ment carried out on 4, in $CDCl_3$ containing 30 μL of [^{13}C]methanol, revealed a long-range coupling between H-21 and the new [^{13}C]methoxy carbon, observed at 53.3 ppm, confirming substitution of methoxy at C-21. Pure 4 was supplied to the Illinois group for direct comparison with ecteinascidin 743. The proton NMR, positive ion FABMS, TLC, and HPLC data strongly suggest that the compounds are identical. The major difference is the relative solubility of the compounds. Our compounds exhibit only limited solubility in $CDCl_3$ (≈2–3 mg/mL) requiring addition of methanol for solubilization while the Illinois group's material appears to be very soluble in $CDCl_3$. In conclusion, the data suggests that the reassignment of our proposed structures 11 and 12 to 3 and 4, respectively, by Rinehart et al.[13] is consistent with the observed spectral data and that 3 and 4 are ecteinascidins 729 and 743 or salts thereof.

The relative stereochemistry of rings A–E was found to be the same as that reported for the structurally related renieramycins[15] and saframycins[14c] through a series of ^{1}H–^{1}H NOE experiments. A strong nuclear Overhauser enhancement of H-12′a was observed upon irradiation of H-8′. Models of other possible structures did not account for this enhancement. We are currently attempting to grow crystals suitable for X-ray diffraction studies to confirm the proposed structures of 3 and 4.

Compounds 3 and 4 are structurally related to the safracins, saframycins, and renieramycins. Both the safracins and saframycins are microbial fermentation products. Experiments to locate a microbial source for the ecteinascidins are in progress. Compounds 3 and 4 are potent in vitro inhibitors of P388 murine leukemia with IC_{50}'s of 0.93 and 1.3 ng/mL, respectively. A mixture of the two compounds (≈1:1) was found to be active in vivo against B-16 murine melanoma (T/C = 188% 0.1 mg/kg QD 1-9[16]) and colon carcinoma 26 (T/C = 147 0.1 mg/kg QD 1-9).

Acknowledgment. We would like to thank Dan Pentek at Yale University for the positive and negative ion FAB mass spectral analysis and the DBMR divers for collection of the organism. This is Harbor Branch Oceanographic Institution Contribution No. 780.

Supplementary Material Available: Experimental procedure for isolation of compounds 3 and 4, proton and carbon NMR data for 3 and 4, and proton and carbon NMR spectra for 3 and 4 (14 pages). Ordering information is given on any current masthead page.

(15) He, H.-y.; Faulkner, D. J. *J. Org. Chem.* **1989**, *54*, 5822–5824.

(16) A (1:1) mixture was tested as we did not have the pure materials at the time of testing. T/C indicates the ratio of the mean day of death of treated mice to that of control mice. A T/C of ≥125% is considered to be active. QD1-9 indicates the dose schedule, i.e., the drug was administered once daily for the first 9 days of the test.

Ecteinascidins 729, 743, 745, 759A, 759B, and 770: Potent Antitumor Agents from the Caribbean Tunicate *Ecteinascidia turbinata*[1]

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Summary: Ecteinascidins 729, 743, 745, 759A, 759B, and 770, tris(tetrahydroisoquinolines) with potent in vivo antitumor activity, have been isolated from the colonial tunicate *Ecteinascidia turbinata*, and their structures have been assigned.

Reports of the potent in vivo efficacy of extracts of the Caribbean tunicate *Ecteinascidia turbinata* date back to 1969, when it was reported that such extracts gave T/C to 272 vs P388 murine leukemia, with four of six cures in one experiment.[5] The extracts were also powerful immunomodulators, but repeated attempts to isolate the compounds responsible for either activity were unsuccessful.[6] Our own concerted efforts to identify the compounds began in 1981, shortly after the Alpha Helix Caribbean Expedition 1978,[7] where a sample of *E. turbinata* showed cytotoxicity in shipboard assays. These efforts culminated in the isolation by 1986 of six compounds—ecteinascidins (Et's) 729, 743, 745, 759A,

