

rate. This suggests that if 1^+ were involved in the reaction, its lifetime, or that of the ion-pair ($1^+ \cdot \text{DCA}^-$), should be considerably less than the singlet lifetime of DCA (12 ns).¹⁷

The present evidence restricts the possible pathways to those shown in Scheme I. A thermally forbidden concerted σ -bond cleavage in 1^+ should require a high activation energy,¹⁸ but the formation of an intermediate short-lived bianthryl diradical (or radical-ion) is a possibility.

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Registry No. 1, 1627-06-1; chloranil, 118-75-2; 9,10-dicyanoanthracene, 1217-45-4; 1,4-dimethoxybenzene, 150-78-7.

(17) $\tau = 12.2$ ns in degassed solution, 11.7 ns under aerated conditions in methylene chloride at room temperature. We thank E. Gudgin and Professor W. R. Ware for this determination.

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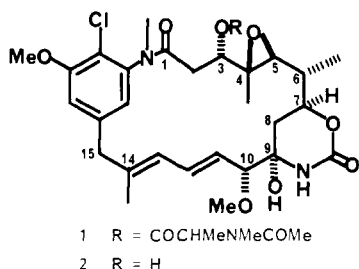
Stereocontrolled Total Synthesis of (\pm)-Maytansinol

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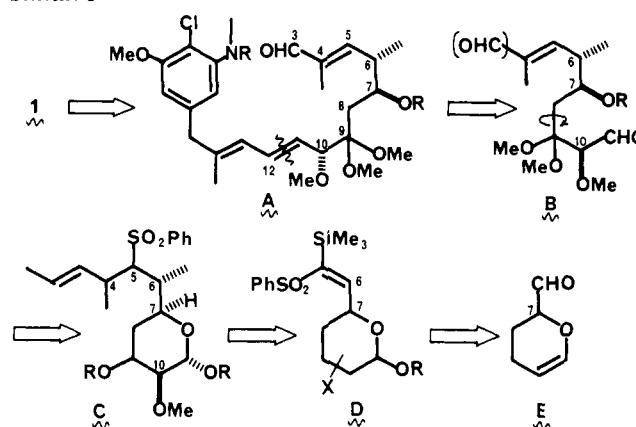
Maytansine (1), a novel ansa-macrocyclic lactam from *May-*



tenus serrata, *M. buchananii*, etc., has significant in vitro cytotoxicity and in vivo antitumor activity.¹ It was recently synthesized by two groups in racemic and optically active forms.² Recent stereochemical advances in the macrocyclic natural product syntheses³ prompted us to describe our new stereocontrolled total synthesis of racemic maytansinol (2). Our goal to this synthesis lies in exploiting the acyclic diastereoselective induction of all of the asymmetric carbons, before closing the 19-membered lactam ring starting from one single asymmetric center in a simple molecule.

The general synthetic strategy toward maytansinoids is illustrated in Scheme I. The common three asymmetric carbons, C-6, -7, and -10 for maytansinoids are included in the intermediate A. Cleavage between C-11 and C-12 of A leads to the pyranosyl ring compound C. The heteroconjugate addition⁴ of MeLi accomplishes the complete acyclic stereoselection in the pyranosyl heteroolefin such as D,⁵ which is preparable from acrolein dimer

Scheme I



E. The high diastereoselective C-C bond formation was facilitated by efficient conformational and chelational control. The current methodology was also designed for elongation of the C-C chain between C-4 and C-5 effected by the α -sulfonyl carbanion, which was finally removed to form an olefin. The stereochemistry of other asymmetric centers were controlled under new *diastereoselective* methods such as epoxidation,⁶ aldol reaction, and so on.

