Synthesis of Methyl 5-(*N*-Benzoyl-*N*-methylamino)-2-methylpenta-2,4-dienoate by Ring-Opening Acylation of an *N*-Alkyltetrahydropyridine

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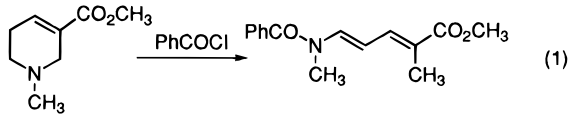
Received November 5, 1996

Iminosugars, in which a nitrogen atom replaces the ring oxygen or anomeric carbon of a saccharide, often display potent and specific activity as glycosidase inhibitors,[1] and many such structures have found application in the emerging field of glycobiology.[2] As part of an ongoing program to synthesize novel azasugar mimics of monosaccharides, we had occasion to investigate the chemistry of arecoline (methyl *N*-methyl-1,2,5,6-tetrahydropyridine-3-carboxylate, **1**), a readily available anthelmintic natural product from the betel nut palm *Areca catechu*.[3] In the course of *N*-demethylation studies on **1** and its congeners, we observed an unexpected and noteworthy high-yielding ring opening to form the *trans, trans*-*N*-acyl-*N*-alkylamino 1,3-diene **2** (eq 1). Over the



(1)

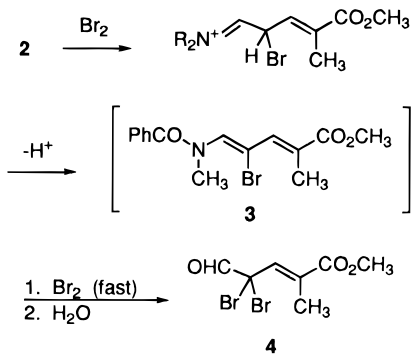
1 **2**

past 20 years, such heteroatom-substituted dienes have found application in Diels−Alder ring constructions.[4,5] More recently, the "push-pull" combination of electron-donating and electron-withdrawing groups evident in dienes related to **2** has been found to exhibit second-harmonic generation activity and other interesting optoelectronic properties.[6]

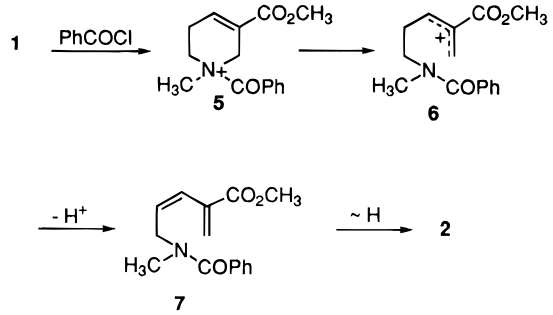
Results and Discussion

In 1983, Allan and Fong reported the successful N-demethylation of **1** using (2,2,2-trichloroethoxy)carbonyl chloride.[7] However, the intermediate (trichloroethyl)-carbamate was known to be sensitive to dialkylamide bases, which posed limits on subsequent alkylation experiments we envisioned. Since a wide range of acyl chlorides have been utilized for N-demethylation,[8] we considered using a nonenolizable acylating agent such as benzoyl chloride. However, when **1** was heated with C_6H_5COCl (xylenes, reflux, 1 day) a single new product, mp 122−123 °C, was formed in 84% yield, exhibiting dramatically different spectral characteristics from **1**. The ^{1}H-NMR spectrum of the product displayed, *inter alia*, three distinct alkene hydrogen resonances and three

Scheme 1



Scheme 2



methyl singlets. Those data, together with the UV spectrum, which revealed an absorbance [$\lambda_{max} = 310$ nm, ($\epsilon = 30\,200$, EtOH)] consistent with its δ-amido-α,β-γ,δ-dienoic ester chromophore, led us to assign structure **2** to the product.

Consistent with its geminal substitution at one terminus of the diene system, which restricts access to the *cisoid* conformation required for Diels−Alder cycloaddition, compound **2** failed to react either with electron-deficient (maleic anhydride, tetracyanoethylene) or electron-rich (vinylene carbonate) dienophiles. The enamide functional group in **2** was also resistant to hydrolysis. However, **2** did react with soft electrophiles, such as bromine in CH_2Cl_2, to afford dibromo aldehyde **4** in 91% yield. When 1 equiv of Br_2 was used, equal amounts of recovered **2** and **4** were isolated, suggesting that a second, more rapid bromination of the initially formed monobromide **3** occurred as shown in Scheme 1. Intermediate bromo diene **3** could not be isolated.

To the best of our knowledge, the ring opening of **1** to **2** is without precedent, although the Hofmann elimination of similar 3,4-unsaturated piperidines has been reported to proceed with ring opening.[9] When benzoyl chloride is replaced with phenyl chloroformate, simple N-demethylation is observed. One plausible mechanism for forming **2** is outlined in Scheme 2. Ring opening of *N*-acyl-*N*-alkylammonium species **5** would furnish allylic cation **6**. Deprotonation of **6** should afford diene **7**, which might then isomerize to the fully conjugated product **2**.

