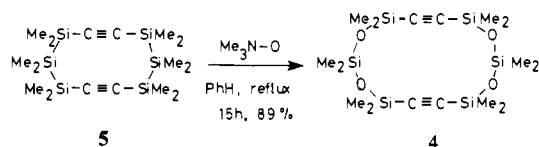
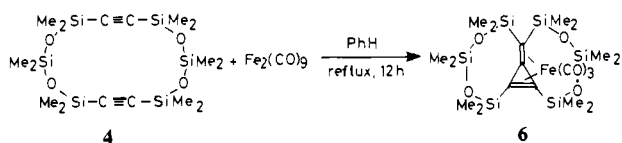


3,3,5,5,7,7,10,10,12,12,14,14-dodecamethyl-4,6,11,13-tetraoxa-3,5,7,10,12,14-hexasilacyclotetradeca-1,8-diyne (**4**) with diiron nonacarbonyl. Compound **4** was prepared from 3,3,4,4,5,5,8,8,9,9,10,10-dodecamethyl-3,4,5,8,9,10-hexasilacyclodeca-1,6-diyne (**5**) by oxidation with trimethylamine *N*-oxide.<sup>12</sup>



The reaction of the diyne **4** with 1.5 equiv of diiron nonacarbonyl in refluxing benzene afforded the novel (methylene-cyclopropene)iron tricarbonyl derivatives **6** in 45.5% yield, as



orange crystals, mp 122–123 °C dec,<sup>13</sup> isolated and purified from the reaction mixture by treatment with silica gel TLC. Its structure was established unequivocally by X-ray diffraction (Figure 1).<sup>14</sup>

The iron atom is bonded to four carbons of the methylene-cyclopropene ligand and three carbonyl groups. It is noteworthy that both  $r(\text{C}_1\text{C}_2)$  (1.479 Å) and  $r(\text{C}_3\text{C}_4)$  (1.397 Å) (to a lesser extent) are elongated by comparing with the corresponding bonds of **1** (1.323 and 1.332 Å, respectively) as determined by microwave spectra.<sup>3c</sup> In contrast, the analogous bond distances in  $r(\text{C}_1\text{C}_3)$  (1.427 Å) and  $r(\text{C}_2\text{C}_3)$  (1.417 Å) are shorter than **1** (1.441 Å).<sup>3c</sup> Unusually wide bond angles were observed for  $\angle\text{SiOSi}$  (163.9° and 158.6°) in comparison with the normal values of disiloxanes (130 ± 10°).<sup>15</sup> The  $\text{C}_3\text{-C}_4$  double bond of **6** is bent to iron by 27.9° from the planar cyclopropene ring.<sup>16</sup>

Apparently, the capability of silicon to undergo 1,2-shifts in disilylalkynes is responsible for the formation of the unusual product reported here. We have previously reported transition-metal-catalyzed intramolecular trimerization of macrocyclic triacetylene **7** to fulvene complexes and benzene derivatives,<sup>11d</sup> and, recently, we have isolated a vinylidene complex **8**, the structure of which was determined by X-ray diffraction, in the reaction of **7** and  $\eta^5$ -cyclopentadienyl(tricarbonyl)manganese.<sup>17</sup> Thermal and photochemical reactions of **8** afforded the corresponding benzene and fulvene derivatives.<sup>17</sup> A similar vinylidene complex must be an intermediate in the present reaction, although we have not isolated it yet.<sup>18</sup>

(11) (a) Sakurai, H.; Nakadaira, Y.; Hosomi, A.; Eriyama, Y. *Chem. Lett.* **1982**, 1971. (b) Sakurai, H.; Nakadaira, Y.; Hosomi, A.; Eriyama, Y.; Kabuto, C. *J. Am. Chem. Soc.* **1983**, *105*, 3359. (c) Sakurai, H.; Nakadaira, Y.; Hosomi, A.; Eriyama, Y.; Kabuto, C. *Chem. Lett.* **1984**, 595. (d) Sakurai, H.; Nakadaira, Y.; Hosomi, A.; Eriyama, Y.; Hiram, K.; Kabuto, C. *J. Am. Chem. Soc.* **1984**, *106*, 8315.