Heteroconjugate addition of MeLi (THF, -78°C , 5 min) to 3 (Scheme II) was followed by treatments with KF (forming 4, its carbanion being generated with *n*-BuLi) and 4-bromo-2-pentene to give alkylated products 5 in 92% yield. Selective opening of the oxyrane ring of 5 with sodium *p*-anisyl oxide (5 equiv in refluxing THF) and subsequent trapping with large excess MeI in one pot gave 6 (87%), which was further converted into 8b (86%) in several steps for a basic cleavage of the glycosidic bond. Thus, 6 was first treated with 2-chloroethanol [containing 10-camphorsulfonic acid (CSA) and $(\text{MeO})_3\text{CH}$ at 80°C for 18 h], and the resulting 7 was oxidized with $\text{CrO}_3\cdot 2\text{Py}$ (CH_2Cl_2 , room temperature, 0.5 h) and then ketalized with $(\text{MeO})_3\text{CH}$ (CSA in MeOH, room temperature 12 h) to give 8a. It was further converted into the 2-phenylsulfonyl ethyl glycoside 8b with sodium thiophenolate (THF, 0°C to room temperature) and then with MCPBA (dry CH_2Cl_2 , 0°C 0.5 h). Reduction of 8b⁷ with NaBH_4 [$\text{EtOH}\cdot\text{THF}$ (4:1), 80°C , 1 h, N_2] afforded the open-chain diol 9a (70%). Each of its two hydroxy groups was selectively protected first with AcCl [1.2 equiv and Py (5 equiv), dry CH_2Cl_2 , 0°C , 20 min] and subsequently with $\text{Me}_2\text{t-BuSiCl}$ (imidazole in DMF, 70°C 30 h) to give 9b (50% overall yield from 7). Ozonolysis of 9b (CH_2Cl_2 , -78°C) and workup with Et_3N produced in 99% yield the stereochemically pure unsaturated aldehyde 10 [^1H NMR δ 1.06 (Me, d, $J = 7$ Hz), 1.78 (Me, s), 3.98 (d, $J = 12$ Hz), 4.38 (dd, $J = 12, 2.5$ Hz), 6.48 (d, $J = 9$ Hz), 9.32 (s); IR ν 1744, 1690 cm^{-1}], which involved the common three asymmetric centers for maytansinoids. 10 was converted in three steps to 11 (91%) by successive treatments with (i) pyridinium tosylate [$\text{MeOH}\cdot(\text{MeO})_3\text{CH}$ (6:1), 0°C , 2 days], (ii) MeONa [1.5 equiv in MeOH, room temperatures, 45 min], and (iii) $\text{CrO}_3\cdot 2\text{Py}$ (6 equiv in CH_2Cl_2 , room temperature, 15 min). The acetal 11 was now ready to be condensed with the aromatic counterpart 15 toward 17. On the other hand, the phosphorus ylide 15 was prepared in seven steps from the known benzyl iodide 12¹⁰ via 13 and 14a-d in 45% overall yield.¹¹ This ylide was reacted with

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(2) (a) Meyers, A. I.; Reider, P.; Campbell, A. L. *J. Am. Chem. Soc.* **1980**, *102*, 6579. (b) Corey, E. J.; Weigel, L. O.; Chamberlin, A. R.; Cho, H.; Hua, D. H. *Ibid.* **1980**, *102*, 6615.

(3) For example: "Organic Synthesis Today and Tomorrow"; Trost B. M., Hutchinson, C. R., Eds.; Pergamon Press New York, 1981.

(4) (a) Isobe, M.; Kitamura, M.; Goto, T. *Tetrahedron Lett.* **1979**, 3465; (b) **1980**, *21*, 4727; (c) *Chem. Lett.* **1980**, 331.

(5) (a) Isobe, M.; Kitamura, M.; Goto, T. *Tetrahedron Lett.* **1981**, *22*, 239. (b) Isobe, M.; Ichikawa, Y.; Goto, T. *Ibid.* **1981**, *22*, 4287.

