Enantioselective Ring Construction: Synthesis of (+)-α-Cuparenone

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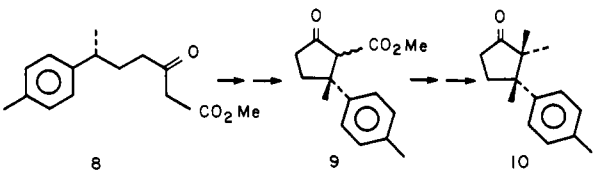
Abstract: Rhodium-catalyzed intramolecular C–H insertion (**8** → **9**) is shown to proceed with retention of absolute configuration. The product β-keto ester **9** is readily carried on to (+)-α-cuparenone (**10**). This represents a general strategy for the enantioselective

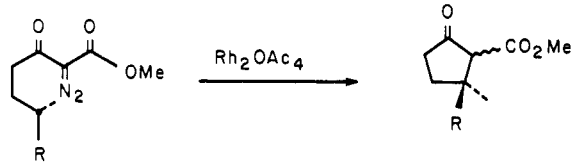


8 9 10

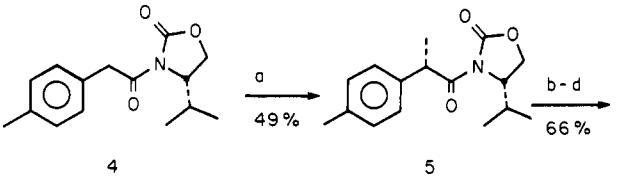
construction of carbocycles containing a chiral quaternary center.

While a variety of methods have been developed for the enantioselective construction of ternary chiral centers,[3] methods for the enantioselective construction of quaternary chiral centers have been slower in coming.[4,8h] We report herein a general strategy for the enantioselective construction of a five-membered ring containing a chiral quaternary center. This approach should be generally useful for the preparation of a wide variety of cyclopentane-containing natural products.

We had previously shown that exposure of a long-chain α-diazo β-keto ester to catalytic amounts of Rh_2OAc_4 in CH_2Cl_2 at room temperature led to smooth intramolecular C–H insertion to give the corresponding cyclopentane (**1** → **2**).[5] We reasoned that if the ternary center at the site of C–H insertion were optically pure and if insertion proceeded with retention of absolute configuration,[6] then the cyclic quaternary center so formed should also be optically pure. We have now shown that such is indeed the case. By combining such stereospecific C–H insertion with any of the methods for enantioselective construction of ternary chiral centers,[3] it should be possible to create a variety of diversely substituted



Scheme I[a]



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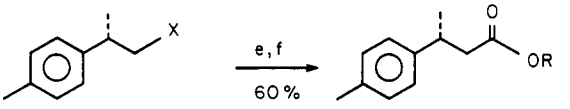
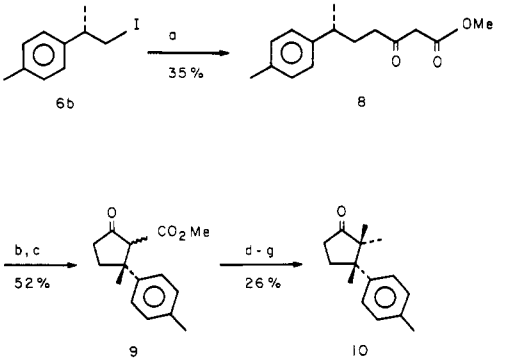


6a, X = OH
6b, X = I
6c, X = SPh

7a, R = H
7b, R = OEt

[a] (a) LDA/THF, CH_3I; (b) $LiAlH_4$; (c) TsCl/pyridine, NaI/acetone; (d) PhSh/NaOEt; (e) Li/naphthalene, CO_2; (f) EtI/K_2CO_3.

Scheme II[a]



6b 8 9 10

[a] (a) Methyl acetoacetate dianion; (b) TsN_3/Et_3N; (c) Rh_2OAc_4/CH_2Cl_2; (d) ethylene glycol/*p*-TsOH; (e) Dibal; (f) HCl-H_2O-CH_2Cl_2/silica gel; (g) L-Selectride, CH_3I.

