$^1$H NMR ($CCl_4$) $\delta$ 1.3 (3 H, d, $J$ = 7 Hz), 2.4–2.9 (2 H, m), 3.4 (1 H, dd, $J$ = 8 Hz, $J'$ = 18 Hz), 7.0–7.7 (4 H, m); IR (NaCl) 1710 cm$^{-1}$ (C=O); mass spectrum (relative abundance), $m/e$ 146 (P, 70), 131 (100), 115 (45), 103 (41), 91 (32), 77 (30), 65 (32), 51 (35), 39 (39).

**Registry No.** 2-Methyl-3-phenylpropionic acid, 1009-67-2; β-chloro-α-methylpropionic acid, 16674-04-7; ethyl β-chloro-α-methylpropionate, 922-29-2; 2,6-dimethyl-1-indanone, 66309-83-9; toluene, 108-88-3; 2-methyl-1-indanone, 17496-14-9; ethyl cyclpropanecarboxylate, 4606-07-9; benzene, 71-43-2.

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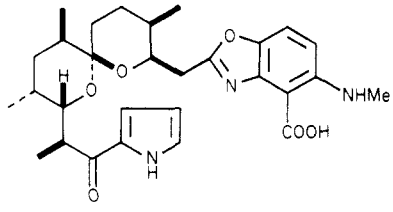
## Preparation and Lithiation of *N*-(*N*,*N*-Dimethylamino)pyrrole: A Useful Reagent for the Preparation of 2-Acylpyrroles

*Summary:* *N*-(*N*,*N*-Dimethylamino)pyrrole can be efficiently lithiated at C(2) with butyllithium and transformed into the corresponding Grignard reagent, which upon condensation with pyridinethiol esters and reductive cleavage of the nitrogen–nitrogen bond provides direct access to 2-acylpyrroles.

*Sir:* In connection with our synthetic efforts in the antibiotic area [cf. A-23187 (1)],[1] we required a mild method for the preparation of 2-acylpyrroles from a suitable pyrrole derivative. Essential to our scheme was the proper choice



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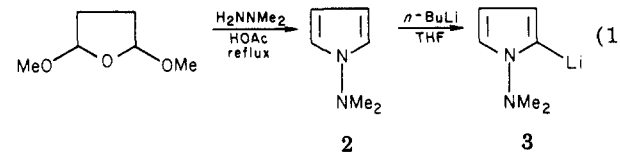
of a protecting group for the pyrrole N–H bond which would facilitate and stabilize carbanion formation at C(2) and, more importantly, be easily removed under extremely mild conditions. The lack of suitably protected pyrrole derivatives[2] which would be amenable to our needs led us to examine the feasibility of employing the previously unreported pyrrole, *N*-(*N*,*N*-dimethylamino)pyrrole (**2**). We report the preparation and facile lithiation of **2** (eq 1) and the utilization of **3** in the preparation of 2-acylpyrroles.

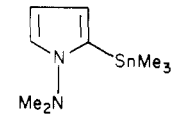
*N*-(*N*,*N*-Dimethylamino)pyrrole (**2**), bp 138–140 °C (distilled from calcium hydride) [$^1$H NMR ($CCl_4$) $\delta$ 2.76 (s, 3 H), 5.81 (t, 1 H), 6.60 (t, 1 H)] was prepared in 57% yield by refluxing (3 h) 2,5-dimethoxytetrahydrofuran and



(1)

2 3

*unsym*-dimethylhydrazine in acetic acid. Lithiation of **2** (1 M in dry tetrahydrofuran) proceeded smoothly (2 h) with 1.0 equiv of *n*-butyllithium, generating the 2-lithiopyrrole **3**. Trapping of **3** with trimethyltin chloride gave 2-(trimethylstannyl)pyrrole **4**, bp 68–70 °C (2.0 mmHg),