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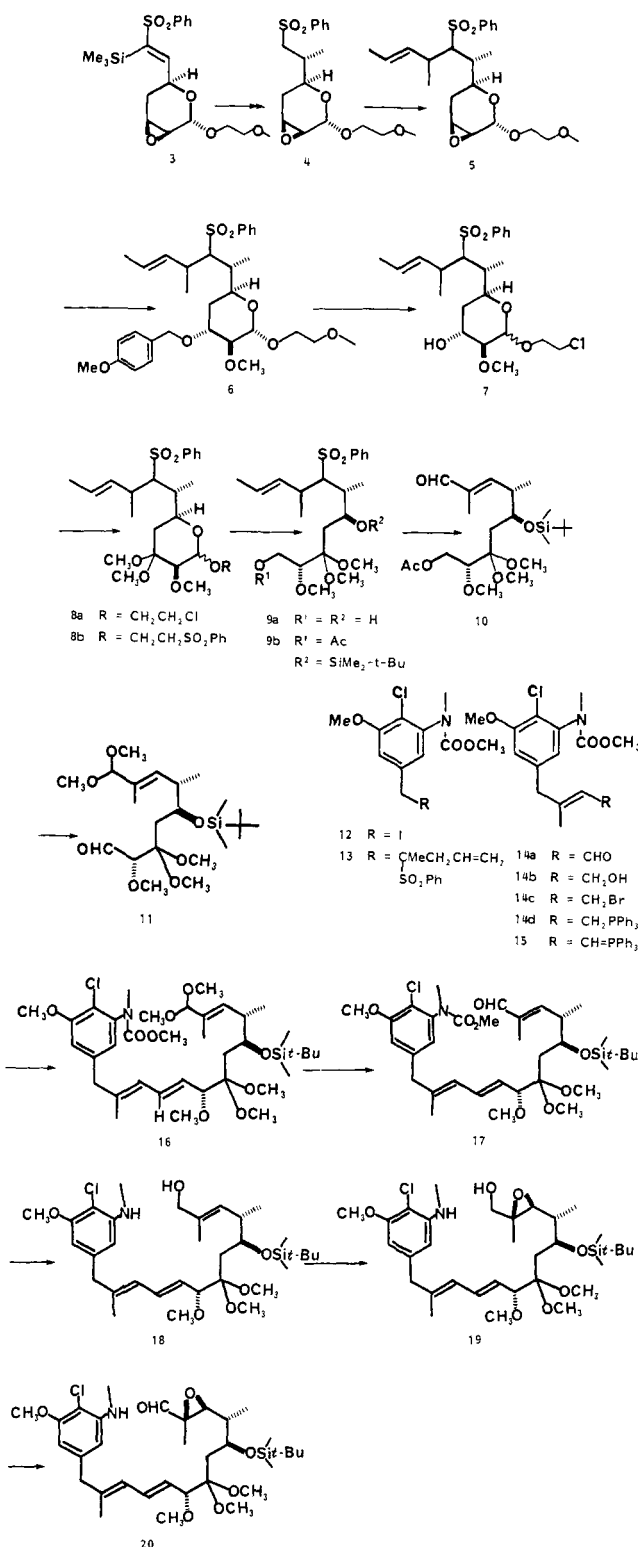
(7) This particular glycoside, 8b, was extremely alkaline labile even in the basicity of NaBH_4 ; see also: Narang, S. A.; Bhanot, O. S.; Goodchild, J.; Wightman, R. J.; Dheer, S. K. *J. Am. Chem. Soc.* **1972**, *94*, 6183.

(8) Usage of Et_3N to decompose ozonide was first reported by Isobe et al. (Isobe, M.; Iio, H.; Kawai, T.; Goto, T. *Tetrahedron Lett.* **1977**, 703).

(9) ^1H NMR spectra were measured in CDCl_3 (δ) at 100 MHz unless specified; IR spectra were taken in CCl_4 .

(10) Gotschi, E.; Schneider, F.; Wagner, H.; Bernaner, K. *Org. Prep. Proced. Int.* **1981**, *13*, 23.