(12) Sakurai, H.; Kira, M.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1167.

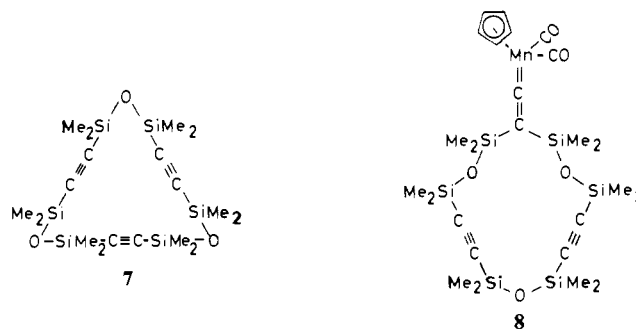
(13) **6**: <sup>1</sup>H NMR ( $\text{CD}_2\text{Cl}_2$ )  $\delta$  0.39 (s, 6 H), 0.28 (s, 12 H), 0.25 (s, 6 H), 0.07 (s, 6 H), 0.06 (s, 6 H); <sup>13</sup>C NMR ( $\text{CD}_2\text{Cl}_2$ )  $\delta$  212.3, 100.3, 96.9, 43.1, 4.6, 3.1, 2.7, 1.4, 1.1, 0.26; <sup>29</sup>Si NMR ( $\text{CD}_2\text{Cl}_2$ )  $\delta$  -0.4, -3.3, -18.7; IR ( $\text{CCl}_4$ ) 2039, 1970  $\text{cm}^{-1}$ ; UV (hexane)  $\lambda_{\text{max}}$  (log  $\epsilon$ ) 216 (4.59), 255 (4.15), 400 nm (2.72); MS,  $m/z$  (rel intensity) 585 ( $\text{M}^+ - 15$ , 0.2), 73 (100). Anal. Calcd for  $\text{C}_{19}\text{FeH}_{36}\text{O}_7\text{Si}_6$ : C, 37.98; H, 6.04. Found: C, 38.21; H, 6.11.

(14) Crystal data:  $\text{C}_{19}\text{FeH}_{36}\text{O}_7\text{Si}_6$ , Fw 600.85, space group *Pbca*,  $a = 20.465$  (2) Å,  $b = 20.854$  (2) Å,  $c = 14.631$  (2) Å,  $V = 6244.2$  (6) Å<sup>3</sup>,  $Z = 8$ ,  $d_{\text{calcd}} = 1.28$   $\text{g cm}^{-3}$ , crystal dimension  $0.20 \times 0.20 \times 0.30$  mm. intensities were measured on a Rigaku diffractometer with use of  $\text{Mo K}\alpha$  radiation within  $2\theta = 55^\circ$ , and independent 7625 reflections within  $|F_o| \geq 3\sigma|F_o|$  were used in the structure refinement. The final *R* factor was 0.055.

(15) Ebsworth, E. A. V. In *Organometallic Compounds of the Group IV Elements*; MacDiarmid, A. G., Ed.; Marcel Dekker: New York, 1968; Vol. 1, Chapter 1.

(16) We have observed similar bending for a  $\text{Mo}(\text{CO})_3$  complex of fulvene derived from **7**.<sup>11d</sup>

(17) Sakurai, H.; Hiram, K.; Nakadaira, Y.; Yamazaki, H., to be published.



**Acknowledgment.** We thank Toshiba Silicone Co., Ltd. for gifts of chlorosilanes. The work was supported in part by the Ministry of Education, Science, and Culture (Grant-in-Aid for Special Project Research, no. 61125004).

**Supplementary Material Available:** Tables of final atomic coordinates, anisotropic temperature factors, and bond lengths and angles (5 pages); tables of observed and calculated structure factors (25 pages). Ordering information is given on any current masthead page.

(18) For vinylidene complexes: Liebeskind, L. S.; Chidambaram, R. J. *Am. Chem. Soc.* **1987**, *109*, 5025 and references cited therein.

