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Quasienantiomeric Levoglucosenone and Isolevoglucosenone Allow the Parallel Kinetic Resolution of a Racemic Nitrone

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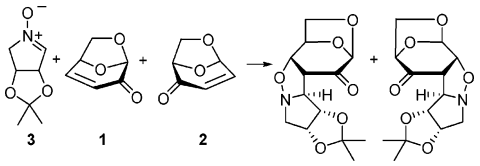
Received November 7, 2007



Cycloadditions of chiral pyrroline *N*-oxides to levoglucosenone (**1**) and isolevoglucosenone (**2**) proceed with a high level of double asymmetric induction. Partial kinetic resolutions (KR) of both enantiomers of a racemic nitrone **3** were achieved, and a parallel kinetic resolution (PKR) experiment allowed the stereoselective divergent synthesis of two quasienantiomeric imino-*C*-disaccharide precursors.

In a Parallel Kinetic Resolution (PKR)[1,2] two quasienantiomeric reagents are used to simultaneously derivatize each enantiomer of a racemate to give two distinct quasienantiomeric products. This strategy is particularly convenient for less efficient kinetic resolutions (KR) where, as racemate conversion increases, the concentration factor allows the reaction with also the less reactive enantiomer to occur, thus lowering the ee of the recovered substrate. During a PKR experiment, in the optimal case where the competing derivatizations occur with similar rates (both enantiomers react simultaneously) and complementary enentioselectivities, products ee values are close to the theoretical limit calculated for the inherent enantioselectivities, regardless of the extent of conversion, and recovery can exceed 90%.

Cycloaddition reactions are nicely suited for KR and PKR experiments,[3] since they occur through a concerted mechanism and with highly organized transition states strongly governed by steric factors. Thanks to double asymmetric induction, the transition states deriving from an enantiopure substrate and the two enantiomers of a racemic partner can significantly differ in terms of energy, resulting in a partial kinetic resolution of the racemate. If two different substrates with similar reactivity and opposite enantioselectivities are used (such as in a PKR experiment), each of them can react with the "matched" enantiomer avoiding formation of minor adducts deriving from "mismatched" interactions. We have used this strategy for the efficient PKR of racemic dihydrophosphole derivatives with two enantiopure cyclic nitrones[4] and of a racemic cyclic nitrone with two different glycals.[5,6]

We noticed that levoglucosenone (**1**) and isolevoglucosenone (**2**) are quasienantiomers,[1c,7] and we envisaged that they could be ideal substrates to be used in PKR experiments. We report here our results on the parallel kinetic resolution (PKR) of a racemic nitrone **3** with **1** and **2** en route to the stereodivergent synthesis of imino-*C*-disaccharide precursors.[8]

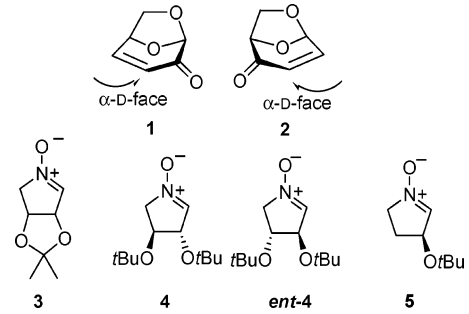


FIGURE 1. Dipolarophiles and nitrones employed.

Levoglucosenone (**1**) is a convenient starting material derived from renewable sources, being produced from the pyrolysis of cellulose.[9] Isolevoglucosenone (**2**) is readily synthesized from D-glucose in four synthetic steps.[10] These two easily available isomers have an intriguing chemical structure: the 1,6-anhydro bridge eliminates the need for protecting groups at the anomeric carbon and at the C-6 OH, and fixes the conformation of the system in such a way that the β-D-face is sterically hindered and reactions occur with high stereochemical control by attack at the α-D-face. The use of **1** and **2** as templates for the design of imino-*C*-disaccharides and analogues has been widely exploited by Vogel and co-workers.[11] The activated double bond in levoglucosenone (**1**) and isolevoglucosenone (**2**) ensures a high reactivity and regioselectivity in 1,3-dipolar cycloadditions. However, while cycloadditions of nitrones and nitrile oxides to