(1) Preliminary reports: (a) Holt, T. G. Ph.D. Dissertation, University of Illinois, Urbana, 1986; *Chem. Abstr.* **1987**, *106*, 193149u; *Diss. Abstr. Int. B* **1987**, *47*, 3771–3772. (b) Rinehart, K. L.; Holt, T. G. U.S. Patent Application Serial No. 872 189, June 9, 1986; PCT Int. Appl. WO8707610, Dec. 17, 1987; *Chem. Abstr.* **1988**, *109*, 811j. (c) Rinehart, K. L. Presented at the 30th Ann. Mtg. Am. Soc. Pharmacognosy, San Juan, Puerto Rico, Aug. 6–10, 1989; paper S:9; cf. Rinehart, K. L.; Holt, T. G.; Fregeau, N. L.; Keifer, P. A.; Wilson, G. R.; Perun, T. J., Jr.; Sakai, R.; Thompson, A. G.; Stroh, J. G.; Shield, L. S.; Seigler, D. S.; Li, L. H.; Martin, D. G.; Grimmelikhuijzen, C. J. P.; Gäde, G. *J. Nat. Prod.*, in press. (d) Rinehart, K. L. Presented at the 2nd Intl. Symp. Mass Spectrom. Health Life Sci., San Francisco, CA, Aug. 27–31, 1989. Cf.: Rinehart, K. L.; Holt, T. G.; Fregeau, N. L.; Staley, A. L.; Thompson, A. G.; Harada, K.-I.; Curtis, J. M.; Rong, L.-S.; Sun, F.; Shield, L. S.; Gäde, G.; Grimmelikhuijzen, C. J. P.; Doughty, C. C.; Grimshaw, C. E. In *Biological Mass Spectrometry*; Burlingame, A. L., McCloskey, J. A., Eds.; Elsevier: Amsterdam, 1990; pp 233–258. (e) Rinehart, K. L. Presented at the 49th Intl. Congress of Pharmaceutical Sciences of F.I.P., Munich, Germany, Sept. 4–9, 1989, Symposium on Bioactive Natural Products. Cf.: Rinehart, K. L.; Shield, L. S. In *Topics in Pharmaceutical Sciences 1989*; Breimer, D. D., Crommelin, D. J. A., Midha, K. K., Eds.; Amsterdam Medical Press B.V.: Noordwijk, The Netherlands, 1989; pp 613–626. (f) Rinehart, K. L. Presented at the 17th Intl. Symp. Chem. Nat. Prod., New Delhi, India, Feb. 4–9, 1990; paper SL 1. Cf.: Rinehart, K. L.; Sakai, R.; Holt, T. G.; Fregeau, N. L.; Perun, T. J., Jr.; Seigler, D. S.; Wilson, G. R.; Shield, L. S. *Pure Appl. Chem.*, in press.

(2) University of Illinois.

(3) Varian.

(4) The Upjohn Co.

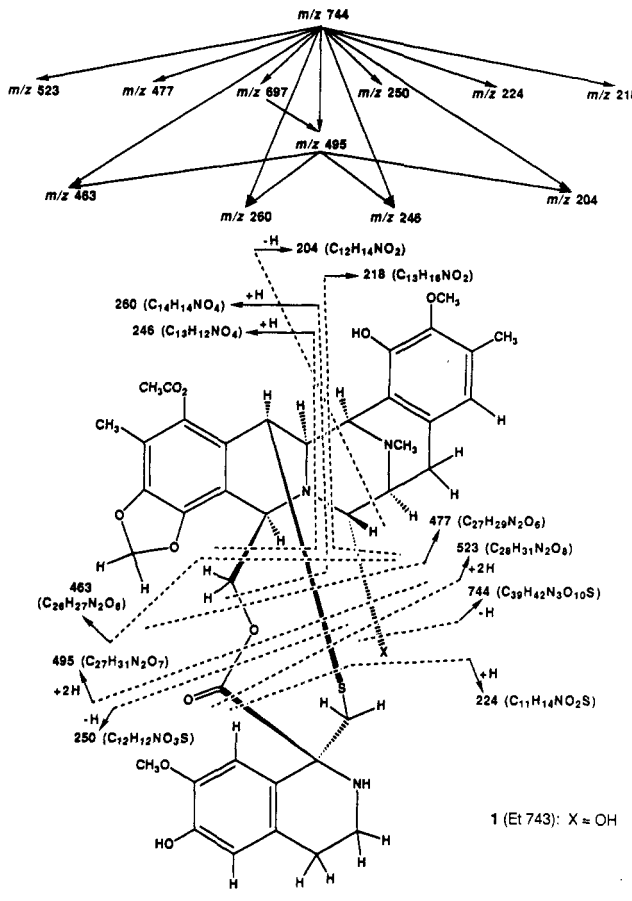
(5) Sigel, M. M.; Wellham, L. L.; Lichter, W.; Dudeck, L. E.; Gargus, J. L.; Lucas, A. H. In *Food-Drugs from the Sea Proceedings 1969*; Youngken, H. W., Jr., Ed.; Marine Technol. Soc.: Washington, DC, 1970; pp 281–294.

