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Sequential Nucleophilic Addition/Intramolecular Cycloaddition to Chiral Nonracemic Cyclic Nitrones: A Highly Stereoselective Approach to Polyhydroxynortropane Alkaloids

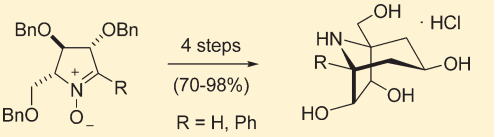
Ignacio Delso,[†,‡] Tomás Tejero,[‡] Andrea Goti,[*,§] and Pedro Merino[*,‡]

[†]Servicio de Resonancia Magnetica Nuclear, CEQMA and [‡]Departamento de Quimica Organica, Instituto de Sintesis Quimica y Catalisis Homogenea (ISQCH), Universidad de Zaragoza, CSIC, 50009 Zaragoza, Aragón, Spain

[§]Dipartimento di Chimica Organica "Ugo Schiff", Università di Firenze, ICCOM-CNR, via della Lastruccia 13, 50019 Sesto Fiorentino (FI), Italy

Supporting Information

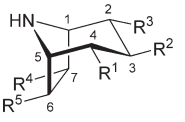
ABSTRACT: Two new polyhydroxylated nortropane analogues closely related with Calystegines have been prepared in excellent chemical yields and complete selectivity. A synthetic strategy based on consecutive nucleophilic allylation, oxidation, and intramolecular dipolar cycloaddition was developed. The formation of key intermediate cycloadducts were observed to take place through the recently confirmed thermally induceded 2-aza-Cope rearrangement of nitrones.



Calystegines are a class of polyhydroxylatednortropane alkaloids that have been isolated from plants in the Convolvulaceae, Solanaceae, and Moraceae families, and they have been shown to strongly inhibit glycosidases (Figure 1).[1]

It has been well-demonstrated for mono- and bicyclic polyhydroxylated alkaloids (e.g., pyrrolidines, indolizidines, and pyrrolizidines) that stereochemical modifications to any of the chiral centers of the molecule (including addition and/or elimination of hydroxyl groups) can dramatically change the biological activities toward the target glycosidases.[2] As a consequence, a considerable synthetic effort has been focused on the synthesis of naturally occurring calystegines.[3] However, much less effort has been devoted to addressing calystegine-type nortropanes.[4] A few syntheses have been reported so far using nitrones as key synthetic intermediates. Shing[5] and Tamayo[6] have used nitrones as early intermediates in the synthesis of calystegines forming the bicyclic system by intramolecular nucleophilic attack of nitrogen to a keto group in the last step, and Kaliappan has reported recently the synthesis of calystegine analogues based on addition of organometallics to a cyclic nitrone.[7] Syntheses of nortropane alkaloids using nitrones as intermediates have been reported by Black,[8] Tufariello,[9] and Davis,[10]

Here we report our own results in the field based on a combination of organometallic addition and intramolecular cycloaddition to nitrones applied for the first time to the synthesis of polyhydroxylated alkaloids. Additional experimental evidence for the 2-aza-Cope rearrangement of alkenyl nitrones[11] has been collected during this study. In order to access heavily hydroxylated nortropanes, we selected nitrone **1** (Scheme 1), readily prepared from D-arabinose in four steps,[12] for this study. The planned strategy involves allylation[13] of nitrone **1** followed by oxidation[14] and further intramolecular 1,3-dipolar cycloaddition of the resulting alkenyl nitrone.[8,15]



	R^1	R^2	R^3	R^4	R^5
A_3	OH	OH	H	H	H
A_5	H	OH	OH	H	H
A_6	OH	H	H	H	OH
B_1	OH	OH	H	OH	H
B_2	OH	OH	OH	H	H
C_1	OH	OH	OH	OH	H

Figure 1. Calystegines isolated from natural sources (numbering is indicated).

Allylation of **1** was carried out at 0 °C with an excess (3.0 equiv) of allylmagnesium bromide and furnished hydroxylamine **2** with complete diastereoselectivity and excellent chemical yield.[16] The relative stereochemistry of the newly generated stereogenic center was confirmed by 2D NMR (NOESY and COSY) experiments. Consistent with our previous reports concerning nucleophilic additions to **1** and related nitrones,[17] the observed high diastereofacial selectivity may be rationalized by steric effects which concur to favor attack of the Grignard reagent on the less hindered *Re* face of the nitrone, *anti* to the vicinal benzyloxy substituent.[18] Oxidation of **2** with manganese(IV) oxide[19] gave nitrone **3** in 73% yield. In addition, the regioisomeric nitrone **4** (24%) and isomerized nitrone **5** (3%) were obtained (Scheme 1). When nitrone **3** was heated in a sealed tube in toluene at 120 °C for 14 h, the cycloadduct **6** was obtained in 97% yield, with complete regio- and stereocontrol, as the only product of the reaction. The configurational assignment of **6** was achieved by careful analyses of 1D and 2D NMR spectra. Catalytic hydrogenolysis (10% $Pd(OH)_2$−C) in acidic methanol furnished the hydrochloride **7** in quantitative yield (Scheme 1).

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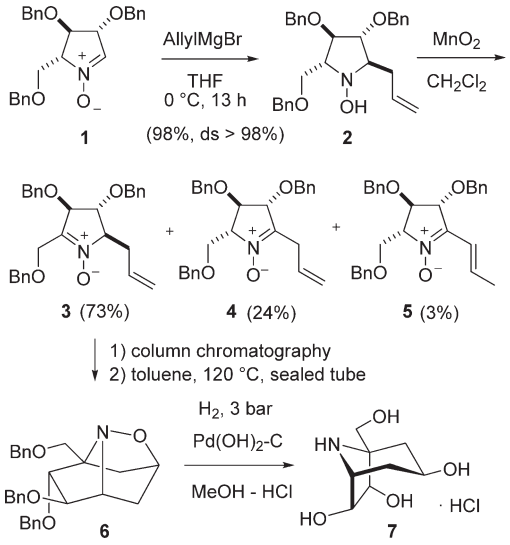
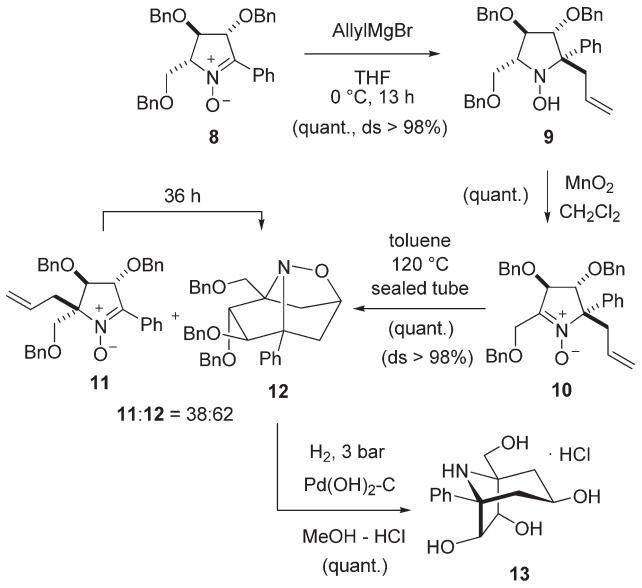
Scheme 1. Synthesis of Polyhydroxylated Nortropane



