Registry No. (±)-1, 90970-18-6; (−)-1, 91049-37-5; (+)-1, 91049-38-6; (±)-2, 90970-19-7; (+)-2, 91049-39-7; (−)-2, 91049-40-0; (±)-4, 90970-20-0; (±)-5, 90970-21-1; 14, 90970-22-2; 15, 90970-23-3; Ia, 90970-24-4; Ib, 90970-25-5; IIa, 90970-26-6; IIb, 90970-27-7; *m*-$(CH_2Br)_2C_6H_4$, 626-15-3; *m*-HOC_6H_4SH, 40248-84-8; CsOH, 21351-79-1.

Supplementary Material Available: X-ray data for 1 and 2 (11 pages). Ordering information is given on any current masthead page.

Total Synthesis of (±)-Dysidin, a Marine Metabolite Containing an *N*-Acyl-*O*-methyltetramic Acid

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The total synthesis of racemic dysidin (3), a unique halogenated marine natural product, is described. This compound along with its diastereomer was prepared by N-acylation of the (±)-5-isopropyl-4-*O*-methyltetramic acid (5) with (±)-(*E*)-5-methyl-3-methoxy-6,6,6-trichloro-2-hexenoic acid (4). Separation of the diastereomers 3 and 18 was effected by fractional crystallization.

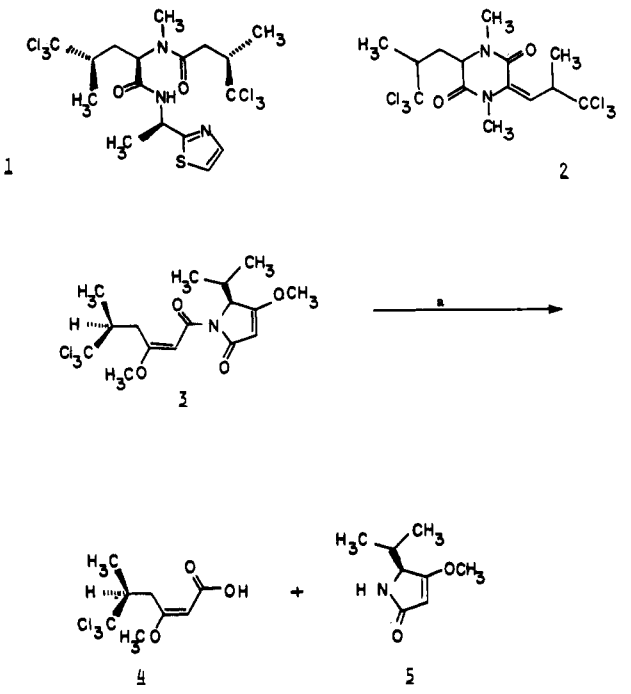
Introduction

At least 15 secondary metabolites have been isolated from the Indopacific sponge, *Dysidea herbacea*.[1] These metabolites belong to a wide variety of structural types including polybrominated diphenyl ethers,[2] nonhalogenated terpenes,[3] and a series of unique polychlorinated metabolites derived from amino acid precursors.[4] Examples of compounds belonging to this latter category are dysidenin (1),[3a] the diketopiperazine 2,[3b] and dysidin (3).[4b] Compounds 1, 2, and 3 pose an interesting synthetic challenge because of the inclusion of a trichloromethyl group in their skeletons. As far as we know, the three natural products 1–3, along with some desmethyl analogues and a diastereomer of 1, are the only naturally occurring compounds which contain the trichloromethyl functionality. In the present study we wish to report the first total synthesis of one of these natural products, namely dysidin (3).

Results and Discussion

During the structure elucidation, it had been shown that basic hydrolysis of dysidin (3) leads to compounds 4 and 5 via scission of the *N*-acyl bond of 3.[4b] This is also a convenient retrosynthetic dissection. A convergent synthesis of 3 from the two fragments 4 and 5 was completed by us.

Scheme I[a]



[a] (a) NaOH.

Preparation of 4. The trichloromethyl group is introduced as early as possible in our synthesis because this group is relatively inert. Thus a convenient starting material is the diastereomeric mixture of 2-bromo-3-methyl-4,4,4-trichlorobutyric acids (6) formed by the radical chain addition of bromotrichloromethane to crotonic acid. The regiochemistry of this addition is similar to the addition of bromotrichloromethane to ethyl crotonate.[5] Treatment of the diastereomeric acids (6) with activated zinc leads to a vigorous, spontaneous reaction. This zinc reduction gave 3-methyl-4,4,4-trichlorobutyric acid (7) in 65% overall yield from crotonic acid.

When the acid chloride 8 was dissolved in methylene chloride and treated with slightly less than 1 equiv of Meldrum's acid[6] and pyridine, the formation of 9 occurred

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(3) (a) Kazlauskas, R.; Murphy, P. T.; Wells, R. J.; Daly, J. J; Schoenholzer, P. *Tetrahedron Lett.* **1978**, 4951. (b) Kazlauskas, R.; Murphy, P. T.; Wells, R. J. *Tetrahedron Lett.* **1978**, 4949. (c) Charles, C.; Braekman, J. C.; Daloze, D.; Tursch, B.; Declercq, J. P.; Germain, G.; Van Meerssche, M. *Bull. Soc. Chim. Belg.* **1978**, *87*, 481. (d) Dunlop, R. W.; Kazlauskas, R.; March, G.; Murphy, P. T.; Wells, R. J. *Aust. J. Chem.* **1982**, *35*, 95. (e) Kashman, Y.; Zviely, M. *Tetrahedron Lett.* **1979**, 3879.