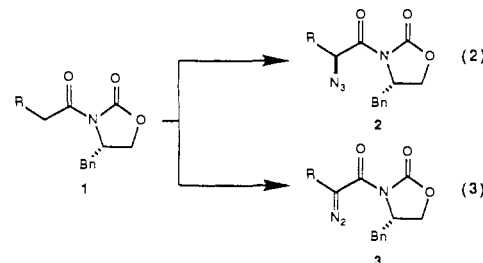
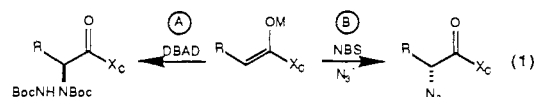
## Electrophilic Azide Transfer to Chiral Enolates. A General Approach to the Asymmetric Synthesis of $\alpha$ -Amino Acids

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Received July 13, 1987

In connection with our interest in developing convenient, general methods for the asymmetric synthesis of  $\alpha$ -amino acids,<sup>1</sup> we recently reported<sup>2</sup> the stereoselective "amination" of chiral imide enolates with di-*tert*-butyl azodicarboxylate (DBAD) (eq 1A).<sup>3</sup>



In an ensuing report<sup>4</sup> we outlined a complementary approach

(1) For complementary approaches based on chiral glycinate synthons, see: (a) Schollkopf, U. *Top. Curr. Chem.* **1983**, *109*, 66–84. (b) Ikegami, S.; Hayama, T.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 3403–3406, and references cited therein. (c) Seebach, D.; Miller, D. D.; Muller, S.; Weber, T. *Helv. Chim. Acta* **1985**, *68*, 949–952, and references cited therein. (d) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1987**, in press. (e) Sinclair, P. J.; Zhai, D.; Reibenspies, J.; Williams, R. M. *J. Am. Chem. Soc.* **1986**, *108*, 1103–1104.

(2) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 6395–6397.

(3) For related studies see: (a) Gennari, C.; Columbo, L.; Bertolini, G. *J. Am. Chem. Soc.* **1986**, *108*, 6394–6395. (b) Trimble, L. A.; Vederas, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 6397–6399. (c) Oppolzer, W.; Moretti, R. *Helv. Chim. Acta* **1986**, *69*, 1923.

involving asymmetric enolate bromination and subsequent azide displacement to afford diastereomerically pure  $\alpha$ -azidoimides (eq 1B).<sup>5</sup> While the former method provided access to a wider range of targets, e.g., *tert*-alkyl and arylglycines, the  $\alpha$ -azido imides and the derived enantiomerically pure  $\alpha$ -azido carboxylic acids perform as nearly ideal protected  $\alpha$ -amino acids. Accordingly, we have investigated the utility of (+)N<sub>3</sub> synthons in the direct electrophilic azidation of basic enolates which incorporates the most desirable features of both of these enolate-based approaches to asymmetric amino acid synthesis (*vide infra*). The purpose of this communication is to disclose the development of highly stereoselective variants of not only this reaction (eq 2) but also the discovery of a protocol for effecting kinetic diazo transfer to basic enolates as well (eq 3).