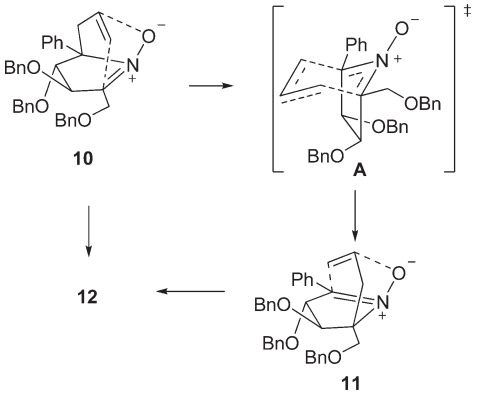
Scheme 2. Synthesis of Phenyl-Substituted Nortropane



In order to study the generality of the process and exploit molecular diversity by introducing an additional substituent at the bridgehead C-5 (calystegine's numbering), the above protocol was applied to the nitrone **8** which was prepared by addition of phenylmagnesium bromide to **1** and subsequent oxidation as described.[20] Allylation of **8** in THF at 0 °C afforded the hydroxylamine **9** in quantitative yield as the only diastereomer. Again, the configurational assignment of **9**, ascertained by NMR techniques, was in agreement with attack to the less hindered *Re* face. In this case, the oxidation of **9** with MnO_2 afforded in quantitative yield only the expected nitrone **10**, as a consequence of C-2 being a quaternary carbon atom (Scheme 2).

Upon heating in toluene at 120 °C in a sealed tube for 14 h, complete conversion of **10** was observed. In contrast to the behavior of **3**, formation of nitrone **11** was also observed in addition to the expected adduct **12**, the ratio **11**:**12** being 38:62.

Scheme 3. Synthesis of Phenyl-Substituted Nortropane



The formation of nitrone **11** is consistent with a thermally promoted 2-aza-Cope rearrangement of nitrone **10** through the cyclic transition state **A** (Scheme 3). The same rearrangement has been detected rarely for both cyclic and acyclic nitrones.[11] We have demonstrated both theoretically and experimentally that the energy barrier of the rearrangement is comparable to that required for the intramolecular cycloaddition.[11] Isolation of nitrone **11** constitutes another clear experimental evidence for such rearrangement. In the case of nitrone **10** the driving force responsible for the rapid formation of **11** is the enhanced stability of the latter due to the conjugation between the nitrone functionality and the phenyl group. The allyl group may migrate only on one face of the nitrone due to its cyclic structure, thus producing a unique stereoisomer. Therefore, this rearrangement may be used in principle for synthesizing nitrones hardly accessible by other means. Indeed, milder heating of **10** at 80 °C furnished the isomeric nitrone **11** as the only product.

From a synthetic point of view, the formation of nitrone **11** is not problematic since intramolecular 1,3-dipolar cycloaddition of **11** would afford the same adduct **12** (Scheme 3). Isomeric nitrones **10** and **11** are connected by chairlike six-membered transition state **A**, corresponding to allylic fragment rearrangement, as demonstrated through theoretical calculations.[11] Indeed, prolonged heating (36 h) of the reaction mixture led to cycloadduct **12** in quantitative yield. Finally, catalytic hydrogenation of **12** under acidic conditions afforded, in quantitative yield, 1-phenyl-*nor*-tropane derivative **13** which was isolated and characterized as the corresponding hydrochloride salt. It is worthy to note that a 5-phenylnortropane related to **13** underwent reductive ring-opening to the corresponding aminocycloheptane by catalytic hydrogenation with Pd/C under similar pressure (40 psi).[8c]

In summary, we have reported a versatile method for the synthesis of polyhydroxylated nortropane analogues related to calystegines, substituted at both bridgehead carbon atoms with defined configuration. These patterns of substitution are otherwise difficult to obtain, and the methodology described here is expected to find further application in the synthesis of nortropane alkaloids.

EXPERIMENTAL SECTION

General Methods. The reaction flasks and other glass equipment were heated in an oven at 130 °C overnight and assembled in a stream of Ar. All reactions were monitored by TLC on silica gel 60 F254; the

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position of the spots was detected with 254 nm UV light or by spraying with one of the following staining systems: 50% methanolic sulfuric acid, 5% ethanolic phosphomolybdic acid, or iodine. Preparative centrifugally accelerated radial thin-layer chromatography (radial chromatography) was performed with solvents that were distilled prior to use; the rotors (1 or 2 mm layer thickness) were coated with silica gel TLC grade with binder and fluorescence indicator, and the eluting solvents were delivered by the pump at a flow rate of 0.5−1.5 mL min^{-1}. Column chromatography was carried out in a MPLC system using silica gel 60 μm. Melting points were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on 400 or 500 instruments in the stated solvent. Chemical shifts are reported in ppm (δ) relative to $CHCl_3$ (δ = 7.26) in $CDCl_3$. Peak assignments were made on the basis of standard COSY and NOESY experiments and according to numbering represented in Figure 1 for compounds **7** and **13**.