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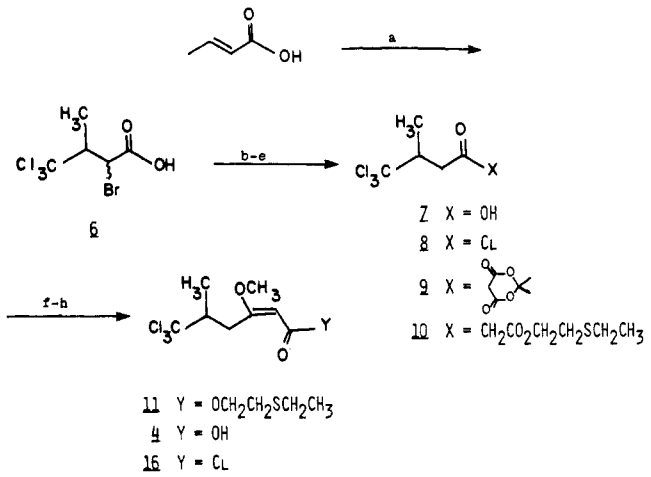
0022-3263/84/1949-3489$01.50/0

Scheme II



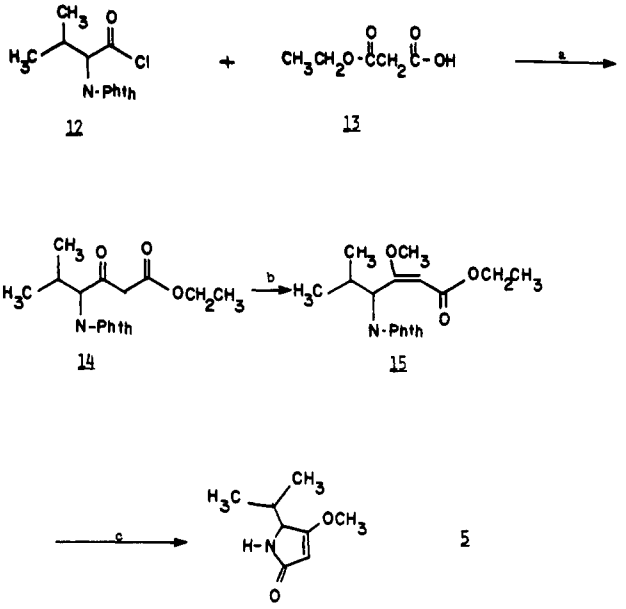
[a] (a) CCl_3Br, AIBN; (b) Zn; (c) $SOCl_2$, DMF; (d) Meldrum's acid, pyridine; (e) $HOCH_2CH_2SCH_2CH_3$; (f) KH, DMS; (g) $R_3O^+BF_4^-$, dilute NaOH; (h) $SOCl_2$, DMF.

in situ. The reactivity of intermediates such as **9** with a wide variety of alcohols, including *tert*-butyl alcohol, was described by Yonemitsu et al.[7] We chose to add 2-(ethylthio)ethanol to the solution of **9** Direct distillation of the reaction mixture led to a 57% overall yield of the β-keto ester **10** from acid chloride **8**. Although a number of keto esters similar to **10** were prepared from simpler alcohols, the choice of the 2-(ethylthio)ethyl ester was dictated by its ease of hydrolysis in a subsequent step.

O-Methylation of the potassium enolate of the β-keto ester **10** was observed when the reaction was carried out in HMPA at 5 °C with dimethyl sulfate. The enol ether **11** was not obtained when the reaction was carried out in methanol or trimethyl orthoformate under acid catalysis. Hydrolysis of **11** to the carboxylic acid **4** is effected by reaction of **11** with a slight excess of trimethyloxonium tetrafluoroborate followed by hydrolysis with dilute NaOH. Mild hydrolysis conditions are required because of the sensitivity of the enol ether and of the trichloromethyl group to either strongly acidic or basic conditions, respectively. The assignment of stereochemistry to **4** was confirmed by X-ray crystallography.[8]

Preparation of the *O*-Methyltetramic Acid 5. The basic heterocyclic nucleus, pyrrolidine-2,4-dione, is an integral part of a number of physiologically active natural products. These compounds include tirandamycin,[9] erythroskyrine,[10] tenuazonic acid,[11] ikarugamycin,[12] and althiomycin.[13] Thus, a series of publications exist which describe the preparation of the pyrrolidine-2,4-dione nucleus.[14] With the exception of two syntheses of this

Scheme III[a]



[a] (a) *n*-BuLi; (b) KH, CH_3OSO_2F; (c) NH_2NH_2.

heterocycle,[14c,g] all of the other published methods utilize a variation of the Dieckmann cyclization as employed in the original route of Lacey.[14a] We found this Dieckmann cyclization acceptable for the preparation of N-alkyl derivatives of tetramic acids. However, we were not able to obtain consistent results for the cyclization of N-unsubstituted derivatives of the pyrrolidine-2,4-dione nucleus by this method. The Dieckmann cyclization was also unattractive to us because of the demonstration by Rinehart of difficulties associated with deacylation or decarboxylation of 3-acyl or 3-carboxyl derivatives.[14f,g]

The original isolators of dysidin (**3**) describe a synthesis of the *O*-methyltetramic acid **5** by Dieckmann cyclization.[4b] Although this procedure provided us with our first synthetic sample of **5**, it became clear that an alternative route to **5** would be desirable. Hence, we set out to explore the possibilities for a more expeditious synthesis of the tetramic acid nucleus **5** with the additional requirement that a new route should allow for synthesis of **5** as an optically pure compound.