In general, the reactions of enolates with arylsulfonyl azides are documented to give several different types of products depending on the course of fragmentation of the presumed intermediate 1-1 adduct.<sup>6</sup> For example, net diazo transfer is the commonly observed path with stabilized enolates,<sup>7</sup> however, the reductive elimination of aryl sulfinate to afford the azide transfer option has been documented in a few specialized cases.<sup>8,9</sup> Of these, the only reported examples of kinetic azide transfer to nonstabilized enolates have been achieved with azetidinones according to the procedure developed by Kuhlein and Jensen.<sup>9</sup> According to this method, the primary reaction product of the lithium enolate with tosyl azide is quenched with Me<sub>3</sub>SiCl at -50 °C, the  $\alpha$ -azide reportedly being formed upon subsequent heating. As a consequence of the lack of generality of the Kuhlein-Jensen azidation reaction to both ester and carboximide enolates, we have systematically studied the principal reaction parameters (metal enolate structure, azide transfer reagent, and quench reagent) and have discovered that either azide transfer (eq 2) or diazo transfer (eq 3) to basic enolates may be achieved by altering these reaction constituents. For example, we have found that the yield of azide transfer increases at the expense of competing diazo transfer as the enolate counterion becomes more electropositive (Li  $\ll$  Na < K) and as the azide transfer reagent becomes more electron-rich and sterically demanding (*p*-nitrobenzenesulfonyl azide<sup>10</sup> (PNBSA) < tosyl azide<sup>11</sup> < trisyl azide<sup>12</sup>). In addition, the quench reagent was found to be an essential ingredient for successful azide transfer. Surprisingly, acetic acid proved to be superior to the silylating agents Me<sub>3</sub>SiCl or Me<sub>3</sub>SiOTf or the stronger acid TFA. Since all of the alkali metal enolates derived from carboximide **1** reacted instantly with all three sulfonyl azides at -78 °C, we speculate that the above factors might be influencing the breakdown of the primary adduct (*vide infra*).

A general procedure for enolate azidation follows: To a cooled (-78 °C) 0.2 M solution of 1.1 equiv of potassium hexamethyldisilylazide (KHMDS), 0.48 M in toluene, in anhydrous THF is added via cannula a cooled (-78 °C) solution (0.3 M in THF) of 1.0 equiv of *N*-acyloxazolidone **1**. After an enolization time of ca. 30 min,<sup>13</sup> a cooled solution (-78 °C) of 1.2 equiv of trisyl

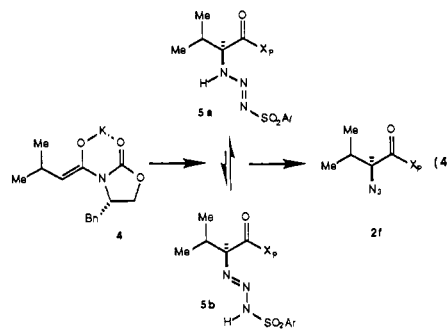
**Table I.** Electrophilic Azide Transfer to *N*-Acylloxazolidones **1** (eq 2)

entry	imide <b>1</b> , R =	kinetic ratio <sup>a</sup> (2 <i>S</i> :2 <i>R</i> )	yield, <sup>b</sup> % <b>2</b>
A	Me	97:3	74 ( <b>2a</b> )
B	CH <sub>2</sub> CH <sub>2</sub> :CH <sub>2</sub>	97:3	78 ( <b>2b</b> )
C	CH <sub>2</sub> Ph	97:3	91 ( <b>2c</b> )
D	Ph	91:9 <sup>c</sup>	82 ( <b>2d</b> )
E	CHMe <sub>2</sub>	98:2	77 ( <b>2e</b> )
F	CMe <sub>3</sub>	>99:1	90 ( <b>2f</b> )

<sup>a</sup>Diastereomer ratios determined by HPLC. <sup>b</sup>Values refer to isolated yields of diastereomerically pure (2*S*:2*R* > 200:1) product. <sup>c</sup>Ratio determined by 500 MHz <sup>1</sup>H NMR spectroscopy.

azide<sup>14</sup> (0.3 M in THF) is added via cannula, and following a reaction time of 1-2 min, 4.6 equiv of glacial acetic acid is added in 1 portion. After either slowly warming to room temperature (10-12 h, 25 °C) or gentle heating (30 min, 30 °C) the  $\alpha$ -azido carboximides **2** are isolated in the indicated yields as single diastereomers (de > 200:1) after chromatographic purification on silica gel (Table I). Due to the stereoregular elution order displayed by the product C<sub>2</sub> diastereomers, the slower eluting<sup>15</sup> minor (2*R*) diastereomeric contaminant is invariably removed by this chromatographic procedure. From the data in Table I it is evident that this azidation reaction enjoys considerable scope while displaying a level of stereoselectivity comparable to that observed in our prior amination study.<sup>2</sup> As in previous reports,<sup>2,4,13</sup> the observed sense of asymmetric induction is consistent with electrophilic attack on the Si face of the chelated *Z* enolate.