(2*R*,3*R*,4*R*,5*R*)-2-Allyl-3,4-bis(benzyloxy)-5-(benzyloxymethyl)pyrrolidin-1-ol (2). To a cooled (0 °C) solution of nitrone **1** (1.0 g, 2.4 mmol) in anhydrous THF (30 mL) was added allylmagnesium bromide (7.2 mL of a 1 M solution in THF, 7.2 mmol) dropwise. After the solution was stirred for 13 h at 0 °C, the reaction was quenched with satd aq NH_4Cl (20 mL). The reaction mixture was diluted with diethyl ether (20 mL), the organic layer was separated, and the aqueous layer was extracted with diethyl ether (2 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, and filtered, and the solvent was eliminated under reduced pressure to afford the crude product which was purified by radial chromatography (hexane−EtOAc, 7:3) to give pure **2** (1.15 g, 98%) as an oil: R_f (hexane−EtOAc, 7:3) = 0.55; $[\alpha]^{22}_D$ = −3 (*c* 0.815, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27−2.37 (m, 1H, $CH_2CH{=}CH_2$), 2.66−2.75 (m, 1H, $CH_2CH{=}CH_2$), 3.37 (dt, *J* = 8.5, 5.1 Hz, 1H, H_2), 3.52−3.57 (m, 1H, H_5), 3.65 (dd, *J* = 9.6, 6.5 Hz, 1H, CH_2OH), 3.80 (dd, *J* = 9.6, 5.2 Hz, 1H, CH_2OH), 3.86 (dd, *J* = 4.8, 2.5 Hz, 1H, H_3), 3.97 (dd, *J* = 4.2, 2.5 Hz, 1H, H_4), 4.45 (d, *J* = 11.8 Hz, 1H, CH_2Ph), 4.47 (d, *J* = 11.9 Hz, 1H, CH_2Ph), 4.51 (d, *J* = 11.8 Hz, 1H, CH_2Ph), 4.54 (d, *J* = 12.0 Hz, 1H, CH_2Ph), 4.54 (d, 1H, *J* = 12.0 Hz, 1H, CH_2Ph), 4.59 (d, *J* = 12.0 Hz, 1H, CH_2Ph), 5.07−5.15 (m, 2H, $CH_2CH{=}CH_2$), 5.86 (dddd, *J* = 16.9, 10.2, 7.5, 6.7 Hz, 1H, $CH_2CH{=}CH_2$), 7.27−7.38 (m, 15H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.6 ($CH_2CH{=}CH_2$), 68.4 (CH_2OBn), 69.5 (C_2), 69.9 (C_5), 71.7 (CH_2Ph), 71.7 (CH_2Ph), 73.4 (CH_2Ph), 84.2 (C_4), 85.3 (C_3), 117.1 ($CH_2CH{=}CH_2$), 127.6 (Ar), 127.7 (Ar), 127.7 (Ar), 127.9 (Ar), 127.9 (Ar), 128.3 (Ar), 128.3 (Ar), 128.4 (Ar), 135.5 ($CH_2CH{=}CH_2$), 138.1 (Ar), 138.2 (Ar), 138.5 (Ar). Anal. Calcd for $C_{26}H_{27}NO_4$: C, 74.80; H, 6.52; N, 3.35. Found: C, 74.73; H, 6.41; N, 3.24.

(2*R*,3*R*,4*R*)-2-Allyl-3,4-bis(benzyloxy)-5-(benzyloxymethyl)-3,4-dihydro-2*H*-pyrrole 1-Oxide (3), (2*R*,3*R*,4*R*)-5-Allyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-3,4-dihydro-2*H*-pyrrole 1-oxide (4), and (2*R*,3*R*,4*R*)-3,4-Bis(benzyloxy)-2-(benzyloxymethyl)-5-((E)-prop-1-enyl)-3,4-dihydro-2*H*-pyrrole 1-Oxide (5). To a cooled (0 °C) solution of **2** (0.919 g, 2 mmol) in CH_2Cl_2 (30 mL) was added activated manganese(IV) oxide (2.09 g, 2.4 mmol). portionwise After 15 min of stirring at 0 °C, the reaction mixture was warmed to room temperature, and stirring was continued until complete disappearance of the starting material (TLC, ca. 2 h). The reaction mixture was filtered through a pad of Celite and anhydrous $MgSO_4$, and the resulting filtrate was evaporated under reduced pressure to give the crude product which was purified by radial chromatography (hexane−EtOAc, 1:1) to give nitrones **3**, **4** and **5**.

3 (0.668 g, 73%): oil; R_f (hexane−EtOAc, 1:1) = 0.42; $[\alpha]^{25}_D$ = −62 (*c* 1.57, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (dddt, *J* = 14.2, 9.9, 7.9, 1.0 Hz, 1H, $CH_2CH{=}CH_2$), 2.85 (dddt, *J* = 14.2, 6.2, 3.7, 1.5 Hz, 1H, $CH_2CH{=}CH_2$), 3.79 (dd, *J* = 2.0, 1.1 Hz, 1H, H_3), 3.89 (ddd, *J* = 9.6, 3.3, 1.5 Hz, 1H, H_2), 4.29 (ddd, *J* = 14.6, 1.5, 1.2 Hz, 1H, CH_2OBn), 4.30 (d, *J* = 11.8 Hz, 1H, CH_2Ph), 4.35 (d, *J* = 11.8 Hz, 1H, CH_2Ph), 4.49 (s, 2H, CH_2Ph), 4.50 (d, *J* = 11.7 Hz, 1H, CH_2Ph), 4.57 (d, *J* = 11.7 Hz, 1H, CH_2Ph), 4.60 (dt, *J* = 14.6, 0.9 Hz, 1H, CH_2OBn), 4.62−4.64 (m, 1H, H_4), 5.02−5.05 (m, 1H, $CH_2CH{=}CH_2$), 5.06−5.08 (m, 1H, $CH_2CH{=}CH_2$), 5.65 (dddd, *J* = 16.6, 10.8, 7.9, 6.2 Hz, 1H, $CH_2CH{=}CH_2$), 7.17−7.31 (m, 15H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.4 ($CH_2CH{=}CH_2$), 62.7 (CH_2OBn), 71.4 (CH_2Ph), 72.5 (CH_2Ph), 73.6 (CH_2Ph), 78.5 (C_2), 79.8 (C_3), 82.8 (C_4), 119.2 ($CH_2CH{=}CH_2$), 127.8 (Ar), 128.0 (Ar), 128.0 (Ar), 128.0 (Ar), 128.1 (Ar), 128.5 (Ar), 128.6 (Ar), 132.5 ($CH_2CH{=}CH_2$), 137.0 (Ar), 137.4 (Ar), 137.5 (Ar), 142.6 (C_5). Anal. Calcd for $C_{29}H_{31}NO_4$: C, 76.12; H, 6.83; N, 3.06. Found: C, 76.33; H, 6.66; N, 2.92.