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(2) For some recent PKRs see: (a) Tanaka, K.; Hagiwara, Y.; Hirano, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 2734−2737. (b) Vedejs, E.; Rozners, E. *Angew. Chem., Int. Ed.* **2001**, *123*, 2428−2429. (c) Chavda, S.; Coulbeck, E.; Coumbarides, G. S.; Dingjan, M.; Eames, J.; Ghilagaber, S.; Yohannes, Y. *Tetrahedron*: *Asymmetry* **2006**, *17*, 3386−3399.

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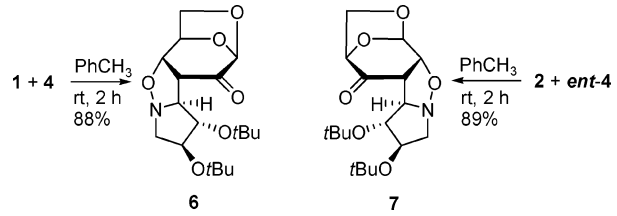
10.1021/jo702403b CCC: $40.75
Published on Web 01/26/2008

SCHEME 1. Double Asymmetric Induction in the Cycloadditions of 1 and 2 to Enantiomeric L- and D-Tartaric Acid Derived Nitrones, Respectively: Synthesis of the "Matched" Adducts 6 and 7



1 have been reported early by Paton and co-workers,[12] use of **2** in cycloaddition chemistry has been proved only recently.[8]

To verify if **1** and **2** could add to chiral nitrones with similar rates and opposite selectivities, two parallel reactions were carried out with enantiomeric nitrones derived from tartaric acids, selecting the expected matched pairs of reagents. Levoglucosenone (**1**)[9] was reacted with 1 equiv of L-tartaric acid derived nitrone **4**[13] in toluene at room temperature, affording after 2 h only the adduct **6** in 88% yield. Analogously, the enantiomeric D-tartaric acid derived nitrone *ent*-**4** afforded with isolevoglucosenone (**2**)[10] the single adduct **7** in 89% yield (Scheme 1).[8] Both cycloadditions were completely regio- and stereoselective, as confirmed by ^{1}H NMR analysis of the crude reaction mixtures. The quasienantiomers "matched" adducts **6** and **7**, whose structure was unambiguously determined by spectral data (including two-dimensional COSY and NOESY NMR spectra), derived from a preferred approach of the nitrones, in an *exo* fashion, to the α face of levoglucosenone (**1**) and isolevoglucosenone (**2**), which avoided repulsive interactions with the vicinal OR group of the nitrones (Figure 2). Yields and reaction times were identical, strengthening the anticipated ability of **1** and **2** to behave as quasienantiomers.

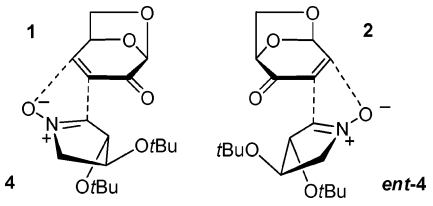
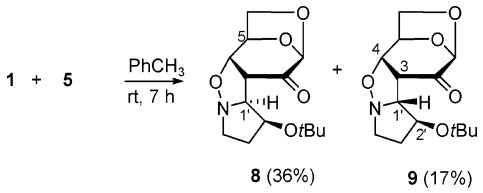


FIGURE 2. Preferred *exo* approaches of nitrones **4** and *ent*-**4** to the α face of levoglucosenone (**1**) and isolevoglucosenone (**2**), *anti* to the 1,6-anhydro bridge and the vicinal *tert*-butoxy.

