rate. This suggests that *if* $1^{+\cdot}$ were involved in the reaction, its lifetime, or that of the ion–pair ($1^{+\cdot}DCA^{-\cdot}$), 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 $1^{+\cdot}$ should require a high activation energy,[18] but the formation of an intermediate short-lived bianthryl diradical (or radical–ion) is a possibility.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Sciences and Engineering Research Council of Canada for support of this research.

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

(17) τ = 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.

(18) Dewar, M. J. S.; Kirschner, S. *J. Am. Chem. Soc.* **1975**, *97*, 2931.

Stereocontrolled Total Synthesis of (±)-Maytansinol

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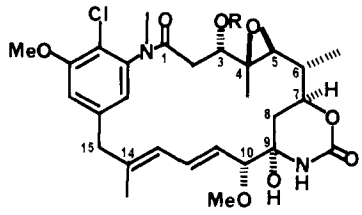
Received April 19, 1982

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



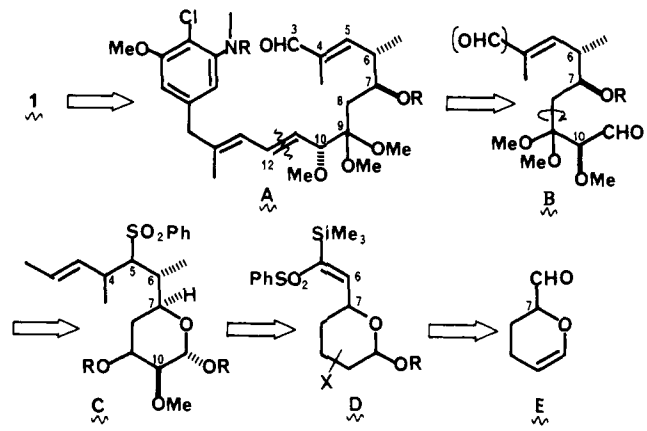
1 R = COCHMeNMeCOMe

2 R = H

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 syntheses[3] prompted us to describe our new stereocontrolled total synthesis of racemic maytansinol (**2**). Our goal to this synthesis lies in exploiting the acylic 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 addition[4] 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 $(MeO)_3CH$ at 80° C for 18 h], and the resulting **7** was oxidized with CrO_3–2Py (CH_2Cl_2, room temperature, 0.5 h) and then ketalized with $(MeO)_3CH$ (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 **8b**[7] with $NaBH_4$ [EtOH–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 Me_2-*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[8] produced in 99% yield the stereochemically pure unsaturated aldehyde **10** [^{1}H NMR δ[9] 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 asymetric centers for maytansinoids. **10** was converted in three steps to **11** (91%) by successive treatments with (i) pyridinium tosylate [MeOH–$(MeO)_3CH$ (6:1), 0 °C, 2 days], (ii) MeONa [1.5 equiv in MeOH, room temperatures, 45 min], and (iii) CrO_3–2Py (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 **12**[10] via **13** and **14a–d** in 45% overall yield.[11] This ylide was reacted with

(1) (a) Kupchan, S. M.; Komoda, Y.; Branfman, A. R.; Dailey, R. G., Jr.; Zimmerly, V. A.; *J. Am. Chem. Soc.* **1972**, *94*, 1345. (b) Kupchan, S. M.; et al. *J. Org. Chem.* **1977**, *42*, 2349. (c) Extensive clinical and biochemical studies reviewed: Komoda, Y.; Kishi, T. In "Anticancer Agent Based on Natural Product Models"; Cassady, J. M., Douros, J. D., Eds.; (P353-389), Academic Press: New York; Chapter 10.

(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.

(6) Isobe, M.; Kitamura, M.; Mio, S.; Goto, T. *Tetrahedron Lett.* **1982**, *23*, 221.

(7) This particular glycoside, **8b**, was extremely alkaline labile even in the basisity 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) ^{1}H 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.