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(3) (a) For a review, see: Martin, S. F. *Tetrahedron* **1980**, *36*, 419. (b) We have recently demonstrated the feasibility of chiral ternary center construction by intramolecular CH insertion: Taber, D. F.; Raman, K. *J. Am. Chem. Soc.* **1983**, *105*, 5935.

(4) For recent progress in this area, see: Meyers, A. I.; Harre, M.; Garland, R. *J. Am. Chem. Soc.* **1984**, *101*, 1146 and references cited therein. See also ref 7h below.

(5) (a) Taber, D. F.; Petty, E. H. *J. Org. Chem.* **1982**, *47*, 4808. (b) For an earlier study of Rh-catalyzed intramolecular CH insertion, see: Wenkert, E.; Davis, L. L.; Mylari, B. L.; Solomon, M. F.; daSilva, R. R.; Shulman, S.; Warnet, R. J.; Ceccherelli, P.; Curini, M.; Pellicciari, R. *J. Org. Chem.* **1982**, *47*, 3242.

(6) That *copper*-catalyzed intramolecular CH insertion proceeds with retention of absolute stereochemistry had been demonstrated: Ledon, H.; Linstrumelle, G.; Julia, S. *Tetrahedron. Lett.* **1973**, 25. In other work, we have shown substantial differences between copper- and rhodium-mediated carbenoid reactions.

(7) Isolation and structure of α-cuparenone: (a) Chetty, G. L.; Dev, S. *Tetrahedron Lett.* **1964**, 73. (b) Irie, T.; Suzuki, T.; Ito, S.; Kurosowa, E. *Tetrahedron Lett.* **1967**, 3187. (c) Benesova, V. *Collect. Czech. Chem. Commun.* **1976**, *41*, 3812.

(8) For representative syntheses of (±)-α-cuparenone see: (a) Parker, W.; Ramage, R.; Raphael, R. *J. Chem. Soc.* **1962**, 1558. (b) Leriverend, P. *Bull. Soc. Chim. Fr.* **1973**, 3498. (c) Wenkert, E.; Buckwalter, B. L.; Craveiro, A. A.; Sanchez, E. L.; Sathe, S. S. *J. Am. Chem. Soc.* **1978**, *100*, 1267. (d) Hayakawa, Y.; Shimizu, F.; Noyori, R. *Tetrahedron Lett.* **1978**, 993. (e) Sakurai, H.; Shirahata, A.; Hosomi, A. *Angew. Chem., Int. Ed. Eng.* **1979**, *18*, 163. (f) Martin, S. F.; Phillips, F. W.; Puckette, T. A.; Colapret, J. A. *J. Am. Chem. Soc.* **1980**, *102*, 5866. (g) Halazy, S.; Zutterman, F.; Krief, A. *Tetrahedron Lett.* **1982**, *23*, 4385. (h) Gadwood, R. C. *J. Org. Chem.* **1983**, *48*, 2098. (i) Greene, A. E.; Lansard, J.-P.; Luche, J. L.; Petrier, C. *J. Org. Chem.* **1983**, 48, 4763. (j) For an alternative enantioselective approach to (+)-α-cuparenone, see: Posner, G. H.; Kogan, T. P.; Hulce, M. *Tetrahedron Lett.* **1984**, *25*, 383.

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quaternary chiral centers. We illustrate this approach by an enantioselective synthesis of (+)-α-cuparenone.[7,8]

The key intermediate in the preparation of the desired cyclization substrate **7** (Scheme I) is chiral iodide **6b**. The precursor alcohol **6a** is readily prepared by diastereoselective alkylation[9] of oxazolidone **4**, followed by $LiAlH_4$ reduction. The diastereomeric α-methylated imides (91:9) are readily separated by open column chromatography. The primary alcohol **6a** was converted to the iodide **6b** by tosylation followed by warming with NaI in acetone.

To assure ourselves of the absolute configuration and optical purity of **6b**, we carried it on to the homologated ester **7b**[10] (Scheme II). Thus, reduction of the derived sulfide **6c** with lithium naphthalenide followed by carboxylation[11] yielded acid **7a**. Esterification[12] gave **7b**, which after chromatography and bulb-to-bulb distillation showed $[\alpha]_D$ −25.1° (lit.[13] +25°, lit.[10] +25.4° for the opposite enantiomer).

