{-1}; ^1H NMR (400 MHz) δ 4.46 (ddd, $^{trans}J_{5a,5}$=12.2 Hz, $J_{5a,10b}$=9.4 Hz, $^{cis}J_{5a,5}$=3.3 Hz, 1H: H_{5a}), 4.34 (ddd, $J_{10a,10b} \approx J_{10a,10} \approx$ 6.7 Hz, $J_{10a,10} \approx$ 3.2 Hz, 1H: H_{10a}), 4.30 (dd, $J_{3,3}$=12.8 Hz, $^{trans}J_{3,4}$=7.3 Hz, 1H: H_3), 4.19 (ddd, $J_{3,3}=^{trans}J_{3,4}$=12.8 Hz, $^{cis}J_{3,4}$=4.9 Hz, 1H: H_3), 3.68 (ddd, $J_{1',1'}$=10.7 Hz, $J_{1',OH}$=6.1 Hz, $J_{1',8}$=4.3 Hz, 1H: $H_{1'}$), 3.51 (ddd, $J_{1',1'}$=10.7 Hz, $J_{1',8} \approx J_{1',OH} \approx$ 5.5 Hz, 1H: $H_{1'}$), 3.33 (dd, $J_{10b,5a}$=9.4 Hz, $J_{10b,10a}$=5.8 Hz, 1H: H_{10b}), 3.14 (m, 1H: H_8), 2.49 (t, $J_{OH,1'}$=6.1 Hz, 1H: OH), 2.19 (m, 1H: H_{10}), 2.06 (m, 2H: H_4, H_5), 1.96 (m, 1H: H_9), 1.80 (m, 1H: H_{10}), 1.68 (m, 2H: H_4, H_5), 1.55 (m, 1H: H_9); ^{13}C NMR δ 171.5 (C_1), 74.5 (C_{5a}), 67.2 (C_{10a}), 64.9 (C_3), 64.5 (C_8), 64.1 ($C_{1'}$), 57.1 (C_{10b}), 27.6/25.5/24.4/22.6 (C_4/C_5/C_9/C_{10}); MS *m/z* 227 (M^+, 5), 196 (100), 71 (37), 41 (32); $[\alpha]_D$=−152.0 (*c* 1.00, $CHCl_3$). Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 58.16; H, 7.52; N, 6.02.

*Cycloaddition of nitrone **1b** to dimethyl fumarate, **11***

Nitrone **1b**, prepared from 500 mg (4.95 mmol) of L-prolinol, was treated with 274 mg (1.90 mmol) of dimethyl fumarate, **11**, in 10 mL of $CHCl_3$ at 61°C for 3 h. Solvent removal and flash chromatography of the reaction crude using AcOEt as eluent afforded 123 mg (45%) of starting **11**, 270 mg (66%) of a 1/1 mixture of (2*S*,3*S*,3a*S*,6*S*)-dimethylhexahydro-6-hydroxymethylpyrrolo[1,2-*b*]isoxazole-2,3-dicarboxylate, **16**, and its (2*R*,3*R*,3a*S*,6*S*)-diastereoisomer, **17**, that was separated by successive flash chromatographies. **16**: IR (film) 3409, 2959, 2882, 1743, 1230 cm^{-1}; ^1H NMR (250 MHz) δ 4.90 (d, $J_{2,3}$=7.7 Hz, 1H: H_2), 3.87 (m, 1H), 3.77 (s, 3H: OCH_3), 3.75 (s, 3H: OCH_3), 3.68 (m, 1H), 3.47 (m, 1H), 3.45 (dd, $J_{3,3a} \approx J_{3,2} \approx$ 7.7 Hz, 1H: H_3), 3.38 (m, 1H), 2.32 (br, 1H: OH), 2.14–1.88 (m, 3H), 1.65 (m, 1H); ^{13}C NMR δ 171.0 (C=O), 170.6 (C=O), 80.6 (C_2), 69.5/66.9 (C_{3a}/C_6), 63.5 ($C_{1'}$), 56.6 (C_3), 52.8 (OCH_3), 52.6 (OCH_3), 26.5/24.4 (C_4/C_5); MS *m/z* 259 (M^+, 6), 228 (100), 108 (75), 59 (30); $[\alpha]_D$=−4.8 (*c* 1.65, $CHCl_3$). **17**: IR (film) 3395, 2952, 2875, 1736, 1230 cm^{-1}; ^1H NMR (250 MHz) δ 4.92 (d, $J_{2,3}$=6.6 Hz, 1H: H_2), 3.92 (m, 2H: H_{3a}, H_3), 3.76 (s, 3H: OCH_3), 3.74 (s, 3H: OCH_3), 3.66 (dd, $J_{1',1'}$=10.8 Hz, $J_{1',6}$=4.0 Hz, 1H: $H_{1'}$), 3.52 (m, 1H: H_6), 3.39 (dd, $J_{1',1'}$=10.8 Hz, $J_{1',6}$=6.6 Hz, 1H: $H_{1'}$), 2.30 (br, 1H: OH), 2.03 (m, 1H), 1.85 (m, 1H), 1.62 (m, 2H); ^{13}C NMR δ 170.5 (C=O), 170.2 (C=O), 76.0 (C_2), 68.5/66.6 (C_{3a}/C_6), 63.7 ($C_{1'}$), 54.3 (C_3), 52.7 (OCH_3), 52.4 (OCH_3), 26.7/26.3 (C_4/C_5); MS *m/z* 259 (M^+, 5), 228 (100), 113 (62), 108 (93), 85 (31), 84 (31), 68 (40), 59 (42); $[\alpha]_D$=−128.0 (*c* 0.75, $CHCl_3$).

