Table I. Representative Urethane-Protected *N*-Carboxy Anhydrides

amino acid	urethane	mp, °C	$[\alpha]^{25}_D$, deg
L-Ala	Fmoc	106–107	+28.7
D-Ala	Fmoc	109–113 dec	−28.7
L-Asn(trityl)	Fmoc	134–137	+29.1
L-Asp(β-*tert*-butyl)	Fmoc	65–70 dec	+22.4
L-Gln(trityl)	Fmoc	123–126	+19.4
L-Glu(γ-*tert*-butyl)	Fmoc	120–123	+29.3
Gly	Fmoc	156–157 dec	00.0
L-Ile	Fmoc	117–118	+25.9
L-Leu	Fmoc	118–120	+38.0
L-Lys(ε-Boc)	Fmoc	81–85	+25.3
L-Met	Fmoc	74–75	+69.3
L-Phe	Fmoc	59–61	+101.9
L-Ser(*O*-*tert*-butyl)	Fmoc	54–57	+27.5
L-Thr(*O*-*tert*-butyl)	Fmoc	124–127	+31.2
L-Trp(N^{in}-formyl)	Fmoc	108 dec	87.9
L-Tyr(*O*-*tert*-butyl)	Fmoc	122–124	+110.6
L-Val	Fmoc	83.5–87	+14.8
L-Ala	Boc	103–104.5	+21.6
L-Ser(*O*-benzyl)	Boc	98–99.5	+47.2
D-Ala	Z	103–104.5	−52.1
L-Phe	Z	105–106	+127.6

reagents will greatly facilitate and enhance the scope of peptide synthesis.

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Supplementary Material Available: Analytical data (mp, IR, ^{1}H NMR, CHN analysis, optical rotation) for all compounds listed in Table I, FAB mass spectrum of crude acyl carrier peptide (65–74), and crystallographic structure determination summary, experimental procedures, data collection, data reduction, structure solution and refinement, tables of general temperature factor expressions and torsional angles, and drawings and unit cell packing diagram of Fmoc-*O*-*tert*-butylthreonine-NCA (27 pages); listing of observed and calculated structure factors of Fmoc-*O*-*tert*-butylthreonine-NCA (7 pages). Ordering information is given on any current masthead page.

Synthesis of Dynemicin A Models

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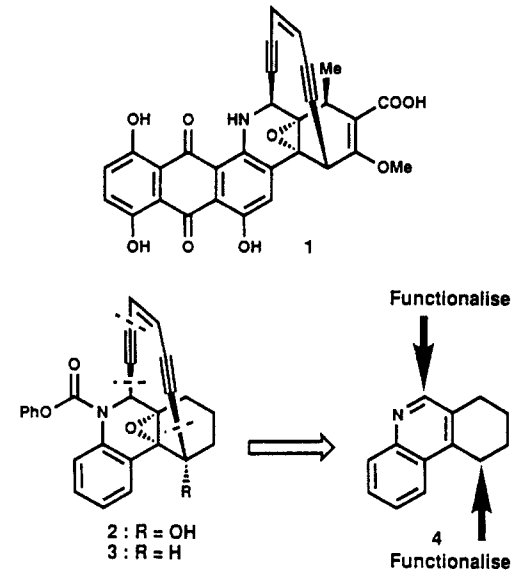
Dynemicin A (**1**, Scheme I) is a potent antibacterial and anticancer agent recently isolated from *Micromonospora chersina*.[1] Its striking molecular structure combines characteristics of both the enediyne[2,3] and the anthracycline[4] classes of antibiotics and presents a considerable challenge to organic synthesis as well as a unique opportunity for the development of new synthetic technology and therapeutic agents. In this communication we report the synthesis, crystal structures, and Bergman-type cyclizations of two novel dynemicin A models (**2** and **3**, Scheme I) containing the nitrogen, epoxide, and enediyne functionalities of the natural product.