The acid chloride of (±)-*N*-phthaloylvaline (**12**) was selected as a convenient starting material for the preparation of **5**. It is also possible to obtain this amino acid derivative in high optical purity.[15] Reaction of the dilithium dianion of the monoethyl ester of malonic acid **13** with the racemic acid chloride **12** yielded the homologated keto ester **14**. This procedure was patterned after the β-keto ester syntheses of Wierenga.[16] This synthetic

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(8) Details of this crystal structure analysis will be published separately, cf., Williard, P. G.; de Laszlo, S. E.; Demoulini, S.; Carpenter, G. B., manuscript in preparation.

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(12) Ito, S.; Hirata, Y. *Bull. Soc. Chem. Jpn.* **1977**, *50*, 227, 1813.

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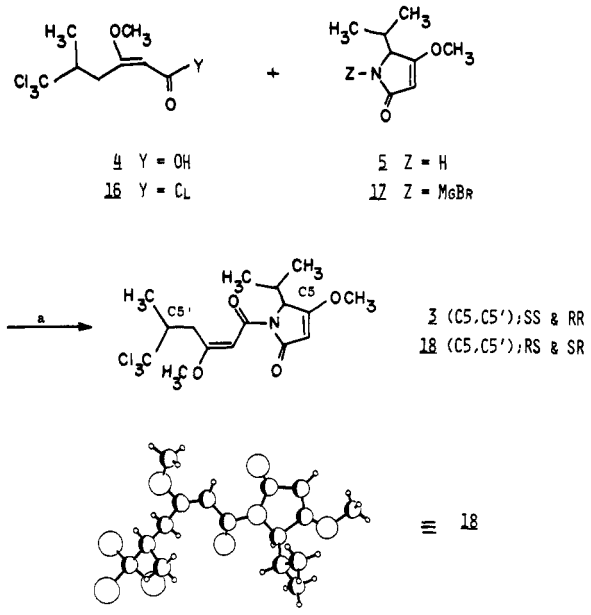
Scheme IV[a]



[a] (a) RMgBr.

transformation is equivalent to the homologation of 8 to 10 which was effected by the Yonemitsu procedure[7] (vide supra). However, it was impossible to effect a reaction of 12 with Meldrum's acid en route to 14. This failure of 12 to react with Meldrum's acid is attributed to the steric inhibition for addition to the carbonyl group of valine. This effect is greatly enhanced by the *N*-phthaloyl protecting group.

Formation of the *O*-methyl enol ether 15 was carried out by treatment of 14 with potassium hydride followed by methyl fluorosulfonate. We assume that the low reactivity of 14 toward O-methylation is also a manifestation of the steric hindrance of the valine moiety. The health hazards associated with methyl fluorosulfonate as a methylating agent preclude its use in other than reasonably small scale reactions.[17] From the NMR spectrum of crude 15, only one stereoisomer, as shown, is observed in this reaction.

For the synthesis of 5 from 15, the *N*-phthaloyl group was removed by refluxing with an excess of hydrazine overnight in anhydrous methanol. Cyclization of the free amine derived from 15 is complete in the same reaction. There is no evidence for the existence of the uncyclized amine. By the sequence of three reactions depicted in Scheme III, the tetramic acid 5 is obtained in 15% overall yield from the valine derivative 12. Efforts to improve this sequence and to utilize optically active starting materials are in progress.

Our synthesis of racemic dysidin (3) was completed as shown in Scheme IV. The carboxylic acid 4 was activated for acylation by treatment with thionyl chloride to yield the acid chloride 16. A suspension of 5 in THF is treated with ethylmagnesium bromide to produce the soluble magnesium salt 17. After addition of 16 to 17 and stirring at room temperature for 24 h, a 48% yield of a 1:1 mixture of two major compounds was obtained. The NMR, IR, and UV spectra of the less polar of the two major isomers are identical with those reported for naturally occurring dysidin (3). We tentatively assigned structure 18, i.e., the diastereomer of dysidin 3, to the more polar of the two major isomers formed in this reaction. Its 250-MHz ^{1}H NMR differs significantly only in the chemical shift of the C-4′ protons from the natural product 3.[4b]

Purification of the reaction mixture by high-pressure liquid chromatography also reveals trace amounts (<2%) of a 1:1 mixture of two slightly less polar compounds. Not enough of these minor products from this reaction were purified for full characterization. However, we concluded from the NMR that these minor products must be the stereoisomers of 3 and 18 which have been isomerized about the enol ether olefin to the *Z* configuration. Isomerization of this olefin is likely to have occurred in the formation of the acid chloride 16 from 4.

