The Hetero Diels−Alder Reactions between D-Mannose-Derived Halonitroso Compounds and Cyclopentadiene: Scope and Limitations

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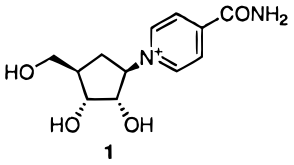
Introduction

Carbocyclic nucleosides have shown potential antiviral,[1−4] antitumor,[5,6] and other biological activities. For example, carbocyclic nicotinamide analogue **1**[7,8] displays antibacterial and antifungal properties, whereas aristeromycin (**2**)[9] and Carbovir (**3**)[10] have potent antiviral activity. Substantial efforts have been directed toward the syntheses of carbocyclic nucleosides and related areas, especially, the development of new methodology for the synthesis of common intermediates used in carbocyclic nucleoside syntheses.



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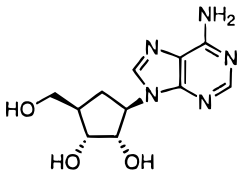

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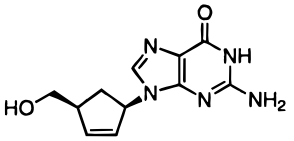

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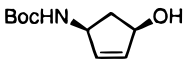

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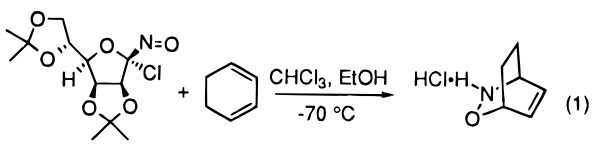
Recently, we reported the synthesis of racemic **4**[11] and *ent*-**4**,[12] important precursors for the synthesis of many carbocyclic nucleosides. Compounds **1**−**3** could be derived from *ent*-**4** by peripheral elaboration. Direct incorporation of purines and other bases using Trost's palladium-mediated reaction[13−16] on the *O*-acetate of **4** will facilitate the synthesis of 4-azacarbocyclic nucleoside derivatives. Asymmetric synthesis of *ent*-**4** or the related 4-amino-cyclopenten-1-ol system has also been reported[15] in the context of synthesis of carbocyclic analogues of "natural" D-nucleosides. However, recent studies showed that several L-nucleosides possess activity comparable to that of D-nucleosides.[17] Asymmetric synthesis of **4** would provide the appropriate intermediate for the synthesis of carbocyclic L-nucleosides.

Results and Discussion

Hetero Diels−Alder reactions of nitroso compounds with dienes have attracted great interest.[18−20] Among them, D-mannose-derived chloronitroso compound **5a** has been used in the synthesis of aminocyclitols[21] and other interesting molecules. In a typical case, highly diastereoselective Diels−Alder reaction of **5a** with cyclohexadiene generated hetero [2.2.2] bicyclic salt **6** in high enantiomeric purity (eq 1).[22−24] While reactions of **5a**



5a **6**

96% ee (1)

with several other dienes were studied, cyclopentadiene was not among those reported. We decided to explore the possibility of utilizing this reaction with cyclopentadiene to provide an alternate route to **4**.

Following literature procedures,[25,26] hydroxyimino lactone **7** was obtained in 70% overall yield from D-mannose. Treatment of **7** with *tert*-butyl hypochlorite furnished chloronitroso derivative **5a** as a blue solid,[22,23] whereas treatment of **7** with *N*-bromosuccinimide afforded bromonitroso derivative **5b** also as a blue solid (Scheme 1).[26]

With chloronitroso compound **5a** in hand, a systematic study of hetero Diels−Alder reactions with cyclopenta-