The L-malic acid derived nitrone **5**,[14] resembling nitrone *ent*-**4**, was expected to form a matched pair with isolevoglucosenone (**2**) and a mismatched one with levoglucosenone (**1**). To obtain models for the "mismatched" diasteroisomers, **1** was reacted with 1 equiv of **5** in toluene at room temperature, affording two adducts **8** and **9** in longer times and with moderate yields (36% and 17%, respectively) (Scheme 2). Their structure was determined by careful analysis of the spectral data. In particular, two-dimensional ROESY spectra showed cross-peaks between signal pairs at δ 4.82 (H-5) and 4.15 (H-1′) in **8** and between

SCHEME 2. Synthesis of the "Mismatched" Adducts 8 and 9



signal pairs at δ 4.17 (H-4) and 3.81 (H-1′), and δ 3.68 (H-3) and 4.27 (H-2′) in **9**. This stereochemical assignment was supported by X-ray crystallographic structure determination of both adducts **8** and **9** (see the Supporting Information).

Compounds **1** and **5** form a "mismatched" pair of stereoisomers, as they cannot approach in the most favored *exo-anti* fashion. Less favored adducts **8** and **9** derived respectively from an *exo* approach *syn* with respect to the vicinal OR group and an *endo* approach *anti* to the vicinal OR group (Figure 3). No adducts deriving from *syn* approaches to the 1,6-anhydro bridge, i.e., to the β-D-face of levoglucosenone, were observed.

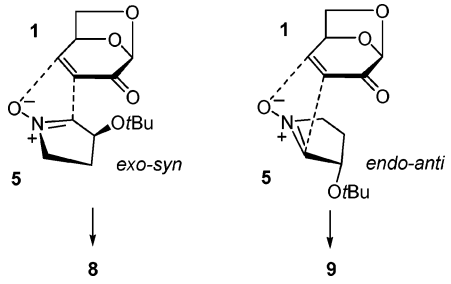


FIGURE 3. "Mismatched" interactions in the approach of levoglucosenone (**1**) to nitrone **5**.

The high facial preference shown by levoglucosenone (**1**) and isolevoglucosenone (**2**) allowed a partial kinetic resolution of both enantiomers of the cis-disubstituted racemic nitrone **3**[15] (Scheme 3). Reaction of **1** with 2 equiv of racemic nitrone **3** in toluene at room temperature afforded after 2 h a major adduct **10** in 22% yield from **3** (44% yield calculated from **1**), with recovery of 50% of enantioenriched (3*R*,4*S*)-nitrone **3** (42% ee).[16] Analogously, reaction of **2** with 2 equiv of racemic nitrone **3** in toluene at room temperature afforded after 2.5 h a major adduct **11** in 32% yield from **3** (64% yield calculated from **2**), and 50% of enantioenriched (3*S*,4*R*)-**3** (54% ee)[16] was recovered.[8] The structure of the major adducts **10** and **11**, deriving from *exo* approaches of the "matched" enantiomers to the α-face of **1** and **2**, were unambiguously determined by spectral data.[17] On the basis of the stereochemical outcome found for cycloaddition of **1** to nitrone **5**, the minor adducts probably derive from *exo*-approaches of the less reactive enantiomers *syn* with respect to the vicinal OR group of the nitrone.

Albeit the shown kinetic resolutions did not afford nitrones **3** with high ee values, the similar reactivity of **1** and **2** toward the opposite enantiomers of a chiral compound, as shown with nitrones **4** and *ent*-**4** (Scheme 1) and in the kinetic resolutions

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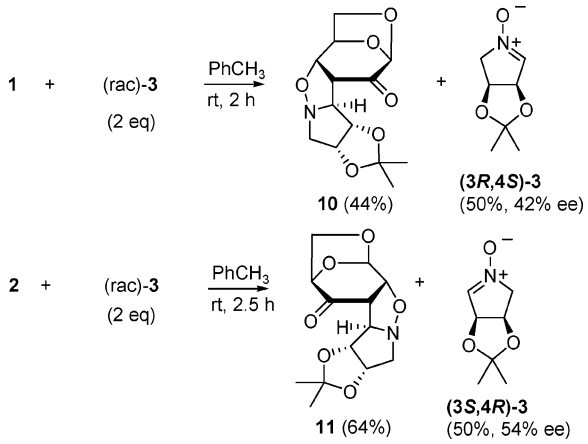
(16) Ee values of the recovered nitrones were determined by ^{1}H NMR experiment with Yb(hfc)$_3$ as a chiral shift reagent.