(6) Sigel, M. M.; McCumber, L. J.; Hightower, J. A.; Hayasaka, S. S.; Huggins, E. M., Jr.; Davis, J. F. *Am. Zool.* **1983**, *23*, 221–227 and references therein.

(7) Rinehart, K. L., Jr.; Shaw, P. D.; Shield, L. S.; Gloer, J. B.; Harbour, G. C.; Koker, M. E. S.; Samain, D.; Schwartz, R. E.; Tymiak, A. A.; Weller, D. L.; Carter, G. T.; Munro, M. H. G.; Hughes, R. G., Jr.; Kuentzel, S. L.; Li, L. H.; Bakus, G. J.; Brusca, R. C.; Craft, L. L.; Young, D. N.; Connor, J. L. *Pure Appl. Chem.* **1981**, *53*, 795–817.

0022-3263/90/1955-4512$02.50/0

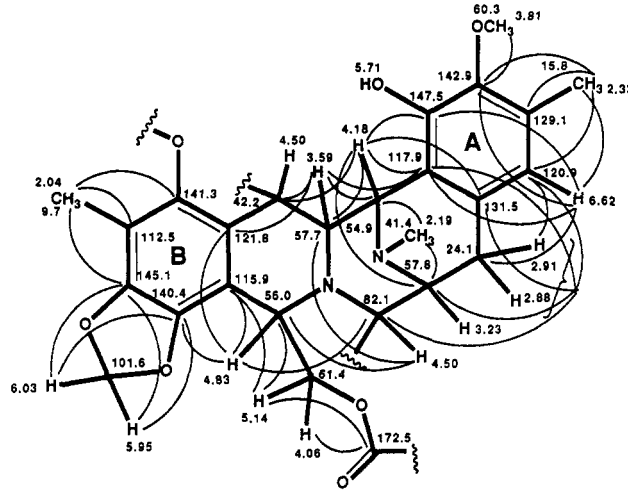
Scheme I



759B, 770—from *E. turbinata*, in yields of (1×10^{-4}) to (1×10^{-5})%.[1a] Key techniques employed for the isolation and preliminary characterization included centrifugal countercurrent chromatography,[8] tissue culture bioautography,[1a,9] moving belt liquid chromatography/fast atom bombardment mass spectrometry (LC/FABMS),[10] and tandem FABMS/MS with collision-induced decomposition,[1d,11,12] as well as the usual 2D homo- and heteronuclear NMR techniques.

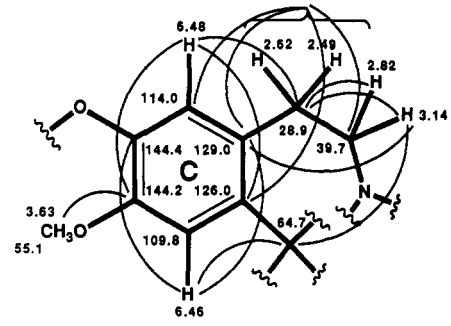
The most abundant ecteinascidin, Et 743 ((1×10^{-4})% yield; IC_{50} 0.5 ng/mL vs L1210 leukemia cells; T/C 167 at 15 μg/kg vs P388 murine leukemia) showed a "molecular" ion at 744.2591 by HRFABMS.[1a] In agreement with the "molecular" formula $C_{39}H_{42}N_3O_{10}S$ (Δ 5.7 mmu), its ^{13}C NMR spectrum contained 39 carbon signals[1a] and electron spectroscopy for chemical analysis (ESCA) indicated a single sulfur atom.