4 (0.22 g, 24%): R_f (hexane−EtOAc, 1:1) = 0.30; $[\alpha]^{25}_D$ = −35 (*c* 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.03 (ddq, *J* = 15.8, 7.3, 1.3 Hz, 1H, $CH_2CH{=}CH_2$), 3.34−3.41 (m, 1H, $CH_2CH{=}CH_2$), 3.76 (dd, *J* = 10.1, 3.3 Hz, 1H, CH_2OBn), 3.92 (dd, *J* = 10.1, 5.7 Hz, 1H, CH_2OBn), 3.59−4.03 (m, 1H, H_2), 4.16 (dd, *J* = 3.0, 1.8 Hz, 1H, H_3), 4.41 (d, *J* = 11.9 Hz, 1H, CH_2Ph), 4.42 (d, *J* = 12.0 Hz, 1H, CH_2Ph), 4.44 (d, *J* = 11.9 Hz, 1H, CH_2Ph), 4.45 (d, *J* = 11.7 Hz, 1H, CH_2Ph), 4.47 (d, *J* = 11.8 Hz, 1H, CH_2Ph), 4.52 (d, *J* = 12.0 Hz, 1H, CH_2Ph), 4.53−4.55 (m, 1H, H_4), 5.05 (ddd, *J* = 10.0, 2.8, 1.4 Hz, 1H, $CH_2CH{=}CH_2$), 5.09 (ddd, *J* = 17.3, 3.2, 1.6 Hz, 1H, $CH_2CH{=}CH_2$), 5.73 (dddd, *J* = 17.2, 10.0, 7.3, 6.3 Hz, 1H, $CH_2CH{=}CH_2$), 7.16 − 7.30 (m, 15H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.6 ($CH_2CH{=}CH_2$), 67.0 (CH_2OBn), 71.6 (CH_2Ph), 71.8 (CH_2Ph), 73.5 (CH_2Ph), 77.7 (C_3), 78.2 (C_2), 84.5 (C_4), 118.8 ($CH_2CH{=}CH_2$), 127.8 (Ar), 127.8 (Ar), 127.9 (Ar), 128.0 (Ar), 128.1 (Ar), 128.2 (Ar), 128.4 (Ar), 128.5 (Ar), 128.6 (Ar), 130.0 ($CH_2CH{=}CH_2$), 137.2 (Ar), 137.3 (Ar), 137.7 (Ar), 144.2 (C_5). Anal. Calcd for $C_{29}H_{31}NO_4$: C, 76.12; H, 6.83; N, 3.06. Found: C, 76.35; H, 6.98; N, 2.96.

5 (27.5 mg, 3%): R_f (hexane−EtOAc, 1:1) = 0.15; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.81 (dd, *J* = 7.5, 1.7 Hz, 3H, $CH{=}CHCH_3$), 3.83 (dd, *J* = 9.9, 3.7 Hz, 1H, CH_2OBn), 3.89 (dd, *J* = 9.9, 6.3 Hz, 1H, CH_2OBn), 4.03−4.08 (m, 1H, H_2), 4.23 (dd, *J* = 2.5, 1.4 Hz, 1H, H_3), 4.35 (d, *J* = 11.3 Hz, 1H, CH_2Ph), 4.41 (d, *J* = 11.3 Hz, 1H, CH_2Ph), 4.44 (d, *J* = 11.8 Hz, 1H, CH_2Ph), 4.49 (d, *J* = 11.8 Hz, 1H, CH_2Ph), 4.49 (d, *J* = 11.8 Hz, 1H, CH_2Ph), 4.55 (d, *J* = 11.8 Hz, 1H, CH_2Ph), 4.94 (s, 1H, H_4), 5.97 (dc, *J* = 12.0, 7.5 Hz, 1H, $CH{=}CHCH_3$), 6.41−6.47 (m, 1H, $CH{=}CHCH_3$), 7.06−7.31 (m, 15H, Ar).

6,7-Bis(benzyloxy)-1-benzyloxymethyl-3,8-epoxy-9-nortropane (6). A solution of nitrone **3** (0.457 g, 1 mmol) was dissolved in anhydrous toluene (25 mL), placed in a sealed tube, and heated at 120 °C under an argon atmosphere for 14 h, at which time the solvent was partially evaporated and the resulting solution was filtered through a pad of silica gel. After the silica was washed with diethyl ether, the resulting solution was evaporated under reduced pressure to afford **6** (0.443 g, 97%) as an oil that did not need any additional purification: $[\alpha]^{25}_D$ = −24 (*c* 0.39, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (dd, *J* = 11.7, 2.9 Hz, 1H, H_{4a}), 1.34 (ddd, *J* = 12.3, 5.0, 3.2 Hz, 1H, H_{2a}), 1.89 (d, *J* = 12.3 Hz, 1H, H_{2b}), 2.12 (dddd, *J* = 11.7, 10.4, 4.6, 3.0 Hz, 1H, H_{4b}), 3.26 (d, *J* = 10.3 Hz, 1H, CH_2OBn), 3.42 (d, *J* = 10.3 Hz, 1H, CH_2OBn), 3.54 (ddd, *J* = 10.5, 2.0, 0.8 Hz, 1H, H_5), 3.83 (d, *J* = 2.6 Hz, 1H, H_7), 4.27 (dd, *J* = 2.6, 1.1 Hz, 1H, H_6), 4.39 (d, *J* = 11.9 Hz, 1H, CH_2Ph), 4.43 (d, *J* = 11.8 Hz, 1H, CH_2Ph), 4.44 (d, *J* = 12.2 Hz, 1H, CH_2Ph), 4.47 (d, *J* = 11.8 Hz, 1H, CH_2Ph), 4.51 (d, *J* = 11.9 Hz, 1H, CH_2Ph), 4.64−4.68 (m, 2H, H_3, CH_2Ph), 7.15−7.28 (m, 15H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.1 (C_2), 39.7 (C_4), 67.3 (C_5), 71.4 (CH_2Ph), 72.2 (CH_2Ph), 72.7 (CH_2OBn), 73.5 (CH_2Ph), 76.8 (C_1), 79.0 (C_3), 83.0 (C_6), 86.9 (C_7), 127.5 (Ar), 127.7 (Ar), 127.7 (Ar), 127.8 (Ar), 127.9 (Ar), 127.9 (Ar), 128.2 (Ar), 128.3 (Ar), 128.4 (Ar), 137.8 (Ar), 138.2 (Ar), 138.4 (Ar). Anal. Calcd for $C_{29}H_{31}NO_4$: C, 76.12; H, 6.83; N, 3.06. Found: C, 76.38; H, 6.87; N, 2.96.

