Conversion of Allylic Alcohols into Allylic Nitromethyl Compounds via a Palladium-Catalyzed Solvolysis: An Enantioselective Synthesis of an Advanced Carbocyclic Nucleoside Precursor[1]

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A two-step reaction sequence to homoallylic nitro compounds from allylic alcohols is presented. Ethoxy carbonylation of the alcohols with ethyl chloroformate provides the corresponding allylic ethyl carbonates in high yields. Exposure of these substrates to catalytic palladium(0) in CH_3NO_2 initiates a reaction sequence, ionization−decarboxylation−nitromethylation, that culminates with the formation of nitroalkenes. The regio- and stereochemical outcomes of the nitromethyl allylation reaction can be explained by the behavior of the transient π-allylpalladium complexes. This methodology serves as a centerpiece for the synthesis of an important carbocyclic nucleoside intermediate.

Introduction

Allylation reactions involving cationic π-allylpalladium complexes provide an effective synthetic methodology for the formation of carbon−carbon and carbon−heteroatom bonds.[2] The combination of high stereospecificity, broad nucleophilic compatibility, and widespread availability of π-allylic precursors account for the reaction's considerable popularity. Still, as measured by the dearth in literature reports, stabilized anions derived from nitroalkanes are underappreciated as nucleophilic components in these reactions. This is rather surprising since the nitro group has played an illustrious role in traditional organic synthesis.[3]

The first examples of couplings between nitronate anions and π-allylpalladium complexes derived from allylic esters[4] were published in 1981 by Wade[5] and Aleksandrowicz.[6] In both instances, researchers used strong base to generate the desired anion prior to the palladium-catalyzed step. A sprinkling of closely related papers by these,[7] and other researchers,[8] followed. Tsuji,[9] Ganet,[8c,10] and Hesse[11] next explored the use of nitroalkanes and their derivatives with allylic carbonates. This modification obviated the need for external base and allowed these allylation reactions to proceed under neutral conditions. Interestingly, despite the fact that the nitro group is well-equipped to stabilize an adjacent carbanion, there are relatively few examples[9,10] of "unactivated" nitroalkanes participating in metal-catalyzed reactions under the exceptionally mild conditions afforded by carbonates.

Our interest in nitroalkane allylation reactions was in response to the challenge of appending the nitromethyl functionality to a cyclopentenyl skeleton in a stereo- and regiocontrolled fashion. The nitromethyl moiety was visualized as a masked hydroxymethyl group that could later be elaborated[12,13] into the pseudo-sugar fragment that distinguishes carbocyclic nucleosides from conventional nucleosides. Success in this venue prompted us to investigate the nitromethylation of other π-allylpalladium complexes prepared from allylic carbonates in the presence of nitromethane. This paper therefore reports the scope, mechanism, and application of this methodology to the practice of organic synthesis.

Results and Discussion

Palladium-Catalyzed Nitromethylation. We have found that palladium(0) catalyzes the addition of unactivated nitroalkanes to vinyl epoxides (eq 1).[12a,14] The

(1)

resulting 5-nitro-2-alken-1-ols are especially versatile intermediates since the nitro group can be readily

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(1) Presented in part by K. A. S. at the Undergraduate Research Conference, April 22, 1989, UCLA and by K. A. S. and D. R. D. at the Joint 45th Northwest/Rocky Mountain Regional Meeting, June 13−15, 1990, Salt Lake City, UT; Abstracts 190 and 220, respectively.

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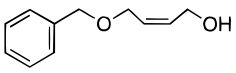
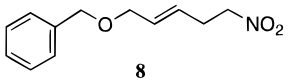
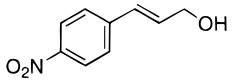
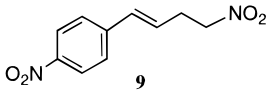
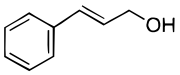
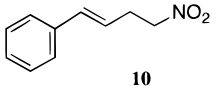
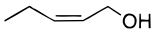
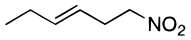
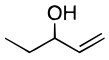
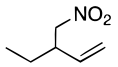
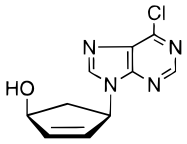
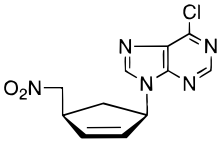
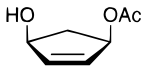
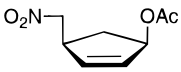
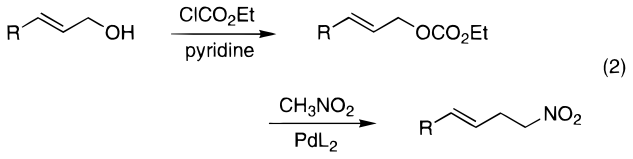
Table 1. Two-Step Conversion of Allylic Alcohols into Homoallylic Nitro Compounds via a Pd(0)-Catalyzed Fragmentation of the Corresponding Ethyl Carbonates

entry	alcohol	carbonate[a]	temp[b]	product(s)	yield, %[c]
1		**1**[d]	rt	 **8**	62[e]
2		**2**	rt	 **9**	74
3		**3**	rt	 **10**	71
4		**4**	65 °C	 **11**	70[f]
5		**5**	65 °C	 **12**	71[g]
6		**6**	50 °C	 **13**	60
7	 **(+)-16**	**7**	0 °C	 **14**	63

[a] Prepared from the corresponding allylic alcohol with pyridine and ethyl chloroformate at 0 °C. [b] Fragmentation temperature. [c] Isolated yields. [d] Determined to be 98.4% cis. [e] E/Z ratio 10:1. [f] Ratio of regioisomers **11** & **12** found to be 3.0:1. [g] Ratio of regioisomers **11** & **12** found to be 3.4:1.

transformed into a wide variety of functionalities. As an extension of this chemistry, we have discovered that palladium also catalyzes the addition of nitromethane to allylic carbonates (eq 2). This reaction opens an additional avenue to synthetically valuable intermediates. For example, upon exposure to palladium, nitromethane adds to the corresponding ethyl carbonate of *cis*-4-(benzyloxy)-2-buten-1-ol (**1**) at room temperature (entry 1, Table 1). The reaction is complete within 35 min and affords a 62% yield of the homoallylic nitro product **8**. The trans stereochemistry was confirmed using ^{1}H NMR spectroscopy (CH=CH, J > 15 Hz). Especially noteworthy is that no bisallylated compound was detected. Bisallylated product often accompanies reactions involving additions of diprotic soft nucleophiles to π-allylpalladium complexes.[15] One might expect that monoallylated nitroalkenes (*e.g.*, **8**) are especially vulnerable to secondary allylation because α-substituted nitro compounds are more acidic than nitromethane.[16] However, since nitromethylation occurs by solvolysis, competition from less-abundant nucleophiles is suppressed.