(17) In both kinetic resolution experiments, the presence of a minor adduct, which was not fully characterized, was visible in the ^{1}H NMR spectrum of the crude reaction mixtures.

SCHEME 3. Partial Kinetic Resolutions of Racemic Nitrone 3 with 1 and 2[a]



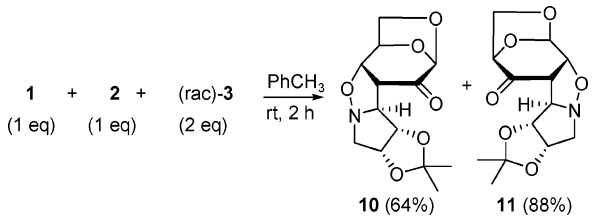
[a] Yields of **10** and **11** based on **1** and **2**, respectively; yields of recovered enriched **3** based on racemic **3**.

of nitrone **3** itself (Scheme 3), suggested that a nearly ideal parallel kinetic resolution (PKR) experiment could be accomplished. Levoglucosenone (**1**) and isolevoglucosenone (**2**) were then reacted with 2 equiv of racemic nitrone **3** in toluene at room temperature. After 2 h, the quasienantiomers **10** and **11** were obtained in a 1:1 ratio, and no traces of the disfavored cycloadducts were detected in the crude mixture. After separation by flash column chromatography, adducts **10** and **11** were obtained in 32% and 44% yields, respectively, calculated with respect to total **3** (Scheme 4). The PKR experiment allows the best utilization of racemic nitrone **3** for the synthesis of two different products in an enantiomerically pure form and in a completely stereoselective manner.

As previously demonstrated, adducts **10** and **11** are direct precursors of directly linked (1→3)-imino-*C*-disaccharides.[8] Imino-*C*-disaccharides[18] are potential inhibitors of glycosidases[19] and glycosyltransferases[20] offering the advantage, with respect to the native disaccharide, of being resistant to acid and enzymatic hydrolysis. It has also been recently found that imino-*C*-disaccharides and analogues are able to inhibit the growth of tumoral cells such as human glioblastoma and melanoma cells.[21]

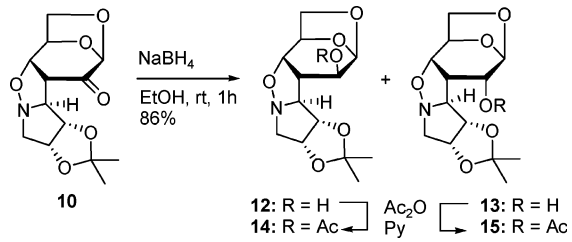
Reduction of **10** with $NaBH_4$ in ethanol at room temperature afforded a 2.2:1 mixture of the two diastereomeric alcohols **12** and **13** in 86% yield, which were better separated as their acetate derivatives **14** and **15** (Scheme 5). Acetylation of the alcohol moiety also allowed structure determination by analysis of the monodimensional NOE spectra of **14** and **15** (see the Supporting Information). Compounds **14** and **15** are precursors of novel D-altro and D-allo derived imino-*C*-disaccharides.[8]

SCHEME 4. Parallel Kinetic Resolution of Nitrone 3 with 1 and 2[a]

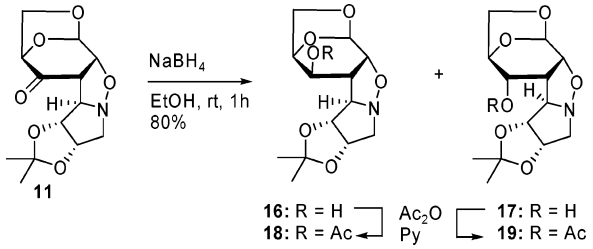


[a] Yields of **10** and **11** based on **1** and **2**, respectively.