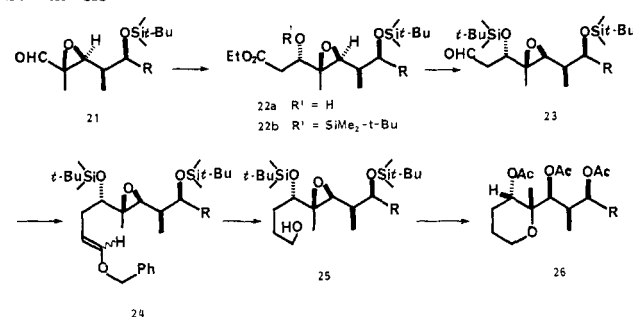
Scheme II



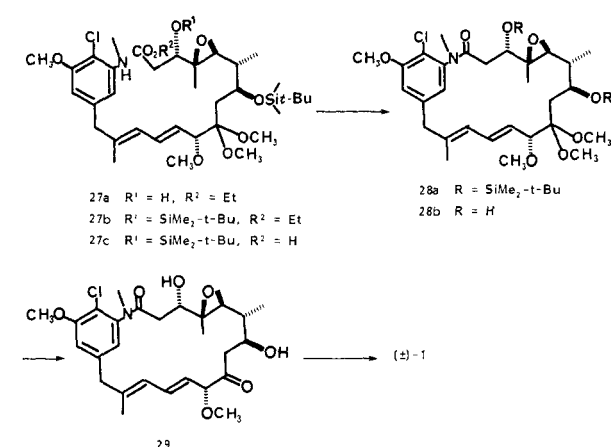
the aldehyde 11 (THF, -63°C to room temperature overnight) to produce the diene 16 (78% yield),¹² which was selectively

(11) In THF 4-lithio-4-(phenylsulfonyl)-1-pentene was added to 12, and the product (13) was treated with ozone and Et_3N at -78°C to give unsaturated aldehyde 14a as a ca. 5:1 *E/Z* olefinic mixture, which was separated. The major *E* isomer [^1H NMR δ 2.04 (Me, s), 10.01 (d, $J = 8$ Hz)] was successively treated with (i) NaBH_4 [EtOH , 0°C , 0.5 h], (ii) PBr_3 , LiBr , and collidine [Et_2O -THF (8:3)], (iii) Ph_3P [nitromethane], and (iv) $t\text{-BuLi}$ [THF-DMF (2:1), -63°C] afforded the 14b, 14c, 14d, and the ylide 15, respectively. The minor isomer *Z*-14a [^1H NMR δ 1.94 (Me, s), 10.07 (d, $J = 8$ Hz)] was in equilibrium with *E*-14a in CH_2Cl_2 and Et_3N , the ratio of *E/Z* being 3:1, and the mixture was separated and used.

Scheme III



Scheme IV



hydrolyzed in 4:1:1 THF- H_2O -AcOH (-10°C , 2 days) and separated with HPLC to provide the common intermediate 17¹³ [^1H NMR (200 MHz) δ 1.02 (Me, d, $J = 7$ Hz), 1.70 (Me, s), 1.76 (Me, s), 1.82 (H-8, dd, $J = 15, 2$ Hz), 2.06 (H-8, dd, $J = 15, 7$ Hz), 3.85 (H-10, d, $J = 7$ Hz), 4.08 (H-7, ddd, $J = 7, 4, 2$ Hz), 5.53 (H-11, dd, $J = 15, 7$ Hz), 5.92 (H-13, d, $J = 11$ Hz), 6.47 (H-12, dd, $J = 15, 11$ Hz), 6.51 (H-5, d, $J = 9$ Hz), 6.68 (Ar 2 H, s), 9.33 (s); m/z 681 (M^+)]

The diastereoselective epoxidation of some olefins into completely syn orientation was unknown until we explored a method⁶ for olefins such as 18. The aldehyde 17 was first reduced with NaBH_4 [MeOH , 0°C , 15 min] and then hydrolyzed with 12 N 1:3 KOH-EtOH (reflux for 22 h) to give the amino alcohol 18 (84%). When treated with $\text{Ti}(\text{O}-i\text{-Pr})_4$ and $t\text{-BuOOH}$ (dry CH_2Cl_2 , -20°C , 1.5 h), the allylic alcohol 18 gave the single epoxide 19 [^1H NMR 1.34, 3.00 (oxirane Me and H)] in 70% yield. The stereocontrol at the C-3 position remained the major problem toward maytansinol (2). To solve the problem, we employed the aldol reaction to get the epoxy aldehyde 20 and several analogous model compounds such as 21 and then examined the stereoisomerism in the products. When lithium salt of ethyl acetate was added to 21 [$\text{R} = (\text{CH}_2)_3\text{CH}_2\text{OSiMe}_2\text{-}t\text{-Bu}$, in THF, -78°C , 25 min], the corresponding aldol 22a and 3-epi-22a was produced (100%) in a ratio of 6:1, whose structural assignment follows. Each isomer was separated with SiO_2 and was respectively converted into six-membered cyclic derivative 26 via the route illustrated in Scheme III.¹⁴ The ^1H NMR spectrum of 26 showed

(12) The geometry of the olefin was a 55:45 *E/Z*-mixture.