(2)

Allylic alcohol entries 1−5 were selected in part for their commercial availability whereas entries 6 and 7 were prepared as starting points for our ongoing synthetic studies on carbocyclic analogs of purine and pyrimidine nucleosides.[17] Our method of nitromethylation is quite versatile since it is compatible with a number of allylic skeletal types. The reaction is effective with both primary and secondary allylic carbonates as well as with cyclic and acyclic substrates. Tertiary allylic carbonates were not examined in this study. Overall yields for the two steps are good with generally high regio- and stereoselectivities.

Previous studies[18] have argued that allylic carbonates are more reactive than their acetoxy counterparts. This assertion was confirmed with the chemoselective nitromethylation of allylic acetoxy carbonate **7** (entry 7). This differential reactivity provides a useful handle for developing selective synthetic processes via the sequential generation of π-allylpalladium complexes. Such a strategy is actualized in the preparation of a nucleoside precursor (*vide infra*).

(15) For example see: Doi, T.; Yanagisawa, A.; Miyazawa, M.; Yamamoto, K. *Tetrahedron: Asymmetry* **1995**, *6*, 389.

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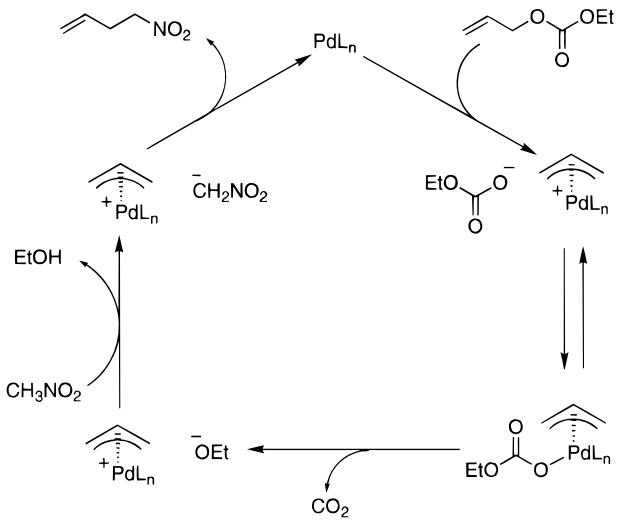
(17) Results from this study will be reported at a later date.

(18) Tsuji, J. *Synthesis* **1990**, 739.

Scheme 1



Mechanistic Considerations. Nitromethylation is believed to proceed via a palladium-induced ionization−fragmentation sequence[19] that concomitantly generates equal concentrations of the transient metal complex and alkoxide base (Scheme 1). Decarboxylation (as evidenced by the evolution of CO_2) ensures irreversibility of this transformation. Rather than attacking the soft, electrophilic π-allyl center directly, unfettered ethoxide abstracts a proton from the solvent nitromethane (pK_a = 10.2),[20] generating the stabilized nitronate that serves as a nucleophile. This cascade of events yields a significantly softer nucleophilic species that readily attacks a terminus of the η^3-allyl system.

π-Allyl intermediates derived from *(Z)*-olefins yield complexes in the anti configuration[21] whereas *(E)*-olefins lead to more stable syn isomers. Accordingly, nucleophilic additions to these transition-metal allyls afford *Z* products in the former case and *E* products in the latter.[22] Yet, in entries 1−5, *E* products are produced overwhelmingly, if not exclusively, regardless of the stereochemistry of the starting carbonate. This suggests that the $\pi-\sigma-\pi$ interconversion[23] between the syn and anti complexes occurs at a faster rate than the nitronate attack.

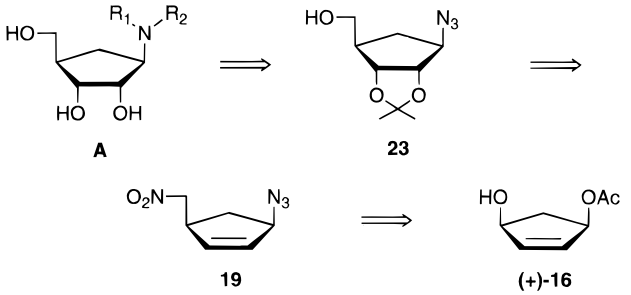
Regiochemical outcomes are influenced by the steric differential between the two termini of unsymmetrical π-allylpalladium complexes. Moreover, when steric and electronic effects act in concert, absolute regiocontrol is possible. This point is readily manifested in entries 1, 6, and 7 where the allylic polar heteroatoms strongly direct nucleophiles toward the more distant and less sterically encumbered terminus of the η^3-allyl system. In the case of carbonates **2** and **3**, which lack a directing heteroatom, preservation of olefin−aromatic conjugation dictates the regiochemical outcome (entries 2 and 3). Entries 4 and 5 show only modest regioselectivity as expected. Of interest is that regioisomeric carbonates **4** and **5** produce surprisingly similar ratios (3.0:1 and 3.4:1, respectively) of nitromethyl adducts **11** and **12**. This evidence suggests that the two reactions travel through a common π-allyl intermediate en route to nitromethylated product.

The nitromethylation reaction is completely stereospecific as evidenced by entries 6 and 7 (*vide infra*). This is consistent with previous mechanistic findings that postulate that palladium approaches the allylic leaving group from the back side prior to ionization.[24] Eventual attack by the nitronate on the π-allyl face opposite the metal would account for the double inversion or observed retention of configuration relative to the original stereogenic center.

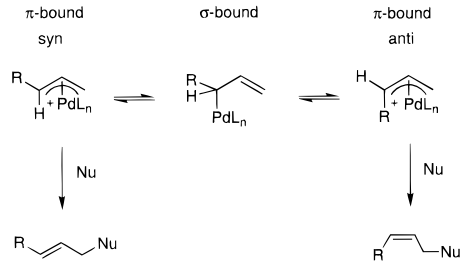
During purification of nitromethyl adduct **8**, we noted the presence of a small amount of the corresponding nitroethyl counterpart (5%). This anomalous result prompted us to assay our distilled nitromethane. GC analysis confirmed the solvent was contaminated with 4.5% of the homologue nitroethane. We were surprised by the disproportionately high percentage of nitroethyl adduct compared to nitromethyl. Nucleophilicity based solely on steric arguments intuitively favors formation of **8**. Consequently, an experiment was designed to measure qualitatively the relative nucleophilicity of nitromethane and nitroethane under our standard conditions. In this reaction, nitromethylation was carried out in a 1:1 nitromethane and nitroethane solvent mixture instead of neat nitromethane. Solvolysis led to complete conversion of carbonate **1** into the corresponding nitroethyl adduct. Such dramatic discrimination between nucleophiles appears driven by the difference in solvent pK_a: 10.2 for nitromethane and 8.5 for nitroethane.[20]