Scheme I. Structure of Dynemicin A (**1**) and Retrosynthetic Disconnection of Model Systems **2** and **3**



The retrosynthetic analysis that led to the present synthetic strategy is outlined in Scheme I (**2**, **3** → **4**). Scheme II[5] summarizes the construction of **2** and **3** starting from quinoline derivative **4**. Thus treatment of **4**[6] with mCPBA in dichloromethane gave the corresponding *N*-oxide, which underwent regiospecific rearrangement[7] upon heating in acetic anhydride to give the acetoxy derivative **5** (62% overall yield). This was converted to the corresponding silyl ether **7** in 92% overall yield by standard methods via hydroxy compound **6**. Addition of phenyl chloroformate[8] to a mixture of compound **7** and ethynylmagnesium bromide at −78 °C led to the formation of compound **8** in 92% yield.[9] Treatment of **8** with mCPBA led to epoxide **9** (85%),[10] which was converted to ketone **11** via alcohol **10** by desilylation followed by oxidation (79% overall). Coupling **11** with vinyl

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‡ Recipient of a Verband Der Chemischen Industrie Doctoral Fellowship, 1989–1990.

(1) (a) Konishi, M.; Ohkuma, H.; Tsuno, T.; Oki, T.; VanDuyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1990**, *112*, 3715–3716. (b) Konishi, M.; Ohkuma, H.; Matsumoto, K.; Tsuno, T.; Kamei, H.; Miyaki, T.; Oki, T.; Kawaguchi, H.; VanDuyne, G. D.; Clardy, J. *J. Antibiot.* **1989**, *42*, 1449–1452. (c) Sugiura, Y.; Shiraki, T.; Konishi, M.; Oki, T. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 3831–3835.

(2) Calicheamicins: (a) Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C.; Morton, G. O.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3464–3466. (b) Lee, M. D.; Dunne, T. S.; Chang, C. C.; Ellestad, G. A.; Siegel, M. M.; Morton, G. O.; McGahren, W. J.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3466–3468.

(3) Esperamicins: (a) Golik, J.; Clardy, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3461–3462. (b) Golik, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohjuma, H.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3462–3464.

(4) (a) *Anthracycline Antibiotics*; El Khadem, H. S., Ed.; Academic Press: New York 1982. (b) Recent Aspects in Anthracyclinone Chemistry; *Tetrahedron* Symposia-in-Print No. 17, Kelly, T. R., Ed.; *Tetrahedron* **1984**, *40*, 4537–4794.

(5) All new compounds exhibited satisfactory spectral and analytical and/or exact mass data. Yields refer to chromatographically and spectroscopically homogeneous materials.

(6) (a) Masamune, T.; Takasugi, M.; Suginome, H.; Yokogama, M. *J. Org. Chem.* **1964**, *29*, 681–685. (b) Curran, D. P.; Kuo, S.-C. *J. Org. Chem.* **1984**, *49*, 2063–2065. (c) Hollingsworth, B. L.; Petrow, V. *J. Org. Chem.* **1948**, *13*, 1537–1541.

(7) Boekelheide, N.; Linn, W. J. *J. Am. Chem. Soc.* **1954**, *76*, 1286–1291.

(8) Comins, D. L.; Myoung, Y. C. *J. Org. Chem.* **1990**, *55*, 292–298.

(9) Compounds **8**–**10** exhibited two sets of ^{1}H and ^{13}C NMR signals (ca. 3:1 ratio), due to the presence of two isomers. This phenomenon disappeared, as expected, upon arrival at intermediate **11** as evidenced by NMR spectroscopy.

(10) The stereochemistry of the epoxide functionality in this compound was tentatively assigned as shown and was confirmed by its subsequent conversion into **2**.