(13) The common intermediate 17 has been converted into *N*-methylmaysenine and maysine, respectively [unpublished results by Isobe, Kitamura, and Goto].

(14) A transformation sequence for 26 as typical example is (i) $\text{Me}_2\text{-}t\text{-BuSiCl}_2$ -imidazole, (ii) LiAlH_4 , and (iii) $\text{CrO}_3\text{-2Py}$, to afford the aldehyde 23. It was further reacted with $\text{Ph}_3\text{P}=\text{CHOCH}_2\text{Ph}$ to yield the vinyl ether 24. Acidic treatment [with 0.1 N HCl-THF (1:5) at room temperature for 12 h] cleaved the primary silyl ether to form the mono-ol which was, after benzylation, hydrogenolyzed with 10% Pd-C [EtOH , 40°C , 22h, H_2] to afford 25 [$\text{R} = (\text{CH}_2)_3\text{CH}_2\text{OBz}$]. Acidic hydrolysis of 25 [with 5% CSA in $\text{CH}_2\text{Cl}_2\text{-MeOH}$] was followed by acetylation to afford the tetrahydropyranyl ether 26 as a single isolable product in more than 64% overall yield.

H-3, at δ 4.64 (br dd, $J = 3.0, 1.5$ Hz),¹⁵ as the equatorial orientation, indicating the right stereochemistry for maytansinol (2).

Similarly, treatment of the epoxy aldehyde **20** with lithium enolate of EtOAc (5 equiv in THF, -78°C , 30 min) now produced the adduct as almost all single isomer **27a** (Scheme IV). Its hydroxy group was protected with $\text{Me}_2\text{-}t\text{-BuSiCl}$ [5 equiv and imidazole (12 equiv) in DMF, 35°C , 12 h], and then the carboxylic ester **27b** was hydrolyzed with a mixture of 3 N 1:5:2 KOH-EtOH-THF (45°C , 7 h) to **27c** (52% overall yield from **20**). Cyclization of the acid **27c** was achieved with mesitylene-sulfonyl chloride^{2b} (20 equiv $i\text{-Pr}_2\text{EtN}$ (20 equiv and $n\text{-Bu}_4\text{NOH}$ in benzene, 40°C) to afford **28a** [^1H NMR δ 1.00 (Me-6, d, $J = 7$ Hz), 1.08 (Me-4), 1.96 (Me-14), 2.94 (H-5, d, $J = 9$ Hz), 3.72 (H-10, d, $J = 8.5$ Hz), 5.24 (H-13, d, $J = 10$ Hz), 5.40 (H-11, dd, $J = 15, 8.5$ Hz), 6.46 (H-12, dd, $J = 15, 10$ Hz), 6.56, 6.72 (Ar 2 H, s); m/z 795 (M⁺)] in 53% yield. Desilylation of **28a** was achieved with $n\text{-Bu}_4\text{NF}$ (5 equiv) only in the presence of MeCN as solvent with THF (2:1), [60°C , 12 h] to form the diol **28b** in 77% yield [m/z 567 (M⁺); IR ν 3500, 1642 cm^{-1}]. The hydrolysis of the dimethyl ketal **28b** with a mixture of 1:3:1 AcOH-THF-H₂O (35°C , 11 h) to give in quantitative yield the ketone **29** [IR ν 1724, 1644 cm^{-1} ; ^1H NMR (200 MHz) δ 0.87 (Me-4), 1.16 (Me-6, d, $J = 6.6$ Hz), 2.55 (H-5, d, $J = 9.5$ Hz), 2.76 (H-8, dd, $J = 17.5, 3.0$ Hz), 6.81, 6.83 (Ar 2 H, d, $J = 2$ Hz); m/z 521 (M⁺)]. Treatment of the keto diol **29** with p -nitrophenyl chloroformate¹⁶ [4 equiv with Py (4 equiv) in dry CH_2Cl_2 , 0°C 15 min] and then with NH_3 [in MeOH with cooling, 20 min] produced maytansinol (2) [^1H NMR (400 MHz) δ 0.84 (Me-4), 1.25 (H-8), 1.29 (Me-6, d, $J = 6.5$ Hz), 1.54 (H-6, m), 1.69 (Me-14), 2.10 (H-2, dd, $J = 13.5, 2.0$ Hz), 2.15 (H-8, d, $J = 14.0$ Hz), 2.28 (H-2, dd, $J = 13.5, 11.0$ Hz), 2.57 (H-5, d, $J = 9.5$ Hz), 3.11, 3.47 (2 H-15, d, $J = 12.5$ Hz), 3.20 (OMe-10), 3.35 (NMe), 3.49 (H-10, d, $J = 9.0$ Hz), 3.54 (H-3, dd, $J = 11.0, 2.0$ Hz), 3.98 (ArOMe), 4.34 (H-7, t, $J = 11.0$ Hz), 5.51 (H-11, dd, $J = 15.0, 9.0$ Hz), 6.14 (H-13, d, $J = 11$ Hz), 6.43 (H-12, dd, $J = 15.0, 11.0$ Hz), 6.80 (Ar H, d, $J = 2$ Hz), 6.98 (or 7.02)¹⁷ (Ar H, d, $J = 2$ Hz)] in 67% overall yield. HPLC and TLC of (\pm)-maytansinol were also superimposable¹⁷ with the authentic maytansinol.