(3*S*,5*R*,6*R*)-1-(Hydroxymethyl)-8-azabicyclo[3.2.1]octane-3,6,7-triol Hydrochloride (7). A solution of cycloadduct **6** (0.2 g, 0.44 mmol) in methanol (10 mL) was treated with $Pd(OH)_2$−C (350 mg)

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and hydrochloric acid (0.5 mL). The resulting mixture was stirred under 3 bar of hydrogen for 6 h. The catalyst was eliminated by filtration through a pad of Celite, the filtrate was treated with 3 M HCl in methanol, and the resulting solution was stirred at room temperature for additional 10 min. The solvent was eliminated under reduced pressure to afford pure **7** (0.1 g, quant) as a white solid: mp >150 °C dec; $[\alpha]26_D$ = +10 (*c* 0.15, H_2O); ^{1}H NMR (400 MHz, D_2O, 60 °C) δ 1.58 (dd, *J* = 14.0, 10.7 Hz, 1H, H_{2a}), 1.68 (ddd, *J* = 14.3, 11.3, 3.2 Hz, 1H, H_{4a}), 2.08 (ddd, *J* = 13.8, 6.0, 1.0 Hz, 1H, H_{2b}), 2.27 (dddd, *J* = 5.7, 4.9, 3.0, 1.4 Hz, 1H, H_{4b}), 3.60 (d, *J* = 12.9 Hz, 1H, CH_2OH), 3.63 (d, *J* = 13.0 Hz, 1H, CH_2OH), 3.74 (t, *J* = 3.0 Hz, 1H, H_5), 4.03−4.05 (m, 1H, H_6), 4.05−4.11 (m, 2H, H_3, H_7); ^{13}C NMR (100 MHz, D_2O) δ 33.2 (C_2), 34.0 (C_4), 61.0 (C_3), 61.4 (CH_2OH), 61.7 (C_5), 69.2 (C_1), 78.1 (C_7), 78.4 (C_6). Anal. Calcd for $C_8H_{16}ClNO_4$: C, 42.58; H, 7.15; N, 6.21. Found: C, 42.76; H, 7.35; N, 6.10.

(2*S*,3*R*,4*R*,5*R*)-2-Allyl-3,4-bis(benzyloxy)-5-(benzyloxymethyl)-2-phenylpyrrolidin-1-ol (9). The reaction of **8** (0.987 g, 2 mmol) with allylmagnesium bromide (6 mL of a solution 1.0 M in hexanes, 6 mmol), as described above for nitrone **1** to give **2**, afforded pure **9** (1.07 g, quant): oil; $[\alpha]^{23}_D$ = −68 (*c* 0.60, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.84 (ddt, *J* = 15.0, 7.5, 1.3 Hz, 1H, CH_2CHCH_2), 3.17 (ddt, *J* = 15.0, 1.3 Hz, 1H, $CH_2CH{=}CH_2$), 3.64 (c, *J* = 5.4 Hz, 1H, H_5), 3.74 (dd, *J* = 9.7, 5.2 Hz, 1H, CH_2OBn), 3.81 (d, *J* = 5.6 Hz, 1H, H_4), 3.82 (dd, *J* = 11.2, 5.6 Hz, 1H, CH_2OBn), 3.98 (d, *J* = 2.0 Hz, 1H, H_3), 4.02 (d, *J* = 11.5 Hz, 1H, CH_2Ph), 4.11 (d, *J* = 11.5 Hz, 1H, CH_2Ph), 4.55 (s, 1H, NO*H*), 4.61 (s, 2H, CH_2Ph), 4.81 (s, 2H, CH_2Ph), 5.00−5.14 (m, 2H, $CH_2CH{=}CH_2$), 5.95 (dddd, *J* = 16,9, 10.2, 7.4, 6.6 Hz, 1H, $CH_2CH{=}CH_2$), 6.86 − 9.91 (m, 2H, Ar), 7.18−7.39 (m, 16H, Ar), 7.54−7.59 (m, 2H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.7 ($CH_2CH{=}CH_2$), 61.5 (C_2), 69.1 (C_5), 71.1 (CH_2OBn), 71.8 (CH_2Ph), 72.0 (CH_2Ph), 73.4 (CH_2Ph), 82.7 (C_4), 86.4 (C_3), 117.5 ($CH_2CH{=}CH_2$), 126.5 (Ar), 127.6 (Ar), 127.6 (Ar), 127.6 (Ar), 127.7 (Ar), 127.8 (Ar), 128.1 (Ar), 128.1 (Ar), 128.4 (Ar), 128.6 (Ar), 136.2 ($CH_2CH{=}CH_2$), 137.5 (Ar), 138.1 (Ar), 138.3 (Ar), 140.9 (Ar). Anal. Calcd for $C_{35}H_{37}NO_4$: C, 78.48; H, 6.96; N, 2.61. Found: C, 78.52; H, 6.81; N, 2.87.