Synthesis of a Carbocyclic Nucleoside Precursor. Preparation of carbocyclic nucleoside precursor **23** hinged on the new nitromethylation methodology. Outlined in Scheme 2 is our retrosynthetic approach to that molecule. We envisioned that the nitromethyl moiety on **19** would serve as a chemical progenitor to the hydroxymethyl function that adorns conventional nucleosides. Germane to this study is the stereo- and regiospecific nitromethylation of the optically pure starting material (+)-**16**.[25,26]

Scheme 2

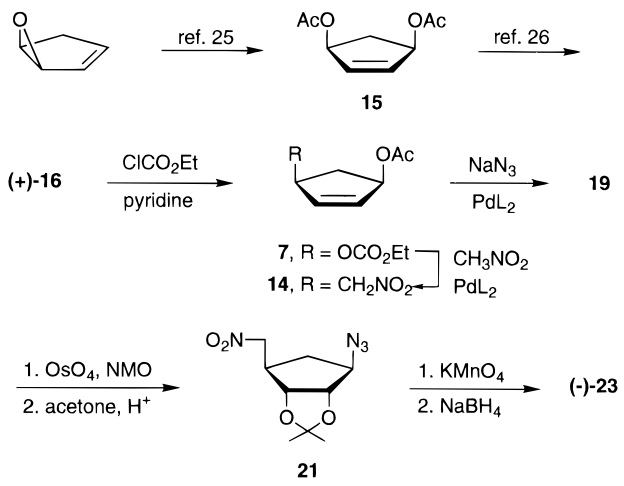


(19) Tsuji, J. *Tetrahedron* **1986**, *42*, 4361.
(20) Reference 16, p 62.
(21) For accepted nomenclature for planar allyl ligands see: Consiglio, G.; Waymouth, R. M. *Chem. Rev.* **1989**, *89*, 257.

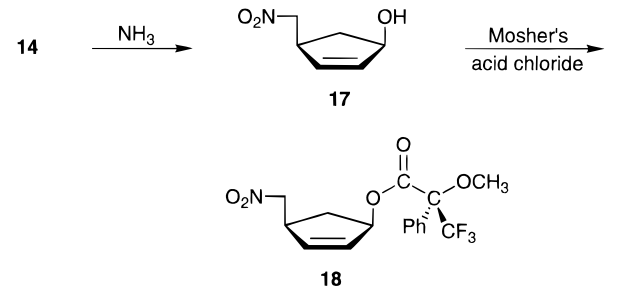


(22) Sjogren, M.; Hansson, S.; Norrby, P.-O.; Akermark, B.; Cucciolito, M. E.; Vitagliano, A. *Organometallics* **1992**, *11*, 3954.
(23) Corradini, P.; Maglio, G.; Musco, A.; Paiaro, G. *Chem. Commun.* **1966**, 618.
(24) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730.
(25) Deardorff, D. R.; Myles, D. C.; MacFerrin, K. D. *Tetrahedron Lett.* **1985**, 5615.

Scheme 3



Scheme 4



The undertaking began with the ethoxycarbonylation of (+)-**16** with ethyl chloroformate in cold pyridine to furnish **7** (R = OCO_2Et; Scheme 3) in near quantitative yield. The nitromethylation step proved particularly challenging due to the unexpected subtle difference in reactivities between the allylic acetate and carbonate functionalities. Fortunately, conditions (0.05 M **7** in 4:1 CH_2Cl_2/CH_3NO_2, 5 mol % Pd, rt) that led predominantly to the desired *cis*-nitromethyl adduct **14** (R = CH_2NO_2; 63% yield), accompanied by a 16% yield of *meso*-diacetate **15**, were identified. Formation of this side product, which presumably results from competitive attack by acetate ion on the π-allylpalladium intermediate that leads to **14**, is strong evidence that the unwanted acetoxy ionization has occurred. We have found that if the above conditions are not enforced, this fragmentation−nitromethylation reaction can lead to other extraneous products such as the *trans*-nitromethyl acetate or the *cis* and *trans*-dinitromethyl adducts.

The nature of these products prompted us to question if the absolute configuration of **14** had been compromised under the above permutating conditions. To verify that the enantiomeric integrity of **14** through ^1H NMR analysis, the Mosher-derived ester[27] derivative **18** was prepared in two steps (Scheme 4). Transformation of nitromethyl acetate **14** with concentrated NH_4OH into the corresponding alcohol **17** followed by esterification with Mosher's acid chloride, (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA) provided **18** in 72% yield. Racemic nitromethyl alcohol *rac*-**17**, precursor to the MTPA diastereomeric control mixture *dia*-**18**, was obtained in one step from the palladium-catalyzed reaction between nitromethane and cyclopentadiene monoepoxide.[12a] NMR analysis on *dia*-**18** at 200 MHz provided enough dispersion to resolve clearly differences between the two diastereomers in both the vinylic and methylene spectral regions of the five-membered ring. To our delight, a comparative analysis with the MTPA ester **18** derived from the enzymatic-nitromethylation pathway illustrated in Scheme 3 revealed an enantiomeric excess >99%.

Already properly configured for a second $Pd(PPh_3)_4$-catalyzed substitution reaction and secure in its optical purity, allylic acetate **14** was reacted with catalyst and NaN_3 in a THF:H_2O (1:1) solution at 52 °C. These conditions[28] provided an excellent means to introduce the surrogate amino function. The desired *cis*-1,4-product **19** was obtained in 68% yield along with the isomeric *cis*-1,2-product (13.5%) **20** (not shown) and a trace of the *trans*-1,4-azide. Longer reaction times, higher temperatures, and larger concentrations of catalyst all favored formation of the thermodynamic *trans*-1,4 product. Accordingly, it is imperative that the reaction be quenched immediately following the consumption of starting material. Allylic azide **20** probably arises via the Winstein rearrangement[29] although 1,2-attack by azide ion on the intermediate π-allyl cannot be ruled out as a contributing mechanism. NMR measurements indicate that the equilibrium ratio of **19** and **20** is 5:1. The tendency for allylic azides to equilibrate has also been a problem in other carbocyclic nucleoside syntheses.[30]

The *cis*-dihydroxylation-protection sequence with OsO_4/NMO and *p*-TSA in 2,2-dimethoxypropane afforded the expected acetonide **21** in 57% yield, and a 10% yield of the undesired all-cis epimer **22** (not shown). Attempts to improve upon this reaction proved frustrating. For example, while the use of cold $KMnO_4$ greatly enhanced stereoselectivity,[31] yields were decreased to an unacceptably low level. Cleavage of the C−N bond in the nitro group by the oxidant is the apparent culprit for the diminished yields.