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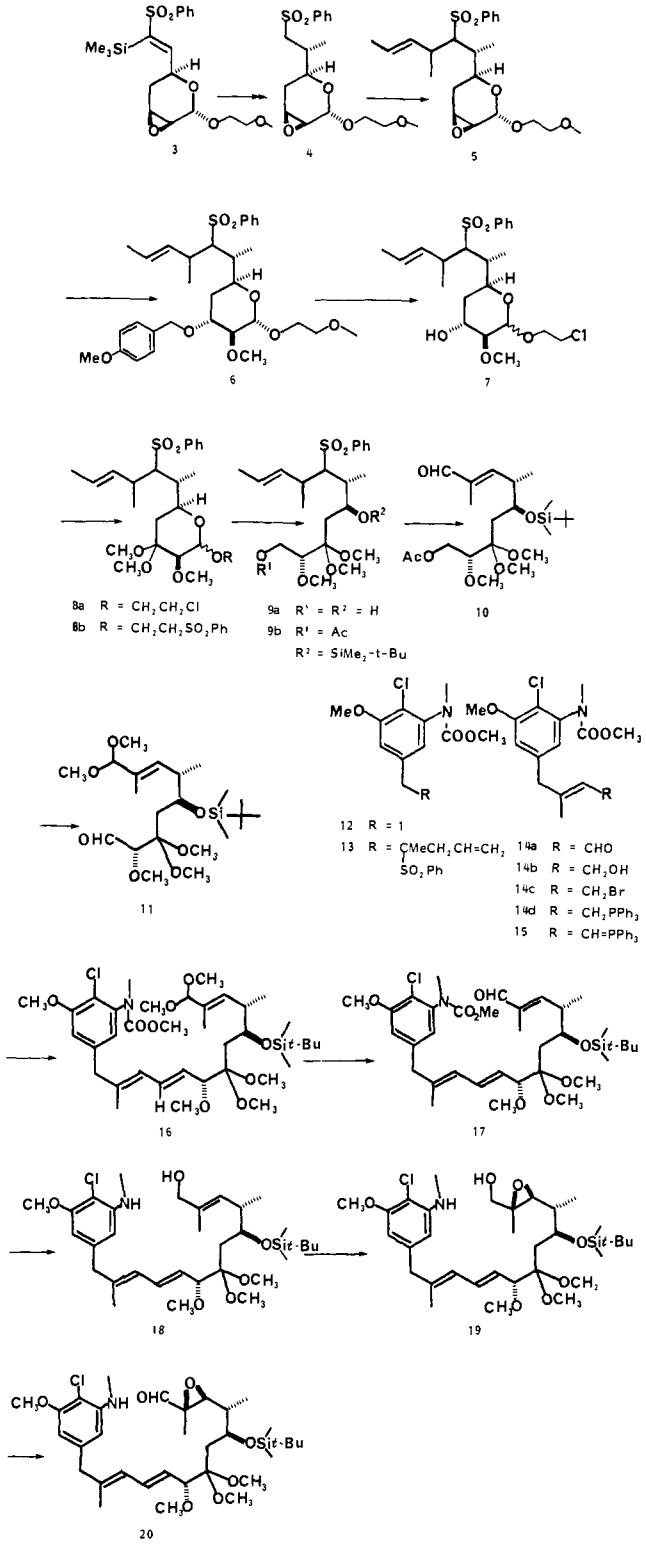
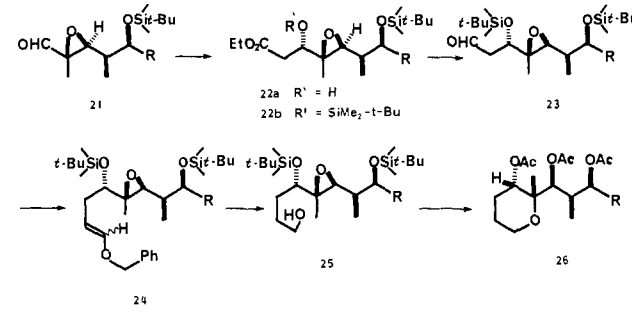
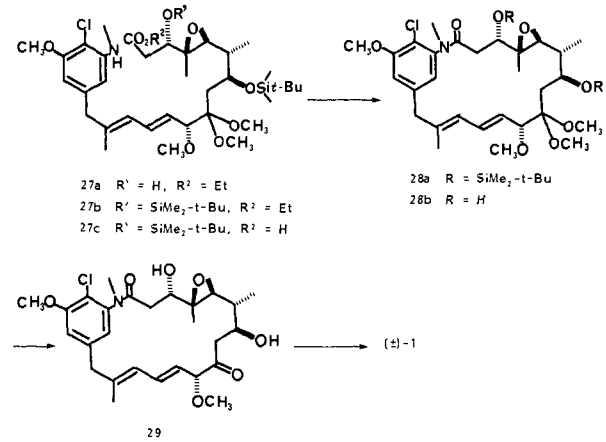
Scheme II



Scheme III



Scheme IV



the aldehyde **11** (THF, −63 °C to room temperature overnight) to produce the diene **16** (78% yield),[12] which was selectively hydrolyzed in 4:1:1 THF–H_2O–AcOH (−10 °C, 2 days) and separated with HPLC to provide the common intermediate **17**[13] [^{1}H 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 diasteroselective epoxidation of some olefins into completely syn orientation was unknown until we explored a method[6] 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 Ti(O-i-Pr)$_4$ and t-BuOOH (dry CH_2Cl_2, −20 °C, 1.5 h), the allylic alcohol **18** gave the single epoxide **19** [^{1}H 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** [R = $(CH_2)_3CH_2OSiMe_2$-t-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 ^{1}H NMR spectrum of **26** showed

(11) In THF 4-lithio-4-(phenylsulfonyl)-1-pentene was added to **12**, and the product (**13**) was treated with ozone and Et_3N[8] at −78 °C to give unsaturated aldehyde **14a** as a ca. 5:1 E/Z olefinic mixture, which was separated. The major E isomer [^{1}H NMRδ 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-BuLi [THF-DMF (2:1), −63 °C] afforded the **14b**, **14c**, **14d**, and the ylide **15**, respectively. The minor isomer Z-**14a** [^{1}H 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.

