The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on 1.0 g of silica gel with 3% EtOAc/petroleum ether. The first 5 mL was discarded. The next 6 mL was concentrated in vacuo to give (+)-α-cuparenone as a colorless oil: 46.5 mg (77%); R_f (10% EtOAc/hexane) 0.40; ^{1}H NMR δ 0.60 (s, 3 H), 1.15 (s, 3 H), 1.24 (s, 3 H), 1.76–2.07 (m, 2 H), 2.32 (s, 3 H), 2.42–2.68 (m, 2 H), 7.00–7.29 (m, 4 H); IR 2.65, 2930, 1734, 1454, 1373 cm^{-1}; $[\alpha]_D^{27}$ +164° (c, 0.001 92, $CHCl_3$) [lit.[9] $[\alpha]_D$ +170° ($CHCl_3$)]; MS 216 (82), 201 (18), 145 (100), 132 (62); exact mass calcd for $C_{15}H_{20}O$ 216.1514, found 216.1507.

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Total Synthesis of (+)-Demethyldysidenin and (−)-Demethylisodysidenin, Hexachlorinated Amino Acids from the Marine Sponge *Dysidea Herbacea*. Assignment of Absolute Stereochemistry

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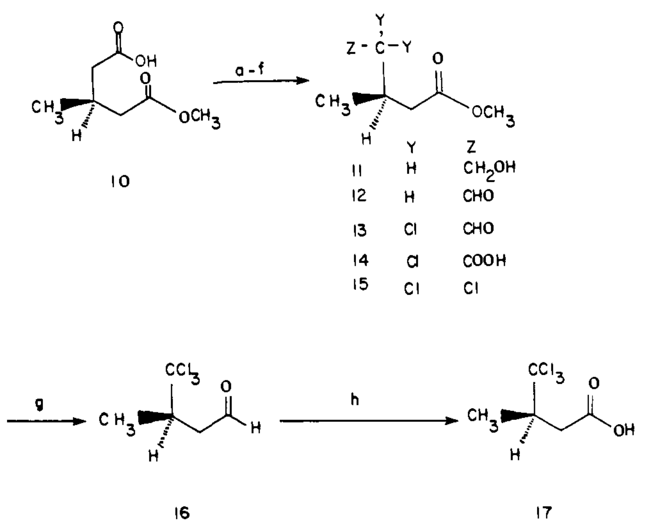
Abstract: The total synthesis of (+)-(2*R*,4*R*)-5,5,5-trichloro-4-methyl-2-[(*R*)-methyl(4,4,4-trichloro-3-methylbutanoyl)-amino]-*N*-[1-(thiazol-2-yl)methyl]pentanamide (**3**), trivial name demethyldysidenin, along with a diastereomer, (−)-demethylisodysidenin (**4**), is described. These compounds are prepared from *R*-(−)-3-methyl-4,4,4-trichlorobutanoic acid (**15**) as the basic building block. The key step of the synthetic scheme is a four-component amino acid synthesis described by Ugi. This asymmetric synthesis leads to a revision of the absolute stereochemistry assigned to the natural products **1–6**.

An unusual set of polychlorinated metabolites has been isolated from the sponge *Dysidea herbacea* collected from various locations in the region of the Great Barrier Reef. The first hexachlorinated metabolite dysidenin (**1**) was reported by Wells et al. without assignment of either relative or absolute stereochemistry.[1] Shortly thereafter a different group also reported the isolation of **1** along with a toxic diastereomer **2** which was named isodysidenin.[2a] Both the relative and the absolute stereochemistry were assigned to this latter substance on the basis of the X-ray diffraction analysis of a derivative of **2**.[2a] The NMR spectra and subsequent chemical correlations between dysidenin (**1**) and isodysidenin (**2**) lead to the conclusion that these two compounds are epimeric at C-5.[2,3] The absolute stereochemistry of the remaining three asymmetric centers in **1** and **2** are assigned identical configurations in both natural products: *R* at both trichloromethyl-bearing carbons, i.e., C-2 and C-7, and *R* at the carbon α to the thiazole moiety, i.e., C-13 as depicted in Figure 1. Most recently, Ireland has questioned the X-ray assignment of absolute stereochemistry for compounds **1** and **2** on the basis of a chemical degradation which proves that C-13 has the *S* absolute configuration in both **1** and **2**.[4] However, any conclusion about the absolute configuration of the entire molecule must be made with caution due to the ease with which the asymmetric center α to a thiazole, i.e., C-13, is known to epimerize.[5]

Extraction of a sample of *D. herbacea* by Erickson and Wells gathered from a different location along the Great Barrier Reef produced four additional polychloro amino acid derived metabolites shown in Figure 1 as compounds **3–6**.[6] Two of these compounds, demethyldysidenin (**3**) and demethylisodysidenin (**4**), are simple demethylated homologues of **1** and **2**. The similarities between the spectral data and especially of the optical rotations of the homologous pairs of compounds, i.e., compound **1**,[1] $[\alpha]^{21}_D$ −98°, compared with **3**,[6] $[\alpha]^{20}_D$ −96°, and compound **2**,[2a] $[\alpha]^{22}_D$ +47°, compared with **4**,[6] $[\alpha]^{20}_D$ +52°, suggest that these pairs share similar stereochemical details, including identical absolute configurations for the three common asymmetric centers at C-2, C-5, and C-7 as shown in Figure 1.[7]

Scheme I[a]



[a] (a) BH_3·THF; (b) PCC; (c) *t*-$BuNH_2$; (d) NCS, H_3O^+; (e) $KMnO_4$; (f) $Pb(OAc)_4$, LiCl; (g) DIBAL; (h) Jones reagent.