(2*S*,3*R*,4*R*)-2-Allyl-3,4-bis(benzyloxy)-5-(benzyloxymethyl)-2-phenyl-3,4-dihydro-2*H*-pyrrole 1-Oxide (10). The oxidation of **9** (1.07 g, 2 mmol), as described above for hydroxylamine **2** to give **3**, afforded pure **10** (1.07 g, quant) as an oil: $[\alpha]^{21}_D$ = −91 (*c* 0.16, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.85 (dd, *J* = 14.3, 8.8 Hz, 1H, $CH_2CH{=}CH_2$), 3.34 (ddt, *J* = 14.3, 5.1, 1.4 Hz, 1H, $CH_2CH{=}CH_2$), 4.31 (d, *J* = 4.5 Hz, 1H, H_3), 4.37 (d, *J* = 0.9 Hz, 2H, CH_2Ph), 4.41 (dd, *J* = 13.4, 1.4 Hz, 1H, CH_2OBn), 4.63 (d, *J* = 11.2 Hz, 1H, CH_2Ph), 4.65 (d, *J* = 11.2 Hz, 1H, CH_2Ph), 4.72 (d, *J* = 11.7 Hz, 1H, CH_2Ph), 4.74 (d, *J* = 11.5 Hz, 1H, CH_2Ph), 4.81 (dd, *J* = 15.3, 4.5 Hz, 1H, H_4), 4.87 (d, *J* = 13.8 Hz, 1H, CH_2OBn), 5.14 (d, *J* = 17.0 Hz, 1H, $CH_2CH{=}CH_2$), 5.23 (d, *J* = 10.1 Hz, 1H, $CH_2CH{=}CH_2$), 5.78 (dddd, *J* = 17.1, 10.2, 8.8, 5.2 Hz, 1H, $CH_2CH{=}CH_2$), 7.01−7.06 (m, 2H, Ar), 7.26−7.46 (m, 18H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 39.7 ($CH_2CH{=}CH_2$), 61.5 (CH_2OBn), 72.4 (CH_2Ph), 73.2 (CH_2Ph), 73.8 (CH_2Ph), 82.7 (C_3), 83.1 (C_4), 83.7 (C_2), 120.8 ($CH_2CH{=}CH_2$), 127.9 (Ar), 127.9 (Ar), 128.0 (Ar), 128.0 (Ar), 128.0 (Ar), 128.2 (Ar), 128.3 (Ar), 128.4 (Ar), 128.5 (Ar), 128.5 (Ar), 131.9 ($CH_2CH{=}CH_2$), 135.8 (Ar), 137.2, (Ar) 137.5 (Ar), 137.6 (Ar), 144.0 (C_5). Anal. Calcd for $C_{35}H_{35}NO_4$: C, 78.77; H, 6.61; N, 2.62. Found: C, 78.90; H, 6.70; N, 2.85.

(1*R*,3*S*,5*S*,6*S*,7*R*)-6,7-Bis(benzyloxy)-1-benzyloxymethyl-3,8-epoxy-5-phenyl-9-nortropane (12). Heating of **10** (0.2 g, 0.36 mmol), as described above for nitrone **3** to give **6**, but for 36 h, afforded pure **12** (0.2 g, quant) as an oil: R_f (EtOAc) = 0.54; $[\alpha]^{26}_D$ = +2 (*c* 0.416, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.61−1.66 (m, 1H, H_{2a}), 2.13 (d, *J* = 11.8 Hz, 1H, H_{4a}), 2.30 (d, *J* = 11.9 Hz, 1H, H_{2b}), 2.53 (ddd, *J* = 11.7, 4.7, 3.0 Hz, 1H, H_1),3.59 (d, *J* = 10.2 Hz, 1H, CH_2OBn), 3.77 (d, *J* = 10.2 Hz, 1H, CH_2OBn), 4.07 (d, *J* = 11.8 Hz, 1H, CH_2Ph), 4.12 (s, 1H, H_6), 4.19 (d, *J* = 11.8 Hz, 1H, CH_2Ph), 4.35 (s, 1H, H_7), 4.56 (d, *J* = 11.8 Hz, 1H, CH_2Ph), 4.66 (d, *J* = 11.8 Hz, 1H, CH_2Ph), 4.67 (d, *J* = 12.0 Hz, 1H, CH_2Ph), 4.84−4.89 (m, 2H, H_5, CH_2Ph),6.81 − 6.87 (m, 2H, Ar), 7.20−7.45 (m, 16H, Ar), 7.55 (d, *J* = 7.5 Hz, 2H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 37.8 (C_2), 47.3 (C_4), 71.7 (CH_2Ph), 72.1 (CH_2Ph), 73.8 (CH_2Ph), 74.7 (CH_2OBn), 75.7 (C_1), 79.0 (C_5), 80.5 (C_3), 84.4 (C_7), 88.2 (C_6), 126.5 (Ar), 127.4 (Ar), 127.5 (Ar), 127.6 (Ar), 127.7 (Ar), 127.8 (Ar), 127.9 (Ar), 128.0 (Ar), 128.1 (Ar), 128.4 (Ar), 128.4 (Ar), 137.7 (Ar), 138.2 (Ar), 138.5 (Ar), 143.2 (Ar). Anal. Calcd for $C_{35}H_{35}NO_4$: C, 78.77; H, 6.61; N, 2.62. Found: C, 78.83; H, 6.460; N, 2.78.

(2*R*,3*R*,4*R*)-2-Allyl-3,4-bis(benzyloxy)-2-(benzyloxymethyl)-5-phenyl-3,4-dihydro-2*H*-pyrrole 1-Oxide (11) and (1*R*,3*S*,5*S*,6*S*,7*R*)-6,7-Bis(benzyloxy)-1-benzyloxymethyl-3,8-epoxy-5-phenyl-9-nortropane (12). A solution of nitrone **10** (0.533 g, 1 mmol) was dissolved in anhydrous toluene (25 mL), placed in a sealed tube, and heated at 120 °C under an argon atmosphere for 14 h, at which time the solvent was partially evaporated and the resulting solution was filtered through a pad of silica gel. After the silica was washed with diethyl ether, the resulting solution was evaporated under reduced pressure, and the residue was purified by radial chromatography using hexane−EtOAc 4:1 as an eluant to afford a 38:62 mixture of compounds **11** and **12**, respectively, in quantitative yield.