Fortuitously, we have found that chromatographic separation of 3 from 18 is unnecessary. When the mixture of these two compounds is allowed to stand at room temperature in a minimum volume of diisopropyl ether/pentane, crystallization began within a few hours. This crystallization was essentially complete after a period of about 24 h. Analysis of these crystals, without further purification, by X-ray crystallography and also by liquid chromatography revealed that racemic isodysidin (18) had fractionally crystallized from the mixture leaving behing almost pure dysidin (3). A computer generated plot of the crystal structure of 18 is given in Scheme IV. The crystals of 18 are somewhat unusual in that they belong to the enantiomorphous space group $P2_1$ and have undergone spontaneous resolution during crystallization.[18] Thus it was possible to obtain the pure, racemic diastereomers dysidin (3) and isodysidin (18) from 4 and 5 in 48% overall yield from the carboxylic acid 4.

Conclusion

In this study, the total synthesis of racemic dysidin (3) has been achieved. This synthesis is completed in a convergent manner by N-acylation of the tetramic acid 5 with the acid chloride 16 derived from 4. No chromatographic separations of diastereomeric mixtures of synthetic intermediates were necessary. Only one separation was required. This proved to be an extremely straightforward fractional crystallization of 3 from its diastereomer 18 in the final step.

A new synthesis of the tetramic acid nucleus 5 has been demonstrated. This route differs fundamentally from the majority of the previous syntheses of the pyrrolidine-2,4-dione skeleton. This route has the potential for the preparation of a variety of 5-alkyltetramic acids as found in several medicinally important natural products. When combined with the lithiation of 3-unsubstituted tetramic acids demonstrated recently by Jones and Peterson,[14k] this tetramic acid synthesis should be generally applicable to the preparation of all naturally occurring tetramic acids. However, the use of methyl fluorosulfonate in the synthetic scheme is a serious limitation, and further investigation to avoid this reagent is under way.

Experimental Section

Melting points were determined with a Thomas Hoover melting point apparatus. The following spectrometers were used to record spectral data: IR, Perkin-Elmer 681; ^{1}H NMR and ^{13}C NMR, Bruker WM-250 (chemical shifts are reported in ppm (δ) downfield from an internal standard (Me_4Si)); UV, Perkin-Elmer 552A. Elemental analyses were performed by the Schwartzkopf Mi-

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(18) The crystallographic asymmetric unit of 18 consists of a pair of enantiomers. Hence the chirality of the crystals of 18 are due solely to the lattice and, unfortunately, not to a resolution of the enantiomeric molecules themselves. Details of this crystal structure will be published separately, cf., Williard, P. G.: de Laszlo, S. E., manuscript in preparation.

croanalytical Lab., Woodside, NY. X-ray crystallography was performed with a Nicolet R3m/E crystallographic system. High-pressure liquid chromatography was done with a Waters 6000a system equipped with a Model 441 absorbance detector.

(±)-2-Bromo-3-methyl-4,4,4-trichlorobutanoic Acid (6). A quantity of 86 g of crotonic acid (0.46 mol) was dissolved in 200 mL of dry distilled bromotrichloromethane (2 mol) and warmed to 90 °C under nitrogen. The mixture was heated for a total of 9 h during which time a total of 15 g (15 mmol) of AIBN was added portionwise. The reaction mixture was monitored by NMR for the disappearance of crotonic acid and appearance of a doublet at δ 5.0 for the proton α to the carboxyl group of compound (6). The reaction mixture was then taken up in 200 mL of diethyl ether and extracted (3 × 100 mL) with 2 N NaOH. The aqueous layer was washed (2 × 50 mL) with ether and acidified with 1 N HCl. The aqueous layer was then extracted with ether (4 × 100 mL), washed with saturated NaCl, and dried over $MgSO_4$. Evaporation in vacuo gave 6 as a pale brown oil 113.15 g (86%). The oil was used in the next reaction without further purification. Spectral analysis indicated that the product consisted of two isomers in an approximate ratio of 2:1: ^{13}C NMR δ 12.78 (q), 43.09 (q), 60.15 (d), 101.4 (s), 173.28 (s) minor isomer; 16.41 (q), 46.41 (d), 54.40 (d), 102.35 (s), 174.09 (s) major isomer; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.61 (d, 3 H, J = 6.6 Hz), 3.31 (dq, 1 H, J = 3.8, 6.6 Hz), 5.01 (d, 1 H, J = 3.8 Hz) major isomer; 1.76 (d, 3 H, J = 6.88 Hz), 3.19 (dq, 1 H, J = 3.11, 6.88 Hz), 5.05 (d, 1 H, J = 3.11 Hz) minor isomer.