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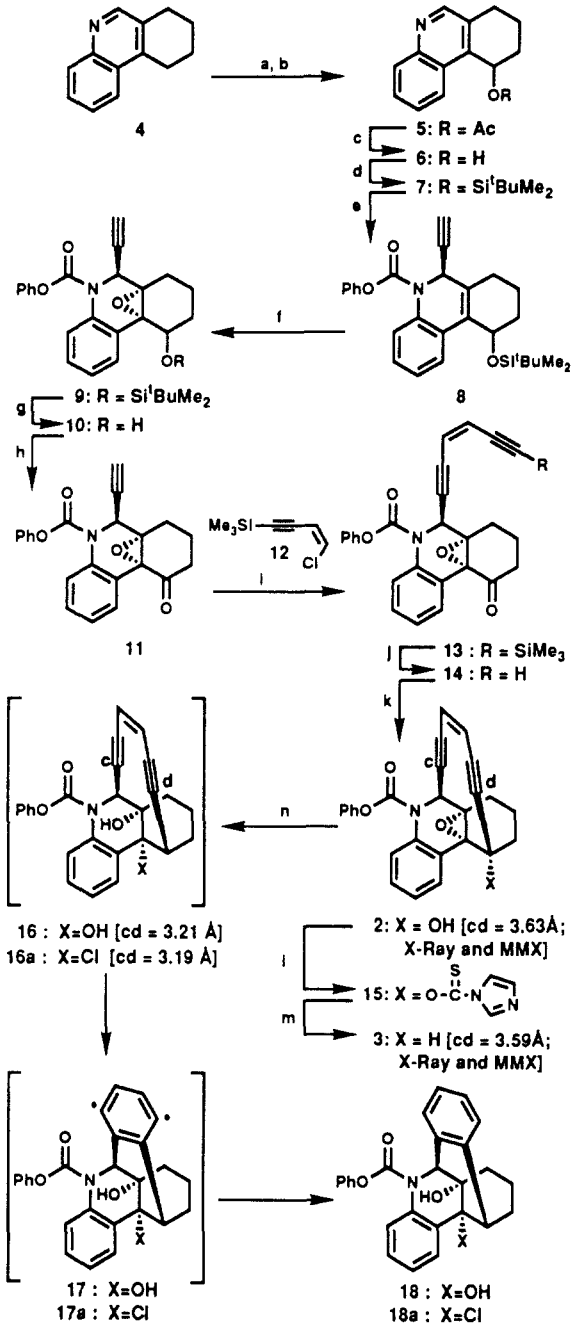
Scheme II. Synthesis and Chemistry of Dynemicin A Model 3[a]



[a] Reagents and conditions: (a) 1.0 equiv of mCPBA, CH_2Cl_2, 25 °C, 1 h, 80%; (b) Ac_2O, reflux, 20 h, 77%; (c) K_2CO_3 (catalytic), MeOH, 25 °C, 1 h, 100%; (d) 1.2 equiv of ^{t}BuMe$_2$SiOTf, 1.4 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 0.5 h, 92%; (e) 3.0 equiv of ethynylmagnesium bromide, 3.0 equiv of PhOCOCl, THF, −78 → 25 °C, 1 h, 92%; (f) 2.0 equiv of mCPBA, CH_2Cl_2, 25 °C, 3 h, 85%; (g) 1.2 equiv of TBAF, THF, 42 °C, 3 h, 95%; (h) 3.0 equiv of PCC, CH_2Cl_2, 4-Å molecular sieves, 25 °C, 1 h, 81%; (i) 1.4 equiv of **12**, 1.5 equiv of *n*-BuNH$_2$, 0.25 equiv of PPh_3, 0.05 equiv of $Pd(OAc)_2$, 0.2 equiv of CuI, PhH, 25 °C, 4 h, 88%; (j) 4.0 equiv of $AgNO_3$, 7.0 equiv of KCN, H_2O, EtOH, THF, 25 °C, 10 min, 90%; (k) 1.1 equiv of LDA, toluene, −78 °C, 1 h, 80% based on 25% recovery of **14**; (l) 3 equiv of thiocarbonyldiimidazole, 0.5 equiv of DMAP, CH_2Cl_2, 25 °C, 48 h, 91%; (m) 2 equiv of *n*-Bu$_3$SnH, AIBN (catalytic), toluene, 75 °C, 2 h, 75%; (n) (i) 0.05 M in benzene–1,4-cyclohexadiene (4:1), 1.2 equiv of TsOH·H_2O, 24 h, 25 °C, 86% (X = OH); or (ii) HCl(g), 40 equiv of 1,4-cyclohexadiene, CH_2Cl_2, 1 min, 25 °C, 82% (X = Cl).

chloride **12** via Pd(0)–Cu(I) catalysis followed by $AgNO_3$–KCN treatment resulted in the formation of the requisite precursor **14** via coupling product **13** (79% overall yield). Finally, treatment of **14** with LDA in toluene–THF at −78 °C gave the first targeted dynemicin A model **2** (80% yield based on 25% recovery of **14**).[11,12]