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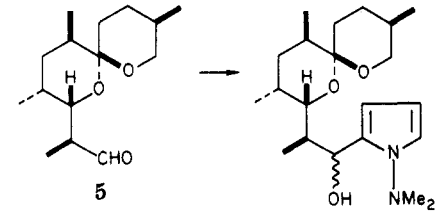
in approximately 80% yield. Regeneration of **3** from **4** could be efficiently carried out by treating a THF solution of **4** cooled to −78 °C with 1.0 equiv of *n*-butyllithium. Trapping of **3** with heptanal and aldehyde **5**[1b] gave rise to adducts **6** (75%) and **7** (70%), respectively. Oxidation ($MnO_2$, $CH_3CN$) of **6** afforded (70%) the corresponding ketone which when subjected to cleavage of the nitrogen–nitrogen bond [$Cr_2(OAc)_4 \cdot 2H_2O$[3] (3.0 equiv), EtOH, RT, 12 h] gave a 95% yield of the 2-acylpyrrole **8**. Attempts to reductively cleave the N–N bond under hydrogenolysis conditions ($H_2$, 10% Pd/C, EtOH) were not encouraging.



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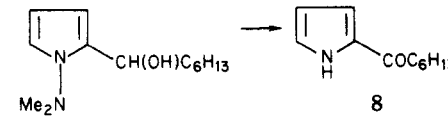
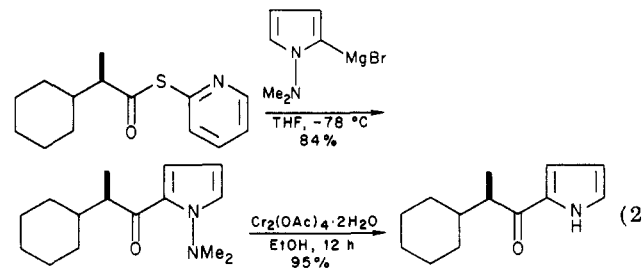


6 8

A direct route to 2-acylpyrroles was achieved by condensation of the Grignard reagent derived from **3** (prepared at 0 °C by treatment of **3** with 1.0 equiv of anhydrous $MgBr_2$ in tetrahydrofuran) with pyridinethiol esters[4] followed by clipping of the N–N bond with chromous acetate (cf. eq 2). Yields for the latter step are generally



(2)

in excess of 95%. Application of this two-step sequence to substrates **9**[5] and **10** provided **11** and **12**, respectively, in excellent overall yield.[6]

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(2) For α lithiation of N-substituted pyrroles, see Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 21. Also see Hasan, I.; Marinelli, E. R.; Lin, C. L.-C.; Fowler, F. W.; Levy, A. B. *J. Org. Chem.* **1981**, *46*, 157.
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(5) The transformation of **9** into **11** was carried out at −10 °C.

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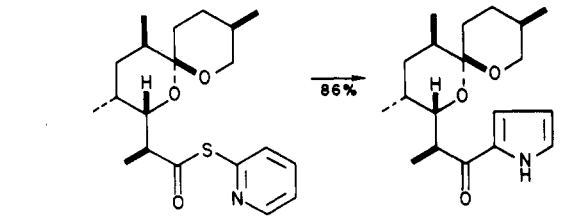


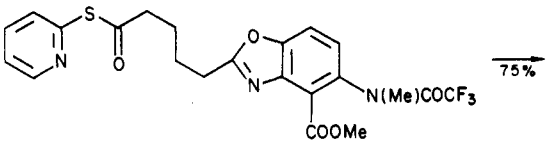


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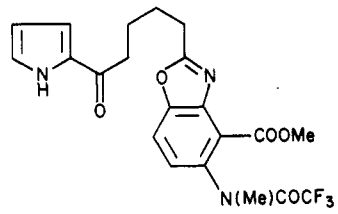


12

The ready availability of *N*-(*N*,*N*-dimethylamino)pyrrole (**2**) coupled with the extreme ease with which it undergoes lithiation, conversion into a Grignard reagent, and removal of the dimethylamino protecting group renders **2** an exceedingly useful reagent in organic synthesis.

**Acknowledgment.** This research was supported by a Public Health Service Research Grant from the National Institute of Allergy and Infectious Diseases (AI-17410). We are indebted to Dr. Heinz Gschwend for valuable discussions.