(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) Me_2-t-BuSiCl–imidazole, (ii) $LiAlH_4$, and (iii) CrO_3–2Py, to afford the aldehyde **23**. It was further reacted with $Ph_3P{=}CHOCH_2Ph$ 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 benzoylation, hydrogenolyzed with 10% Pd–C [EtOH, 40 °C, 22h, H_2] to afford **25** [R = $(CH_2)_3CH_2OBz$]. Acidic hydrolysis of **25** [with 5% CSA in CH_2Cl_2–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 Me_2-t-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 mesitylenesulfonyl chloride[2b] (20 equiv i-Pr_2EtN (20 equiv and n-Bu_4NOH in benzene, 40 °C) to afford **28a** [^{1}H 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-Bu_4NF (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–H_2O (35 °C, 11 h) to give in quantitative yield the ketone **29** [IR ν 1724, 1644 cm^{-1}; ^{1}H 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 chloroformate[16] [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**) [^{1}H 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 (±)-maytansinol were also superimposable[17] with the authentic maytansinol.

We have now accomplished the total synthesis of (±)-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 (±)-maysine and (±)-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 ^{1}H 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. (±)-**2**, 57103-68-1; (±)-**3**, 77943-81-8; (±)-**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; (±)-**10**, 82598-99-0; (±)-**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; (±)-**16**, 82599-05-1; (±)-**17**, 82599-06-2; (±)-**18**, 82599-07-3; (±)-**19**, 82599-08-4; (±)-**20**, 82599-15-3; (±)-**21**, 82614-15-1; (±)-**22a**, 82599-09-5; (±)-3-*epi*-**22a**, 82637-92-1; (±)-**22b**, 82599-10-8; (±)-**23**, 82599-11-9; (±)-**24**, 82614-16-2; (±)-**25**, 82599-13-1; (±)-**26**, 82599-14-2; (±)-3-*epi*-**26**, 82659-78-7; (±)-**27a**, 82599-16-4; (±)-**27b**, 82599-17-5; (±)-**27c**, 82599-18-6; (±)-**28a**, 82614-17-3; (±)-**28b**, 82599-19-7; (±)-**29**, 82599-20-0; 4-bromo-2-pentene, 1809-26-3; sodium p-anisyoxide, 53942-86-2; 2-chloroethanol, 107-07-3; 4-lithio-4-(phenylsulfonyl)-1-pentene, 82599-01-7; ethyl acetate lithium salt, 56267-15-3; (±)-maysine, 72880-43-4; (±)-N-methylmaysenine, 67045-55-0; Ph_3P=$CHOCH_2Ph$, 82599-12-0.

(15) The epitriacetate corresponding to **26** derived from 3-epi-**26** showed axial H-3 at δ 4.93 (dd, J = 10, 2.5 Hz) at 400 MHz.

(16) Lestinger, R. L.; Ogilvie, K. K. *J. Org. Chem.* **1967**, *32*, 296.

(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.[1b] 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.

Microwave Structure Determination for the Furan–HCl Complex

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Received June 14, 1982

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 calculations[1] and calorimetric studies[2] 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. Transtions observed for furan–H^{35}Cl 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 ^{35}Cl 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 Å^2, 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 HCl[5] 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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(1) A. Hinchliffe, *Adv. Mol. Relaxation Interact. Processes*, **18**, 21 (1980).
(2) M. Tsuda, H. Touhara, K. Nakanishi, K. Kitaura, and K. Morokuma, *J. Am. Chem. Soc.*, **100**, 7189 (1978).
(3) T. J. Balle and W. H. Flygare, *Rev. Sci. Instrum.*, **52**, 33 (1981).
(4) T. J. Balle, E. J. Campbell, M. R. Keenan, and W. H. Flygare, *J. Chem. Phys.*, **72**, 922 (1980).
(5) M. D. Harmony, V. W. Laurie, R. L. Kuczkowski, R. H. Schwendeman, D. A. Ramsey, F. J. Loving, W. J. Lafferty, and A. G. Maki, *J. Phys. Chem. Ref. Data*, **8**, 619 (1979).
(6) F. Mata, M. C. Martin, and G. O. Sorensen, *J. Mol. Struct.*, **48**, 157 (1978).

0002-7863/82/1504-4999$01.25/0