(1) Kazlauskas, R.; Lidgard, R. O.; Wells, R. J. *Tetrahedron Lett.* **1977**, 3183.
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(3) The numbering system for these compunds was adopted to conform to the existing literature.
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(5) Biskupiak, J. E.; Ireland, C. M. *J. Org. Chem.* **1983**, *48*, 2302.
(6) Erickson, K. L.; Wells, R. J. *Aust. J. Chem.* **1982**, *35*, 31.

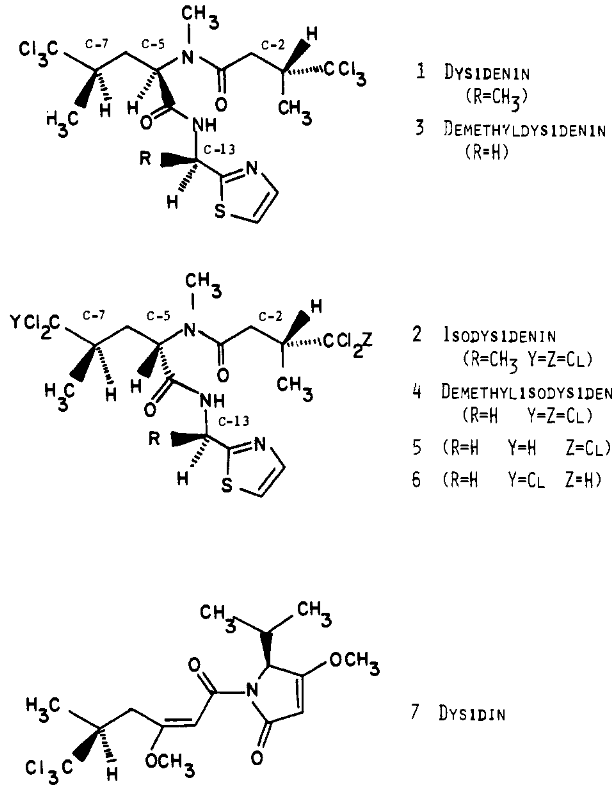


Figure 1.

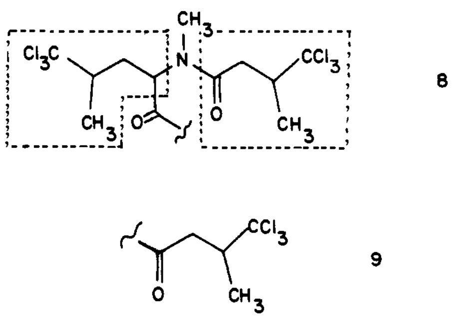


Figure 2.

A total synthesis of optically pure 13-demethylisodysidenin (**4**) could be of value since **4** is reported to exhibit antihypertensive activity when administered iv.[8] We wish to report an extremely short and efficient preparation of the two optically pure compounds **3** and **4** with configurations as shown in Figure 1. It is clear that this synthetic route can be utilized for the total synthesis of either enantiomer of any of the natural products **1–6**. The total synthesis of compounds **1–6** in the dysidenin/isodysidenin series complements our total synthesis of racemic dysidin (**7**), another polychlorinated *Dysidea* metabolite, and it also represents the first synthetic route to optically pure *Dysidea* metabolites.[9]

Results

The partial structure **8** given in Figure 2 represents the main carbon skeleton of the natural products **1–4**. The dashed lines in structure **8** depict the major synthetic dissection of these compounds. Preparation of an optically active five-carbon unit corresponding to **9** should provide the basic building block for a total synthesis of optically pure **1–4**. A preparative route to racemic 3-methyl-4,4,4-trichlorobutyric acid, a synthetic equivalent of **9**, was described in our synthesis of dysidin (**7**);[9] however, this route is not adaptable to the preparation of optically active compounds. Hence, we now describe a route to optically active *Dysidea* metabolites.

As a starting material for an asymmetric synthesis, the half-acid ester of β-methylglutaric acid was chosen. It is possible to obtain pure enantiomers of this compound by resolution with either cinchonidine or quinine.[10] We chose the *S*-(−) enantiomer **10**, shown in Scheme I, to match the absolute configuration originally assigned to C-2 and C-7 in compounds **1–6**.[2,6] Thus the *S*-(−) half-acid ester **10** is elaborated to optically pure **3** and **4** as described below.

The free carboxylic acid of *S*-(−)-**10** is transformed into an aldehyde **12** by reduction to the alcohol **11** with diborane–THF,[11] followed by reoxidation with pyridinium chlorochromate.[12] Two chlorine atoms are introduced into **12** by treatment of its corresponding *tert*-butyl imine with NCS.[13] The α,α-dichloro aldehyde **13** is oxidized with $KMnO_4$[14] to the carboxylic acid **14**. By adapting Kochi's procedure for the Hunsdiecker reaction,[15] we are able to obtain optically active trichloromethyl ester **15** upon oxidative decarboxylation of **14** with lead tetracetate in the presence of lithium chloride. The overall yield for the transfor-