In the first of a two-step sequence, the nitromethyl function was converted into the corresponding aldehyde under basic Nef conditions[32] ($KMnO_4$, KOH, MeOH). The instability of this carbonyl intermediate dictated that the subsequent reduction step be carried out immediately. Exposure to excess $NaBH_4$ resulted in the successful preparation of optically active **23** $[\alpha]^{19}_D$ −35.2° (*c* 0.515, $CHCl_3$) in a 44% two-step yield. The same carbocycle has been previously prepared from D-erythrose in 22 steps by Tadano et al.[33] Structure proof and enantiopurity determinations for azido alcohol **(−)-23** were realized through an exact match with the authentic spectra (NMR, IR, UV-vis) and optical rotation data ($[\alpha]^{19}_D$ −35.2° (*c* 1.05, $CHCl_3$)) generously provided by Professor Tadano. Tadano and co-workers have used this advanced nucleoside precursor in the formal synthesis of the notable carbocyclic nucleoside (−)-aristeromycin (**A**, NR_1R_2 = adenine).

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Conclusions

We have shown that nitromethylation of allylic carbonates via a palladium-induced fragmentation reaction is a viable adjunct to existing synthetic methodologies. The reaction proceeds with predictable regio- and stereospecificity in good to very good yield. A mechanism, catalytic in palladium, has been proposed to account for the observed products. Finally, the utility of this new methodology was demonstrated with a linear, formal synthesis of aristeromycin.

Experimental Section

General. All reactions were carried out in flame-dried glassware under positive pressure of dry N_2. Pyridine, nitromethane, and CH_2Cl_2 were distilled under N_2 from CaH_2. THF was distilled under N_2 from a midnight blue solution of sodium benzophenone ketyl. Ethyl chloroformate, osmium tetraoxide, *N*-methylmorpholine *N*-oxide (NMO), triphenylphosphine (PPh_3), and palladium catalysts, tris(dibenzylideneacetone)dipalladium(0) (DBA_3Pd_2) and tetrakis(triphenylphosphine)palladium(0) (PdL_4), were commercially available from Aldrich and used without further purification. Starting material alcohols were purchased from Lancaster unless otherwise indicated. (−)-MTPA-Cl was prepared from (+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid.[27] Solutions were concentrated by rotary evaporation using water aspirator (ca. 30 Torr). Separations were performed by radial chromatography, and TLC analyses were conducted on Baker Si 250 precoated glass plates (0.25 mm). Plates were developed using either ethanolic *p*-anisaldehyde reagent or phosphomolybdic acid. Optical rotations were obtained in a 1-cm^3 water-jacketed microcell. Isomeric ratios were determined by gas chromatograph using a HP-101 column (25 m). Chromatographed products were distilled bulb-to-bulb and submitted to UC Riverside Mass Spectrometry Facility for HRMS and Desert Analytics for elemental analyses.

Illustrative Example for the Ethoxycarbonylation of Allylic Alcohols. *cis*-4-(Benzyloxy)-2-butenyl Ethyl Carbonate (1). A flask purged with N_2 was charged with pyridine (0.4 M, 7.0 mL). Next, 0.47 mL of *cis*-4-(benzyloxy)-2-buten-1-ol (97% cis, 2.81 mmol, 500 mg) was syringed into the flask. The solution was cooled to 0 °C with an ice−water bath, and cold ethyl chloroformate (4.21 mmol, 0.34 mL) was syringed in dropwise over 5 min. Upon completion of addition, the ice−water bath was removed and the reaction was monitored by TLC analysis (6:1 hexanes−EtOAc, R_f 0.63). The reaction was quenched by diluting with ether, followed by extraction of the organic layer with 8 mL portions of saturated NH_4Cl (3 ×), 1 N HCl (3 ×), and saturated $NaHCO_3$ (3 ×). The organic layer was then dried over $MgSO_4$ and concentrated under reduced pressure. Radial chromatography (4 mm plate, 12:1 hexanes−EtOAc) was effected on 760 mg of crude product. Removal of solvent *in vacuo* afforded 659 mg (93% yield) **1** as a colorless oil: 98.4% cis by GC; ^{1}H NMR ($CDCl_3$) δ 7.32 (m, 5H), 5.92−5.68 (m, 2H), 4.69 (d, J = 6.2 Hz, 2H), 4.52 (s, 2H), 4.20 (q, J = 6.9 Hz, 2H), 1.31 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 155.0, 138.0, 131.3, 128.4, 127.8, 127.7, 126.2, 72.5, 65.7, 64.0, 63.4, 14.3; IR (neat) 1745, 1710, 1450, 1375 cm^{-1}; HRMS (CI) calcd for $C_{14}H_{19}O_4$ (MH^+) 251.1283, found 251.1285.

Ethyl *p*-nitrocinnamyl carbonate (2): yellow solid; 77−99% yield; mp 34.2−35.0 °C; bp (bulb-to-bulb) 142 °C at 0.38 Torr; ^{1}H NMR ($CDCl_3$) δ 8.19 (br d, J = 8.9 Hz, 2H), 7.52 (br d, J = 8.9 Hz, 2H), 6.76 (br d, J = 15.9 Hz), 6.45 (dt, J = 15.9, 5.8 Hz, 1H), 4.83 (dd, J = 5.8, 1.3 Hz, 2H), 4.24 (q, J = 7.2 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 154.8, 147.4, 142.5, 131.5, 127.7, 127.1, 123.9, 123.9, 67.1, 64.2, 14.1; IR (neat) 2985, 2941, 1745, 1597, 1516 cm^{-1}; HRMS calcd for $C_{12}H_{13}O_5N$ (M^+) 251.0794; found 251.0797.

(*E*)-Cinnamyl ethyl carbonate (3): clear oil; 85% yield; R_f 0.45 (1:1 hexanes−EtOAc); bp (bulb-to-bulb) 96−100 °C at 0.18 Torr; ^{1}H NMR ($CDCl_3$) δ 7.34−7.17 (m, 5H), 6.61 (br d, J = 15.9 Hz, 1H), 6.23 (dt, J = 15.9, 6.3 Hz, 1H), 4.71 (dd, J = 6.3, 1.2 Hz, 2H), 4.15 (q, J = 7.1 Hz, 2H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 154.8, 135.9, 134.3, 128.3, 127.9, 126.4, 122.4, 67.8, 63.7, 14.0; IR ($CDCl_3$) 2984, 1748, 1448 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{14}O_3$ (M^+) 206.0943, found 206.0954.

Ethyl (*Z*)-2-pentenyl carbonate (4): colorless oil; 88% yield; R_f 0.59 (3:1 hexanes−CH_2Cl_2); bp (bulb-to-bulb) 60 °C at 0.40 Torr; 89.2% cis by GC; ^{1}H NMR ($CDCl_3$) δ 5.75−5.47 (m, 2H), 5.67 (dd, J = 7.1, 0.8 Hz, 2H), 4.19 (q, J = 7.2 Hz), 2.13 (dq (app br quintet), J = 8.0 Hz), 1.30 (t, J = 7.2 Hz, 3H), 0.99 (t, J = 7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 155.0, 137.1, 122.3, 63.5, 63.1, 20.7, 14.0, 13.7; IR (neat) 2969, 1745, 1464, 1374 cm^{-1}.