Some insight into the mechanism and associated counterion effects observed for the azidation reaction was obtained from the isolation of the intermediate triazine **5** (eq 4). This sensitive



compound was prepared from the potassium enolate derived from **1** (R = CHMe<sub>2</sub>) as described above with the following exception: After the acetic acid quench, the reaction was held at -30 °C for ca. 13 h prior to isolation. After chromatographic purification, **5a** and **5b** were obtained as a 3:1 tautomeric mixture in 60% yield.<sup>16</sup> Solutions of **5a-b** in THF were subjected to a range of reagents which could have been responsible for the decomposition of these triazines to azide **2f** (eq 4). Surprisingly, acetic acid is not an effective catalyst for this reaction at 25 °C; however, potassium acetate is highly effective in promoting triazine decomposition. Since lithium acetate is also an ineffective catalyst, it appears that the counterion effects noted in the preceding discussion are not expressed in the formation of the triazine intermediate as originally anticipated but in triazine decomposition!

During the course of these studies, conditions for effecting diazo transfer to these substrates has also been discovered (eq 3).<sup>17</sup> In

(4) Evans, D. A.; Ellman, J. A.; Dorow, R. L. *Tetrahedron Lett.* **1987**, *28*, 1123-1126.

(5) For a related study, see: Oppolzer, W.; Pedrosa, R.; Moretti, T. *Tetrahedron Lett.* **1986**, *27*, 831-834.

(6) For examples, see: Hendrickson, J. B.; Wolfe, W. A. *J. Org. Chem.* **1968**, *33*, 3610-3618. Also, see: ref 7.

(7) For reviews on diazo transfer, see: (a) Regitz, M. *Synthesis* **1972**, 351-373. (b) Regitz, M.; Maas, G. *Diazo Compounds, Properties and Synthesis*, Academic Press: New York, NY, 1986; Chapter 13.

(8) (a) Weininger, S. J.; Kohen, S.; Mataka, S.; Koga, G.; Anselme, J. P. *J. Org. Chem.* **1974**, *39*, 1591-1592. (b) Hakimelahi, G. H.; Just, G. *Synth. Commun.* **1980**, *10*, 429-435.

(9) (a) Kuhlein, K.; Jensen, H. *Liebigs Ann. Chem.* **1974**, 369-402. (b) Wasserman, H. H.; Hlasta, D. J. *J. Am. Chem. Soc.* **1978**, *100*, 6780-6781. (c) Bevilacqua, P. F.; Keith, D. D.; Roberts, J. L. *J. Org. Chem.* **1984**, *49*, 1430-1434.

(10) Reagan, M. T.; Nickon, A. *J. Am. Chem. Soc.* **1968**, *90*, 4096-4105.

(11) *p*-Toluenesulfonyl azide, see: ref 7a.

(12) 2,4,6-Triisopropylbenzenesulfonyl azide: Harmon, R. E.; Wellman, G.; Gupta, S. K. *J. Org. Chem.* **1973**, *38*, 11-16.

(13) (a) Evans, D. A.; Morrissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346-4348. (b) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737-1739.

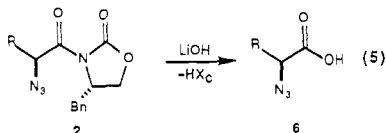
(14) Trisyl azide has also been recommended for effecting direct diazo transfer to hindered enolates under phase transfer conditions: Lombardo, L.; Mander, L. *Synthesis* **1980**, 368-369.

(15) This order of elution was observed with CH<sub>2</sub>Cl<sub>2</sub>-hexane mixtures. In some cases the elution order was reversed with hexane-EtOAc solvent systems.

(16) No information is available on the stereochemistry of either of these tautomers. <sup>1</sup>NMR saturation-transfer experiments carried out on these isomers at ambient probe temperature indicated that tautomer interconversion was occurring at the approximate rate of 10<sup>-1</sup>-1 s<sup>-1</sup> in CDCl<sub>3</sub>.