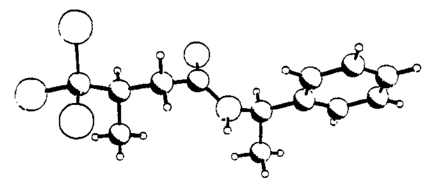
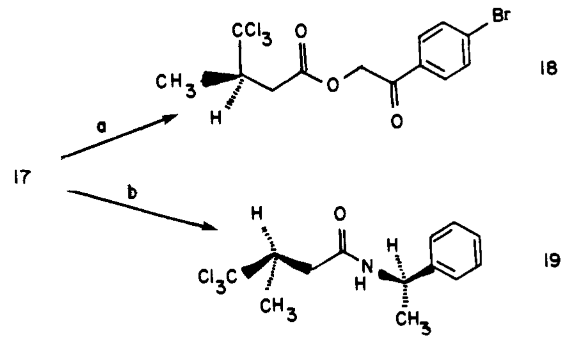


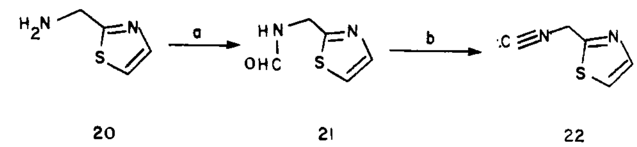
Figure 3. Computer-generated plot of **19**.

Scheme II[a]



[a] (a) 2,4′-Dibromoacetophenone, (b) (*R*)-(+)-(α-methylbenzyl)-amine.

Scheme III[a]



[a] (a) HCOOH, (b) $COCl_2$.

(7) Erickson and Wells themselves put forth this argument for the similarity of compounds **1** with **3** and **2** with **4**.[6] Hence, we have assumed that the structures which these authors have assigned to **3** and **4** were assigned to the same enantiomorphous series as compuds **1** and **2**. However, these authors have given a systematic name to diastereomeric structures for dysidenin (**1**) and isodysidenin (**2**) and to enantiomeric structures for demethyldysidenin (**3**) and demethylisodysidenin (**4**) on page 32 of ref 5. Private communication with Prof. Erickson has established that all six natural products, **1–6** as dipicted in Figure 1 in this manuscript, were meant to be assigned according to the precedent in ref 2a.

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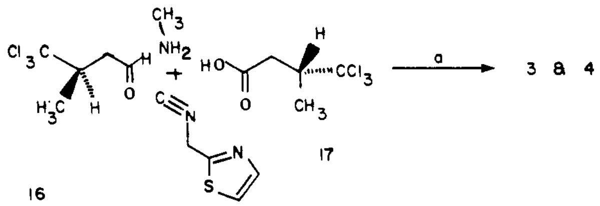
Scheme IV



16   17   22

mation of optically pure **10** into **15** is 21%.

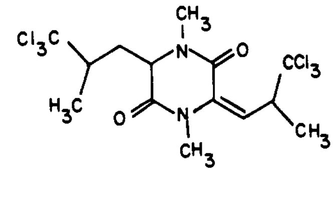
DIBAL reduction of **15** produces the aldehyde **16** in 68% yield. Subsequent oxidation of **16** with Jones reagent yields the acid **17**. Carboxylic acid **17** was converted into the two derivatives shown in Scheme II. A *p*-bromophenacyl ester **18** was prepared from synthetic **17** in order to compare its optical rotation with the same derivative prepared by Tursch et al. from naturally occurring **1** and **2**.[2b] A second derivative, i.e., the optically active *N*-(α-phenethyl)amide **19**, was prepared from D-(+)-α-phenethylamine and **17**. This amide **19** was subjected to X-ray diffraction analysis.[16] A computer-generated plot of this structure is given in Figure 3. The absolute configuration of **19** is unamibiguous since the absolute configuration of the starting amine is well-defined.[17] The absolute stereochemistry of the trichloromethyl-bearing carbon in compound **19** is consistent with the literature assignment of absolute stereochemistry for (−)-methyl hydrogen β-methylglutarate **10**,[10] which is utilized as the starting material.

The thiazole ring in compounds **3** and **4** is introduced starting from 2-(aminomethyl)thiazole (**20**). Compound **20** was reported previously in the literature.[18] Treatment of **20** with formic acid and removal of water with a Dean-Stark apparatus gives the formamide **21**. Compound **21** is dehydrated to the isonitrile **22** by treatment with phosgene and triethylamine (Scheme III).[19]

An extremely efficient preparation of optically pure (+)-13-demethyldysidenin (**3**) and (−)-13-demethylisodysidenin (**4**) can be achieved by utilizing the "four-component peptide synthesis" described by Ugi.[20] A one-pot combination of the synthetic intermediates **16**, **17**, and **22** with methylamine produces the optically pure compounds **3** and **4** in 31% total yield as shown in Scheme IV. Chromatographic separation of **3** and **4** is effected by either flash chromatography[21] or by liquid chromatography on silica. Thus, we can obtain optically pure (+)-(2*R*,5*R*,7*R*)-13-demethyldysidenin (**3**) and (−)-(2*R*,5*S*,7*R*)-13-demethylisodysidenin (**4**) in 17% and 13% yields, respectively, after this chromatography. *The optical rotations of* +97° and −48° *for our synthetic 3 and 4 are equivalent in magnitude but opposite in sign to those of the naturally occurring compounds, which are reported as −96°* and *+52°, respectively.*[6]

Discussion

Logical arguments for the assignment of complete stereochemical details to the *Dysidea* metabolites **3** and **4** are given as follows. The zinc-mediated dechlorination of naturally occurring (−)-**3** and (+)-**4** leads to a pair of enantiomers.[6] This result clearly establishes that these compounds are epimeric at C-5. Assignment of the correct relative configuration at C-5 in these two compounds is based upon the chiroptic similarity of **1** with **3** and of **2** with **4** as noted by Erickson and Wells[6,22] (vide supra). Our synthesis



23

Figure 4.

of the optically active (+)-**3** and (−)-**4**, with configurations as given in Figure 1, clearly proves that the naturally occuring compounds have the opposite absolute configurations from those shown in Figure 1.