(±)-3-Methyl-4,4,4-trichlorobutanoic Acid (7). In a clean, dry 1-L three-neck flask fitted with condensor, 250 mL dropping funnel, and stopper was placed 32.7 g (0.5 mol) of activated zinc under nitrogen. To this flask was added 200 mL of freshly opened, reagent grade methylene chloride. This suspension was treated dropwise with a solution of 113 g (0.4 mol) of bromo trichloro acid 6 dissolved in 200 mL of methylene chloride. The acid (6) was added at such a rate so as to maintain a gentle reflux. After the addition was over and reflux ended, the mixture was warmed for about 2 h to give a light green, clear solution with a small amount of unreacted zinc dust. This solution was poured into a separatory funnel and washed with water (400 mL) containing 50 mL of concentrated HCl. This must be done carefully as effervescence does occur. The CH_2Cl_2 layer is washed with water (2 × 50 mL) followed by saturated NaCl (2 × 50 mL). After drying over $MgSO_4$, the solution is evaporated in vacuo to give a pale yellow solid. Only a small sample of this compound was purified for analysis by recrystallization from ether/pentane, mp 74–75 °C. The remaining material was used without further purification (yield 76%, 55 g): ^{13}C NMR δ 17.02 (q), 38.23 (t), 51.45 (d), 104.45 (s), 177.33 (s); IR ($CHCl_3$) 2600–3600, 1710, 1410, 1380, 1285, 1240, 1070, 965, 900, 870 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.42 (d, 3 H, J = 6 Hz), 2.47 (dd, 1 H, J = 10, 17 Hz), 3.07–3.21 (m, 2 H). Anal. Calcd for $C_5H_7Cl_3O_2$: C, 29.22; H, 3.41; Cl, 51.79. Found: C, 29.60; H, 3.47; Cl, 52.13.

(±)-3-Methyl-4,4,4-trichlorobutanoyl Chloride (8). Carboylic acid 7 (10.25 g, 0.05 mol) is treated with an excess of thionyl chloride in a round-bottom flask fitted with a reflux condenser. A catalytic amount of dry DMF was added giving rise to an exothermic reaction. The mixture was gently refluxed for 1 h and then cooled. After the condenser was replaced with a distilling head, the excess thionyl chloride was removed by distillation under vacuum (30 mmHg) at room temperature. The acid chloride was recovered by distillation at 104 °C (30 mmHg): yield, 8.06 g, 72%; ^{13}C NMR δ 16.74 (q), 50.69 (t), 51.56 (d), 103.38 (s), 171.41 (s); IR ($CHCl_3$) 2990, 2930, 1780, 1460, 1400, 1380, 1350, 1270, 1125, 1070, 985, 950, 870 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.44 (dd, 3 H, J = 6.4, 1.0 Hz), 3.01 (dd, 1 H, J = 9.5, 17.4 Hz), 3.11–3.22 (m, 1 H), 3.67 (dm, 1 H, J = 17.2 and other smaller couplings). Anal. Calcd for $C_5H_6Cl_4O$: C, 26.81; H, 2.68; Cl, 63.36. Found: C, 27.78; H, 2.91; Cl, 62.47.

(±)-2-(Ethylthio)ethyl 5-Methyl-3-oxo-6,6,6-trichlorohexanoate (10). To 5.47 g (0.038 mol) of Meldrum's acid[6] dissolved in 50 mL of dry CH_2Cl_2 under N_2 was added at −5 °C 6.33 g (0.08 mol) of dry pyridine. To this solution was added dropwise over 20 min the acid chloride 8 (8.92 g, 0.04 mol). This solution was stirred for 1 h at −5 °C and $^1/_2$ h at room temperature. The mixture was then extracted (4 × 15 mL) with 1 N HCl. The organic layer was washed with water (1 × 15 mL) and dried with $MgSO_4$. Evaporation of the solvent gives a dark oil weighing 13 g (0.038 mol, 100% yield). This crude product was used directly in the next step.

A quantity of 11.7 g (0.035 mol) of the above product was dissolved in 75 mL of dry benzene under N_2. To this solution was added 2-(ethylthio)ethanol (11.24 g, 0.106 mol) and the resulting mixture was refluxed for 3 h. Carbon dioxide evolution could be observed if a mineral oil bubbler was attached. The benzene was then removed on a rotary evaporator and the product distilled at 0.075 mmHg. After a substantial forerun of XS alcohol at 40 °C, the ester was recovered at 150–155 °C in an overall yield of 57% from the acid chloride 8: ^{13}C NMR δ 14.80 (q), 17.13 (q), 26.22 (t), 30.08 (t), 46.73 (t), 49.37 (t), 50.23 (d), 64.37 (t), 105.00 (s), 166.38 (s), 198.91 (s); IR ($CHCl_3$) 2760, 2920, 1740, 1715, 1450, 1405, 1375, 1357, 1310, 1200, 1150, 1070, 965 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.27 (t, 3 H, J = 7.41 Hz), 1.34 (d, 3 H, J = 6.5 Hz), 2.58 (q, 2 H, J = 7.41 Hz), 2.77 (t, 2 H, J = 7.0 Hz), 3.24–3.33 (m, 3 H), 3.52 (s, 2 H), 4.30 (t, 2 H, J = 7.0 Hz). Anal. Calcd for $C_{11}H_{17}Cl_3O_3S$: C, 39.35; H, 5.07; Cl, 31.71; S, 9.54. Found: C, 40.11; H, 5.48; Cl, 30.49; S, 9.84.