SCHEME 5. Reduction of Adduct 10



SCHEME 6. Reduction of Adduct 11



Analogously, reduction of **11** with $NaBH_4$ in ethanol at room temperature afforded a 1:1 mixture of the two diastereomeric alcohols **16** and **17** in 80% yield, which were separated as their acetate derivatives **18** and **19** (Scheme 6, see the Supporting Information for stereochemistry assignment). Acetates **18** and **19** are precursors of imino-*C*-disaccharides of the D-gulo and D-allo series, respectively.

In conclusion, we demonstrated that levoglucosenone (**1**) and isolevoglucosenone (**2**) undergo nitrone cycloadditions with high levels of double asymmetric induction. They are nearly ideal reagents to be used for parallel kinetic resolutions (PKR) of racemic nitrones, being able to add simultaneously to the two enantiomers with similar rates and complementary selectivities, thus affording cleanly two quasienantiomeric adducts without formation of minor isomers. Reduction of the C=O bond of the adducts furnished precursors of novel imino-*C*-disaccharides belonging to different sugar series. Work is underway in our laboratory to expand the scope of this strategy.

Experimental Section

Matched Cycloaddition to Levoglucosenone (1): Synthesis of Adduct 6. A solution of nitrone **4** (91.2 mg, 0.4 mmol) and levoglucosenone (**1**, 51 mg, 0.4 mmol) in toluene (0.8 mL) was stirred at room temperature for 2 h. After concentration under reduced pressure, purification of the crude reaction mixture by flash column chromatography (eluent pentane/AcOEt, 3:2) gave **6** as a white solid (R_f 0.3, 125 mg, 0.35 mmol, 88%): mp 110−113 °C; $[\alpha]^{25}_D$ −46.5 (*c* 0.76, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.19 (s, 1H, H-1), 4.85 (d, J = 5.1 Hz, 1H, H-5), 4.49 (d, J = 7.2 Hz, 1H, H-4), 3.96−3.89 (m, 3H, Ha-6, Hb-6, H-2′), 3.87−3.86 (m,

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1H, H-1′), 3.82−3.79 (m, 1H, H-3′), 3.72 (dd, J = 13.4, 5.3 Hz, 1H, Ha-4′), 3.36 (dd, J = 7.2, 4.1 Hz, 1H, H-3), 2.85 (dd, J = 13.4, 2.3 Hz, 1H, Hb-4′), 1.20 (s, 9H, $(CH_3)_3C-O$), 1.17 (s, 9H, $(CH_3)_3C-O$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 197.1 (s, C-2), 100.4 (d, C-1), 81.5 (d, C-2′), 76.8 (d, C-4), 76.5 (d, C-3′), 74.5 (s, $(CH_3)_3C-O$), 74.3 (s, $(CH_3)_3C-O$), 73.9 (d, C-1′), 73.0 (d, C-5), 66.0 (t, C-6), 63.0 (t, C-4′), 53.2 (d, C-3), 28.4 (q, 3 C, $(CH_3)_3C-O$), 28.3 (q, 3C, $(CH_3)_3C-O$); MS, m/z (%) 355 (M^+, 5), 298 ($M^+ - t$Bu, 3), 242 (4), 57 (100); IR (KBr) 2983, 2932, 2905, 1738, 1733, 1393, 1366 cm^{-1}. Anal. Calcd for $C_{18}H_{29}NO_6$ (355.43): C, 60.83; H, 8.22; N, 3.94. Found: C, 60.91; H, 8.52; N, 4.14.