The absolute stereochemistry of three of the four asymmetric centers of dysidenin (**1**) isodysidenin (**2**) is also now established unequivocally as follows. Ireland proved that naturally occurring **1** and **2** have the *S*-absolute configuration at C-13.[4,5] Zinc dechlorination of **1** and **2** led to a pair of diastereomers.[2b] These two results can only be interpreted by having **1** and **2** epimeric at C-5. The *p*-bromophenacyl ester **18** derived from our synthetic *R*-(−) acid **17** had an optical rotation opposite to that observed from the same derivative prepared from a hydrolysis product of naturally occurring **1** and **2**.[2b] Hence, the absolute configuration at C-2 of naturally occurring **1** and **2** must be *S*.

Although not rigorously established by any of the experimental work described above, it is certain that the absolute stereochemistry of C-7 in naturally occurring **1** and **2** is *S* also. This conclusion is based upon acceptance of the relative configurations of these compounds assigned by X-ray crystallography.[2b] These assignments are extended to compounds **3–6** on the basis of the comparisons made by Erickson and Wells.[6]

It appears that an erronous assignment of absolute configuration for compound **2** was originally made from the X-ray data.[2b] This assignment of configuration had been applied by others to the entire series of polychlorinated amino acid derived *Dysidea* metabolites.[6] In light of the work of Ireland[5] and this total synthesis, these absolute configurations for the entire series of *Dysidea* metabolites **1–6** should now be revised. Thus, the natural products **1–6** have the opposite absolute configurations from those shown in Figure 1.

Conclusion

The absolute configuration of the trichloromethyl-bearing carbon atom of dysidin (**7**), i.e., C-5 of structure **7** in Figure 1 was assigned as *S* by Hofheinz and Oberhansli.[23] There is no reason to doubt this assignment since the X-ray data are clearly presented. Our current revision of the absolute configurations of the natural products **1–6** gives the trichloromethyl-bearing carbons, i.e., C-2 and C-7 in structures **1–6** in Figure 1, the *S*-absolute configuration also. It seems very likely to us that the one remaining polychlorinated *Dysidea* metabolite whose stereochemistry remains unassigned, i.e., compound **23**[24] shown in Figure 4, will also prove to be *S* at the two asymmetric centers bearing the trichloromethyl groups. Synthetic work leading to optically pure **23** is in progress in order to establish this point.

Experimental Section

(+)-Methyl 3-Methyl-5-oxopentanoate (12). To 4.42 g (20.5 mmol) of pyridinium chlorochromate in 25 mL of dry methylene chloride was added 2.0 g (13.7 mmol) of the resolved alcohol **11**[11] dissolved in 5 mL of methylene chloride. The mixture grew dark and was stirred at room

(16) The final agreement factors for the crystal structure of compound **19** was R_w = 0.0464. Details of this structure will be published separately, c.f.: Williard, P. G.; de Laszlo, S. E.; Carpenter, G. B., manuscript in preparation.

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(22) It has been correctly pointed out by a referee that this is not a watertight argument. However, it has not been possible to crystallize either compound **3** or **4** and subject either one to X-ray diffraction analysis to establish this point unambiguously. We would liked to emphasize that both both compounds **3** and **4** are natural products and that it is proven that they differ only in configuration at C-5.[6] Hence, in the unlikely event of a misassignment of configuration at C-5 it will simply be a matter of exchanging trival names for these two compounds to correct such an error.

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temperature for 3 h and then diluted with 100 mL of dry ether. Following decantation of the liquid, the solid was washed with ether (3 × 10 mL), and the resulting combined organic phases were filtered through Florisil to give a colorless solution. The solution was evaporated in vacuo and distilled to give 1.24 g (63%) of a colorless oil **12**: bp 52 °C (2 mmHg); $[\alpha]^{15}_D$ +4.64° ($CHCl_3$, *c* 7.56); ^1H NMR ($CDCl_3$, 60 MHz) δ 1.05 (d, 3 H, *J* = 5.5 Hz), 2.1–2.6 (m, 5 H), 3.7 (s, 3 H), 9.77 (t, 1 H, *J* = 1 Hz); ^{13}C NMR ($CDCl_3$) 20.15 (q), 25.42 (d), 40.79 (t), 50.19 (t), 51.43 (q), 172.52 (s), 201.12 (d); IR (neat) 3500, 2950, 2720, 1735, 1725, 1432, 1362, 1300, 1255, 1210, 1165, 1085, 1008 cm^{-1}. Anal. Calcd for $C_7H_{12}O_3$: C, 58.33; H, 8.33. Found: C, 57.59; H, 8.05.