We have now accomplished the total synthesis of (\pm)-maytansinol. The total synthesis of racemic maytansinol involves the solution of the crucial problem that all of the asymmetric centers were prepared ahead of 19-membered lactam ring closure, thus, that only one asymmetric center was present in the original starting material, acrolein dimer, and all other six asymmetric centers in **2** were intramolecularly induced in high stereospecificity. We have also finished the syntheses of (\pm)-maysine and (\pm)- N -methylmaysenine along this line.¹³

Acknowledgment. We are indebted to Professors Ohtake and Seto, and Dr. Nakayama at the University of Tokyo and Dr. Kondo at Nagoya University for measurements of high-field ^1H NMR spectra. We thank Drs. Kishi and Hashimoto at Central Research Division of Takeda Chem. Ind. Ltd. Osaka, Japan, for authentic samples, and also to T. Yamamoto for his assistance to this work. This research was financially supported by a grant-in-aid for scientific research from the Japanese Ministry of Education, Science, and Culture.

Registry No. (\pm)-**2**, 57103-68-1; (\pm)-**3**, 77943-81-8; (\pm)-**4**, 77890-94-9; **5**, 82598-93-4; **6**, 82598-94-5; **7**, 82598-95-6; **8a**, 82614-13-9; **8b**, 82598-96-7; **9a**, 82598-97-8; **9b**, 82598-98-9; (\pm)-**10**, 82598-99-0; (\pm)-**11**, 82614-14-0; **12**, 82599-00-6; **13**, 82599-02-8; (E)-**14a**, 67705-17-3; (Z)-**14a**, 82599-21-1; (E)-**14b**, 67705-16-2; (E)-**14c**, 74510-49-9; (E)-