(±)-(*E*)-2-(Ethylthio)ethyl 5-Methyl-3-methoxy-6,6,6-trichloro-2-hexenoate (11). A quantity of 0.144 g of 24% KH in oil (3.6 mmol KH) was weighed into a two-neck 25-mL flask. The oil was removed by washing with pentane and drying under a stream of nitrogen. To this was added 10 mL of dry HMPA at 5 °C followed by dimethyl sulfate (1.13 g, 9.0 mmol). The mixture was stirred at 5 °C for 5 min and then the β-keto ester 10 (1.0 g, 3.0 mmol) in 3 mL of HMPA was added dropwise. H_2 evolution occurred and the mixture turned pale brown. It was stirred at 5 °C for 1 h at which time it was a pale brown clear solution. The ice bath was removed and the mixture stirred for a further 30 min. The solution was pured into 15 mL of water and extracted (4 × 15 mL) with pentane. The pentane extracts were then washed (3 × 5 mL) with 1 N NaOH and then dried over $MgSO_4$. Evaporation in vacuo was followed by flash chromatography over silica gel with 50% CH_2Cl_2/hexanes to give 0.74 g of colorless oil (11): yield 71%; ^{13}C NMR δ 14.86 (q), 15.72 (q), 26.26 (t), 30.55 (t), 34.84 (t), 52.59 (d), 55.63 (q), 62.88 (t), 92.87 (d), 105.59 (s), 166.75 (s), 172.71 (s); IR ($CHCl_3$) 2965, 2930, 1700, 1620, 1452, 1437, 1382, 1366, 1280, 1200, 1180, 1132, 1090, 1072, 1050, 1000, 957, 905, 822 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.26 (d, 3 H, J = 6 Hz), 1.27 (t, 3 H, J = 7.3 Hz), 2.59 (q, 2 H, J = 7.3 Hz), 2.78 (t, 2 H, J = 6.9 Hz), 3.02 (m, 1 H), 3.16 (dd, 1 H, J = 3.5, 12.7 Hz), 3.42 (m, 1 H), 3.68 (s, 3 H), 4.25 (t, 2 H, J = 6.9 Hz), 5.15 (s, 1 H); UV λ_{max} (95% EtOH) 235 (ε 14 200). Anal. Calcd for $C_{12}H_{19}Cl_3O_3S$: C, 41.22; H, 5.44; Cl, 30.44. Found: C, 41.51; H, 5.53.

(±)-(*E*)-5-Methyl-3-methoxy-6,6,6-trichloro-2-hexenoic Acid (4). A quantity of 0.106 g (0.3 mmol) of the ester 11 was dissolved in 0.5 mL of dry nitromethane under nitrogen and cooled to 0 °C. To this solution was added 0.054 g (0.36 mmol) of trimethyloxonium tetrafluoroborate. The mixture was stirred for 15 min, at which time TLC (silica gel) indicated that the nonpolar ester had been converted to highly polar sulfonium salt. The nitromethane was then removed in vacuo and replaced by 3 mL of 1 N NaOH. This mixture was stirred for 45 min at room temperature. The basic solution was washed with ether (3 × 1 mL) and then carefully acidified to pH 5.0 with 1 N HCl and extracted with ether (5 × 1 mL). The ethereal extracts were washed once with 2 mL of water and dried over $MgSO_4$. After evaporation in vacuo, 4 was recovered as a white crystalline solid, 58.5 mg (74% yield). This solid was not purified further but could be recrystallized from ether/pentane: mp 136–137 °C; ^{13}C NMR δ 15.73 (q), 35.16 (t), 52.66 (d), 55.87 (q), 92.58 (d), 105.47 (s), 172.81 (s), 174.72 (s); IR ($CHCl_3$) 3500–2400, 2935, 2990, 1690, 1609, 1455, 1438, 1380, 1360, 1295, 1247, 1190, 1160, 1090, 1035, 958, 830 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.26 (d, 3 H, J = 6.6 Hz), 3.03 (m, 1 H), 3.26 (m, 2 H), 3.70 (s, 3 H), 5.15 (s, 1 H); UV λ_{max} (95% ethanol) 232 (ε 13 400). Anal. Calcd for $C_8H_{11}Cl_3O_3$: C, 36.73; H, 4.21; Cl, 40.69. Found: C, 37.34; H, 4.58; Cl, 40.52.

(±)-(*E*)-5-Methyl-3-methoxy-6,6,6-trichloro-2-hexenoyl Chloride (16). A quantity of 20 mg (0.077 mmol) of the acid 4 was dissolved in 0.75 mL of dry benzene under nitrogen. To this was added via syringe 8 μL (0.115 mmol) of neat thionyl chloride and a catalytic amount (0.5 μL) of dry dimethylformamide. The solution was refluxed for 1 $^1/_2$ h and then evaporated in vacuo.

The oily product was used directly in the acylation of the tetramic acid **5**: crude yield, 19 mg, 92%; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.23 (d, 3 H), 2.8–3.4 (m, 3 H), 3.8 (s, 3 H), 5.45 (s, 1 H).