Methyl 3-Methyl-4,4-dichloro-5-oxopentanoate (13). To 1.114 g (7.74 mmol) of the aldehyde (**12**) in a 25-mL round-bottom flask at 10 °C was added 0.56 g (7.74 mmol) of *tert*-butylamine. The solution was stirred for 20 min at which time 15 mL of CCl_4 was added. The solution was then dried over $MgSO_4$. Following vacuum filtration, 2.24 g (16.8 mmol) of *N*-chlorosuccinimide was added to the stirred solution. The suspension was then stirred overnight. The succinimide was removed by vacuum filtration and the filtrate evaporated in vacuo. The product was hydrolyzed by stirring with 25 mL of 0.1 N HCl. The pH of the solution was kept acidic by periodic addition of 1 drop of concentrated HCL. After 2.5 h the reaction mixture was extracted with ether (4 × 10 mL), and the combined organic layers were dried over $MgSO_4$ and evaporated in vacuo to give 1.26 g (72%) of a mixture of the aldehyde (**13**) and its hydrate. The material was not characterized further, but was used immediately in the next reaction.

(+)-5-Methyl 2,2-Dichloro-3-methylpentanedioate (14). To a rapidly stirred mixture of 1.18 g (5.54 mmol) of the aldehyde (**13**) in 10 mL of water was added 1.31 g (8.31 mmol) of potassium permanganate. The purple solution was warmed in a 65 °C oil bath for 20 min during which time the solution turned dark brown. On cooling to room temperature the excess potassium permanganate was reduced by addition of 2 mL of saturated $NaHSO_3$ solution. The mixture was made basic by addition of solid $NaHCO_3$ and was then filtered through Celite to give a clear colorless solution. Acidification by addition of concentrated HCl was followed by ether extraction (4 × 10 mL), and the combined ethereal extracts were dried over $MgSO_4$, filtered, and evaporated in vacuo. The acid **14** was distilled at 150–155 °C (2 mmHg) to give 0.96 g (76%) of a colorless oil: $[\alpha]^{15}_d$ +15.52° ($CHCl_3$, *c* 4.49); ^1H NMR ($CDCl_3$, 60 MHz) δ 1.21 (d, 3 H, *J* = 6 Hz), 2.40 (dd, 1 H, *J* = 10, 16 Hz); 2.82 (m, 1 H), 3.0–3.3 (m, 1 H), 3.73 (s, 3 H); ^{13}C NMR ($CDCl_3$) 15.88 (q), 37.23 (t), 42.59 (d), 52.17 (q), 89.27 (s), 167.62 (s), 172.77 (s); IR ($CHCl_3$) 3500–2500, 3020, 2975, 2940, 1730, 1430, 1378, 1360, 1280, 1255, 1170, 1070, 1030, 1000, 868, 825 cm^{-1}. Anal. Calcd for $C_7H_{10}Cl_2O_4$: C, 36.78, H, 4.40. Found: C, 36.90; H, 4.33.

(+)-Methyl 3-Methyl-4,4,4-trichlorobutanoate (15). In a dry 10-mL two-neck flask fitted with condenser and N_2 inlet was weighed 0.30 g (1.3 mmol) of the acid **14**. A quantity of 2 mL of dry benzene was added, and the solution was rapidly stirred while being continuously swept with a stream of N_2 for 5 min. To the resulting solution was added 0.19 g (0.44 mmol) of lead tetracetate, which gave a yellow solution. To the resulting solution was added 0.018 g (0.44 mmol) of lithium chloride. The mixture was heated at 80–85 °C until the solution turned colorless and no more CO_2 was evolved. The mixture, which contained a fine white precipitate, was washed into a separatory funnel with 10 mL of ether and extracted with 7% perchloric acid (2 × 5 mL) followed by saturated $NaHCO_3$ solution (3 × 5 mL). The organic layer was dried over $MgSO_4$ and evaporated in vacuo to give 0.05 g (0.23 mmol) of the ester (**15**). The yield was 52% with respect to lead tetracetate, 72% with respect to acid **14** used.

The $NaHCO_3$ extracts were acidified and extracted with ether (3 × 10 mL). The combined organic extracts were then dried over $MgSO_4$ and evaporated in vacuo to give 0.23 g (1.0 mmol) of recovered acid **14**.

This reaction was repeated with the recovered acid **14** until sufficient ester **15** had been synthesized. The combined products were then distilled at 95 °C (30 mmHg) to give a colorless oil: $[\alpha]^{15}_D$ +20.91° ($CHCl_3$, *c* 5.16); ^1H NMR ($CDCl_3$, 60 MHz) δ 1.38 (d, 3 H, *J* = 6 Hz), 2.38 (dd, 1 H, *J* = 10, 16 Hz), 2.9–3.3 (m, 2 H), 3.74 (s, 3 H); ^{13}C NMR ($CDCl_3$) 16.99 (q), 38.17 (t), 51.74 (q), 51.81 (d), 104.78 (s), 171.18 (s); IR (neat) 2980, 2940, 1735, 1430, 1378, 1360, 1275, 1250, 1190, 1170, 1070, 1000, 960, 900, 860, 840, 790, 767 cm^{-1}. Anal. Calcd for $C_6H_9Cl_3O_2$: C, 32.84; H, 4.10. Found: C, 33.58; H, 4.17.

