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.

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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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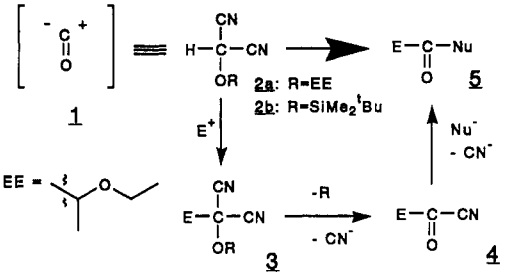
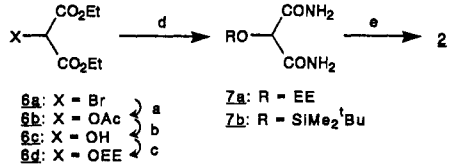
Summary: A new acyl anion equivalent, the protected hydroxymalonitrile **2**, has been developed as a masked activated ester equivalent. Alkylation or allylation of **2a** proceeded in high yields under mild basic or neutral conditions, respectively. Treatment of the tosylimine **18** with **2a** gave 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]

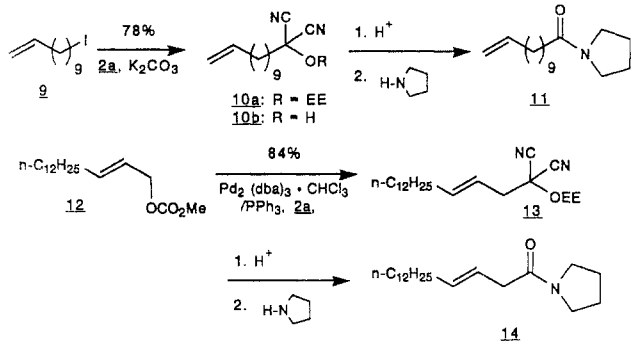


[a] (a) KOAc/DMF; (b) K_2CO_3/EtOH; (c) ethyl vinyl ether/*p*-TsOH; (d) excess NH_3/EtOH; (e) $Et_3N^+SO_2N^-CO_2Me$ (**8**)/THF.

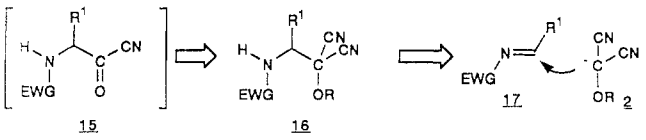
(1) Hase, T. A. *Umpoled Synthons, A Wiley-Interscience Publication*; Wiley & Sons: New York, 1987; and references cited therein.
(2) Although the preparation of 2-cyano-1,3-dithiane and its alkylation have been reported, transformation to the acyl cyanide has not been achieved. (a) Khatri, H. N.; Walborsky, 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.

0022-3263/90/1955-4515$02.50/0

Scheme III. Reaction of 2 with an Alkyl Halide or Allyl Carbonate



Scheme IV. Strategy for the Synthesis of α-Amino Acid Having a Masked Activated Ester Functionality



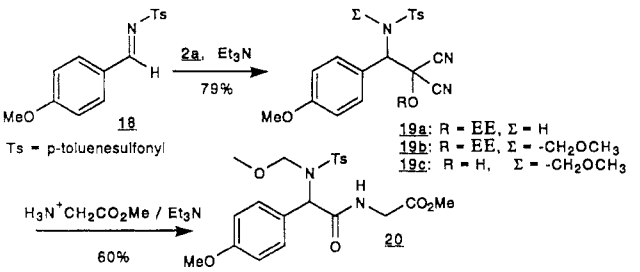
conversion from **2** to **5**. The latter feature is especially important for the synthesis of amino acids and peptides.[5]

For the synthesis of **2**, the key step was the formation of two cyano groups by the dehydration of the diamide **7** (Scheme II). The bromide **6a** was transformed to **6d** in three steps in 63% overall yield. The diethyl ester **6d** was converted to **7a** with excess ammonia in ethanol. The dehydration reaction of **7a** was accomplished with the reagent 8[6] and gave **2a**[7] in 74% yield. The reagent **2a** is a colorless oil and storable for more than 1 month if it is diluted with ether suspended with a trace amount of potassium carbonate.

In order to know the reactivity of **2a**, the typical alkylation and allylation reactions were carried out (Scheme III). Reaction of 1-iodo-10-undecene (**9**) with **2a** by using potassium carbonate[8] in acetone for 8.5 h gave **10a** in 78% yield. The palladium-catalyzed reaction of the allyl carbonate[9] **12** with **2a** in tetrahydrofuran (THF) for 2 h gave **13** in 84% yield. Accordingly, it is proved that **2a** exhibits a similar reactivity as the ordinary active methyne compounds and the C–C bond formation smoothly proceeds under very mild conditions.

Transformation of **10a** to the activated ester followed by amide formation was accomplished as follows. The ethoxyethyl group of **10a** was deprotected with trifluoroacetic acid (TFA) in dichloromethane (CH_2Cl_2) for 24 h. After removal of TFA, a mixture of the crude alcohol **10b** and 3 equiv of pyrrolidine in CH_2Cl_2 was stirred for 30 min and gave the amide **11** in 76% yield from **10a**. The compound **13** was also converted to the β,γ-unsaturated amide **14** in 60% yield. It is noteworthy that the α,β-unsaturated

Scheme V. Synthesis of a Dipeptide



amide was not detected at all.[10] Thus, generation of the activated ester from **10a** (or **13**) and the following amide bond formation smoothly proceeded under the mild conditions.