**Registry No.** **2**, 78307-76-3; **3**, 78307-77-4; **4**, 78307-78-5; **5**, 78307-79-6; **6**, 78328-70-8; **7**, 78307-80-9; **8**, 73252-31-0; **9**, 78307-81-0; **10**, 78307-82-1; **11**, 78307-83-2; **12**, 78328-71-9; 2,5-dimethoxytetrahydrofuran, 696-59-3; *unsym*-dimethylhydrazine, 57-14-7; heptanal, 111-71-7; 1-(dimethylamino)-2-heptanoylpyrrole, 78307-84-3; *S*-(2′-pyridyl) 2-cyclohexylpropanethioate, 78307-85-4; 1-(dimethylamino)-2-bromopyrrole, 78307-86-5; 1-(dimethylamino)-2-(2-cyclohexylpropanoyl)pyrrole, 78307-87-6; 2-(2-cyclohexylpropanoyl)-pyrrole, 78307-88-7.

(6) All new compounds reported have been fully characterized by spectral analysis (NMR, IR) and combustion or high-resolution mass spectral analysis.

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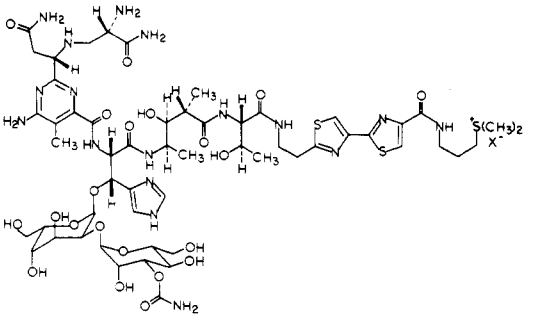
## Synthesis of the Carbohydrate Moiety of Bleomycin

*Summary:* The synthesis of the disaccharide 2-*O*-(3-*O*-carbamoyl-α-D-mannopyranosyl)-L-gulopyranose has been achieved in good yield via the silver triflate promoted coupling of 2,4,6-tri-*O*-acetyl-3-*O*-(*N*-acetylcarbamoyl)-α-D-mannopyranosyl bromide (**7**) with both benzyl 3,4,6-tri-*O*-benzyl-β-L-gulopyranoside (**5**) and 3,4-di-*O*-benzyl-1,6-anhydro-β-L-gulopyranose (**12**).

*Sir:* Bleomycin $A_2$ (**1**), one of a family of structurally related antibiotics derived from *Streptomyces*,[1] is the major component of a mixture of bleomycins used clinically for the treatment of certain malignancies.[2] Biochemically,



**1**

bleomycin mediates the cleavage of DNA, and this property may well constitute the basis for its anticancer activity.[3] To facilitate an understanding of the structural basis of the biological and biochemical activities of the bleomycins, there has been considerable interest in their chemistry, and numerous reports have appeared descriptive of the modification[4] of this natural product as well as the synthesis of components of the bleomycins.[5] Reported herein is the first synthesis of the carbohydrate moiety[6] of bleomycin and certain observations regarding synthetic approaches useful for its elaboration.

Benzyl 3,4,6-tri-*O*-benzyl-β-L-gulopyranoside (**5**) was obtained from L-gulose,[7] the latter of which was acetylated[8] and then converted to 3,4,6-tri-*O*-acetyl-1,2-*O*-(1-methoxyethylidene)-β-L-gulopyranose (**2**) via an intermediate tetraacetyl gulopyranosyl bromide (HBr–HOAc, then $CH_3OH$, $(C_2H_5)_4N^+Br^-$, Hünigs base). Ortho ester **2** was

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(2) (a) Crooke, S. T. "Bleomycin: Current Status and New Developments"; Carter, S. K., Crooke, S. T., Umezawa, H., Eds.; Academic Press: New York, 1978; p 1 ff. (b) Carter, S. K. *Ibid.* p 9 ff.

(3) Hecht, S. M. "Bleomycin: Chemical, Biochemical and Biological Aspects"; Hecht, S. M., Ed.; Springer-Verlag: New York, 1979; p 1 ff.

(4) For example, see Tanaka, W.; Takita, T. *Heterocycles* **1979**, *13*, 469.

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(6) The technically simpler synthesis of 2-*O*-(α-D-mannopyranosyl)-L-gulopyranose (i.e., the carbohydrate lacking the carbamoyl moiety of bleomycin) has recently been reported; see Tsuchiya, T.; Miyake, T.; Kageyama, S.; Umezawa, S.; Umezawa, H.; Takita, T. *Tetrahedron Lett.* **1981**, *22*, 1413.

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