Mismatched Cycloaddition to Levoglucosenone (1): Synthesis of 8 and 9. A solution of nitrone **5** (791 mg, 5.04 mmol) and levoglucosenone (**1**, 634 mg, 5.04 mmol) in toluene (10 mL) was stirred at room temperature for 7 h. After concentration under reduced pressure, purification of the crude reaction mixture by flash column chromatography (eluent petroleum ether/AcOEt, 2:3) gave pure **9** (R_f 0.48, 196 mg, 0.69 mmol, 17%) and pure **8** (R_f 0.37, 519 mg, 1.83 mmol, 36%). **8**, white solid: mp 101−103 °C; crystals for X-ray crystal structure determination were obtained by slow evaporation from diisopropyl ether. $[\alpha]^{26}_D$ −80.2 (c 0.77, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.20 (s, 1H, H-1), 4.82−4.81 (m, 1H, H-5), 4.30 (dd, J = 6.6, 1.5 Hz, 1H, H-4), 4.19−4.10 (m, 2H, H-1′, H-2′), 4.00−3.91 (m, 2H, Ha-6, Hb-6), 3.60 (d, J = 7.0 Hz, 1H, H-3), 3.27−3.00 (m, 2H, Ha-4′, Hb-4′), 2.00−1.70 (m, 2H, Ha-3′, Hb-3′), 1.19 (s, 9H, $(CH_3)_3C-O$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 198.0 (s, C-2), 100.4 (d, C-1), 78.1 (d, C-4), 74.2 (s, $(CH_3)_3C$-O), 73.4 (d, C-5), 70.8, 69.7 (2d, C-1′, C-2′), 65.4 (t, C-6), 53.6 (t, C-4′), 50.7 (d, C-3), 33.6 (t, C-3′), 28.1 (q, 3 C, $(CH_3)_3C-O$); MS, m/z (%) 283 (M^+, 16), 226 ($M^+ - t$Bu, 44), 209 (6), 96 (55), 58 (89), 55 (100); IR (KBr) 2983, 2937, 2881, 1741, 1366 cm^{-1}. Anal. Calcd for $C_{14}H_{21}NO_5$ (283.32): C, 59.35; H, 7.47; N, 4.94. Found: C, 59.51; H, 7.70; N, 5.05. **9**, white solid: mp 105−107 °C; crystals for X-ray crystal structure determination were obtained by slow evaporation from AcOEt. $[\alpha]^{25}_D$ −148.9 (c 0.48, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.17 (s, 1H, H-1), 4.76 (d, J = 5.3 Hz, 1H, H-5), 4.27 (ddd, J = 6.4, 4.0, 2.1 Hz, 1H, H-2′), 4.17 (d, J = 7.9 Hz, 1H, H-4), 3.90 (dd, J = 7.7, 5.5 Hz, 1H, Ha-6), 3.86 (dd, J = 7.7, 1.0 Hz, 1H, Hb-6), 3.81 (dd, J = 9.3, 4.0 Hz, 1H, H-1′), 3.68 (dd, J = 8.8, 8.4 Hz, 1H, H-3), 3.41 (ddd, J = 13.8, 7.8, 2.1 Hz, 1H, Ha-3′), 3.24 (ddd, J = 13.8, 10.5, 7.5 Hz, 1H, Hb-3′), 2.40−2.33 (m, 1H, Ha-4′), 1.74−1.69 (m, 1H, Hb-3′), 1.16 (s, 9H, $(CH_3)_3C-O$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 196.5 (s, C-2), 100.1 (d, C-1), 77.2 (d), 76.6 (d), 74.1 (s, $(CH_3)_3C-O$), 73.2 (d), 65.5 (t, C-6), 54.1 (t, C-4′), 51.4 (d, C-3), 33.9 (t, C-3′), 28.7 (q, 3C, $(CH_3)_3C-O$); MS, m/z (%) 283 (M^+, 17), 226 ($M^+ - t$Bu, 64), 156 (36), 126 (67), 84 (61), 82 (67), 80 (100), 57 (74); IR (KBr) 2974, 2906, 1726 cm^{-1}. Anal. Calcd for $C_{14}H_{21}NO_5$ (283.32): C, 59.35; H, 7.47; N, 4.94. Found: C, 59.17; H, 7.48; N, 4.80.