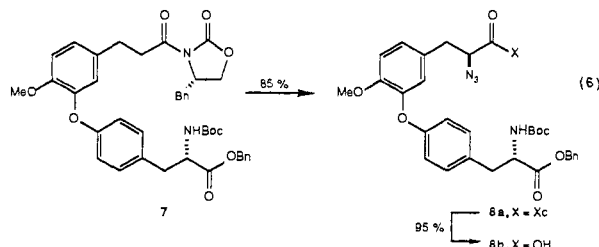
experiments that have not been fully optimized, we have found that the sodium enolate derived from **1** affords good yields of  $\alpha$ -diazoidimides **3** upon reaction with *p*-nitrobenzenesulfonyl azide, (PNBSA).<sup>18</sup> Thus, the sodium enolate derived from **1** (R = CH<sub>2</sub>Ph) and NaHMDS, on treatment with 1.2 equiv of PNBSA (THF, -78 °C, 30 min), afforded an 85% yield of diazocarbonyl imide **3** (R = CH<sub>2</sub>Ph) after quenching the reaction with a pH 7 phosphate buffer.

The racemization-free removal of the chiral auxiliary from the  $\alpha$ -azido imides **2** has proven to be a facile process (eq 5). Relevant hydrolysis and transesterification studies carried out on the  $\alpha$ -azido carbonyl imides diastereomeric to **2** have already been reported.<sup>4</sup> In a similar fashion, the hydrolysis of **2c** (R = CH<sub>2</sub>Ph), chosen as a representative unhindered substrate, with 2.0 equiv of LiOH (3:1 THF-H<sub>2</sub>O, 0.05 M in **2**, 0 °C, 30 min)<sup>4</sup> afforded the (2*S*) azido acid **6c** (R = CH<sub>2</sub>Ph) in quantitative yield with no detectable racemization.<sup>19</sup> Even the highly racemization prone azide **2d** (R



= Ph), when hydrolyzed under the above conditions, afforded a quantitative yield of (2*S*)-azidophenylacetic acid (**6d**) (R = Ph) having a minimum enantiomeric purity of 99.5%. In the most sterically demanding case, treatment of **2f** (R = CMe<sub>3</sub>) with LiOH as described above (0 °C, 1.5 h) resulted in predominant attack at the oxazolidone carbonyl. However, a dramatic improvement in selectivity was achieved in the hydrogen peroxide-mediated hydrolysis<sup>20</sup> of this substrate. Thus, a 0.05 M solution of **2f** in 3:1 THF-H<sub>2</sub>O containing 4 equiv of H<sub>2</sub>O<sub>2</sub> was treated with 2.0 equiv of LiOH (0 °C, 30 min) to afford the enantiomerically pure acid **6f**, isolated in 98% yield by a simple extraction procedure, along with a 98% recovery of the chiral auxiliary. This hydrolysis procedure has proven to be the most generally useful protocol yet discovered for regioselective carboximide hydrolysis.<sup>21</sup>

One of the distinct advantages of this azidation reaction is its applicability to the construction of polyfunctional amino acids. The example shown below serves to illustrate this point (eq 6).



Treatment of **7** with 2.2 equiv of KHMDS followed by 1.1 equiv of trisyl azide according to the conditions detailed above afforded an 85% yield of the diastereomerically pure azide **8a** after chromatographic purification. Finally, **8a** may be selectively hydrolyzed to the fully differentiated isodityrosine derivative **8b** without concomitant benzyl ester hydrolysis in 96% yield by using the basic hydrogen peroxide procedure described above.<sup>22</sup>

(17) Previous attempts to effect direct diazo transfer to related imide enolates were unsuccessful: Doyle, M. P.; Dorow, R. L.; Terpstra, J. W.; Rodenhouse, R. A. *J. Org. Chem.* 1985, 50, 1663-1666.

(18) The scope of this reaction with other enolates is currently under active investigation.

(19) The optical purity of the azido acids was determined by capillary gas chromatographic analysis of their derived (+)-MTPA-amide methyl esters as previously described in ref 2 and 4.

(20) The enhanced reactivity of hydroperoxide over hydroxide in active ester hydrolysis is well-documented: Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* 1968, 90, 2622-2637.