FABMS/MS was critical in locating the three nitrogen atoms in three units of similar size and composition, differing mainly in the numbers of oxygens (Scheme I).[1a] The UV spectrum [λ_{max} 287 nm (ε 6200), 240 (sh, 15 000), end absorption 202 (81 000), bathochromic shift in base], while unremarkable, agreed with that expected for a tris(multioxygenated benzene). A portion of the molecule (unit A) appeared to be identical with a unit in safracin B[13] since the ^{13}C and ^1H chemical shifts[14] were nearly the same and the key FAB mass spectral peaks (Scheme I) at m/z 204.1027 (Δ −0.2 mmu) and 218.1174 (Δ 0.7 mmu) were also prominent for safracin B. Heteronuclear multiple-bond correlation (HMBC)[15] spectroscopy confirmed unit A, as shown.



A second aromatic unit (unit B) was constructed from HMBC, as shown, and demonstrated (again by HMBC) to overlap unit A. The latter observation had already been adumbrated by the FABMS/MS data (Scheme I), with the A and B units together in the m/z 495 ion.

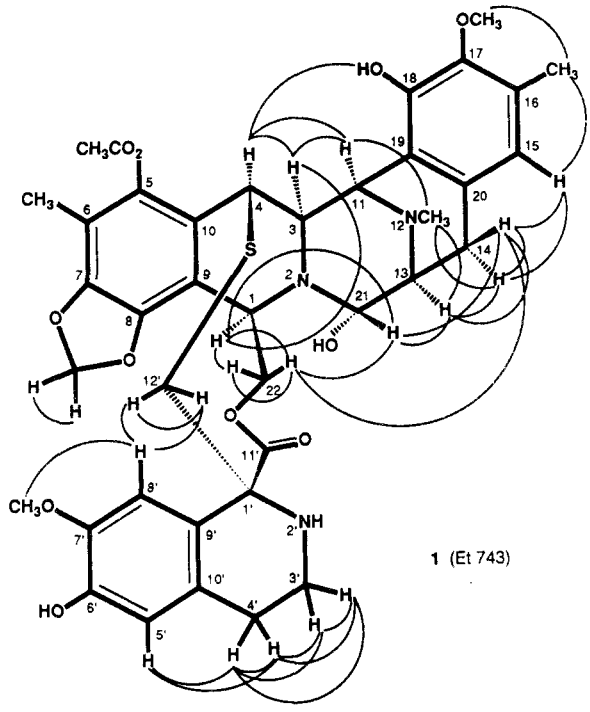
The third aromatic unit (unit C) was also identified by HMBC, as shown.[16] A proton can be attached to the pendant oxygen in unit C since mass spectral fragments associated with unit C shift by 14 mass units in di-*O*-methyl Et 743 and by 42 mass units in di-*O*-acetyl Et 743.



By a similar argument, the acetyl group (CH_3CO, δ_{13C} 20.4 and 168.3, δ_{1H} 2.28, HMBC, HETCOR) can be assigned to the pendant oxygen in unit B since fragments associated with it do not shift in either Et 743 derivative, whereas