(+)-3-Methyl-4,4,4-trichlorobutanal (16). In a dry 10-mL round-bottom flask 0.32 g (1.46 mmol) of the ester (**15**) was dissolved in 4 mL of dry toluene under N_2. The solution was cooled to −78 °C and 1.04 mL (1.53 mmol) of 1.48 M DIBAL in toluene was added dropwise. The solution was stirred for 1 h and then quenched with 1 mL of 1 N HCL. The mixture was diluted with 10 mL of ether and allowed to warm to room temperature. The etheral layer was removed and washed with 1 N HCL (2 × 1 mL) and then dried over $MgSO_4$ and evaporated in vacuo. The colorless oil was distilled in a Kugelrohr apparatus at 75 °C (30 mmHg) to give 0.188 g (1.0 mmol) of aldehyde (**16**): 68% yield, $[\alpha]^{16}_D$ +24.95° ($CHCl_3$, *c* 2.99); ^1H NMR ($CDCl_3$, 60 MHz) δ 1.38 (d, 3 H, *J* = 6 Hz), 2.58 (ddd, 1 H, *J* = 9, 18, 2 Hz), 3.0–3.5 (m, 2 H), 9.78 (brs, 1 H); ^{13}C NMR ($CDCl_3$) 17.29 (q), 47.78 (t), 49.35 (s), 104.86 (s), 198.09 (s); IR ($CHCl_3$) 2970, 2930, 2720, 1722, 1455, 1432, 1410, 1378, 1348, 1280, 1235, 1170, 1120, 1070, 1000, 960, 927, 868 cm^{-1}. Anal. Calcd for $C_5H_7Cl_3O$: C, 31.69; H, 3.69; Found C, 32.83; H, 3.99.

(+)-3-Methyl-4,4,4-trichlorobutanoic Acid (17). To a solution of 94 mg (0.5 mmol) of the aldehyde **16** in 1 mL of acetone at 15 °C was added dropwise Jones reagent until a persistent orange color was observed. After 10 min, the orange color was removed by dropwise addition of isopropyl alcohol. The reaction mixture was diluted with 5 mL of ether followed by 1 mL of water to dissolve the inorganic residue. Following removal of the ethereal phase, the aqueous phase was reextracted with 5 mL of ether. The combined ethereal phases were washed with water (1 × 5 mL) and saturated NaCl (1 × 5 mL) and dried over $MgSO_4$. The colorless solution was evaporated in vacuo to give an oil which crystallized on standing to give 0.087 g (4.34 mmol): yield 85%; $[\alpha]^{15}_D$ +25.15° ($CHCl_3$, *c* 1.36); ^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); ^{13}C NMR 17.02 (q), 38.23 (t), 51.45 (d), 104.45 (s), 177.33 (s); IR $CHCl_3$ 3600–2600, 1710, 1410, 1380, 1285, 1240, 1070, 965, 900, 870 cm^{-1}. Anal. Cacld for $C_5H_7Cl_3O_2$: C, 29.22; H, 3.41; Cl, 51.79. Found: C, 28.97; H, 3.03; Cl, 51.28.

(*R*)-(+)-Ethyl 2-(4-Bromophenyl)-2-oxo-3-methyl-4,4,4-trichlorobutanoate (18). To 68 mg (0.33 mmol) of the acid **17** in 1 mL of water was added 1 N NaOH until a clear solution was observed. The solution was made neutral by dropwise addition of 1 N HCl. To this solution was added 0.1 g (0.36 mmol) of *p*-bromophenacyl bromide dissolved in 2 mL of EtOH. The solution was refluxed for 2.5 h, cooled, and then evaporated in vacuo. Flash chromatography over silica gel eluting with 5% ethyl acetate in hexanes gave 43.3 mg of the ester **18**:[2b] yield 32%, mp 92–93 °C, $[\alpha]^{15}_D$ +8.89° ($CHCl_3$, *c* 0.87).

(*R*,*R*)-(+)-*N*-[(1-phenyl)ethyl]-3-methyl-4,4,4-trichlorobutanamide (19). To 0.063 g (0.3 mmol) of the acid **17** dissolved in 1 mL of dry benzene was added 55 mg (0.46 mmol) of thionyl chloride. The solution was refluxed for 1 h under N_2 and cooled to room temperature at which time 0.53 g (4.4 mmol) of (*R*)-(+)-1-phenethylamine[17,25] was added followed by 5 mL of dry ether. The mixture was stirred for 20 min. The resulting suspension was further diluted with 10 mL ether in a separatory funnel and extracted with H_2O (1 × 5 mL), followed by 1 N HCl (2 × 5 mL) and saturated $NaHCO_3$ solution (2 × 5 mL). The ethereal layer was dried over $MgSO_4$ and evaporated in vacuo to give 77.2 mg (0.25 mmol) of the amide **19**; yield 81%. After recrystallization from diisopropyl ether **19** had a mp of 155–157 °C: $[\alpha]^{15}_D$ +79.0° ($CHCl_3$, *c* 0.96); ^1H NMR ($CDCl_3$, 250 MHz) δ 1.36 (d, 3 H, *J* = 6.5 Hz), 1.49 (d, 3 H, *J* = 6.94 Hz), 2.17 (dd, 1 H, *J* = 10, 15 Hz), 2.94 (dd, 1 H, *J* = 2.7, 14.6 Hz), 3.18 (m, 1 H), 5.12 (dq, 1 H, *J* = 7.27, 6.94 Hz), 6.10 (brd, 1 H, *J* = 7.27, Hz), 7.31 (m, 5 H); ^{13}C NMR ($CDCl_3$) 16.85 (q), 21.73 (q), 40.40 (t), 49.17 (d), 51.95 (d), 105.25 (s), 126.17 (d), 127.51 (d), 128.74 (d), 142.93 (s), 168.93 (s); IR ($CHCl_3$) 3420, 3310, 3080, 3055, 3020, 3000, 2920, 2860, 1660, 1500, 1448, 1375, 1270, 1238, 1068, 1010, 950, 902, 800 cm^{-1}; UV (95% ETOH) λ_{max} 201 (ε 16 300). Anal. Calcd for $C_{13}H_{16}Cl_3NO$: C, 50.57; H, 5.19. Found: C, 50.91; H, 5.64.