Ethyl 1-penten-3-yl carbonate (5): colorless oil; 47% yield; R_f 0.37 (4:1 hexanes−CH_2Cl_2); bp (bulb-to-bulb) 27 °C at 0.40 Torr; ^{1}H NMR ($CDCl_3$) δ 5.79 (overlapping ddd, J = 17.3, 11.7, 6.9 Hz, 1H), 5.23 (m, 2H), 4.99 (ddd (app br q), J = 6.9 Hz, 1H), 4.18 (q, J = 7.3 Hz, 2H), 1.78−1.70 (m, 2H), 1.30 (t, J = 7.3 Hz, 3H), 0.92 (dd (app t), J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 154.6, 135.9, 117.1, 79.8, 63.5, 27.2, 14.1, 9.1; IR (neat) 2976, 1744, 1263, 992 cm^{-1}; HRMS (CI) calcd for $C_8H_{15}O_3$ (MH^+) 159.1021, found 159.1012.

(+)-(1*S*,4*R*)-4-(6-Chloro-9*H*-purin-9-yl)-2-cyclopentenyl Ethyl Carbonate (6). The alcohol was reacted with ethyl chloroformate in 1:1 CH_2Cl_2−pyridine with 4 Å sieves, and upon completion the reaction was diluted with EtOAc followed by extraction of the organic layer with saturated NH_4Cl (3 ×), 1 N HCl (3 ×), and saturated $NaHCO_3$ (3 ×). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. Residual pyridine was removed *in vacuo*. The crude material was passed through a plug of SiO_2 and chromatographed via radial chromatography (4 mm plate, solvent gradient, starting 1:1, then 3:1 EtOAc−hexane) yielding **6** as a colorless solid in 80% yield: mp 94.8−95.9 °C; R_f 0.52 (3:1 EtOAc−hexanes); $[\alpha]^{25}_D$ −9.20° (*c* 0.915, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.76 (s, 1H), 8.20 (s, 1H), 6.44 (dt, J = 5.4, 3.9 Hz, 1H), 6.22 (dd, J = 5.4, 2.1 Hz, 1H), 5.77 (m, 1H), 5.68 (br dt, J = 7.2, 2.6 Hz, 1H), 4.20 (q, J = 7.2 Hz, 2H), 3.16 (overlapping dt, J = 15.2, 8.0 Hz, 1H), 2.04 (dt, J = 15.2, 3.4 Hz, 1H), 1.31 (t, J = 7.2 Hz, 3H); IR ($CDCl_3$) 1734.1, 1591.4, 1550.5, 1402.3 cm^{-1}; HRMS (FAB) calcd for $C_{13}H_{14}O_3N_4Cl$ (MH^+) 309.0754, found 309.0771. Anal. Calcd: C, 50.58; H, 4.24; N, 18.15. Found: C, 50.46; H, 4.16; N, 17.87.

(+)-(1*S*,4*R*)-4-Acetoxy-2-cyclopentenyl Ethyl Carbonate (7). To a N_2-flushed flask containing 115.0 mg (0.810 mmol) of **2** ($[\alpha]^{26}_D$ +67.6° (*c* 1.46, $CHCl_3$)) was added 2 mL of pyridine (0.04 M). The clear, colorless solution was stirred in an ice−water bath for 10 min prior to the dropwise addition of cold ethyl chloroformate (0.465 mL, 4.86 mmol) over a 15 min period. The reaction was judged complete by TLC analysis (3:1 hexanes−EtOAc, R_f 0.50) in about 1 hour. (Since the starting material lies under the UV-active pyridine streak, the glass TLC slide was heated on a hotplate to remove the pyridine prior to staining.) The reaction was quenched by the addition of aqueous saturated NH_4Cl solution and then layered with ether. The organic phase was washed three times each with saturated NH_4Cl, ice-cooled 1 N HCl, and saturated $NaHCO_3$ solution. The organic phase was then dried over $MgSO_4$, vacuum filtered, and concentrated by rotary evaporation. The residue was dissolved twice in 20 mL of heptane and azeotroped under aspirator vacuum to remove the final traces of pyridine. Following exposure to high vacuum, 168 mg (96.6%) of clear oil was obtained. A slight enrichment in purity may be realized by chromatographing the product **7** over SiO_2 using 4:1 hexanes−EtOAc: $[\alpha]^{25}_D$ −9.71° (*c* 1.605, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.10 (br s, 2H), 5.50 (ddd, J = 7.5, 3.7, 1.0 Hz, 1H), 5.44 (ddd, J = 7.5, 3.7, 1.0 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 2.87 (dt (app quintet), J = 7.5, 15.0 Hz, 1H), 2.02 (s, 3H), 1.80 (dt, J = 3.8, 15.0 Hz, 1H), 1.28 (t, J = 7.1 Hz, 3H); IR (neat) 2990, br 1740, 795 cm^{-1}; HRMS (CI) calcd for $C_{10}H_{18}NO_5$ (MNH_4^+) 232.1185, found 232.1205.

Illustrative Example of the Pd-Catalyzed Fragmentation−Nitromethylation Reaction. *cis*-4-(Benzyloxy)-1-nitro-3-pentene (8). A flask was purged with N_2 and charged with nitromethane (6.0 mL, 0.2 M). Carbonate **1** (1.20 mmol, 300 mg) was dissolved in a portion of nitromethane and was subsequently syringed into the flask followed by PPh_3 (10 mol%, 31 mg) and DBA_3Pd_2 (2.5 mol%, 27 mg). After 35 min,

the reaction was judged complete by TLC analysis. The reaction was concentrated under reduced pressure, followed by elution with ether (30 mL) through a glass frit layered with $MgSO_4$ and SiO_2. (This step ensures removal of the palladium catalyst.) After concentration of the solution under reduced pressure, purification was effected via radial chromatography (2 mm plate, 12:1 hexanes−EtOAc). Concentration of the solution *in vacuo* yielded 165 mg (62% yield) of **8** as a clear oil: 10:1 trans−cis by GC; ^{1}H NMR ($CDCl_3$) δ 7.33 (m, 5H), 5.72 (m, 2H), 4.50 (s, 2H), 4.43 (t, J = 6.9 Hz, 2H), 3.98 (dd, J = 4.4, 1.1 Hz, 2H,), 2.75 (dt (app br q), J = 6.9, 5.5 Hz, 2H); ^{13}C ($CDCl_3$) δ 138.2, 131.1, 128.5, 128.4, 127.8, 127.8, 127.7; IR (neat) 1555, 1500, 1455, 1430 cm^{-1}; HRMS (CI) calcd for $C_{12}H_{16}O_3N$ (MH^+) 222.1130, found 222.1138.