(8) Ito, Y. *CRC Crit. Rev. Anal. Chem.* **1986**, *17*, 65–143.
(9) Holt, T. G.; Rinehart, K. L., manuscript in preparation.
(10) (a) Stroh, J. G.; Rinehart, K. L., Jr.; Cook, J. C.; Kihara, T.; Suzuki, M.; Arai, T. *J. Am. Chem. Soc.* **1986**, *108*, 858–859. (b) Stroh, J. G. Ph.D. Dissertation, University of Illinois, Urbana, 1986.
(11) (a) *Tandem Mass Spectrometry*; McLafferty, F. W., Ed.; Wiley: New York, 1983. (b) Busch, K. L.; Glish, G. L.; McLuckey, S. A. *Mass Spectrometry/Mass Spectrometry: Techniques and Applications of Tandem Mass Spectrometry*, VCH: New York, 1988.
(12) (a) Rinehart, K. L.; Namikoshi, M.; Thompson, A. G.; Shield, L. S.; Gäde, G.; Grimmelikhuijzen, C. J. P.; Nothacker, H.-P.; Carmichael, W. W.; Sivonen, K.; Doughty, C. C.; Grimshaw, C. E. In *Proc. 2nd Int. Symp. Mass Spectrom. Health Life Sci.*; Burlingame, A. L., McCloskey, J. A., Eds.; in press. (b) Rinehart, K. L.; Gäde, G.; Grimmelikhuijzen, C. J. P.; Shield, L. S.; Namikoshi, M.; Carmichael, W. W.; Sivonen, K.; Thompson, A. G.; Doughty, C. C.; Grimshaw, C. E. In *Proc. 4th Intl. Symp. Nat. Prod. Chem.*; Karachi, Pakistan, Jan. 27–Feb. 2, 1990, Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, in press. (c) Rinehart, K. L.; Thompson, A. G.; Rong, L.; Milberg, R. M.; Curtis, J. M.; Sun, F. In *Proc. 37th ASMS Conf. Mass Spectrom. Allied Topics*; Miami Beach, FL, May 21–26, 1989, pp 1128–1130.
(13) (a) Ikeda, Y.; Matsuki, H.; Ogawa, T.; Munakata, T. *J. Antibiot.* **1983**, *36*, 1284–1289. (b) Cooper, R.; Unger, S. *J. Antibiot.* **1985**, *38*, 24–30.
(14) All NMR values are for $CDCl_3$ solutions.
(15) Bax, A.; Summers, M. F. *J. Am. Chem. Soc.* **1986**, *108*, 2093–2094.
(16) The aromatic hydrogens of unit C were initially assigned in two separate aromatic rings,[1a,c,f] each bearing a single aromatic hydrogen, since neither the protons nor their attached carbons are correlated in any way with one another.

Scheme II



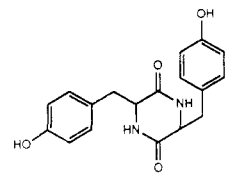
1 (Et 743)

they are 42 mass units less in deacetyl Et 743. Unfortunately, the protons and carbons in unit C are not correlated by HMBC with those in unit A or B or with the remaining units of the molecule, a methylene (CH_2, $\delta_{^{13}C}$ 42.2, $\delta_{^1H}$ 2.37 and 2.18, COSY, HETCOR) and a sulfide (S).

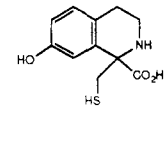
Chemical shift and lack-of-coupling arguments require the methylene carbon to be attached to the quaternary carbon of unit C as well as to the sulfide link; chemical shift arguments require the quaternary carbon in unit C (δ 64.7) to be attached to the nitrogen in that unit, the sulfide must by stability and chemical shift arguments be attached to the aryl methine (δ 42.2), and the carbonyl must by chemical shift arguments be attached to the quaternary carbon.[17] The remaining bond should then join the nitrogen of unit C to the aminomethine carbon of unit B.[19] However, the chemical shifts of that carbon (δ 82.0) and hydrogen (δ 4.50) are unexpectedly far downfield for a $-CH(N<)_2$ unit,[20] but exactly that expected for a –CH(OH)–N< unit, as found in safracin B. Consequently, the structure of Et 743 is assigned as 1 (X = OH) (Scheme II), the molecule undergoing dehydration during FABMS. The same phenomenon (dehydration, lack of FAB M + H) has been observed in FABMS on safracin B[13b] and saframycin Mx1.[21] Confirmation of this carbinolamine hypothesis is provided by the negative ion HRFAB mass spectrum of 1 in a diethanolamine matrix, which gives M – H at 760.2514 ($C_{39}H_{42}N_3O_{11}S$, Δ 2.6 mmu). The hydroxyl is readily exchanged (cf. cyanide below); treatment with a trace of methanol gives the *O*-methyl analogue (1, X = OCH_3; M – H 774.2679, $C_{40}H_{44}N_3O_{11}S$, Δ 1.8 mmu, by negative ion HRFABMS) for which the carbinol amine carbon, C-21, has shifted to δ 91.8 ($CDCl_3$).