While iodide **6b** is not an efficient alkylating agent, dianion alkylation[14] of methyl acetoacetate led to **8** in acceptable yield (Scheme II). Diazo transfer[15] followed by rhodium-catalyzed cyclization[5] then proceeded smoothly to give **9** as a diastereomeric mixture.

The remaining problem was to convert ester **8** to the geminally dialkylated cyclopentanone **10**. To this end, the β-keto ester was converted to the corresponding α-methylene ketone by a modification of the three-step procedure of Marx.[16,17] Reductive alkylation[18] then proceeded smoothly to give **10**. α-Cuparenone **10** so prepared[8j] showed $[\alpha]_D$ +164° (lit.[7] +170°, 96% optically pure), confirming that rhodium-catalyzed intramolecular C–H insertion does indeed proceed with retention of absolute configuration. This observation is pertinent to the investigation, currently under way in other laboratories,[19] of the mechanism of rhodium-mediated *inter*molecular C–H insertion.

The development of methods for enantioselective ring construction is currently a pressing concern of synthetic organic chemistry.[20] As synthetic targets become more sophisticated, and especially as convergent strategies become increasing important in synthetic planning, the development of general methods for enantioselective ring construction will be essential. The approach outlined herein, diastereoselective alkylation followed by stereospecific C–H insertion, should be general for the construction of a five-membered ring containing a chiral quaternary center.

Experimental Section

Preparation of 4. Acylation was carried out by following the procedure of Evans.[8] Thus, *p*-tolylacetic acid (21.32 g, 0.142 mol) was placed in a 250-mL round-bottomed flask with a magnetic stir bar and 100 mL of methylene chloride. Dimethylformamide (100 μL) was added, the flask was immersed in an ice/water slurry, oxalyl chloride (21.65 g, 0.171 mol) was added, and the mixture was stirred magnetically for 10 min at 0 °C. The mixture was then allowed to warm to room temperature, stirred overnight, and concentrated in vacuo to give a brown oil.

A flame-dried 500-mL three-necked round-bottomed flask equipped with a magnetic stir bar and maintained under N_2 was charged with chiral 5-isopropyl-3-oxazolid-2-one (15.05 g, 0.117 mol) and 200 mL of dry THF. The flask was immersed in a dry ice/acetone slurry, and the mixture was stirred magnetically. *n*-BuLi (88.8 mL, 1.45 M in hexane, 0.129 mol) was then added, and the mixture was stirred for 30 min. The crude acid chloride prepared above was then taken up in a little THF and added in one portion. The mixture was stirred 30 min, then the cooling bath was removed, and the mixture was stirred an additional 100 min at room temperature. The reaction mixture was diluted with aqueous NH_4Cl, extracted with CH_2Cl_2, and washed with aqueous $NaHCO_3$. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was distilled bulb to bulb (bp 120–145 °C (0.5 mmHg)) then recrystallized from methanol/water to give **4** as a colorless needles, 16.7 g (55%): R_F (10% EtOAc/hexane) 0.18; ^1H NMR δ 0.80 (t, J = 7 Hz, 6 H), 2.15 (m, 1 H), 2.21 (s, 3 H), 3.71–4.20 (m, 3 H), 3.99 (s, 2 H), 6.62–6.83 (m, 4 H); IR 2960, 2925, 1780, 1690, 1363, 1198, 1171; MS 261 (18), 132 (100), 105 (20); exact mass calcd for $C_{15}H_{19}NO_3$ 261.1365, found 261.1353.