4-Nitro-1-(*p*-nitrophenyl)butene (9): yellow solid; 74% yield; mp 77.0−78.5 °C; R_f 0.60 (2:1 hexanes−EtOAc); bp (bulb-to-bulb) 160 °C at 0.40 Torr; ^{1}H NMR ($CDCl_3$) δ 8.19 (br d, J = 8.9 Hz, 2H), 7.46 (br d, J = 8.9 Hz, 2H), 6.60 (br d, J = 15.9 Hz, 1H), 6.32 (dt, J = 15.9, 6.9 Hz, 1H), 4.56 (t, J = 6.7 Hz, 2H), 2.97 (ddt (app br q), J = 6.7, 1.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 147.4, 142.8, 132.2, 128.2, 126.9, 124.0, 74.5, 30.6; IR (neat) 2356, 1556, 1519, 1345 cm^{-1}; HRMS calcd for $C_{10}H_{10}O_4N_2$ (M^+) 222.0641, found 222.0650.

4-Nitro-1-phenylbutene (10): colorless oil; 71% yield; R_f 0.55 (5:1 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$) δ 7.4−7.15 (m, 5H), 6.51 (br d, J = 15.8 Hz, 1H), 6.09 (dt, J = 15.8, 7.0 Hz, 1H), 4.48 (t, J = 7.0 Hz, 2H), 2.89 (ddt (app br q), J = 7.0, 1.2, 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 136.5, 134.1, 128.6, 127.8, 126.3, 122.9, 75.0, 30.7; IR ($CHCl_3$) 2860, 1558, 1500, 1450 cm^{-1}.

(*E*)-1-Nitro-3-hexene (11) and 3-Ethyl-4-nitro-1-butene (12). Carbonate **4** (300 mg, 1.90 mmol) was added to a flask charged with 9.0 mL of nitromethane (0.2 M). The flask was fitted with a cold finger condenser and purged with N_2. The solution was heated to a 65 °C oil bath temperature followed by addition of PPh_3 (10 mol %, 50 mg) and DBA_3Pd_2 (2.5 mol %, 43 mg). Ionization−decarboxylation of the carbonate was confirmed by immediate bubbling of CO_2 gas. The reaction was monitored and judged compete by TLC analysis (ca. 1.5 h). (High volatility of the desired product precluded the use of rotary evaporation with heat for the removal of nitromethane.) Accordingly, the entire reaction mixture was chromatographed over 40 g of SiO_2 with 6:1 hexanes−CH_2Cl_2 as the eluent. All product spots were collected for GC analysis and were subsequently separated via radial chromatography (2 mm plate, 10:1 hexanes−CH_2Cl_2). Concentration *in vacuo* yielded 175 mg of a colorless oil containing inseparable regioisomers **11** and **12**, 3.0:1, respectively, from **4** in 71% yield (3.4:1 from **5** in 70% yield): R_f 0.35 (4:1 hexanes−CH_2Cl_2); bp (bulb-to-bulb) 30 °C at 0.28 Torr; ^{1}H NMR ($CDCl_3$) δ 5.63 (dtt, J = 15.4, 6.2, 1.1 Hz, 1H, **11**), 5.33 (dtt, J = 15.4, 6.6, 1.5 Hz, 1H, **11**), 5.16 (dd, J = 9.9, 1.5 Hz, 1H, **12**), 5.14 (d, J = 17.3 Hz, 1H, **11**), 4.39 (t, J = 6.94 Hz, 2H, **11**), 4.39 (dd, J = 11.7, 4.4 Hz, 1H, **12**), 4.29 (dd, J = 11.7, 8.77 Hz, 1H, **12**), 2.9−2.7 (m, 2H, **12**), 2.67 (dq, J = 6.9, 1.1 Hz, 2H, **11**), 2.01 (br quintet, J = 7.3 Hz, 2H, **11**), 1.56−1.20 (m, 2H, **12**), 0.96 (t, J = 7.3 Hz, 3H, **11**), 0.95 (dd, J = 7.7, 7.3 Hz, 3H, **12**); IR (neat) 2924, 1601, 1492, 1452 cm^{-1}; HRMS (CI) calcd for $C_6H_{12}O_2N$ (MH^+) 130.0868, found 130.0864.

(+)-(3*R*, 5*S*)-3-(6-Chloro-9*H*-purin-9-yl)-5-(nitromethyl)-1-cyclopentene (13). A flask containing 650 mg (2.11 mmol) of carbonate **6** was charged with 10.5 mL of nitromethane (0.2 M) followed by addition of DBA_3Pd_2. The mixture was heated with an oil bath at 50 °C for 30 min after which 0.062 mL (3 mol %) of triisopropyl phosphite was added via syringe. Shortly thereafter, evolution of a gas was observed. The reaction was judged complete by TLC (3:1 EtOAc−hexanes, R_f 0.46) after 20 min. The solution was concentrated under reduced pressure and passed through a glass frit layered with $MgSO_4$ (4 g) and SiO_2 (7 g) with 170 mL of EtOAc. The solvent was concentrated and the residue purified via radial chromatography (4 mm plate, 1:1 EtOAc−hexanes) and afforded 350 mg of a crystalline colorless solid (**13**) with mp 130.4−131.8 °C (recrystallized from MeOH) in 60% yield: $[\alpha]^{25}_D$ +29.97° (*c* 0.94, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.75 (s, 1H), 8.12 (s, 1H), 6.24 (dt, J = 5.4, 2.1 Hz, 1H), 6.05 (dt, J = 5.4, 2.1 Hz, 1H), 5.82 (m, 1H), 4.63 (d, J = 6.4 Hz, 2H), 3.66 (m, 1H), 3.09 (dt, J = 14.2, 8.5 Hz, 1H), 1.94 (dt, J = 14.2, 6.4 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 151.5, 151.2, 148.9, 145.8, 135.7, 131.2, 130.8, 78.2, 60.2, 42.9, 34.5 cm^{-1}; IR ($CDCl_3$) 3092, 3064, 1588, 1562, 1556, 1494; HRMS (FAB) calcd for $C_{11}H_{11}O_2N_5Cl$ (MH^+) 280.0602, found 280.0601. Anal. Calcd: C, 47.24; H, 3.60; N, 25.04. Found: C, 47.27; H, 3.56; N, 24.95.