The structure assigned is amply substantiated by mass spectrometric fragmentations, as outlined in Scheme I. The relative stereochemistry assigned at C-1, C-3, C-11, and C-13 in Et 743 (1) is derived from extensive NOE correlations, as shown in Scheme II, and is the same as in safracins[13,22] and saframycins;[21,23] that at C-21 is the same as in safracins and saframycins (where C-21 and H-21 appear with similar chemical shifts and coupling constants); that at C-4 is tentative, based on lack of observed coupling for H-3 and H-4; that at C-1 is arbitrary. The absolute stereochemistry shown is the same as in bromosafracin A,[22] but is also arbitrary.

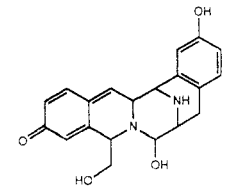
Biosynthetically, the three tetrahydroisoquinoline units presumably arise, as usual,[24] from condensation of carbonyl groups with dopa or dopamine equivalents, perhaps involving the intermediate diketopiperazine 2. Unit B would then be formed by condensation with a serine-derived glycoaldehyde and unit C from a cysteine-derived β-mercaptopyruvic acid. Nucleophilic addition of the cysteine-derived thiol 3 to a quinone methide, e.g. 4, and lactone formation would link the two units (A–B and C). Methylations, oxidations, and acetylation would complete the structure.



2



3



4

Assignment of Et 743 (1) allows assignment of other ecteinascidins as well. Et 729 (*N*-demethyl-1, X = OH; 10^{-5}%; $C_{38}H_{39}N_3O_{10}S$, M + H, 730.2493, Δ –5.9 mmu; T/C 214 at 3.8 μg/kg vs P388 murine leukemia and 246 at 10 μg/kg vs B16 melanoma), the most active antitumor agent, is the *N*-demethyl analogue (lacking δ 2.19); Et 745 (1, X = H; (2×10^{-5})%; $C_{39}H_{43}N_3O_{10}S$, M + H, 746.2775, Δ –2.8 mmu; IC_{50} 88 ng/mL vs L1210; T/C 111 at 250 μg/kg vs P388 murine leukemia) arises from reduction of the carbinolamine unit of Et 743 (replacement of OH by H), and Et 770 (1, X = CN; $C_{40}H_{43}N_4O_{10}S$, M + H, 771.2704, Δ –0.4 mmu) is the cyanoamine analogue (CN replacement of OH). Et 770 can be formed by treatment of Et 743 with

(17) (a) The detailed argument goes as follows. The δ 42.2 methylene carbon is not attached to nitrogen because its protons are too far upfield (cf. C-3′), not attached to the δ 42.1 or 82.1 methines due to lack of splitting, not attached to the ester carbonyl due to lack of long-range correlation of its protons with δ 172.5, and must, therefore, be attached to the quaternary carbon (δ 64.7) and to the sulfide. This quaternary carbon is sufficiently deshielded that it must be attached to nitrogen. The sulfide is not attached to the nitrogen or the quaternary carbon due to instability (N–S bond, episulfide), not attached to the carbonyl (a standard ester at δ 172.5) or the 82.1 ppm methine since a sulfur is not sufficiently deshielding, and must, therefore, be attached to the δ 42.1 methine. The carbonyl carbon is not attached to nitrogen since it is a standard ester (δ 172.5), not a urethane; not attached to the too highly deshielded methine at 82.1 ppm; and must, therefore, be attached to the quaternary carbon at δ 64.7. (b) These attachments are in part confirmed by total correlation spectroscopy (TOCSY)[18] experiments in which both protons of the isolated methylene show correlations to the methine protons along the top of units A and B (4.50, 4.18 and 3.59 ppm), and by the loss of CH_2=SH in the FABMS/MS spectra.

(18) Braunschweiler, L.; Ernst, R. R. *J. Magn. Reson.* **1983**, *53*, 521–528.

(19) The structure which would result from this junction has been proposed for Et 743 (and a similar structure for Et 729) by Wright et al. (adjacent communication). The correct placement of substituents on rings B and C was first proposed by the Harbor Branch group (O. J. McConnell, private communication).

(20) Pretsch, E.; Clerc, T.; Seibl, J.; Simon, W. *Tables of Spectral Data for Structure Determination of Organic Compounds*; Springer-Verlag: Berlin, 1983; p C10.

(21) Trowitzsch-Kienast, W.; Irschik, H.; Reichenbach, H.; Wray, V.; Höfle, G. *Liebigs Ann. Chem.* **1988**, 475–481.