Preparation of 5. Alkylation was carried out in the manner of Evans.[8] Thus, a flame-dried three-necked 500-mL round-bottomed flask equipped with a magnetic stir bar and under N_2 was charged with diisopropylamine (8.35 g, 82.7 mmol) and THF (150 mL). *n*-BuLi (31.7 mL, 2.21 M in hexane, 69.7 mmol) was added in one portion, and the resulting mixture was stirred 10 min at 0 °C. The flask was cooled to −78 °C in a dry ice/acetone slurry; then the acylated oxazolidone prepared above (16.56 g, 63.4 mmol) in 25 mL of THF was added dropwise over 5 min. A bright yellow color was produced. The solution was stirred 30 min at −78 °C; then methyl iodide (45.0 g, 317 mmol) was added in one portion. The cooling bath was removed and stirring was continued for an additional 2 h. The reaction mixture was diluted with aqueous HCl and extracted with Et_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed[21] on 500 g of silica gel with a linear gradient elution progressing from petroleum ether to 5% EtOAc/petroleum ether. The first 12 L was discarded. The next $11^1/_2$ L was concentrated in vacuo to give the major diastereomer as an oil (7.285 g, 49%), R_f (10% EtOAc/Hexane) 0.30. The next $2^1/_2$ L was discarded. The next 4 L contained the undesired diastereomer. The next 4 L contained a mixture of the undesired diastereomer and the starting material. The next 6 L contained the starting material. The fractions containing a mixture of products were rechromatographed to give a total yield of 0.703 g, R_f (10% EtOAc/Hexane) 0.248 of the minor diastereomer and 1.474 g of recovered starting material. Major diastereomer: ^1H NMR δ 0.89 (d, J = 7 Hz, 6 H), 1.45 (d, J = 7 Hz, 3 H), 2.26 (s, 3 H), 2.41 (m, 1 H), 3.95 (d, J = 7 Hz, 2 H), 4.23 (m, 1 H), 4.97 (q, J = 6 Hz, 1 H), 6.85–7.10 (m, 4 H); IR 2955, 2920, 1776, 1690, 1358, 1196 cm^{-1}; MS 275 (16), 146 (100), 119 (33), 118 (20); exact mass calcd for $C_{11}H_{21}NO_3$ 275.1521, found 275.1519.

Preparation of Alcohol 6a. A 250-mL round-bottomed flask equipped with a magnetic stir bar and placed in an ice/water slurry was charged with the major diastereomer from above (7.03 g, 25.6 mmol) and 100 mL of THF. LAH (3.07 g, 76.7 mmol) was added over 10 min, the mixture was stirred an additional 10 min, the cooling bath was removed, and the mixture was stirred an additional 40 min. Excess LAH was quenched by successive dropwise addition of H_2O (3 mL), 15% NaOH (3 mL), and H_2O (9 mL). The mixture was filtered, the solids were washed with Et_2O, and the filtrate was concentrated in vacuo. The residue after concentration was extracted with petroleum ether, leaving behind crystalline oxazolidone that could be recycled. The combined organic extracts were washed with water, dried over K_2CO_3, concentrated in vacuo, and distilled bulb to bulb to give alcohol **5** as a colorless oil: 3.73 g (97%); bp 70–95 °C (0.5 mm); R_f (10% EtOAc/hexane) 0.14; ^1H NMR δ 1.23 (d, J = 8 Hz, 3 H), 2.35 (s, 3 H), 2.92 (m, 1 H), 3.24 (s,