The suggested mechanism for forming **7** would also explain a longstanding observation in a closely related tropane alkaloid system, where demethylation of anhydroecgonine ethyl ester **8** took place with extensive ring

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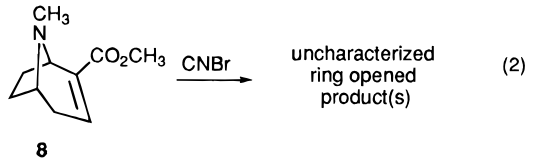
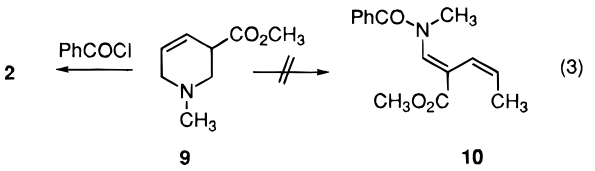
S0022-3263(96)02070-1 CCC: $14.00

opening (eq 2).[10] Attempts to transform the known[7] β,γ-





unsaturated isomer **9** into diene **10** using benzoyl chloride were unsuccessful (eq 3). Only diene **2** was formed in 72% yield, suggesting that **9** isomerized to **1** under the conditions of acylation.

Experimental Section

Reactions were performed under an argon atmosphere using oven-dried glassware. Xylenes were distilled over 4 Å molecular sieves. Melting points are uncorrected. NMR spectra were recorded at room temperature. Arecoline **1** was prepared from commercially available arecoline hydrobromide (Aldrich Chemical Co.) using a known procedure.[7]

Preparation of Diene 2. A suspension of freshly distilled benzoyl chloride (0.31 mL, 2.70 mmol), K_2CO_3 (300 mg, 2.16 mmol), and arecoline (280 mg, 1.80 mmol) in xylenes (5 mL) was heated at reflux for 24 h, and then the reaction mixture was cooled to room temperature and filtered. The filtrate was washed with 5 M NaOH (1 × 2 mL) and 1 M HCl (1 × 2 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel 60 (230−400 mesh) flash chromatography, eluting with 3:1 hexanes:ethyl acetate, to afford diene **2** (390 mg, 84%) as a white solid: mp 122−123 °C; R_f 0.17; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.46 (br s, 5 H), 7.15−7.40 (m, 1 H), 7.07 (d, 1 H, J = 11.5 Hz), 5.88 (dd, 1 H, J = 11.7, 11.5 Hz), 3.71 (s, 3 H), 3.33 (s, 3 H), 1.93 (s, 3 H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 170.7, 168.8, 137.2, 134.3, 130.8, 128.6, 128.0, 125.5, 123.7, 106.3, 51.6, 20.6, 12.5; IR (KBr) 1930, 1720, 1675, 1630 cm^{-1}; UV (λ_{max}, EtOH) 205 nm (ϵ = 31 300), 310 nm (ϵ = 30 200); EIMS m/e 259 (M^+), 105 (100).

Preparation of Dibromoaldehyde 4. To a solution of diene **2** (50 mg, 0.19 mmol) in CH_2Cl_2 (2 mL) was added bromine in CH_2Cl_2 (1 M, 0.4 mL, 0.40 mmol) dropwise at −78 °C. When the addition was complete, the resulting solution was stirred for 5 min at −78 °C, and then treated with water (0.5 mL) and warmed to room temperature. After evaporation of the solvent, the residue was purified by flash column chromatography using 5:1 hexanes:EtOAc to give **4** (52 mg, 91%) as a colorless oil: R_f 0.28; ^{1}HNMR (300 MHz, $CDCl_3$) δ 9.19 (s, 1 H), 7.66 (s, 1 H), 3.85 (s, 3 H), 2.22 (s, 3 H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 185.7, 169.4, 152.8, 128.9, 54.4, 54.3, 27.8; IR (CH_2Cl_2) 2940, 1745, 1710, 1610 cm^{-1}; EIMS m/e 298 (0.7), 300 (1.4), 302 (0.7), all M^+, 96 (100).

Acknowledgment. We thank the National Institutes of Health (GM 35712) for generous financial assistance. Support of the Cornell Nuclear Magnetic Resonance Facility by the NSF (CHE 7904825; PGM 8018643) and NIH (RR02002) is gratefully acknowledged.

Supporting Information Available: ^{1}H-NMR and ^{13}C-NMR spectra for **2** and **4** (4 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.

JO962070N

Additions and Corrections

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Arun K. Ghosh* and Wenming Liu. Total Synthesis of (+)-Sinefungin.

Page 6175, footnote 9. The following reports of total synthesis of sinefungin and analogs of sinefungin regrettably were omitted: (e) Barton, D. H. R.; Gero, S. D.; Negron, G.; Quiclet-Sire, B.; Samadi, M.; Vincent, C. *Nucleosides Nucleotides* **1995**, *14*, 1619. (f) Barton, D. H. R.; Gero, S. D.; Lawrence, F.; Robert-Gero, M.; Quiclet-Sire, B.; Samadi, M. *J. Med. Chem.* **1992**, *35*, 63. (g) Barton, D. H. R.; Gero, S. D.; Quiclet-Sire, B.; Samadi, M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 981.

JO964030P