14d, 82599-03-9; (E)-**15**, 82599-04-0; (\pm)-**16**, 82599-05-1; (\pm)-**17**, 82599-06-2; (\pm)-**18**, 82599-07-3; (\pm)-**19**, 82599-08-4; (\pm)-**20**, 82599-15-3; (\pm)-**21**, 82614-15-1; (\pm)-**22a**, 82599-09-5; (\pm)-3-*epi*-**22a**, 82637-92-1; (\pm)-**22b**, 82599-10-8; (\pm)-**23**, 82599-11-9; (\pm)-**24**, 82614-16-2; (\pm)-**25**, 82599-13-1; (\pm)-**26**, 82599-14-2; (\pm)-3-*epi*-**26**, 82659-78-7; (\pm)-**27a**, 82599-16-4; (\pm)-**27b**, 82599-17-5; (\pm)-**27c**, 82599-18-6; (\pm)-**28a**, 82614-17-3; (\pm)-**28b**, 82599-19-7; (\pm)-**29**, 82599-20-0; 4-bromo-2-pentene, 1809-26-3; sodium p -anisoyl, 53942-86-2; 2-chloroethanol, 107-07-3; 4-lithio-4-(phenylsulfonyl)-1-pentene, 82599-01-7; ethyl acetate lithium salt, 56267-15-3; (\pm)-maysine, 72880-43-4; (\pm)- N -methylmaysenine, 67045-55-0; $\text{Ph}_3\text{P}=\text{CHOCH}_2\text{Ph}$, 82599-12-0.

Microwave Structure Determination for the Furan-HCl Complex

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The structure of the furan-HCl complex in the gas phase has been determined from measurements of rotational transition frequencies. Analysis of the data indicates a planar structure for the complex with an oxygen-chlorine distance of 3.27 (1) Å.

It is well-known that furan has a high probability of being protonated in acidic solutions. Molecular orbital calculations¹ and calorimetric studies² for furan-HX complexes have been carried out. Furan has a conjugated π -electron system and an oxygen atom, so complexes of this type should provide information on the relative importance of these properties for hydrogen-bond formation. Actual structure measurements on these complexes are helpful in evaluating the numerous molecular orbital calculations on hydrogen-bonded complexes.

The microwave rotational transitions were observed by using a pulsed-nozzle Fourier transform spectrometer developed by Balle, Flygare, and co-workers.^{3,4} A gas mixture of 3% furan plus 3% hydrogen chloride in argon was pulsed into the evacuated microwave cavity consisting of 28-cm diameter spherical mirrors.

The "free induction decay" emission signal following the microwave pulses was digitized, averaged, and Fourier transformed to obtain the spectra. Transitions observed for furan-H³⁵Cl were $3_{03} \rightarrow 4_{04}$, $4_{14} \rightarrow 5_{15}$, $4_{04} \rightarrow 5_{05}$, $4_{23} \rightarrow 5_{24}$, $4_{22} \rightarrow 5_{23}$, $4_{13} \rightarrow 5_{14}$, $5_{15} \rightarrow 6_{16}$, $5_{05} \rightarrow 6_{06}$, $5_{24} \rightarrow 6_{25}$, $5_{23} \rightarrow 6_{24}$, and $5_{14} \rightarrow 6_{15}$. Hyperfine structure due to the ³⁵Cl quadrupole coupling was observed on all transitions and aided in the assignment of rotational quantum numbers to the observed transitions. The observed spectral line positions followed the pattern expected for a planar molecule.

The line centers were fit by using the rotational constants A , B , and C and distortion constants D_{JK} and D_J as adjustable parameters. Values obtained are $A = 9499$ (26) MHz, $B = 1003.93$ (1) MHz, $C = 904.32$ (1) MHz, $D_{JK} = 228.892$ (2) kHz, and $D_J = 0.24$ (17) kHz.

The inertial defect is 2.25 amu Å², which is not excessively large for a planar complex of this type. Similar values were obtained for the planar "T"-shaped complexes involving acetylene and hydrogen halides. The experimentally determined geometries of HCl⁵ and furan^{5,6} were used in order to obtain the structure of the complex. It would be expected that the H-Cl bond length would increase slightly on complex formation, but since the H atom is close to the center of mass of the complex, this would not

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(17) In connection to the identification of maytansinol, it should be strongly noted that the signal corresponding to one of the two aromatic protons has been reported as δ 7.05 by Kupchan et al.¹⁸ and as δ 6.91 by Meyers et al.^{2a} (no value reported in ref 2b). We found that this signal appeared at different chemical shifts depending upon the concentration of **2**: the higher in concentration, the lower in chemical shifts, while the other aromatic signal at δ 6.8 and other signals sparingly changed irrespective of the concentration.