(9) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.
(10) Meyers, A. I.; Smith, R. K. *Tetrahedron Lett.* **1979**, 2749.
(11) Screttas, C. G.; Micha-Screttas, M. *J. Org. Chem.* **1978**, *43*, 1064.
(12) Moore, G. G.; Foglia, T. A.; McGahan, T. J. *J. Org. Chem.* **1979**, *44*, 2425.
(13) Honwad, V. K.; Rao, A. S. *Tetrahedron* **1964**, *20*, 2921.
(14) Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.
(15) Regitz, M.; Hocker, J.; Liedhegener, A. "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. V, p 197.
(16) Marx, J. N.; Norman, L. R. *J. Org. Chem.* **1975**, *40*, 1602.
(17) Huet, F.; Lechevallier, A.; Pellet, M.; Conia, J. M. *Synthesis* **1978**, 63.
(18) Fortunato, J. M.; Ganem, B. *J. Org. Chem.* **1976**, *41*, 2194.
(19) Jones, W. D.; Feher, F. J. *J. Am Chem. Soc.* **1984**, *106*, 1650 and references cited therein.
(20) Several strategies for the enantioselective preparation of carbocycles have been reported. For leading references, see the following. (a) Intermolecular Diels–Alder reaction: Ensley, H. E.; Parnell, C. A.; Corey, E. J. *J. Org. Chem.* **1978**, *43*, 1610. Horton, D.; Machinami, T. *J. Chem. Soc., Chem. Commun.* **1981**, 88. (b) Intramolecular Diels–Alder reaction: Nicolaou, K. C.; Papahatjis, D. P.; Claremon, D. A.; Dolle, R. E., III, *J. Am. Chem. Soc.* **1981**, *103*, 6967. Roush, W. R.; Gillis, H. R.; Ko, A. I. *J. Am. Chem. Soc.* **1982**, *104*, 2269. (c) Intermolecular alkylation: Meyers, A. I.; Williams, D. R.; Erickson, G. W.; White, S.; Druelinger, M. *J. Am. Chem. Soc.* **1981**, *103*, 3081. (d) Intramolecular alkylation: Quinkert, G.; Schwartz, U.; Stark, H.; Weber, W.-D. Baier, H.; Adam, F. Durner, G. *Angew. Chem., Int. Ed. Engl.* 1980, *19*, 1029. Yamamoto, K.; Tsuji, J. *Tetrahedron Lett.* **1982**, *23*, 3089. (e) Conjugate addition: Kogen, H.; Tomioka, K.; Hashimoto, S.-I.; Koga, K. *Tetrahedron* **1981**, *37*, 3951. Posner, G. H.; Hulce, M.; Mallamo, J. P.; Drexler, S. A.; Clardy, J. *J. Org. Chem.* **1981**, *46*, 5246. (f) Intramolecular aldol condensation: Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. Trost, B. M.; Curran, D. P. *J. Am Chem. Soc.* **1980**, *102*, 5699. (g) Cyclopropanation: Mukaiyama, T.; Fujimoto, K.; Takeda *Chem. Lett.* **1979**, 1207. Monpert, A.; Martelli, J.; Gree, R.; Carrie, R. *Tetrahedron Lett.* **1981**, *22*, 1961. (h) Biomimetic polyolefin cyclization: Demailly, G.; Solladie, G. *Tetrahedron Lett.* **1980**, *21*, 3355. Johnson, W. S.; Berner, D.; Dumas, D. J.; Nederlof, P. J. R.; Welch, J. *J. Am. Chem. Soc.* **1982**, *104*, 3508. (i) [2 + 2] Cycloaddition: Houge, C.; Frisque-Hesbain, A. M.; Mockel, A.; Declerq, J. P.; Germain, G.; Van Meerssche, M. *J. Am. Chem. Soc.* **1982**, *102*, 2920.
(21) Taber, D. F. *J. Org. Chem.* **1982**, *47*, 1351.

1 H), 3.67 (d, J = 7 Hz, 2 H), 7.15 (s, 4 H); IR 3400 (br), 2925, 2870, 1445, 1380, 1367, 1027, 1010 cm^{-1}; $[\alpha]^{27}$D −47.7° (c 0.002 57, EtOH); MS 150 (16), 119 (100); exact mass calcd for $C_{10}H_{14}O$ 150.1045, found 150.1043.

Preparation of Iodide 6b. A 100-mL round-bottomed flask equipped with a magnetic stir bar was charged with alcohol **5** (3.38 g, 22.5 mmol) and 35 mL of pyridine. The flask was immersed in an ice/water slurry and *p*-toluenesulfonyl chloride (8.59 g, 45.1 mmol) was added. Stirring was continued for 1 h, after which the flask was placed in a freezer overnight. The reaction mixture was diluted with aqueous HCl, extracted with CH_2Cl_2, and washed with aqueous $NaHCO_3$. The combined organic extracts were dried over K_2CO_3 and concentrated in vacuo. The residue was transferred to a 100-mL round-bottomed flask equipped with a magnetic stir bar. Acetone (20 mL) was added, followed by NaI (10.13 g, 67.5 mmol), and copper-bronze powder (0.2 g). The mixture was refluxed with stirring for 4.5 h. The cooled reaction mixture was diluted with aqueous $Na_2S_2O_3$ and extracted with petroleum ether. The combined organic extracts were dried over K_2CO_3, filtered, and concentrated in vacuo. The residue was chromatographed on 60 g of silica gel with petroleum ether. The first 250 mL was discarded. Concentration of the next 400 mL gave 4.5 g (76%) of the iodide **6**, R_f (hexane) 0.32.