11 (0.202 g, 38%): oil; R_f (hexane−EtOAc, 4:1) = 0.36; $[\alpha]^{23}_D$ = +8 (*c* 0.35, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.54 (d, *J* = 7.1 Hz, 2H, $CH_2CH{=}CH_2$), 3.53 (d, *J* = 10.2 Hz, 1H, CH_2OBn), 4.22 (d, *J* = 10.2 Hz, 1H, CH_2OBn), 4.33 (d, *J* = 11.5 Hz, 1H, CH_2Ph), 4.50 (d, *J* = 11.7 Hz, 1H, CH_2Ph), 4.51 (d, *J* = 11.5 Hz, 1H, CH_2Ph), 4.67 (d, *J* = 11.2 Hz, 1H, CH_2Ph), 4.69 (d, *J* = 11.5 Hz, 1H, CH_2Ph), 4.74 (d, *J* = 11.8 Hz, 1H, CH_2Ph), 4.80 (d, *J* = 4.3 Hz, 1H, H_3), 5.01 (dd, *J* = 10.2, 2.0 Hz, 1H, $CH_2CH{=}CH_2$), 5.15 (ddt, *J* = 17.1, 2.1, 1.2 Hz, 1H, $CH_2CH{=}CH_2$), 5.33 (d, *J* = 4.3 Hz, 1H, H_4), 5.82 (ddt, *J* = 17.4, 10.1, 7.3 Hz, 1H, $CH_2CH{=}CH_2$), 7.10−7.13 (m, 2H, Ar), 7.26 −7.32 (m, 8H, Ar), 7.34−7.41 (m, 5H, Ar), 7.43−7.47 (m, 3H, Ar), 8.41−8.45 (m, 2H, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.9 ($CH_2CH{=}CH_2$), 68.5 (CH_2Ph), 71.2 (CH_2OBn), 72.8 (CH_2Ph), 73.6 (CH_2Ph), 78.5 (C_3), 82.1 (C_2), 83.7 (C_4), 120.1 ($CH_2CH{=}CH_2$), 127.7 (Ar), 127.7 (Ar), 127.8 (Ar), 127.8 (Ar), 128.0 (Ar), 128.0 (Ar), 128.2 (Ar), 128.3 (Ar), 128.4 (Ar), 128.5 (Ar), 130.2 (Ar), 131.7 ($CH_2CH{=}CH_2$), 137.6 (Ar), 137.7 (Ar), 137.8 (Ar), 139.1 (C_5). Anal. Calcd for $C_{35}H_{35}NO_4$: C, 78.77; H, 6.61; N, 2.62. Found: C, 78.54; H, 6.40; N, 2.45.

12 (0.331 g, 62%). The physical and spectroscopic properties were identical to those of the same compound obtained by heating at 120 °C for 36 h as described above.

(3*S*,5*S*,6*R*)-1-(Hydroxymethyl)-5-phenyl-8-azabicyclo[3.2.1]-octane-3,6,7-triol (13). The hydrogenation of **12** (0.533 g, 1 mmol), as described above for cycloadduct **6** to give **8**, afforded pure **13** (0.3 g, quant) as a white solid: mp >150 °C dec; $[\alpha]^{27}_D$ = +21 (*c* 0.34, H_2O); ^{1}H NMR (500 MHz, D_2O) δ 1.77−1.86 (m, 2H, H_{2a}, H_{4a}), 2.24 (dd, *J* = 13.9, 5.9 Hz, 1H, H_{4b}), 2.63 (dd, *J* = 14.1, 5.9 Hz, 1H, H_{2b}), 3.81 (d, *J* = 12.9 Hz, 1H, CH_2OH), 3.84 (d, *J* = 12.9 Hz, 1H, CH_2OH), 4.15 (s, 1H, H_7), 4.41 (tt, *J* = 11.4, 6.0 Hz, 1H, H_3), 4.50 (s, 1H, H_6), 7.26 (d, 1H, *J* = 7.5 Hz, Ar), 7.39 (t, 1H, *J* = 7.4 Hz, Ar), 7.47 (t, 1H, *J* = 7.6 Hz, Ar); ^{13}C NMR (100 MHz, D_2O) δ 32.6 (C_4), 44.6 (C_2), 61.2 (C_3), 62.8 (CH_2OH), 68.3, 71.8 (C_5), 79.7 (C_7), 80.4 (C_6), 125.1 (Ar), 128.3 (Ar), 128.9 (Ar), 136.3 (Ar). Anal. Calcd for $C_{14}H_{20}ClNO_4$: C, 55.72; H, 6.68; N, 4.64. Found: C, 55.83; H, 6.45; N, 4.86.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. ^{1}H and ^{13}C NMR spectra of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author
*E-mail: pmerino@unizar.es, andrea.goti@unifi.it.

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REFERENCES

(1) (a) Biastoff, S.; Draeger, B. In *The Alkaloids: Chemistry and Biology*; Cordell, G. A., Ed.; Academic Press: Oxford, 2007; Vol. 64, pp 49−102. (b) Draeger, B. *Nat. Prod. Rep.* **2004**, *21*, 211–223. (c) Molyneux, R. J.; Nash, R. J.; Asano, N. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon Press: Oxford, 1996; Vol. 11, pp 303−343.

(2) For recent examples and reviews, see: (a) Pandey, G.; Grahacharya, D.; Shashidhara, K. S.; Khan, M. I.; Puranik, V. C. *Org. Biomol. Chem.* **2009**, *7*, 3300–3307. (b) Li, R.; Bols, M.; Rousseau, C.; Zhang, X.-G.; Wang, R. W.; Qing, F. L. *Tetrahedron* **2009**, *65*, 3717–3727. (c) D'Alonzo, D.; Guaragna, A.; Palumbo, G. *Curr. Med. Chem.* **2009**, *16*, 473–505. (d) Baumann, D.; Bennis, K.; Ripoche, I.; Thery, V.; Troin, Y. *Eur. J. Org. Chem.* **2008**, 5289–5300. (e) Alam, M. A.; Kumar, A.; Vankar, Y. D. *Eur. J. Org. Chem.* **2008**, 4972–4980.