***N*-(Thiazol-2-yl)methylformamide (21).** A quantity of 1.38 g (12.1 mmol) of 2-(methylamino)thiazole (**20**)[18] was dissolved in 20 mL of toluene to which 2.8 g (61 mmol) of formic acid was added. The solution was refluxed under a Dean-Stark trap in an oil bath at 150 °C. Periodic removal of the azeotroped water followed over a total of 3 h. The residue was evaporated in vacuo and distilled at 121 °C (1 mmHg). A pale yellow oil was recovered weighing 1.4 g: yield 82%; ^1H NMR ($CDCl_3$, 60 MHz), δ 4.78 (d, 2 H, *J* = 6.2 Hz), 7.25 (brs, 1 H), 7.31 (d, 1 H, *J* = 3.3 Hz), 7.69 (d, 1 H, *J* = 3.3 Hz), 8.27 (brs, 1 H); ^{13}C NMR ($CDCl_3$) 39.33 (t), 119.62 (d), 142.16 (d), 161.83 (d), 167.43 (s); IR (neat) 3750, 3020, 2920, 2860, 1770, 1510, 1410, 1375, 1330, 1225, 1170, 1130, 1050, 955, 870, 740 cm^{-1}; UV (95% EtOH) λ_{max} 239, 202 (ε 4300, 4900). Anal. Calcd for $C_5H_6N_2OS$: C, 42.25; H, 4.22; N, 19.72. Found: C, 42.14; H, 4.11; N, 19.57.

Thiazol-2-ylmethyl Isocyanide (22). In a dry 25-mL round-bottom flask was weighed 0.5 g (3.52 mmol) of the formamide **21** to which was added 2 mL of CH_2Cl_2 and 1.15 mL (8.22 mmol) of dry triethylamine. This mixture was cooled in an ice bath under positive N_2 pressure. A quantity of 3.52 mL (3.52 mmol) of 1 M phosgene in CH_2Cl_2 was added dropwise. An exothermic reaction was observed; a precipitate of triethyl ammonium chloride formed and the mixture turned brown. After 15 min, 10 mL of saturated Na_2CO_3 solution was added and a thick glu-

(25) This optically active amine was purchased from Aldrich Chemical Co. and used without further purification.

tinous precipitate formed. The CH_2Cl_2 solution was decanted and the solid washed further with 3 × 10 mL of CH_2Cl_2. The combined extracts were dried over $MgSO_4$, evaporated in vacuo and distilled at 100 °C (30 mmHg) to give a pale brown oil **22**: yield 0.293 g (67%); ^1H NMR ($CDCl_3$, 60 MHz) δ 4.99 (br s, 2 H), 7.40 (d, 1 H, J = 4 Hz), 7.78 (d, 1 H, J = 7 Hz); ^{13}C NMR ($CDCl_3$) 43.28 (t), 120.60 (d), 143.30 (d), 160.98 (s), 161.12 (s); IR (neat) 3100, 3080, 2960, 2920, 2140, 1498, 1430, 1322, 1255, 1180, 1140, 1050, 940, 770, 730 cm^{-1}; UV (95%, EtOH), λ_{max} 240, 210 (ϵ 4300, 2700). Anal. Calcd for $C_5H_4N_2S$: C, 48.38; H, 3.22. Found: C, 47.94; H, 3.26.

13-Demethyldysidenin (3) and 13-Demethylisodysidenin (4). In a 5-mL round-bottom flask containing 80 mg (0.42 mmol) of the aldehyde **16** dissolved in 0.5 mL of MeOH was added a solution of 87 mg (0.42 mmol) of the acid **17**, 50 mg (0.42 mmol) of the isonitrile (**22**), and 0.132 mL (0.42 mmol) of 3.2 M CH_3NH_2/MeOH in 1.5 mL of methanol. This mixture was stirred at room temperature for 65 h and then diluted with 20 mL of CH_2Cl_2 and extracted with 1 N HCl (2 × 5 mL) followed by 5% $NaHCO_3$ (1 × 5 mL). The organic phase was dried over $MgSO_4$ and evaporated in vacuo to give a brown oil. The oil was flash chromatographed over silica eluting with 45% hexanes/55% ethyl ether to give 69 mg (0.13 mmol) of a mixture of **3** and **4**, yield 30.7%. This mixture was separated by HPLC using a Waters 5μ Silica Radial Pak Cartridge eluting with 65% diethyl ether/35% hexanes at 3 mL/min. The compound 13-demethyldysidenin (**3**) eluted at 4.83 min and 13-demethylisodysidenin (**4**) eluted at 5.55 min. A total of 29.5 mg of 13-demethylisodysidenin and 37.3 mg of 13-demethyldysidenin was recovered from this chromatography. Spectral data for these compounds are given as follows.