Preparation of Sulfide 6c. A mixture of thiophenol (259 mg, 2.354 mmol), NaOH (94 mg, 2.354 mmol), and iodide **6b** (510 mg, 1.962 mmol) in 5 mL of EtOH was refluxed for 1.5 h. The reaction mixture was then cooled and partitioned between H_2O and ether. The combined ether extracts were washed with 10% NaOH solution, dried over Na_2SO_4, and concentrated in vacuo. The residue was chromatographed over 30 g of silica gel with 1% EtOAc/petroleum ether. The first 250 mL was discarded. The next 300 mL was concentrated in vacuo to give the sulfide (425 mg, 90%) as a colorless oil: R_f (hexane) 0.29; ^{1}H NMR δ 1.35 (d, J = 7 Hz, 3 H), 2.30 (s, 3 H), 2.90–3.21 (m, 3 H), 7.1–7.3 (m, 9 H); IR 3080, 3040, 2980, 2940, 1590, 1520, 1490, 1445, 1100, 1035 cm^{-1}; MS 242 (100), 132 (57), 124 (56), 120 (45), 11 (45), 117 (37), 105 (52), 91 (59); exact mass calcd for $C_{16}H_{18}S$ 242.113, found 242.1095.

Preparation of Acid 7a. A lithium naphthalenide solution in 2 mL of THF, prepared by the method of Screttas et al.[11] using 256 mg (2 mmol) of naphthalene and 14 mg (2 mmol) of lithium, was cooled to −60 °C. To this was added 242 mg (1 mmol) of sulfide **11**. The solution turned dark yellow brown. The mixture was stirred while warming to −20 °C then cooled again to −60 °C. A slurry of dry ice in ether was added to the reaction mixture. The brown color was discharged. The mixture was allowed to warm to room temperature then diluted with 5 mL of H_2O followed by 200 mg of NaOH and 0.1 mL of 30% H_2O_2. This mixture was stirred for 2 h and then extracted twice with hexane. The aqueous layer was acidified with 10% HCl and extracted with 3 × 50 mL of ether. The combined ether extracts were dried over Na_2SO_4 and concentrated in vacuo to give 145 mg (81%) of acid **7a** as a colorless oil: ^{1}H NMR 1.29 (d, J = 7 Hz, 3 H), 2.30 (s, 3 H), 2.5–2.7 (m, 2 H), 3.24 (q, J = 7 Hz, 1 H), 7.1 (s, 4 H), 11.1 (s, 1 H); IR 3050, 2990, 1710, 1510, 1450, 1265, 900 cm^{-1}; MS 178 (50), 132 (14), 122 (23), 120 (23), 119 (100), 118 (23), 91 (34); exact mass calcd for $C_{11}H_{14}O_2$ 178.099, found 178.099.

Preparation of Ester 13. The esterification of acid **12** was carried out by the method of Moore et al.[12] Thus, a mixture of acid (80 mg, 0.449 mmol), K_2CO_3 (155 mg, 1.12 mmol), and ethyl iodide (280 mg, 1.8 mmol) in 2 mL of acetone was refluxed for 2 h. The reaction mixture was then cooled, diluted with 10% aqueous HCl, and extracted with 3 × 20 mL ether. The ethereal extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on 5 g of silica gel with 2% EtOAc/petroleum ether. The first 20 mL was discarded. Concentration of the next 20 mL provided ester **7b** (69 mg, 74%) as a colorless oil; R_f (10% EtOAc/Hexane) 0.65; ^{1}H NMR δ 1.18 (t, J = 7 Hz, 3 H), 1.27 (d, J = 7 Hz, 3 H), 2.30 (s, 3 H), 2.54 (m, 2 H), 3.24 (q, J = 6 Hz, 1 H), 4.07 (q, J = 7 Hz, 2 H), 7.1 (s, 4 H); IR 2990, 2930, 1735, 1510, 1450, 1365, 1260, 1035 cm^{-1}; MS 206 (100), 135 (74), 120 (52), 119 (50), 115 (64), 105 (45), 91 (81); exact mass calculated for $C_{13}H_{18}O_2$ 206.131, found 206.129; $[\alpha]_D$ −25.1° ($CHCl_3$).