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Scheme 1

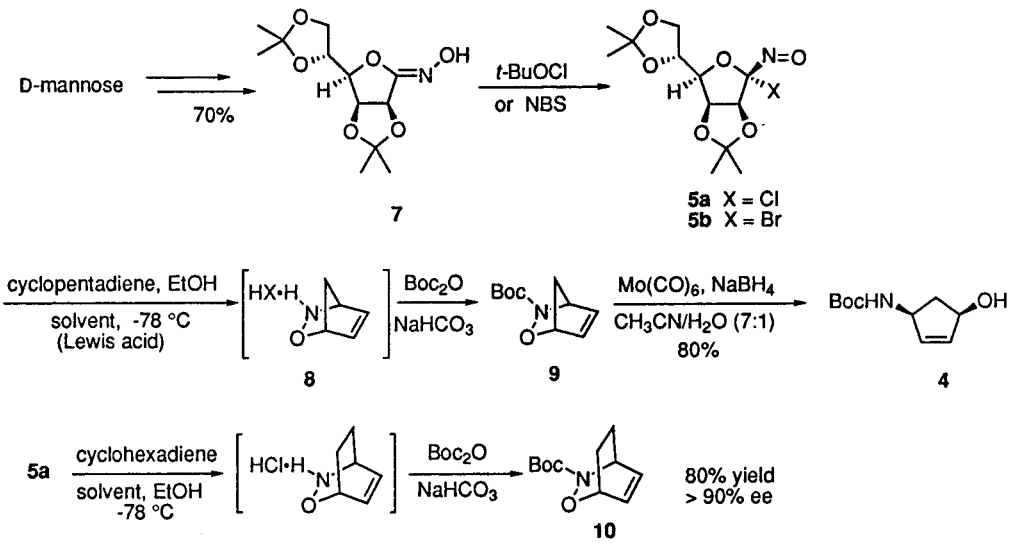

Table 1. Asymmetric Hetero Diels–Alder Reactions of 5 with Cyclopentadiene

entry	solvent	Lewis acid (equiv)	yield of **9** from **5** (%)	ee (%)
1	Et_2O	none	49	57
2	Et_2O	$ZnCl_2$ (0.6)	50	60
3	THF	Et_2AlCl (0.2)	25	73
4	THF	$TiCl_4$ (1.1)	67	75
5	CH_2Cl_2	$TiCl_4$ (1.1)	dec	
6	toluene	none	8[a]	89
7	toluene	Et_2AlCl (0.2)	12[a]	93
8	toluene	none	75	76
9	toluene	Et_2AlCl (0.2)	61	84
10	toluene	$Ti(OiPr)_3Cl$ (0.3)	76	78
11	toluene	$Ti(OiPr)_4$ (0.3)	58	76
12	toluene	$Ti(OiPr)_4$/L-DET[b] (1.0)	77	70
13	toluene	$Ti(OiPr)_4$/D-DET[b] (1.0)	80	75
14[c]	Et_2O/ toluene (2:1)	none	75	74
15[d]	toluene	none	52	75
16[d]	toluene	Et_2AlCl (0.2)	60	60

[a] **8** was separated and kept overnight at room temperature before Boc_2O protection. [b] DET = diethyl tartrate. [c] Diels–Alder reaction temperature was −100 °C. [d] Results from hetero Diels–Alder reactions utilizing bromonitroso derivative **5b** as the dienophile.

diene was undertaken (Table 1). The cycloaddition was studied under a range of conditions including changes in reaction temperature, solvent systems, and addition of Lewis acids as well as the method of product isolation. As opposed to its [2.2.2] bicyclic counterpart **6**, the resulting [2.2.1] bicyclic salt **8** formed from the reaction was not stable. Separation of salt **8** and overnight drying at room temperature resulted in significant decomposition (entries 6 and 7). Thus, in most cases, the Diels–Alder reaction product was further protected with Boc_2O to provide **9** which is stable and can be purified. Most of the reactions were performed at −78 °C. The results summarized in Table 1 indicate that, in general, the enantiomeric excess of **9** formed from the reaction of **5** with cyclopentadiene is lower than that reported for the formation of **6** from cyclohexadiene. Lowering the reaction temperature to −100 °C did not improve the selectivity (entry 14). In most cases, EtOH was added at the beginning of the Diels–Alder reactions to facilitate release of the chiral auxiliary. However, in a control reaction, delayed addition of EtOH until after the initial Diels–Alder adduct formed had no detrimental effect on product formation. While solvent variation was found to affect the diastereoselectivity of the Diels–Alder reactions (entries 1 and 8), addition of various Lewis acids had little influence on the diastereoselectivity. D-Mannose-derived bromonitroso compound **5b** was less stable than its chloronitroso counterpart **5a**, and its Diels–Alder reaction had not been reported previously. For comparison, the cycloaddition of **5b** with cyclopentadiene was also studied briefly (entries 15 and 16). Interestingly, the diastereoselectivity of the Diels–Alder reaction decreased with the addition of Lewis acid. Once bicyclic compound **9** was obtained, reduction of the N–O bond with $Mo(CO)_6$ provided **4** in moderate yield.[27,28] After several attempts, we found that addition of $NaBH_4$ improved the yield of the reduction to 80% and also simplified the workup.