(±)-Ethyl 5-Methyl-4-phthalimido-3-oxohexanoate (14). To 2.24 g (17 mmol) of monoethyl malonate in 25 mL of dry THF at −70 °C was added dropwise 16.2 mL of 2.1 M butyllithium in hexanes (34 mmol). This gave a white suspension which was warmed slowly to −5 °C and then recooled to −78 °C. To the mixture was added, all at once, the acid chloride of *N*-phthaloylvaline (**12**) (2.65 g, 10 mmol) in 7 mL of dry THF. The solution was stirred for 20 min, then poured into a mixture of 35 mL of 1 N HCl and 70 mL of ether at room temperature, and stirred for 5 min. The mixture was separated and the aqueous layer extracted with ether (2 × 20 mL). The combined ethereal layers were washed with 10% $NaHCO_3$ (3 × 15 mL), were dried over $MgSO_4$, and then evaporated in vacuo to give an oil. The oil was flash chromatographed over silica gel eluting with CH_2Cl_2 to give an oil: 1.68 g (53%); ^{13}C NMR δ 13.97 (q), 19.03 (q), 20.80 (q), 27.43 (d), 46.97 (t), 61.39 (t), 63.95 (d), 123.71 (d), 131.77 (s), 134.49 (d), 166.44 (s), 167.76 (s), 196.43 (s); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.84 (d, 3 H, *J* = 6.86 Hz), 1.08 (d, 3 H, *J* = 6.75 Hz), 1.18 (t, 3 H, *J* = 7.07 Hz), 2.78 (m, 1 H), 3.51, 3.37 (ABq, 2 H, *J* = 16 Hz), 4.09 (q, 2 H, *J* = 7.07 Hz), 4.61 (d, 1 H, *J* = 8.1 Hz), 7.77–7.92 (m, 4 H); UV λ_{max} (95% EtOH) 221 (ε 40 800). Anal. Calcd for $C_{17}H_{19}NO_5$: C, 64.35; H, 5.99; N, 4.42. Found: C, 64.39; H, 6.16; N, 4.12.

(±)-Ethyl (*E*)-5-Methyl-4-phthalimido-3-oxo-2-hexenoate (15). In a dry clean two-neck flask fitted with a nitrogen inlet and stopper was placed 2.3 g of 24% potassium hydride in oil (3.3 mmol of KH). This was washed with pentane under a stream of nitrogen to remove the mineral oil. To the dry powder was added 6 mL of dry HMPA and the mixture was cooled to 5 °C. The β-keto ester **14** (0.96 g, 3.0 mmol) was added over 2 min in 2 mL of HMPA. Hydrogen evolution was readily observed. The mixture was stirred for 20 min at which time it was a light brown color. To this was added, all at once, 0.75 mL of methyl fluorosulfonate. ***CAUTION*: *methyl fluorosulfonate is an extremely toxic and carcinogenic reagent*.**[17] The darker color disappeared immediately and the reaction mixture was stirred for 5 min and quenched in a saturated solution of $NaHCO_3$ (2 mL). The mixture was then poured into 20 mL of water and extracted with pentane (5 × 10 mL). The pentane extracts were then washed with 1 N NaOH (2 × 5 mL). The organic layer was dried over $MgSO_4$ and evaporated in vacuo. The oil was flash chromatographed over silica gel eluting with 30% ether hexanes to give a colorless oil in a yield of 0.53 g (53%): bp 140 °C (0.5 mmHg); ^{13}C NMR δ 14.29 (q), 19.81 (q), 20.49 (q), 27.13 (d), 59.90 (t), 61.21 (q), 62.13 (d), 99.95 (d), 123.37 (d), 131.85 (s), 134.02 (d), 165.05 (s), 166.98 (s), 167.87 (s); IR ($CHCl_3$) 3020, 2960, 1710, 1630, 1465, 1378, 1348, 1325, 1220, 1170, 1065, 885 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.88 (d, 3 H, *J* = 6.58 Hz), 1.06 (d, 3 H, *J* = 6.6 Hz), 1.26 (t, 3 H, *J* = 7.1 Hz), 2.9–3.8 (m, 1 H), 3.92 (s, 3 H), 4.12 (q, 2 H, *J* = 7.1 Hz), 4.32 (d, 1 H, *J* = 11.12 Hz), 5.53 (s, 1 H), 7.73–7.86 (4 H); UV λ_{max} (95% EtOH) 221 (ε 41 000). Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.27; H, 6.34; N, 4.23. Found: C, 65.15; H, 6.27; N, 4.18.

(±)-5-(1-Methylethyl)-4-methoxy-Δ^{3,4}-pyrrolin-2-one (5). The enol ester **15** (0.195 g, 0.6 mmol) was dissolved in 4 mL of dry methanol. To this was added 0.075 g (2.35 mmol) of 97% hydrazine. The mixture was heated to reflux for 24 h. The reaction mixture was cooled to room temperature and 4 mL of water was added followed by careful acidification to pH 5.0 with 1 N HCl. The mixture was filtered through Celite and then 10% $NaHCO_3$ was added to bring the mixture to pH 8.5. The reaction mixture was extracted with chloroform (4 × 3 mL) and the combined organic layers were dried over $MgSO_4$. Evaporation in vacuo gave rise to 56 mg of pale yellow solid (55%) tetramic acid (**5**). This could be recrystallized from benzene: mp 172–173 °C (lit. 172–174 °C); ^{13}C NMR δ 15.44 (q), 19.32 (q), 29.56 (d), 58.09 (q), 62.87 (d), 94.52 (d), 174.89 (s), 177.68 (s); IR ($CHCl_3$) 3450, 3215, 3000, 2960, 2935, 2870, 1675, 1620, 1455, 1440, 1355, 1336, 1200, 1170, 1010, 978, 950, 895, 805 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.8 (d, 3 H, *J* = 6.81 Hz), 1.01 (d, 3 H, *J* = 7.0 Hz), 2.08 (m, 1 H), 3.78 (s, 3 H), 3.99 (d, 1 H, *J* = 3.1 Hz), 5.02 (d, 1 H, *J* = 1 Hz), 5.85 (broad, 1 H); UV λ_{max} (95% EtOH) 211 (ε 14 200). Anal. Calcd for $C_8H_{13}NO_2$: C, 61.93; H, 8.39; N, 9.03. Found: C, 61.34; H, 8.37; N, 8.94.