Preparation of β-Keto Ester 8. The alkylation was carried out by the method of Weiler.[14] Thus, a flame-dried 100-mL three-necked round-bottomed flask equipped with a magnetic stir bar and maintained under N_2 was charged with 50% NaH (3.36 g, 70.0 mmol) and 25 mL of THF. The flask was chilled in an ice/water slurry, then methyl acetoacetate (6.25 g, 53.8 mmol) was added dropwise over 15 min. After an additional 15 min of stirring *n*-BuLi (20.8 mL, 2.85 M in hexane, 59.2 mmol) was added in one portion, and stirring was continued an additional 30 min. Iodide (7.00 g, 26.9 mmol) was added in one portion, the cooling bath was removed, and stirring was continued an additional 30 min. The mixture was diluted with a mixture of dilute aqueous HCl and brine and extracted with Et_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on 50 g of silica gel with 500 mL of petroleum ether then 5% EtOAc/petroleum ether. The first 100 mL was discarded. The second 100 mL was concentrated in vacuo to give the starting iodide as an oil (2.253 g). The next 400 mL was discarded. The next 250 mL was concentrated in vacuo to give the alkylated β-keto ester **8** as a yellowish oil (1.566 g, 35% based on unrecovered iodide: R_f (10% EtOAc/hexane) 0.24; ^{1}H NMR δ 1.23 (d, J = 7 Hz, 3 H), 1.69–2.12 (m, 2 H), 2.30–2.54 (m, 2 H), 2.34 (s, 3 H), (m, 1 H), 3.35 (s, 2 H), 3.70 (s, 3 H), 7.07 (s, 4 H); IR 2955, 1745, 1715, 1650, 1622, 1444, 1229 cm^{-1}; $[\alpha]^{27}$ −23.2° (c 0.001 610, EtOH); MS (NH_3, C/I) 266 (5), 249 (6), 231 (10), 132 (100), 119 (36); exact mass calcd for $C_{15}H_{19}O_3$ (M − H) (methane, C/I) 247.1334; found 247.1272. Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.58%; H, 8.06%. Found: C, 72.54%; H, 8.05%.

Preparation of Cyclized Keto Ester 9. Diazo transfer was carried out by the method of Regitz.[15] Thus, a 25-mL round-bottomed flask equipped with a magnetic stir bar was charged with *p*-toluenesulfonyl azide (0.895 g, 4.54 mmol) and triethylamine (0.834 g, 0.26 mmol). The β-keto ester **8** (1.025 g, 4.13 mmol) in 10 mL of acetonitrile was added, and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with 10% aqueous NaOH and extracted with Et_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on 50 g of silica gel with 3% EtOAc/petroleum ether. The first 50 mL was discarded. The next 800 mL was concentrated in vacuo to give the diazo ester as an oil, 871.6 mg (77%), R_f (10% EtOAc/hexane) 0.30.

This oil was transferred to a flame-dried, 100-mL round-bottomed flask equipped with a magnetic stir bar and maintained under N_2. Methylene chloride (50 mL), dried by filtering through anhydrous K_2CO_3, was added, followed by rhodium(II) acetate dimer (17.4 mg, 2% by weight). The mixture was stirred at room temperature until evolution of nitrogen ceased (30 min). The reaction mixture was concentrated in vacuo to give **8** as a colorless oil: 0.523 g (67%); R_f (10% EtOAc/hexane) 0.35; ^{1}H NMR δ 1.32, 1.45, 1.62 (s, s s, 3 H total), 1.88–2.68 (m, 4 H), 2.51 (s, 3 H), 3.36, 3.58, 3.72 (s s s, 3 H total), 3.43, 3.63 (s s s, 1 H total), 7.04–7.28 (m, 4 H); IR 2970, 1759, 1725, 1657, 1614, 1207, 1034 cm^{-1}; MS (CH_4, C/I) 246 (1), 215 (2), 189 (86), 188 (72), 171 (100), 132 (67); exact mass calcd for $C_{15}H_{18}O_3$ 246.1256, found 246.1245.