(22) Ueda, I.; Kawana, S.; Ikeda, Y.; Matsuki, H.; Ogawa, T. *Acta Crystallogr.* **1984**, *C40*, 1578–1580.

(23) Arai, T. In *Natural Products Isolation, Separation Methods for Antimicrobials, Antivirals and Enzyme Inhibitors*; Wagman, G. H., Cooper, R., Eds.; Elsevier: Amsterdam, 1989; J. Chromatogr. Lib., Vol. 43; Chapter 5.

(24) (a) Schütte, H. R. In *Biosynthese der Alkaloids*; Mothes, K., Schütte, H. R., Eds.; VEB Deutscher Verlag der Wissenschaften: Berlin, 1969; pp 367–419. (b) Herbert, R. B. *The Biosynthesis of Secondary Metabolites*; Chapman and Hall: London, 1981; pp 113–125.

KCN, and the corresponding cyano compound (*N*-demethyl-1, X = CN) is derived from Et 729 by like treatment. Et 759A and Et 759B (M – H_2O = $C_{39}H_{41}N_3O_{11}S$ by HRFABMS) are tentatively assigned as *N*-oxides of Et 743.[25]

The structures assigned the ecteinascidins are related to those of the microbially derived safracins[13] and saframycins,[21,23] as well as of the sponge-derived renieramycins[26] and xestomycin,[27] but show greater in vitro and in vivo antitumor activity than those reported for the saframycins or safracins. No antitumor activity has been reported for the renieramycins or xestomycin.

Acknowledgment. This work was supported in part by a grant from the National Institute of Allergy and Infectious Diseases (AI 04769 to K.L.R.) and the Mass Spectrometry Laboratory, School of Chemical Sciences, in part by a grant from the National Institute of General Medical Sciences (GM 27029 to K.L.R.). N.L.F. also appreciates fellowships from the University of Illinois and The Proctor & Gamble Company and a Traineeship from The National Institutes of Health-Cell and Molecular Biology Training Program.

Supplementary Material Available: Table I, ^{13}C and ^{1}H NMR data for ecteinascidin 743; Table II, comparison of the ^{13}C NMR data for ecteinascidin 743 in different solvents; Table III, ^{1}H NMR data for ecteinascidins 743, 729, 745, and 770; Table IV, short- and long-range ^{1}H–^{1}H COSY correlations for ecteinascidin 743; Table V, HMBC data for ecteinascidin 743; Table VI, COLOC data for ecteinascidin 743; Table VII, TOCSY data for ecteinascidin 743; Table VIII, ROESY data for ecteinascidin 743; Table IX, ESCA results for ecteinascidin 743; Table X, high-resolution positive ion FABMS data on ecteinascidin 743; Table XI, high-resolution negative ion FABMS data on ecteinascidin 743; Table XII, high-resolution positive ion FABMS data on other ecteinascidins; Table XIII, comparison of major FABMS ions for ecteinascidins and derivatives; Figure 1, ^{1}H NMR spectrum of ecteinascidin 743; Figure 2, ^{13}C NMR spectrum of ecteinascidin 743; Figure 3, COSY spectrum of ecteinascidin 743; Figure 4, HMQC spectrum of ecteinascidin 743; Figure 5, HMBC spectrum of ecteinascidin 743; Figure 6, COLOC spectrum of ecteinascidin 743; Figure 7, TOCSY spectrum of ecteinascidin 743; Figure 8, ROESY spectrum of ecteinascidin 743; Figure 9, positive ion FABMS spectrum of ecteinascidin 743; Figure 10, positive ion FABMS/MS spectrum of ecteinascidin 743 (22 pages). Ordering information is given on any current masthead page.

(25) The designations Et 729, 743, 745, 759A, 759B, and 770 were originally employed[1a,b] as indicative of the compounds' molecular weights and are retained to avoid confusion, in spite of their real (hydrated) molecular weights—Et 729 (747), Et 743 (761), Et 759A, B (777).