The enantiomeric excess (ee) of **9** was measured through chiral shift studies with chiral shift reagent Eu(hfc)$_3$ using ^{1}H NMR. The ee value derived from this study was confirmed by measuring the diastereomeric ratio of the Mosher esters[29] of **4** using ^{19}F NMR (for entry 8). The absolute stereochemistry of the product was derived based on literature precedent.[24] Under the scale we tested (from 0.5 to 20 g of **5a**), the ee was satisfactory. However, later, when we scaled up the reaction (50 g of **5a**) under conditions indicated in entry 8, we noticed a significant drop in diastereoselectivity of the Diels–Alder reaction as reflected by the low ee of isolated bicyclic product (44% ee vs 76% measured for **9**) under otherwise similar conditions. The cause of this decrease is unclear at this time and further investigation of this effect is needed.

The significant difference in the diastereoselectivity between the reaction of **5a** with cyclopentadiene and cyclohexadiene promoted us to further examine the latter reaction. Following the literature procedure,[22,23] compound **6** was obtained in 71% yield and this salt was quite stable. More importantly, one-pot protection with Boc_2O of the Diels–Alder adduct **6** without prior separation

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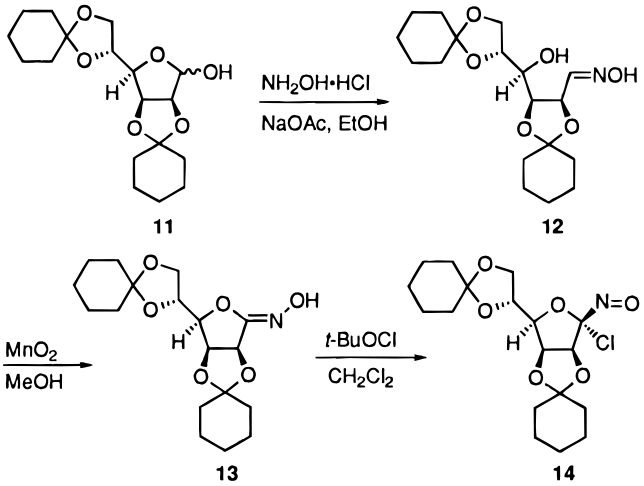
Scheme 2



provided the desired protected bicyclic derivative **10** in very high yield (80%) as well as high ee (>90%) in either toluene or chloroform as the Diels−Alder reaction solvent. The only difference was that, at −78 °C, the reaction in toluene proceeded much slower than that in chloroform. These results independently confirmed the previous report and further demonstrated that the dienes used in this type of reaction significantly affect the diastereoselectivity of the reactions. In a related study, another chloronitroso analogue **14** with diols protected as the cyclohexanone adducts was also synthesized from **11**[30,31] (Scheme 2). Unfortunately, its Diels−Alder reaction with cyclopentadiene only afforded similarly moderate diastereoselectivity (70% ee).

In conclusion, we explored novel hetero Diels−Alder reactions between D-mannose-derived halonitroso compounds and cyclopentadiene. Interestingly, the diastereoselectivity of the hetero Diels−Alder reaction between **5a** and cyclopentadiene is not as high as originally expected on the basis of related studies with cyclohexadiene. However, this methodology provided an effective and novel alternate route to **4**, an important intermediate for syntheses of carbocyclic nucleoside and other functionally rich small molecules.