*Cycloaddition of nitrone **1b** to methyl (E)-6-benzoyloxy-2-hexenoate, **12***

Nitrone **1b**, prepared from 250 mg (2.47 mmol) of L-prolinol, was treated with 183 mg (0.74 mmol) of methyl (*E*)-6-benzoyloxy-2-hexenoate, **12**, in 10 mL of $CHCl_3$ at 61°C for 5 d. Solvent removal and flash chromatography of the reaction crude using hexane/AcOEt 1/1 as eluent afforded 98 mg (53%) of starting **12** and 122 mg (45%) of (2*S*,3*R*,3a*S*,6*S*)-methyl 2-(3-benzoyloxypropyl)-hexahydro-6-hydroxymethylpyrrolo[1,2-*b*]isoxazole-3-carboxylate, **18**: IR (film) 3381, 2952, 2924, 2860, 1721, 1278 cm^{-1}; ^1H NMR (400 MHz) δ 8.00 (d, $J \approx$ 6.7 Hz, 2H: $2H_{o\text{-Ph}}$), 7.52 (t, $J \approx$ 7.3 Hz, 1H: $H_{p\text{-Ph}}$), 7.39 (t, $J \approx$ 7.3 Hz, 2H: $2H_{m\text{-Ph}}$), 4.30 (t, $J_{3'',2''}$=6.1 Hz, 2H: $2H_{3''}$), 4.27 (ddd, $J_{2,3} \approx$ 10.0 Hz, $J_{2,1''} \approx$ 7.9 Hz, $J_{2,1''} \approx$ 3.7 Hz, 1H: H_2), 4.01 (ddd, $J_{3a,3} \approx$ 10.4 Hz, $^{cis}J_{3a,4} \approx {}^{trans}J_{3a,4} \approx$ 6.7 Hz, 1H: H_{3a}), 3.70 (m, 1H: $H_{1'}$), 3.68 (s, 3H: OCH_3), 3.48 (m, 1H: $H_{1'}$), 3.23 (m, 1H: H_6), 3.12 (dd, $J_{3,3a}=J_{3,2}$=9.4 Hz, 1H: H_3), 2.44 (br, 1H: OH), 1.95–1.77 (m, 5H: H_4, H_5, $H_{1''}$, $2H_{2''}$), 1.70 (m, 1H: $H_{1''}$), 1.63–1.53 (m, 2H: H_4, H_5); ^{13}C NMR δ 170.7 (C=O), 166.5 (C=O), 132.8/130.3/129.5/128.3 (Ph), 76.4 (C_2), 68.2 (C_{3a}), 65.9 (C_6), 64.5/63.6 ($C_{3''}$/$C_{1'}$), 56.2 (C_3), 51.9 (OCH_3), 28.7/27.0/25.5/25.3 (C_4/C_5/$C_{1''}$/$C_{2''}$); MS *m/z* 363 (M^+, 1), 332 (23), 105 (100), 77 (42); $[\alpha]_D$=−90.5 (*c* 1.62, $CHCl_3$). Anal. Calcd for $C_{19}H_{25}NO_6$: C, 62.80; H, 6.93; N, 3.85. Found: C, 62.81; H, 7.00; N, 3.88.

*Cycloaddition of nitrone **1b** to dimethyl acetylenedicarboxylate, **13***

Nitrone **1b**, prepared from 250 mg (2.47 mmol) of L-prolinol, was treated with 351 mg (2.47 mmol) of dimethyl acetylenedicarboxylate, **13**, in 15 mL of AcOEt at room temperature overnight. Solvent removal and flash chromatography of the crude product using hexane/AcOEt 2/1 as eluent afforded 290 mg (83%) of starting **13** and 82 mg (40%) of (3a*S*,6*S*)-dimethyl 3a,4,5,6-tetrahydro-6-hydroxymethylpyrrolo[1,2-*b*]isoxazole-2,3-dicarboxylate, **19**: IR (film) 3409, 2952, 2882, 1750, 1715, 1651, 1441, 1314, 1251, 1202, 1131, 1061 cm^{-1}; ^1H NMR (250 MHz) δ 4.81 (dd, $^{trans}J_{3a,4} \approx {}^{cis}J_{3a,4} \approx 6.3$ Hz, 1H: H_{3a}), 3.82 (s, 3H: OCH_3), 3.71 (m, 1H: $H_{1'}$), 3.68 (s, 3H: OCH_3), 3.52 (dd, $J_{1',1'}$=11.3 Hz, $J_{1',6}$=5.5 Hz, 1H: $H_{1'}$), 3.44 (m, 1H: H_6), 2.48 (br, 1H: OH), 2.23 (m, 1H: H_4), 1.98 (m, 1H: H_4), 1.83 (m, 1H: H_5), 1.60 (m, 1H: H_5); ^{13}C NMR δ 162.5 (C=O), 159.2 (C=O), 151.2 (C_2), 109.3 (C_3), 72.0/69.3 (C_{3a}/C_6), 62.4 ($C_{1'}$), 53.1 (OCH_3), 51.7 (OCH_3), 30.5/23.7 (C_4/C_5); MS *m/z* 257 (M^+, 9), 226 (100), 198 (52), 59 (44); $[\alpha]_D$=−253.0 (*c* 2.30, $CHCl_3$). Anal. Calcd for $C_{11}H_{15}NO_6$: C, 51.36; H, 5.88; N, 5.44. Found: C, 51.27; H, 5.97; N, 5.21.

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