Kinetic Resolution of Racemic 3: Synthesis of Adduct 10. A solution of nitrone (±)-**3** (53.4 mg, 0.34 mmol) and levoglucosenone (**1**, 21.4 mg, 0.17 mmol) in toluene (0.34 mL) was stirred at room temperature for 2 h. After concentration under reduced pressure, purification of the crude reaction mixture by flash column chromatography with an eluent of increasing polarity afforded pure **10** (R_f 0.23, eluent pentane/AcOEt, 3:2, 21 mg, 0.074 mmol, 22%) and the recovered (+)-**3** (R_f 0.29, eluent AcOEt/MeOH, 15:1, 27 mg, 0.172 mmol, 50%). **10**, white solid: mp 136−138 °C; $[\alpha]^{25}_D$ +21.4 (c 0.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.22 (s, 1H, H-1), 4.91−4.87 (m, 1H, H-3′), 4.82−4.80 (m, 1H, H-5), 4.76 (dd, J = 6.5, 1.7 Hz, 1H, H-2′), 4.35 (d, J = 8.4 Hz, 1H, H-4), 3.93 (dd, J = 5.9, 1.6 Hz, 1H, H-1′), 3.90−3.88 (m, 2H, Ha-6, Hb-6), 3.45 (dd, J = 12.9, 2.1 Hz, 1H, Ha-4′), 3.12 (dd, J = 8.1, 6.0 Hz, 1H, H-3), 3.08 (dd, J = 12.9, 5.5 Hz, 1H, Hb-4′), 1.51 (s, 3 H, $(CH_3)_2C$), 1.31 (s, 3H, $(CH_3)_2C$); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 196.0 (s, C-2), 112.7 (s, $(CH_3)_2C$), 99.6 (d, C-1), 82.4 (d, C-2′), 79.2 (d, C-3′), 76.1 (d, C-4), 75.6 (d, C-1′), 74.7 (d, C-5), 65.7 (t, C-6), 59.3 (t, C-4′), 51.4 (d, C-3), 26.6 (q, $(CH_3)_2C$), 25.0 (q, $(CH_3)_2C$); MS, m/z (%) 283 (M^+, 100), 268 (M^+ − Me, 34), 183 (55), 110 (71), 82 (59), 55 (85); IR (KBr) 2979, 2926, 1732, 1376, 1114 cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO_6$ (283.28): C, 55.12; H, 6.05; N, 4.94. Found: C, 55.51; H, 6.29; N, 4.60.

Parallel Kinetic Resolution (PKR) of Racemic 3: Synthesis of Compounds 10 and 11. A solution of nitrone (±)-**3** (126 mg, 0.80 mmol), levoglucosenone (**1**, 51.0 mg, 0.40 mmol), and isolevoglucosenone (**2**, 51.0 mg, 0.40 mmol) in toluene (1 mL) was stirred at room temperature for 2 h. After concentration under reduced pressure. Purification of the crude reaction mixture by flash column chromatography afforded pure **11** (R_f 0.4, eluent pentane/AcOEt, 2:3, 100 mg, 0.35 mmol, 44%) and pure **10** (R_f 0.35, eluent pentane/AcOEt, 2:3, 75 mg, 0.26 mmol, 32%).

Acknowledgment. We thank Cassa di Risparmio di Firenze for granting a 400 MHz spectrometer. This work was supported by a research grant from the University of Florence (Progetto Giovani Ricercatori 2002) and by MiUR- Rome project PRIN 2005032057.

Supporting Information Available: General Experimental Methods, experimental procedures for the preparation of compounds **1** and **12**−**19**, crystallographic information files (CIFs) for compounds **8** and **9**, and copies of ^{1}H and ^{13}C NMR spectra of all new pure compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO702403B