Based upon the above observation, we attempted to apply **2a** to the synthesis of α-amino acids and peptides. The strategy is shown in Scheme IV. Reaction of "*activated* imine"[11] **17** with **2** gives the N-*protected* amine **16**. Its carbonyl moiety is in a *protected* form at this stage (**16**), but is readily converted to the *activated* ester in the next step (**15**).

The reaction of the tosylimine **18**[12] with **2a** in the presence of a catalytic amount of triethylamine gave **19a**, which was subsequently converted to **19b** upon treatment with chloromethyl methyl ether and diisopropylethylamine (Scheme V). The isolated yield of **19b**[13] was 79% yield from **2a**. Isolation of **19a** resulted in slow decomposition, giving **18**, *p*-toluenesulfonamide, and anisaldehyde. Presumably the reversible process occurred on the silica gel column. However, the structure of **19a** was definitely confirmed by ^1H and ^{13}C NMR spectra. The ethoxyethyl group of **19b** was deprotected with Amberlyst 15[14] in methanol to give **19c**.[15] The crude **19c** was treated with 1.2 equiv of glycine methyl ester hydrochloride and triethylamine in THF to give **20** in 61% yield from **19b**. Thus, the first synthesis of α-amino acid having a "masked" activated ester functionality was accomplished.

In conclusion, we developed, for the first time, the acyl anion equivalent of an activated ester. Application to the synthesis of a dipeptide via an α-amino acid having a "masked" activated ester was also first accomplished. We are actively pursuing to extend this new methodology to the synthesis of optically active unnatural amino acids and peptides not easily available through the ordinary methods.

Supplementary Material Available: Full characterization data for **2a,b**, **10a**, **11**, **13**, **14**, **19b**, and **20** along with a detailed procedure (9 pages). Ordering information is given on any current masthead page.

(5) Preparation of α,α-dicyanoepoxides and their reaction with hydrazines probably via the acyl cyanide has been reported. Legrel, P.; Baudy-Floc'h, M.; Robert, A. *Synth. Commun.* **1987**, 306.

(6) Claremon, D. A.; Phillips, B. T. *Tetrahedron Lett.* **1988**, *29*, 2155.

(7) We also synthesized **2b** in 78% yield from **7b**. **2b** is storable for more than 1 month without dilution and/or in the absence of potassium carbonate. The stability of **2** seems to depend upon the protective group.

(8) Use of stronger bases such as lithium hexamethyldisilazide, lithium diisopropylamide, and sodium hydride gave **10a** in low yields. Stork has reported that the cyanohydrin ether of formaldehyde is too unstable to generate carbanion because of its self-condensation. Fortunately, however, the bases which deprotonate **2** but do not induce the self-condensation, can be used in our case. Stork, G.; Ozorio, A. A.; Leong, A. Y. W. *Tetrahedron Lett.* **1978**, 5175.

(9) Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y. *Tetrahedron Lett.* **1982**, *23*, 4809. Tsuji, J. *Pure Appl. Chem.* **1989**, *61*, 1673.

(10) Transformation of γ,δ-unsaturated cyanohydrins to β,γ-unsaturated ketones without the isomerization has been reported. Takahashi, T.; Shimizu, K.; Doi, T.; Tsuji, J. *J. Am. Chem. Soc.* **1988**, *110*, 2674. Takahashi, T.; Nemoto, H.; Kanda, Y.; Tsuji, J.; Fukazawa, Y.; Okajima, T.; Fujise, Y. *Tetrahedron* **1987**, *43*, 5499.

(11) In the imine **17**, an EWG *activates* the C=N bond. Recently, therefore, a number of synthetic studies by using EWG-activated imines or iminium ions have been reported. (a) Yamada, J.; Satô, H.; Yamamoto, Y. *Tetrahedron Lett.* **1989**, *30*, 5611. (b) Yamamoto, Y.; Schmid, M. *J. Chem. Soc., Chem. Commun.* **1989**, 1310. (c) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1984**, *40*, 4367. (d) Esch, P. M.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron Lett.* **1988**, *29*, 367. (e) Shono, T. *Tetrahedron* **1984**, *40*, 811. (f) Sisko, J.; Weinreb, S. M. *J. Org. Chem.* **1990**, *55*, 393.

(12) Albrecht, R.; Kresze, G.; Mlakar, B. *Chem. Ber. Jahr.* **1964**, *97*, 483.

(13) A mixture of diastereomers (ca. ~1:1) was observed in ^1H and ^{13}C NMR spectroscopy.

(14) Bongini, A.; Cardillo, G.; Orena, M.; Sandri, S. *Synthesis* **1979**, 618.

(15) The resulting crude **19c** was pure enough to be analyzed by ^1H and ^{13}C NMR spectroscopy, in which a single isomer was observed since one of the two asymmetric centers of **19b** disappeared after removal of the ethoxyethyl (EE) group.