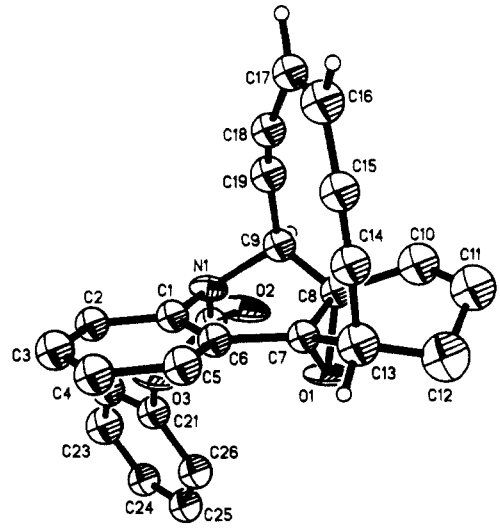


Figure 1. ORTEP drawing of the dynemicin A model **3**. Hydrogen atoms are omitted for clarity. Distance cd (C_{19}–C_{14}) = 3.59 Å. Angles: C_{17}–C_{18}–C_{19} = 170.2°; C_9–C_{19}–C_{18} = 162.0°; C_{14}–C_{15}–C_{16} = 170.1°; C_{13}–C_{14}–C_{15} = 163.7°.

To obtain a closer model to dynemicin A, the tertiary hydroxy group in **2** was removed to form compound **3** via thionoimidazolide **15** as summarized in Scheme II (68% overall yield).

Compound **3** undergoes the novel cascade of reactions shown in Scheme II. Thus, upon treatment with *p*-toluenesulfonic acid in benzene–1,4-cyclohexadiene (3:1, 0.05 M) at 25 °C for 24 h, **3** was converted to product **18** in 86% yield, presumably via intermediates **16** and **17**. Protonation of the epoxide group in **3** apparently initiates formation of diol **16** (distance cd = 3.21 Å, MMX), which undergoes spontaneous Bergman cyclization[13] to form benzenoid diradical **17**. This is, in turn, rapidly trapped by the hydrogen donor present to furnish cyclized product **18**. The use of anhydrous HCl in CH_2Cl_2 in the presence of 1,4-cyclohexadiene also resulted in triggering of the cyclization cascade leading to **18a** (82% yield) presumably via the intermediacy of **16a** (cd = 3.19 Å, MMX) and **17a**. These cyclizations are analogous to those observed for dynemicin A.[1]

Compound **3** crystallized from ether–petroleum ether as colorless prisms (mp 251–252 °C dec). X-ray crystallographic analysis confirmed its structure (see ORTEP drawing, Figure 1) and revealed some interesting structural features. The following angles reflect considerable deviation of the acetylenic groupings from linearity: C17–C18–C19 = 170.2°; C9–C19–C18 = 162.0°; C14–C15–C16 = 170.1°; and C13–C14–C15 = 163.7°. The distance between carbons C14 and C19 (cd distance) was found to be 3.59 Å, which agrees well with the values derived for the MMX minimized structure of **3** (3.59 Å) and from the X-ray crystallograpic analysis of dynemicin A (3.54 Å).[1a,14] It is in-

(11) For a key reference describing the first synthesis of calicheamicinone, see: (a) Cabal, M. P.; Coleman, R. S.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 3253–3255. For other selected studies of model systems in the area of calicheamicins–esperamicins, see: (b) Nicolaou, K. C.; Zuccarello, G.; Ogawa, Y.; Schweiger, E. J.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 4866–4868. (c) Nicolaou, K. C.; Ogawa, Y.; Zuccarello, G.; Kataoka, H. *J. Am. Chem. Soc.* **1988**, *110*, 7247–7248. (d) Schoenen, F. J.; Porco, J. A., Jr.; Schreiber, S. L.; VanDuyne, G. D.; Clardy, J. *Tetrahedron Lett.* **1989**, *30*, 3765–3768. (e) Magnus, P.; Lewis, R. T.; Huffman, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 6921–6923. (f) Kende, A. S.; Smith, C. A. *Tetrahedron Lett.* **1988**, *29*, 4217–4220.

(12) X-ray crystallographic analysis of **2** confirmed its structure (see supplementary material for details). The Bergman-type cyclization of this model system induced by acid was accompanied by pinacol rearrangement leading to a novel polycyclic framework. Details will be reported in the full account of this work.