(21) For additional examples documenting the scope of this method, see: Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.*, submitted for publication.

(22) This experiment was carried out by J. A. Ellman in this laboratory.

**Acknowledgment.** Support has been provided by the National Institutes of Health, Eli Lilly, and Upjohn. The NIH BRS Shared Instrumentation Grant Program 1 S10 RR01748-01A1 is also acknowledged for providing NMR facilities.

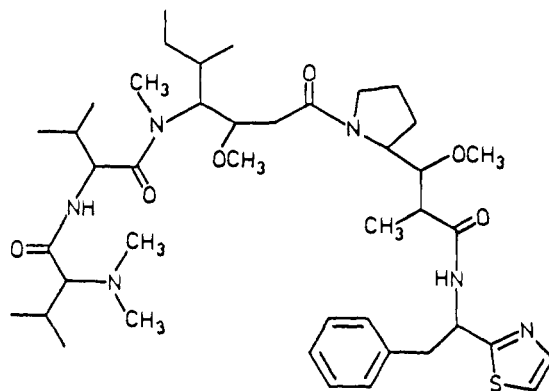
**Supplementary Material Available:** Detailed general procedures for azidation and hydrolysis as well as full spectral data (IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR) are provided (4 pages). Ordering information is given on any current masthead page.

## The Isolation and Structure of a Remarkable Marine Animal Antineoplastic Constituent: Dolastatin 10<sup>1a</sup>

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Received April 1, 1987

Exceptionally potent biological properties exhibited by the sea hare *Dolabella auricularia* have been recorded for nearly two millennia.<sup>2</sup> In 1972 we found Indian Ocean specimens of this captivating sea hare to yield extracts that proved very effective (over 100% increase in life span) against the U.S. National Cancer Institute's (NCI) murine P388 lymphocytic leukemia (PS system).<sup>3</sup> Subsequently, we isolated nine new (and powerful) cell growth inhibitory and/or antineoplastic peptides designated dolastatins 1-9<sup>2a,b</sup> and two cytotoxic terpenes.<sup>2c</sup> Due to the dolastatins potency, the sea hare seems to require only vanishingly small quantities (ca. ~1 mg each from 100 kg),<sup>2b</sup> making isolation and structural elucidation<sup>2a</sup> of these peptides exceptionally challenging. Now we are pleased to report that our 15-year effort directed at discovering the most important *Dolabella auricularia* antineoplastic constituents has resulted in isolation and structural determination of a unique linear pentapeptide herein named dolastatin 10 (**1**). To our knowledge, dolastatin 10 is the most active



DOLASTATIN 10

1

(1) (a) Contribution 136 of the series "Antineoplastic Agents". Consult the following for part 135: Dell'Aquila, M. L.; Nguyen, H. T.; Herald, C. L.; Pettit, G. R.; Blumberg, P. M. *J. Biol. Chem.*, in press. (b) Polysciences, Inc., Paul Valley Industrial Park, Warrington, PA 18976. (c) Physical and Analytical Chemistry, The Upjohn Co., Kalamazoo, MI 49001. (d) Midwest Center for Mass Spectrometry, The University of Nebraska-Lincoln, Lincoln, NB 68588.

(2) For leading references refer to the following: (a) Pettit, G. R.; Kamano, Y.; Brown, P.; Gust, D.; Inoue, M.; Herald, C. L. *J. Am. Chem. Soc.* 1982, 104, 905. (b) Pettit, G. R.; Kamano, Y.; Fujii, Y.; Herald, C. L.; Inoue, M.; Brown, P.; Gust, D.; Kitahara, K.; Schmidt, J. M.; Doubek, D. L.; Michel, C. J. *J. Nat. Prod.* 1981, 44, 482. (c) Pettit, G. R.; Herald, C. L.; Ode, R. H.; Brown, P.; Gust, D. J.; Michel, C. *J. Nat. Prod.* 1980, 43, 752.

(3) Schmidt, J. M.; Pettit, G. R. *Experientia* 1978, 34, 659.