13-Demethyldysidenin (3): $[\alpha]^{14}{}_D$ +96.07° ($CHCl_3$, c 0.41); ^1H NMR ($CDCl_3$, 250 MHz) δ 1.36 (d, 3 H, J = 6.34 Hz), 1.36 (d, 3 H, J = 6.39 Hz), 1.93 (ddd, 1 H, J = 4.1, 10.5, 14.6 Hz), 2.24 (m, 1 H), 2.49 (dd, 1 H, J = 9.2, 16.1 Hz), 2.64 (dd, 1 H, J = 13.1, 14.4 Hz), 3.01 (s, 3 H), 3.11 (dd, 1 H, J = 2.4, 16.3 Hz), 3.31 (m, 1 H), doublet of ABq, A 4.62 (1 H, J = 5.3, 16.1 Hz), B 4.84 (1 H, J = 6.5, 16.1 Hz), 5.41 (dd, 1 H, J = 4.16, 11.8), 7.13 (brt, 1 H, J = 5.51 Hz), 7.28 (d, 1 H, J = 3.23 Hz), 7.69 (d, 1 H, J = 3.27 Hz); ^{13}C NMR ($CDCl_3$) 16.25, 17.20, 30.65, 30.65, 37.47, 40.73, 51.52, 51.88, 53.91, 105.18, 105.48, 119.26, 142.44, 166.50, 169.44, 172.10; IR ($CHCl_3$) 3400, 2985, 2920, 1675, 1632, 1510, 1455, 1378, 1298, 1267, 1250, 1140, 1100, 1062, 960, 905 cm^{-1}; UV (95% EtOH) λ_{max} 201 (ϵ 15 500); mass spectra (EI) m/e 533 (M), 496, 390, 382, 356, 202 (base peak), 166, 141, 123, 113, 98, 57, 42.

13-Demethylisodysidenin (4): $[\alpha]^{15}{}_D$ −48.5° ($CHCl_3$, c 0.59); ^1H NMR ($CDCl_3$, 250 MHz), δ 1.33 (d, 1 H, J = 6.5 Hz), 1.38 (d, 1 H, J = 6.5 Hz), 1.49 (ddd, 1 H, J = 4.5, 9.9, 13.4 Hz), 2.47, (dd, 1 H, J = 9.3, 16.2 Hz), 2.65 (m, 1 H), 2.94 (ddd, 1 H, J = 2.6, 10.3, 13.0 Hz), 3.02 (s, 3 H), 3.06 (dd, 1 H, J = 2.5, 17.5 Hz), 3.27 (m, 1 H), doublet of ABq, A 4.65 (1 H, J = 16.1, 5.3 Hz), B 4.87 (1 H, J = 16.1, 6.7 Hz), 5.31 (dd, 1 H, J = 4.7, 10.2 Hz), 7.13 (brt, 1 H, J = 5.6 Hz), 7.29 (d, 1 H, J = 3.3 Hz), 7.69 (d, 1 H, J = 3.3 Hz); ^{13}C NMR ($CDCl_3$) 16.6, 17.42, 31.37, 37.58, 40.78, 51.76, 51.86, 54.72, 105.24, 105.53, 119.39, 142.49, 166.80, 169.27, 171.65; IR ($CHCl_3$) 3400, 2990, 2935, 1680, 1510, 1456, 1413, 1400, 1380, 1290, 1240, 1140, 1120, 1065, 955, 905, 870, 840 cm^{-1}; UV (95% EtOH) λ_{max} 202 (ϵ 14 000); mass spectrum (EI) m/e 496, 390, 382, 202 (base peak), 166, 149, 141, 98, 57, 42.

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One-Way Photoisomerization of *cis*-Stilbene via a Cation Radical Chain Mechanism

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Abstract: Quenching of singlet 9,10-dicyanoanthracene by *cis*- or *trans*-stilbene in acetonitrile solution leads to a steady-state mixture consisting of 98.8% *trans*- and 1.2% *cis*-stilbene. Quantum yields for isomerization of *cis*-stilbene increase with increasing stilbene concentration, solvent polarity, salt concentration, and decreasing light intensity. These effects are attributed to a cation radical chain process in which the *cis*-stilbene cation radical isomerizes to the more stable *trans*-stilbene cation radical, which undergoes electron hole transfer to neutral *cis*-stilbene in competition with back electron transfer to the dicyanoanthracene anion radical. One-electron oxidation of *cis*-stilbene substantially lowers the activation energy for isomerization. In the presence of oxygen, the cation radical isomerization mechanism is suppressed and photooxygenation of *cis*- and *trans*-stilbene occurs.

The cation radicals of unsaturated and strained hydrocarbons undergo a variety of isomerization and cycloaddition reactions with activation energies substantially lower than those of the neutral molecules.[1-3] Generation of cation radicals via electron transfer to an electronically excited electron acceptor can result in quantum yields for cation radical isomerization or cyclodimerization in excess of unity.[3a] For example, Evans[4] observed that the naphthalene-sensitized isomerization of hexamethyl(Dewar benzene) to hexamethylbenzene in polar solvent can occur with high quantum yield ($\Phi \sim 80$ for 1.7 M reactant) as a consequence of a cation radical chain process (Scheme I). Electron-transfer from the Dewar benzene (D) to naphthalene

Scheme I. Cation Radical Chain Mechanism for the Naphthalene (A)-Sensitized Isomerization of Hexamethyl(Dewar benzene) (D) to Hexamethylbenzene (B)

$$A^* + D \rightarrow A^{-\cdot} + D^{+\cdot}$$
$$D^{+\cdot} \rightarrow B^{+\cdot}$$
$$D + B^{+\cdot} \rightarrow D^{+\cdot} + B$$

Scheme II. Electron-Transfer-Initiated Isomerization of a Trans Olefin via Formation of the Olefin Triplet

$$^*A^1 + t\text{-}D \rightarrow {}^1(A^{-\cdot}t\text{-}D^{+\cdot})^* \rightarrow {}^3(A^{-\cdot}t\text{-}D^{+\cdot})^* \rightarrow A + {}^3t\text{-}D \rightarrow c\text{-}D$$

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