(13) (a) Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25–31. Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660–661. Lockhart, T. P.; Gomita, P. B.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4091–4096. (b) Darby, N.; Kim, C. V.; Salaun, J. A.; Shelton, K. W.; Takadar, S.; Masamune, S. *J. Chem. Soc., Chem. Commun.* **1971**, 1516–1517. (c) Wong, H. N. C.; Sondheimer, F. *Tetrahedron Lett.* **1980**, *21*, 217–220.

teresting to note the considerable shortening of the cd distance in going from **3** to **16** (cd = 3.21 Å, MMX) and **16a** (cd = 3.19 Å, MMX).[15]

The described chemistry supports epoxide opening[1c] as a triggering mechanism for the action of dynemicin A, paves the way for the total synthesis of this natural product, and suggests the potential of these and related systems as novel DNA-cleaving molecules and anticancer agents.

Acknowledgment. We thank Dr. Raj Chadha, University of California, San Diego, for the X-ray crystallographic analysis of compounds **2** and **3** and Drs. Dee H. Huang and Gary Siuzdak, Research Institute of Scripps Clinic, for their NMR and mass spectroscopic assistance, respectively. This work was financially supported by the National Institutes of Health and the Research Institute of Scripps Clinic.

Supplementary Material Available: A listing of R_f, ^1H and ^{13}C NMR, and mass spectral data for compounds **2**, **3**, **9–11**, **13–15**, **18**, and **18a**, X-ray crystallographic data for compounds **2** and **3**, and NMR spectra of compounds **2**, **3**, **8–11**, **13–15**, **18**, and **18a** (41 pages). Ordering information is given on any current masthead page.

(14) The calculated distance between these acetylenic carbons in dynemicin A was found to be 3.40 Å. See: Semmelhack, M. F.; Gallagher, J.; Cohen, D. *Tetrahedron Lett.* **1990**, *31*, 1521–1522.

(15) Although this distance is often a useful guide, of course it is not necessarily the only criterion for cyclization in these systems, as strain considerations are also important; see: Magnus, P.; Fortt, S.; Pitterna, T.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 4986–4987. Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 5367–5369 and references cited therein.

Chloromethyl Cations in Cryogenic SbF_5 Matrices and the Generation of Carbocations from Hydrocarbons

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Trichloromethyl cation and other metastable halonium ions have previously been produced and spectroscopically characterized as matrix photoionization and photolysis products of halomethanes.[1-3] Recently, Olah et al.[4,5] succeeded in preparing trihalomethyl cations under long-lived stable ion conditions in superacid solutions at −78 °C. In this communication we report that chloromethyl cations can also be prepared in cryogenic antimony pentafluoride matrices from carbon tetrachloride, chloroform, and methylene chloride, respectively, by the application of the same technique used in the preparation and spectroscopic identification of carbocations.[6] In addition, the trichloromethyl cation has been shown to be an excellent reagent for the generation of carbocations from corresponding hydrocarbons in the SbF_5 matrix.

Codeposition of the above named chloromethanes with SbF_5 at 77 K on a CsI window and subsequent warming to 150 K produced the corresponding ions, i.e., CCl_3^+, $CHCl_2^+$, and $(ClCH_2)_2Cl^+$, as ion pairs with $Sb_2F_{10}Cl^-$ which were identified by their IR spectra (Table I). The spectral assignments can be supported by the following arguments.

CCl_3^+. This ion was first observed by Jacox[7] in the argon matrix at 14 K among the products of ultraviolet and microwave radiation decomposition of chloroform.[8a] They assigned the strong absorption band at 1037 cm^{-1} to the asymmetrical C–Cl stretching vibration. This relatively high frequency is indicative of a partial double-bond character of this bond as predicted from the canonic resonance structures:

$$Cl_2C^+-Cl \leftrightarrow Cl_2C{=}Cl^+$$

In the solid SbF_5 matrix this band appeared at 1040 cm^{-1} and was also present at 1045 cm^{-1} in the vibrational spectrum of $CHCl_2^+$ (see Table I). Its appearance at 150 K was accompanied by the disappearance of the absorption at 785 cm^{-1} characteristic for the C–Cl stretching vibration in carbon tetrachloride.

Table I. Infrared Frequencies of Chloromethyl Cations

starting material	cation	IR data, cm^{-1} lit.	this work
CCl_4	CCl_3^+	1035[a]	1040 (vs)
$CHCl_3$	$CHCl_2^+$	3033[b]	
		1291	1290 (s)
		1045	1045 (vs)
		845	850 (s)
CH_2Cl_2	$(ClCH_2)_2Cl^+$		3070 (m), 3068 (m), 2980 (m), 1233 (w), 1030 (s), 870 (vs), 796 (s), 780 (s)

[a] Reference 7. [b] Reference 8.