(+)-(1*R*,4*S*)-1-Acetoxy-4-(nitromethyl)-2-cyclopentene (14). Carbonate **7** (22.4 mg, 0.105 mmol) was weighed into a flame-dried flask under a N_2 atmosphere and then dissolved in a mixture of nitromethane (0.35 mL) and CH_2Cl_2 (1.75 mL). PPh_3 (5.0 mg, 0.021 mmol, 20 mol%) was added to the colorless solution followed by the catalyst, DBA_3Pd_2 (4.8 mg, 0.0052 mmol, 5 mol %). Initially the solution turned dark brown, but gradually became lighter until a bright yellow color was achieved, usually after 5 min. The reaction progress was monitored by TLC (4:1 hexanes−EtOAc, R_f 0.30) and judged complete in typically 15−60 min. The reaction mixture was diluted with ether and washed through a premoistened (ether) plug of layered $MgSO_4$ and silica gel (40−140 mesh) with anhydrous ether. The solvent was removed under reduced pressure. The crude material was chromatographed over SiO_2 (7 g) with 10:1 hexanes−EtOAc as the eluent. Concentration under high vacuum produced a 15.3 mg mixture of **14** and **15** in a 4:1 ratio (63% and 16%, respectively) as measured by NMR. Scale-up to gram quantities of reactants afforded more modest yields (45−55%) of **14**. Further chromatography under similar conditions led to pure **14**: $[\alpha]^{27}_D$ +83.4° (*c* 1.535, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 5.98 (br s, 2H), 5.63 (ddd, J = 7.6, 3.4, 0.9 Hz, 1H), 4.43 (dd, J = 12.4, 6.7 Hz, 1H), 4.31 (dd, J = 12.4, 7.9 Hz, 1H), 3.40 (m, 1H), 2.57 (dt (app quintet), J = 15.2, 7.8 Hz, 1H), 2.02 (s, 3H), 1.62 (dt, J = 15.2, 3.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 169.9, 134.7, 132.3, 78.7, 75.7, 42.0, 33.5, 20.5; IR (neat) 2950, 1727, 1551, 1377, 1243 cm^{-1}; HRMS (CI) calcd for $C_8H_{12}NO_4$ (MH^+) 186.0766, found 186.0774.

***cis*-4-Cyclopentene-1,3-diol diacetate (15)**: ^{1}H NMR ($CDCl_3$) δ 6.06 (s, 2H), 5.51 (m, 2H), 2.85 (overlapping dt, J = 7.5, 15 Hz, 1H), 2.02 (s, 6H), 1.71 (dt, J = 3.8, 15 Hz, 1H).

(+)-(1*R*,4*S*)-4-(Nitromethyl)-2-cyclopenten-1-ol (17). A solution of **14** (50 mg, 0.27 mmol) in 2 mL of concd NH_4OH was stirred at rt under N_2 for 3 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography using 12 g of SiO_2 and a 1:1 hexanes−EtOAc solvent system. Removal of solvent *in vacuo* provided 36.3 mg (94% yield) as a colorless oil: $[\alpha]^{25}_D$ +19.91 (*c* 0.905, MeOH); ^{1}H NMR ($CDCl_3$) δ 5.98 (dt, J = 5.6, 2.0 Hz, 1H), 5.86 (ddd, J = 5.6, 2.0, 1.0 Hz, 1H), 4.87 (m, 1H), 4.46 (dd, J = 12.3, 6.6 Hz, 1H), 4.37 (dd, J = 12.3, 7.4 Hz, 1H), 3.33 (m, 1H), 2.56 (ddd (app quintet), J = 14.2, 7.9, 7.6 Hz, 1H), 1.70 (br s, 1H), 1.52 (ddd (app dt), J = 14.2, 4.4, 4.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 136.3, 132.3, 79.5, 75.6, 42.4, 36.7; IR (neat) 3361, 2916, 1556, 1381, 1084 cm^{-1}; HRMS calcd for $C_6H_8O_2N$ (M^+ − OH) 126.0555, found 126.0548.

Preparation of the (*R*)-(+)-MTPA Ester of (+)-(1*R*,4*S*)-4-(Nitromethyl)-2-cyclopenten-1-ol (18). A solution of **17** (18.1 mg, 0.127 mmol), (*R*)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride (96 mg, 0.38 mmol), and pyridine (0.70 mL, 0.18 M in **17**) stirred at rt under N_2 for 12 h. The reaction was quenched with 5 mL of H_2O, layered with ether, and transferred to a separatory funnel. The aqueous phase was extracted (8 ×) with ether. The combined extracts were dried over $MgSO_4$, filtered, and concentrated. The final traces of pyridine were removed by azeotroping with heptane. The residual viscous oil was purified by radial chromatography (1 mm plate, 4:1 hexanes−EtOAc). The spot at TLC R_f 0.31 was collected and concentrated *in vacuo* to give 33.9 mg (77% yield) of **18** as a colorless oil: $[\alpha]^{23}_D$ +102.5° (*c* 1.055, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.55−7.35 (m, 5H, 6.05 (br s, 2H), 5.85 (m, 1H), 4.25 (dd, J = 12.7, 6.8 Hz, 1H), 4.12 (dd, J = 12.7, 8.0 Hz, 1H), 3.51 (s, 3H), 3.40 (m (app dq), 1H), 2.57 (dt (app quintet), J = 15.0, 7.6 Hz, 1H), 1.68 (dt, J = 15.0, 2.9 Hz, 1H); IR (neat) 2952, 1745, 1553, 1379, 1270, 1172 cm^{-1}; HRMS (CI) calcd for $C_{16}H_{20}O_5N_2F_3$ (MNH_4^+) 377.1324, found 377.1324.

Preparation of the (*R*)-(+)-MTPA Ester of *cis*-(±)-4-(Nitromethyl)-2-cyclopenten-1-ol (*dia*-18). See the preparation of **18** above. The NMR spectrum consists of a 1:1

diastereomeric mixture of spectrum **18** (above) overlapping with the following diastereomer: ^{1}H NMR ($CDCl_3$) δ 7.55−7.35 (m, 5H), 6.09 (br s, 2H), 5.84 (m, 1H), 4.30 (dd, J = 12.6, 6.5 Hz, 1H), 4.15 (dd, J = 12.6, 8.2 Hz, 1H), 3.49 (s, 3H), 3.41 (m, 1H), 2.58 (dt (app quintet), J = 15.0, 7.6 Hz, 1H), 1.78 (dt, J = 15.0, 3.0 Hz, 1H).

(+)-(3*R*,5*S*)-3-Azido-5-(nitromethyl)-1-cyclopentene (19). To a stirred solution of allylic acetate **14** (108 mg, 0.583 mmol) in THF (1.16 mL, 0.25 M) was added in one portion to a solution of NaN_3 (80.0 mg, 1.23 mmol) in water (1.23 mL). The reaction vessel was immersed into an oil bath held at 52 °C. After 5 min, $Pd(PPh_3)_4$ (13.5 mg, 0.0117 mmol) was added. The reaction was followed by TLC analysis and judged complete in 20 min. The mixture was passed through a 40−140 silica gel plug with ether. The solvent was concentrated to approximately 75 mL, dried over $MgSO_4$, and vacuum filtered. Purification via radial chromatography (1 mm plate, 6:1 hexanes−EtOAc) afforded, after concentration *in vacuo*, 54.0 mg (67.7% yield) of the *cis*-1,4 product **19** and 10.8 mg (13.5% yield) of the *cis*-1,2 product **20**.