Experimental Section

General methods have been described previously.[32]

General Procedure for Diels−Alder Reaction. To a solution of chloronitroso compound **5a**[22,23] in toluene at −78 °C were added cyclopentadiene (3 equiv), Lewis acid (if necessary), and EtOH (10 equiv). The blue solution was stirred at −78 °C until the color disappeared. The solution was adjusted to pH 8−9 using aqueous 1 M $NaHCO_3$ and the reaction temperature was allowed to raise to 0 °C. To this mixture was added the solution of Boc_2O (1.2 equiv) in THF, and the reaction was stirred overnight at 0 °C. After removal of THF, the mixture was extracted with EtOAc and the combined organic layers were washed with brine and dried. Filtration and concentration in vacuo gave the crude product. Flash chromatography (EtOAc:hexanes 2:3) afforded **9** as a white solid: mp 47−49 °C; ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 9H), 1.73 (d, J = 8.4 Hz, 1H), 1.99 (dt, J = 8.4, 2.0 Hz, 1H), 4.98 (br, 1H), 5.21 (m, 1H), 6.41 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 27.98, 47.96, 64.84, 81.81, 83.36, 132.76, 133.94, 158.37; IR (KBr) 2982, 1739 (br), 1700, 1370, 1332, 1286, 1252, 1162 (br), 844 cm^{-1}; HRMS [MH$^+$] calcd for $C_{10}H_{16}NO_3$ 198.1130, found 198.1135. Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.75; H, 7.84; N, 7.02.

(1*R*,4*S*)-4-(*N*-*tert*-Butylcarbamoyl)-2-cyclopenten-1-ol (4). To a solution of **9** (570 mg, 2.89 mmol) in CH_3CN-H_2O (23 mL, 7:1) was added $Mo(CO)_6$ (1.19 g, 4.5 mmol). After 10 min, $NaBH_4$ (57 mg, 1.5 mmol) was added to the reaction mixture and the mixture was refluxed for 2 h. The solid was filtered off. After removal of all the solvent in vacuo, the black slurry was chromatographed (EtOAc:hexanes 3:2) to give **4** (460 mg, 80%) as a white solid: mp 64−65.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 9H), 1.53 (m, 1H), 2.72 (dt, J = 14.4, 7.8 Hz, 1H), 3.32 (br, 1H), 4.44 (m, 1H), 4.68 (m, 1H), 5.01 (d, J = 8.4 Hz, 1H), 5.84 (m, 1H), 5.97 (dt, J = 5.7, 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.37, 41.34, 54.81, 75.09, 79.53, 134.15, 136.00, 155.25; IR (KBr) 3330, 2985, 1680 (br), 1510 cm^{-1}; HRMS [MH$^+$] calcd for $C_{10}H_{18}NO_3$ 200.1287, found 200.1289. Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.32; H, 8.60; N, 7.03. Found: C, 60.29; H, 8.70; N, 7.04.

(1*R*,4*S*)-*N*-(*tert*-Butoxycarbonyl)-3-aza-2-oxabicyclo[2.2.2]-oct-5-ene (10). Following the general procedure, compound **10** was obtained as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.31−1.54 (m, 2H), 1.46 (s, 9H), 2.05−2.24 (m, 2H), 4.73 (m, 2H), 6.55 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 20.47, 23.51, 28.09, 50.04, 70.57, 81.44, 131.48, 131.63, 157.61; IR (neat) 2968, 2940, 1737, 1696, 1370, 1162 cm^{-1}; HRMS [MH$^+$] calcd for $C_{11}H_{18}NO_3$ 212.1287, found 212.1279. Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: 62.35; H, 7.96; N, 6.74.