$CHCl_2^+$. An extensive list of experimental frequencies for this ion is available,[8] but attempts to prepare it in superacid from chloroform have so far been unsuccessful. However, we succeeded in generating it in the cryogenic matrix. At 150 K, signals of the codeposited chloroform in SbF_5 changed, with the appearance of three strong new signals characteristic of the $CHCl_2^+$ ion (Table I). The scaled theoretical vibrational frequencies[8b] for the three observed bands (in cm^{-1}) are 1365 (H–C–Cl in-plane bend), 1013 (C–Cl asymmetric stretch), and 818 (C–Cl symmetric stretch). When the matrix was warmed to 200 K, the original signals disappeared and new signals at 3020, 1375, 1150, and 1113 cm^{-1} became visible. By comparison with the known data[9] (3036, 1373, 1152, and 1117 cm^{-1}), we believe that these signals belong to CHF_3 formed by halogen exchange and partial diffusion from the matrix material. This exchange reaction is likely to be responsible for the failure to produce this ion in superacids.

$(ClCH_2)_2Cl^+$. In the matrix experiment with CH_2Cl_2, a complicated spectrum was obtained at 150 K which because of its complexity cannot belong to the $CHCl_2^+$ ion. Since in the analogous reaction with SbF_5 in liquid SO_2 the bis(chloromethyl)chloronium ion (**1**) was formed,[5] we believe that the observed spectrum belongs to this ion. When the matrix was warmed to 200 K, signals belonging to CH_2F_2 appeared which must have been formed by an exchange reaction similar to the one described above. In this case the chemical ionization of CH_2Cl_2 differs from the photoionization in the argon matrix where $CHCl_2^+$ is formed. The chemical ionization probably first produces the unstable CH_2Cl^+ ion, which reacts immediately with the unreacted methylene chloride, forming the chloronium ion (**1**).

Generation of Carbocations. At 75 K, a thin film of SbF_5 was deposited on the CsI window by using the already described apparatus,[6a] followed by the concomitant deposition of SbF_5, CCl_4, and the respective hydrocarbon. If the matrix is allowed to warm slowly to about 150 K, the progress of reactions 1 and 2 can be followed spectroscopically. In the isodesmic reaction (2), the first-formed trichloromethyl cation is consumed by the hydrocarbon as the equilibrium is shifted in favor of the thermodynamically more stable carbocation. A demonstration of this

$$CCl_4 + SbF_5 = CCl_3^+ + SbClF_5^- \quad (1)$$

$$CCl_3^+ + RH = R^+ + CHCl_3 \quad (2)$$

(1) Ault, B. S.; Andrews, L. *J. Chem. Phys.* **1975**, *63*, 1411.
(2) Kelsall, B. J.; Andrews, L. *J. Mol. Spectrosc.* **1983**, *97*, 362.
(3) Andrews, L.; Dyke, J. M.; Jonathan, N.; Keddar, N.; Morris, A. *J. Chem. Phys.* **1983**, *79*, 4650.
(4) Olah, G. A.; Heiliger, L.; Prakash, G. K. S. *J. Am. Chem. Soc.* **1989**, *111*, 8020.
(5) Olah, G. A.; Bruce, M. R. *J. Am. Chem. Soc.* **1979**, *101*, 4765.
(6) (a) Vančik, H.; Sunko, D. E. *J. Am. Chem. Soc.* **1989**, *111*, 3742. (b) Koch, W.; Liu, B.; DeFrees, D. J.; Sunko, D. E.; Vančik, H. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 185.
(7) Jacox, M.; Milligan, D. E. *J. Chem. Phys.* **1971**, *54*, 3935.
(8) (a) Jacox, M. *Chem. Phys.* **1976**, *12*, 51. (b) Kafafi, S. A.; Hudgens, J. W. *J. Phys. Chem.* **1989**, *93*, 3474.
(9) Shimanouchi, T. *Tables of Molecular Vibration Frequencies Consolidated, Vol. 1. Natl. Stand. Ref. Data Ser.* **1972**, *39*.

0002-7863/90/1512-7418$02.50/0