Major isomer **19**: $[\alpha]^{25}_D$ +178.6° (*c* 1.4, $CHCl_3$); R_f 0.31 (6:1 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$) δ 5.95 (br s, 2H), 4.47 (m, 1H), 4.44 (dd, J = 12.6, 6.6 Hz, 1H), 4.31 (dd, J = 12.6, 8.1 Hz, 1H), 3.34 (m, 1H), 2.58 (dt, J = 14.4, 8.2 Hz, 1H), 1.62 (dt, J = 14.4, 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 134.6, 132.4, 79.1, 66.2, 42.9, 34.2; IR (neat) 2923, 2096, 1552, 1380, 1368, 1248 cm^{-1}: HRMS (CI) calcd for $C_6H_9O_2N_4$ (MH^+) 169.0726, found 169.0736.

Minor isomer **20**: R_f 0.36 (6:1 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$) δ 6.16 (m, 1H), 5.92 (m, 1H), 4.67 (dd, J = 14.0, 8.3 Hz, 1H), 4.43 (dd, J = 14.0, 7.0 Hz, 1H), 4.50 (m, 1H), 3.07 (m (app sextet), 1H), 2.54 (m, 1H), 2.26 (ddq, J = 17.0, 8.0, 2.5 Hz, 1H); IR (neat) 2940, 2101, 1553, 1380, 1250 cm^{-1}.

(−)-(1*R*,2*R*,3*S*,4*R*)-4-Azido-1-(nitromethyl)-2,3-(isopropylidenedioxy)cyclopentane (21). To a N_2-flushed flask containing a solution of **19** (167.6 mg, 0.9970 mmol) in 3.3 mL of an 8:1 acetone−water solution was added NMO (350.4 mg, 2.991 mmol). The reaction vessel, equipped with a glass-coated magnetic stirbar, was placed in a salt−ice bath in which the temperature was held between −5 and −15 °C prior to the addition of a small crystal of OsO_4. TLC analysis indicated that the reaction was complete in 2 h (R_f 0.32, 1:1 hexanes−EtOAc). The mixture was then eluted through a SiO_2 plug with 400 mL of ether and concentrated under reduced pressure. The crude diols were chromatographed over SiO_2 (9 g, 40−140) with 200 mL of 1:1 hexanes−EtOAc. All of the eluent was collected and concentrated under vacuum to afford 202 mg of a yellow oil. The diols were then transferred to a flame-dried flask and dissolved in 4.95 mL of freshly distilled acetone and 20 drops of 2,2-dimethoxypropane. Two crystals of *p*-TSA were added to the solution, and the reaction was stirred for 1 h before it was quenched by passing it through a $MgSO_4/SiO_2$ plug with ether. The solvent was removed under vacuum, and the crude mixture of acetonides **21** and **22** was purified by radial chromatography (2 mm plate, 6:1 hexanes−EtOAc). The spot at TLC R_f 0.29 was collected and concentrated *in vacuo* to give 56.6% yield of **21** as a colorless oil.

Major isomer **21**: $[\alpha]^{26.5}_D$ −28.1° (*c* 1.31, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.65−4.35 (m, 2H), 4.55 (dd, J = 13.1, 7.8 Hz, 1H), 4.39 (dd, J = 13.1, 7.2 Hz, 1H), 4.05 (m, 1H), 2.88 (m (app dq), 2.39 (ddd, J = 14.2, 7.8, 5.6 Hz, 1H), 1.60 (br d, J = 14.2 Hz, 1H), 1.44 (s, 3H), 1.27 (s, 3H): ^{13}C NMR ($CDCl_3$) δ 111.7, 84.7, 82.7, 66.6, 43.7, 32.3, 29.5, 26.4, 24.1; IR (neat) 2989, 2938, 2113, 1552, 1378, 1212 cm^{-1}; HRMS (CI) calcd for $C_9H_{15}O_4N_4$ (MH^+) 243.1093, found 243.1080.

Minor isomer **22**: The spot at TLC R_f 0.16 was collected and concentrated in vacuo to give 24.1 mg (10% yield) of **22** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 4.65 (dd, J = 14.0, 7.8 Hz, 1H), 4.63 (m, 2H), 4.41 (dd, J = 6.7, 14.0 Hz, 1H), 3.30 (m, 1H), 3.28 (m, 1H), 1.98 (ddd (app br quintet), J = 11.6, 5.9, 5.9 Hz, 1H), 1.79 (ddd (app q), J = 11.9, 11.8, 11.8 Hz, 1H), 1.47 (s, 3H), 1.29 (s, 3H); IR (neat) 2983, 2938, 2105, 1450, 1376 cm^{-1}.

(−)-(1*R*,2*R*,3*S*,4*R*)-4-Azido-1-(hydroxymethyl)-2,3-(isopropylidenedioxy)cyclopentane (23). To a stirring, ice−water cooled solution of compound **21** (142.9 mg, 59 mmol) in MeOH (4.2 mL) was added dropwise over 5 min a freshly prepared solution of KOH (87%, 42.1 mg, 0.65 mmol) in MeOH (6.5 mL). After an additional 15 min, a freshly prepared solution of $KMnO_4$ (74.7 mg, 0.470 mmol) and $MgSO_4$ (51.9 mg, 0.430 mmol) in 10.5 mL of H_2O was added dropwise over 15 min. The reaction stirred at 0 °C for 45 min and was then quenched by passing it through a Celite plug with ether. Brine was added and the aqueous layer extracted with 1:1 ether−EtOAc (5 ×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 108 mg of crude aldehyde. The unstable aldehyde was immediately dissolved in 2-propanol (5.1 mL), cooled in an ice−water bath, and combined with $NaBH_4$ (107 mg, 0.78 mmol). The reaction ran at rt and was judged complete in about 1 h using TLC analysis. The mixture was cooled in an ice−water bath, layered with ether, and quenched with the addition of H_2O. When the gas evolution had ceased, a saturated NaCl solution was added and the aqueous phase was extracted with EtOAc (7 ×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. Column chromatography performed over SiO_2 with 3:1 hexanes−EtOAc to provided 8 mg of recovered **21** and 54 mg (45.5% yield) of pure **23**: $[\alpha]^{19}_D$ −35.2° (*c* 0.515, $CHCl_3$); R_f 0.26 (3:1 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$) δ 4.55 (dd, J = 6.2, 1.6 Hz, 1H), 4.43 (dd, J = 6.2, 1.9 Hz, 1H), 3.95 (ddd, J = 6.7, 4.4, 6.7 Hz, 1H), 3.63 (d, J = 6.4 Hz, 2H), 2.39−2.20 (m, 2H), 1.63 (br s, 1H), 1.60 (m, 1H), 1.44 (s, 3H), 1.27 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 111.6, 85.2, 82.6, 67.0, 63.8, 47.2, 32.0, 26.7, 24.3; IR (neat) 3436, 2988, 2936, 2105, 1455, 1440, 1381, 1376, 1263, 1211, 1161, 1065, 1039, 865 cm^{-1}; HRMS (CI) calcd for $C_9H_{16}O_3N_3$ (MH^+) 214.1192, found 214.1183.

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Supporting Information Available: Copies of the ^{1}H NMR spectra for compounds **1-15**, **17-22**, and *dia*-**18** (20 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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