2,3:5,6-Di-*O*-cyclohexylidene-D-mannose Oxime (12). A 250 mL round-bottom flask was charged with ethanol (60 mL), lactol **11**[30,31] (7.48 g, 22 mmol), NH_2OH·HCl (2.45 g, 35.2 mmol), and NaOAc (2.95 g, 36 mmol), and the reaction was stirred at 60 °C for 1.5 h. The ethanol was removed in vacuo and the residue was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with EtOAc once. The combined organic layers were washed with saturated $NaHCO_3$ and brine and dried over Na_2SO_4. Filtration and concentration afforded a white solid. Recrystalization (hexanes) afforded **12** (6.88 g, 88%) as white crystals: mp 144−145.5 °C; ^{1}H NMR (DMSO-d_6) δ 1.33−1.67 (m, 20 H), 3.14 (t, J = 7.5 Hz, 1H), 3.84−3.93 (m, 3H), 4.50 (d, J = 8.1 Hz, 1H), 4.61 (d, J = 7.5 Hz, 1H), 5.16 (dd, J = 4.0, 7.5 Hz, 1H), 6.92 (d, J = 3.9 Hz, 1H), 11.11 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 23.44, 23.65, 23.70, 24.65, 24.73, 33.91, 34.60, 35.30, 36.28, 65.69, 69.46, 71.39, 75.23, 76.57, 108.62, 108.75, 149.93; IR (KBr) 3372, 1451 cm^{-1}; HRMS [MH$^+$] calcd for $C_{18}H_{30}NO_6$ 356.2073, found 356.2047. Anal. Calcd for $C_{18}H_{29}NO_6$: C, 60.83; H, 8.22; N, 3.94. Found: C, 60.85; H, 8.11; N, 4.02.

2,3:5,6-Di-*O*-cyclohexylidene-1-*C*(hydroxyimino)-D-mannofuranose (13). To a stirred solution of oxime **12** (5.80 g, 16.3 mmol) in methanol was added freshly made MnO_2[33] (5.35 g, 61 mmol), and the reaction was stirred at rt. The mixture was filtered through Celite, and the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 and washed with 1 M citric acid aqueous solution and brine. The organic layer was stirred at rt overnight. Concentration provided a white solid. Recrystalization (CH_2Cl_2−hexanes) afforded **13** (5.0 g, 89%) as a white solid: mp 165−167 °C; ^{1}H NMR (DMSO-d_6) δ 1.33−1.55 (m, 20H), 3.85 (dd, J = 5.1, 8.4 Hz, 1H), 4.03 (dd, J = 6.3, 8.4 Hz, 1H), 4.33 (pseudo-q, J = 5.8 Hz, 1H), 4.38 (dd J = 3.6, 6.6 Hz, 1H), 4.75 (dd, J = 3.3, 5.7 Hz, 1H), 5.12 (d, J = 5.7 Hz, 1H), 9.80 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 23.42, 23.45, 23.55, 23.63, 24.32, 24.59, 34.32, 34.85, 35.74, 35.98, 65.06, 72.34, 76.82, 77.01, 81.27, 108.80, 112.96, 155.45; IR (KBr) 3409, 1692 cm^{-1}; HRMS [MH$^+$] calcd for $C_{18}H_{28}NO_6$ 354.1916, found 354.1904. Anal. Calcd for $C_{18}H_{27}NO_6$: C, 61.17; H, 7.70; N, 3.96. Found: C, 61.30; H, 7.58; N, 3.89.

2,3:5,6-Di-*O*-cyclohexylidene-1-*C*-nitroso-α-D-mannofuranosyl Chloride (14). To a solution of **13** (4.23 g, 12 mmol) in CH_2Cl_2 at −10 °C was added dropwise a solution of *t*-BuOCl in CH_2Cl_2 in 20 min. The solution was stirred further for 40 min at −10 °C. Concentration provided crude product as an oil. Chromatography (EtOAc:hexanes 1:5) afforded **14** (4.56 g, 98%) as a blue thick oil: ^{1}H NMR ($CDCl_3$) δ 1.22−1.67 (m, 20H), 4.05

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(dd, J = 1.8, 9.0 Hz, 1H), 4.13 (dd, J = 6.3, 9.0 Hz, 1H), 4.27 (dd, J = 3.6, 7.5 Hz, 1H), 4.51−4.57 (m, 1H), 4.97 (dd, J = 3.6, 5.4 Hz, 1H), 5.52 (d, J = 5.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 23.51, 23.60, 23.84, 24.04, 24.72, 25.07, 34.35, 34.68, 35.03, 36.52, 66.16, 71.79, 78.79, 82.51, 84.49, 110.20, 115.80, 125.45; IR (neat) 1578, 1450 cm^{-1}; HRMS [MH^+] calcd for $C_{18}H_{27}ClNO_6$ 388.1527, found 388.1530.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for **14** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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