(3) (a) Boyer, F.-D.; Lallemand, J.-Y. *Tetrahedron* **1994**, *50*, 10443–10458. (b) Asano, N.; Kato, A.; Kizu, H.; Matsui, K.; Griffiths, R. C.; Jones, M. G.; Watson, A. A.; Nash, R. J. *Carbohydr. Res.* **1997**, *304*, 173–178. (c) Boyer, F. D.; Hanna, I. *Tetrahedron Lett.* **2001**, *42*, 1275–1277. (d) Skaanderup, P. R.; Madsen, R. *Chem. Commun.* **2001**, 1106–1107. (e) Marco-Contelles, J.; de Opazo, E. *J. Org. Chem.* **2002**, *67*, 3705–3717. (f) Koulocheri, S. D.; Pitsinos, E. N.; Haroutounian, S. A. *Synthesis* **2002**, 1707–1710. (g) Skaanderup, P. R.; Madsen, R. *J. Org. Chem.* **2003**, *68*, 2115–2122. (h) Garcia-Moreno, M. I.; Mellet, C. O.; Fernandez, J. M. G. *Eur. J. Org. Chem.* **2004**, 1803–1819. (i) Csuk, R.; Prell, E.; Reissmann, S. *Tetrahedron* **2008**, *64*, 9417–9422. (j) Chen, Y.-L.; Redlich, H.; Bergander, K.; Froelich, R. *Org. Biomol. Chem.* **2007**, *20*, 3330–3339. (k) Monrad, R. N.; Pipper, C. B.; Madsen, R. *Eur. J. Org. Chem.* **2009**, 3387–3395. (l) Chagnault, V.; Compain, P.; Lewinski, K.; Ikeda, K.; Asano, N.; Martin, O. R. *J. Org. Chem.* **2009**, *74*, 3179–3182. (m) Moosophon, P.; Baird, M. C.; Kanokmedhakul, S.; Pyne, S. G. *Eur. J. Org. Chem.* **2010**, 3337–3344. (n) Moosophon, P.; Baird, M. C.; Kanokmedhakul, S.; Pyne, S. G. *Eur. J. Org. Chem.* **2010**, 3337–3344.

(4) (a) Garcia-Moreno, M. I.; Benito, J. M.; Ortiz Mellet, C.; Garcia Fernandez, J. M. *J. Org. Chem.* **2001**, *66*, 7604–7614. (b) Garcia-Moreno, M. I.; Mellet, C. O.; Garcia Fernandez, J. M. *Tetrahedron* **2007**, *63*, 7879–7884. (c) Aguilar, M.; Gloster, T. M.; Garcia-Moreno, M. I.; Mellet, C. O.; Davies, G. J.; Llebaria, A.; Casas, J.; Egido-Gabas, M.; Fernandez, J. M. G. *ChemBioChem* **2008**, *9*, 2612–2618. (d) Chagnault, V.; Compain, P.; Lewinski, K.; Ikeda, K.; Asano, N.; Martin, O. R. *J. Org. Chem.* **2009**, *74*, 3179–3182.

(5) Shing, T. K. M.; Wong, W. F.; Ikeno, T.; Yamada, T. *Org. Lett.* **2007**, *9*, 207–209.

(6) Lo, Re, D.; Franco, F.; Sanchez-Cantalejo, F.; Tamayo, J. A. *Eur. J. Org. Chem.* **2009**, 1984–1993.

(7) Kaliappan, K. P.; Das, P.; Chavan, S. T.; Sabharwal, S. G. *J. Org. Chem.* **2009**, *74*, 6266–6274.

(8) (a) Bapat, J. B.; Black, D. St.C.; Brown, R. F. C.; Ichlov, C. *Aust. J. Chem.* **1972**, *25*, 2445–2450. (b) Black, D. St. C.; Craig, D. C.; Edwards, G. L.; Laaman, S. L. *Tetrahedron Lett.* **1998**, *39*, 5849–5852. (c) Black, D. St.C.; Craig, D. C.; Edwards, G. L.; Laaman, S. L. *Bioorg. Chem.* **1999**, *27*, 91–99.

(9) (a) Tufariello, J. J.; Trybulski, E. J. *J. Chem. Soc., Chem. Commun.* **1973**, 720. (b) Tufariello, J. J.; Mullen, G. B.; Tegeler, J. J.; Trybulski, E. J.; Wong, S. C.; Ali, S. A. *J. Am. Chem. Soc.* **1979**, *101*, 2435–2442. (c) Tufariello, J. J. *Acc. Chem. Res.* **1979**, *12*, 396–403.

(10) Davis, F. A.; Theddu, N.; Edupuganti, R. *Org. Lett.* **2010**, *12*, 4118–4121.

(11) Merino, P.; Tejero, T.; Mannucci, V. *Tetrahedron Lett.* **2007**, *48*, 3385–3388See also ref 8a.

(12) Cardona, F.; Faggi, E.; Liguori, M.; Cacciarini, A.; Goti, A. *Tetrahedron Lett.* **2003**, *44*, 2315–2318.

(13) For previous work on allylation of acyclic nitrones, see: (a) Merino, P.; Delso, I.; Mannucci, V.; Tejero, T. *Tetrahedron Lett.* **2006**, *47*, 3311–3314. (b) Merino, P.; Mannucci, V.; Tejero, T. *Tetrahedron* **2005**, *61*, 3335–3347. For a review on allylation of C═N systems, see: (c) Merino, P.; Tejero, T.; Delso, I.; Mannucci, V. *Compr. Org. Synth.* **2005**, *2*, 479–498.

(14) For oxidation of cyclic hydroxylamines to nitrones, see: (a) Revuelta, J.; Cicchi, S.; Goti, A.; Brandi, A. *Synthesis* **2007**, 485–504. (b) Merino, P. In *Science of Synthesis*; Padwa, A., Bellus, D., Eds.; George Thieme:: Stuttgart, 2004; Vol. 27, pp 511−584.

(15) For previous reports on intramolecular dipolar cycloadditions of alkenyl cyclic nitrones toward tropanes, see: Shing, T. K. M.; Wong, W. F.; Ikeno, T.; Yamada, T. *Org. Lett.* **2007**, *9*, 207–209.

(16) No better results were obtained and longer reaction times were needed on carrying out the reaction at lower temperatures (−15 and −80 °C) or in the presence of Lewis acids such as $ZnCl_2$, $Zn(OTf)_2$, Et_2AlCl, and $BF_3 \cdot Et_2O$.

(17) Merino, P.; Delso, I.; Tejero, T.; Cardona, F.; Marradi, M.; Faggi, E.; Parmeggiani, C.; Goti, A. *Eur. J. Org. Chem.* **2008**, 2929–2947.

(18) Merino, P.; Tejero, T.; Revuelta, J.; Cicchi, S.; Goti, A. *Eur. J. Org. Chem.* **2004**, 776–782.

(19) Cicchi, S.; Marradi, M.; Goti, A.; Brandi, A. *Tetrahedron Lett.* **2001**, *42*, 6503–6505.

(20) Merino, P.; Delso, I.; Tejero, T.; Cardona, F.; Goti, A. *Synlett* **2007**, 2651–2654.