(26) (a) He, H.-y.; Faulkner, D. J. *J. Org. Chem.* **1989**, *54*, 5822–5824. (b) Frincke, J. M.; Faulkner, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 265–269.
(27) Gulavita, N. K.; Scheuer, P. J.; De Silva, E. D. Abstracts, Indo-United States Symposium on Bioactive Compounds from Marine Organisms, Goa, India, Feb. 23–27, 1989; p 28.

Development of a New Acyl Anion Equivalent for the Preparation of Masked Activated Esters and Their Use To Prepare a Dipeptide

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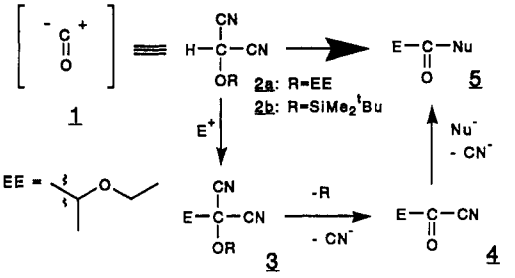
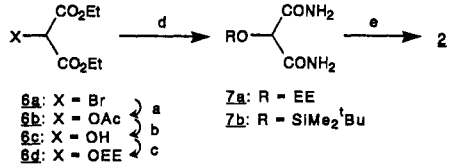
Summary: A new acyl anion equivalent, the protected hydroxymalonitrile **2**, has been developed as a masked activated ester equivalent. Alkylation or allylation of **2a** proceeded in high yields under mild basic or neutral conditions, respectively. Treatment of the tosylimine **18** with **2a** gave the dipeptide **20** via the α-amino acid having a masked activated functionality **19a**.

A number of "masked acyl anions" have been developed,[1] and they play an important role in organic synthesis. However, the chemistry on "masked activated esters" has been virtually unknown.[2,3] We report the first synthesis of a *masked acyl anion* for the preparation of an *activated ester* and its application to the synthesis of a dipeptide via the α-amino acid[4] having a masked activated ester functionality. Our strategy is summarized in Scheme I. The reaction of **2** with an electrophile will give **3**, which can subsequently undergo elimination of R and a cyano group, resulting in the formation of **4**. Treatment with a nucleophile will produce **5**. Accordingly, **2** acts as a synthetic equivalent of **1**. Further, both the protected form **3** and the activated form **4** of esters intervene during the

Scheme I. The Strategy via a Masked Activated Ester



Scheme II. Synthesis of 2[a]



[a] (a) KOAc/DMF; (b) K_2CO_3/EtOH; (c) ethyl vinyl ether/*p*-TsOH; (d) excess NH_3/EtOH; (e) $Et_3N^+SO_2N^-CO_2Me$ (**8**)/THF.

(1) Hase, T. A. *Umpoled Synthons, A Wiley-Interscience Publication*; Wiley & Sons: New York, 1987; and references cited therein.
(2) Although the preparation of 2-cyano-1,3-dithiane and its alkylation have been reported, transformation to the acyl cyanide has not been achieved. (a) Khatri, H. N.; Walborsky, H. M. *J. Org. Chem.* **1978**, *43*, 734. (b) Hannick, S. M.; Kishi, Y. *J. Org. Chem.* **1983**, *48*, 3833.
(3) The reaction of acyl cyanide with trimethylsilyl cyanide to 1,1-dicyano-1-(silyloxy) compound has been reported. However, its acyl anion analogue has not been synthesized. Hünig, S.; Schaller, R. *Angew Chem., Int. Ed. Engl.* **1982**, *21*, 36.
(4) For the recent synthesis of α-amino acids: (a) O'Donnell, M. J., Ed. *α-Amino Acid Synthesis*; *Tetrahedron-in-Print number 33*; Pergamon: Oxford, 1988; p 5253. (b) Mooiweer, H. H.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1989**, *45*, 4627. (c) Ermert, P.; Meyer, J.; Stucki, C.; Schneebeli, J.; Obrecht, J.-P. *Tetrahedron Lett.* **1988**, *29*, 1265. (d) Wakamatsu, H.; Uda, J.; Yamakami, N. *J. Chem. Soc., Chem. Commun.* **1971**, 1540. (e) Harding, K. E.; Davis, C. S. *Tetrahedron Lett.* **1988**, *29*, 1891. (f) Yamamoto, Y. *Acc. Chem. Res.* **1987**, *20*, 243.

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