Dysidin and Isodysidin (3 and 18). In a clean dry 10-mL, two-neck flask fitted with a nitrogen inlet was weighed 33.5 mg (0.22 mmol) of tetramic acid (**5**). To this was added 2 mL of dry THF and the mixture was cooled to 0 °C. The tetramic acid did not all dissolve. To this mixture was added dropwise slowly 73.2 μL of a solution of MeMgBr (2.95 M in ether) (0.22 mmol). A vigorous evolution of methane was observed. To this clear colorless solution was added all of the trichloromethyl enol acid chloride **16** which had been prepared from 0.20 mmol of the acid **4** and which was dissolved in 0.5 mL of dry THF. The mixture was allowed to stir for 24 h at room temperature at which time it was quenched by addition of 1 mL of saturated $NaHCO_3$. The mixture was diluted with 10 mL of water and extracted with 4 × 10 mL of ether. The ethereal layers were combined, dried over $MgSO_4$, and then flash chromatographed over silica gel eluting with 15% ethyl acetate/cyclohexane. This chromatography gave 37.5 mg of a 1:1 mixture of pure dysidin (**3**) and isodysidin (**18**) (48% yield with respect to the acid **4**) which was contaminated by <2% of some isomeric material.

Dysidin (**3**) and isodysidin (**18**) were separated by HPLC with a column of μ-Porasil (7.8 × 30 cm) eluting with 15% ethyl acetate/cyclohexane at 3 mL/min. Dysidin (**3**) eluted at 22.6 min, and isocysidin (**18**) at 23.5 min. Peak shaving gave pure isomers by NMR. By this liquid chromatography 7 mg of pure dysidin (**3**) was obtained. However it was subsequently found to be unnecessary to perform this chromatography since isodysidin (**18**) fractionally crystallized from an ether/pentane solution as a pure compound, mp 144–145 °C. The mother liquor contained almost pure dysidin (**3**) which was contaminated with a trace amount of isodysidin (**18**). The spectral data of synthetic materials are as follows. Dysidin (**3**): ^{13}C NMR δ 15.56, 15.92, 18.84, 29.03, 35.81, 52.71, 55.88, 58.24, 64.02, 94.92, 96.39, 105.6, 164.81, 170.4, 173.0, 179,17; IR ($CHCl_3$) 2955, 2920, 2850, 1708 (broad), 1655, 1622, 1450, 1385, 1338, 1315, 1292, 1240, 1168, 1090, 995, 962, 900, 870 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.75 (d, 3 H, *J* = 6.9 Hz), 1.12 (d, 3 H, *J* = 7.2 Hz), 1.26 (d, 3 H, *J* = 5.8 Hz), 2.57 (dqq, 1 H, *J* = 2.8, 7.7 Hz), 3.0–3.12 (m, 1 H), 3.15 (dd, 1 H, *J* = 3.4, 13.5 Hz), 3.46 (dd, 1 H, *J* = 10.5, 13.5 Hz), 3.76 (d, 3 H), 3.84 (s, 3 H), 4.68 (d, 1 H, *J* = 2.75 Hz), 5.06 (s, 1 H), 6.84 (s, 1 H). Isodysidin (**18**): ^{13}C NMR δ 15.60, 15.95, 18.82, 29.07, 35.81, 52.67, 55.86, 58.24, 64.03; 94.93, 96.27, 105.83, 164.77, 170.78, 172.97, 179.16; IR ($CHCl_3$) 2920, 1708, 1659, 1623, 1315, 1169; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.76 (d, 3 H, *J* = 6.95 Hz), 1.12 (d, 3 H, *J* = 7.17 Hz), 1.29 (d, 3 H, *J* = 6.35 Hz), 2.56 (m, 1 H), 3.03 (m, 1 H), 3.30 (m, 1 H), 3.75 (s, 3 H), 3.83 (s, 3 H), 4.66 (d, 1 H, *J* = 2.81 Hz), 5.05 (s, 1 H), 6.83 (s, 1 H); UV λ_{max} (MeOH) 264 (ε 43 500) 228 (ε 8130). Anal. Calcd for $C_{16}H_{22}Cl_3NO_4$: C, 48.20; H, 5.56; Cl, 26.68. Found: C, 48.19; H, 5.60; Cl, 26.77.

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Registry No. **3**, 91279-96-8; **4**, 91238-94-7; **5**, 91238-95-8; **6** (isomer 1), 91238-96-9; **6** (isomer 2), 91238-97-0; **7**, 91279-97-9; **8**, 91238-98-1; **9**, 91265-41-7; **10**, 91265-42-8; **11**, 91238-99-2; **12**, 74958-23-9; **13**, 1071-46-1; **14**, 91239-00-8; **15**, 91239-01-9; **16**, 91239-02-0; **18**, 91279-98-0; crotonic acid, 3724-65-0; bromotrichloromethane, 75-62-7; meldrum's acid, 2033-24-1; 2-(ethylthio)ethanol, 110-77-0.