Preparation of (+)-α-Cuparenone (10). Following the procedures of Marx[16] and Conia,[17] a flask equipped with a magnetic stir bar and Dean-Stark water trap was charged with keto ester **9** (522 mg, 2.12 mmol) and 10 mL of toluene. Ethylene glycol (0.59 mL, 10.6 mmol) and a crystal of *p*-toluenesulfonic acid were added and the mixture was refluxed overnight. The reaction mixture was diluted with aqueous $NaHCO_3$, extracted with Et_2O, dried over Na_2SO_4, and concentrated in vacuo. The residue was placed in a 25-mL round-bottomed flask equipped with a magnetic stir bar, and 5 mL of toluene was added. The flask was cooled to 0 °C in an ice/water slurry and diisobutylaluminum hydride (5.67 mL, 1.5 M in toluene, 8.5 mmol) was added over 2 min. The resulting solution was stirred an additional 30 min. Excess Dibal was decomposed with NaF (1.6 g, 40 mmol) and H_2O (1 mL). The reaction mixture was filtered, the solids were washed with CH_2Cl_2, and the filtrate was concentrated in vacuo. The resulting ketal alcohol was placed in a 25-mL round-bottomed flask equipped with a magnetic stir bar. Methylene blue (5 mg) and CH_2Cl_2 (11 mL) were added, and the solution was cooled to 0 °C in an ice/water slurry. Silica gel (60–200 mesh, 3.57 g)[15b] and concentrated aqueous HCl (0.57 mL) were added, and the mixture was stirred for 40 min. K_2CO_3 (1 g) was added, and stirring was continued for an additional 5 min. The reaction mixture was filtered, the solids were washed with CH_2Cl_2, and the filtrate was concentrated in vacuo. The residual oil was chromatographed on 10 g of silica gel with 2% EtOAc/petroleum ether. The first 120 mL was discarded. The next 50 mL was concentrated in vacuo to give the α-methylene ketone was a colorless oil: 90.5 mg (33%); R_f (10% EtOAc/hexane) 0.42; ^{1}H NMR δ 1.57 (s, 3 H), 1.67–2.52 (m, 4 H), 2.33 (s, 3 H), 5.24 (s, 1 H), 6.19 (s, 1 H), 6.96–7.21 (m, 4 H); IR 2960, 2930, 1720, 1629, 1254, 1233, 1080, 942 cm^{-1}; MS 200 (100), 185 (62), 157 (27.5), 143(61), 129 (48), 115 (15); exact mass calcd for $C_{14}H_{16}O$ 200.1201, found 200.1181.

Reductive alkylation was carried out by the method of Ganem.[18] Thus, to a flame-dried 5 -mL round-bottomed flask equipped with a magnetic stir bar and maintained under N_2 was added the above enone (56.3 mg, 0.282 mmol) and 565 μL of THF. The flask was immersed in a dry-ice/acetone slurry. L-Selectride (Aldrich) (310 μL, 1 M in THF, 0.310 mmol) was added in one portion, and stirring was continued for 1 h. Methyl iodide (175 μL, 2.82 mmol) was then added in one portion, and stirring was continued an additional 5 min. The cooling bath was removed, and stirring was continued an additional 1 h. 10% NaOH (1.2 mL) and 30% H_2O_2 (0.6 mL) were then added, and the mixture was stirred for an additional 30 min. The mixture was diluted with saturated aqueous $NaHCO_3$, extracted with Et_2O, and washed with aqueous NaCl.

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, 0.00192, $CHCl_3$) [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.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the National Cancer Institute, DHHS (CA 22757 and CA 34383), for support of this work. We express our appreciation to Professor Evans for sharing his experimental procedures with us prior to publication.

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

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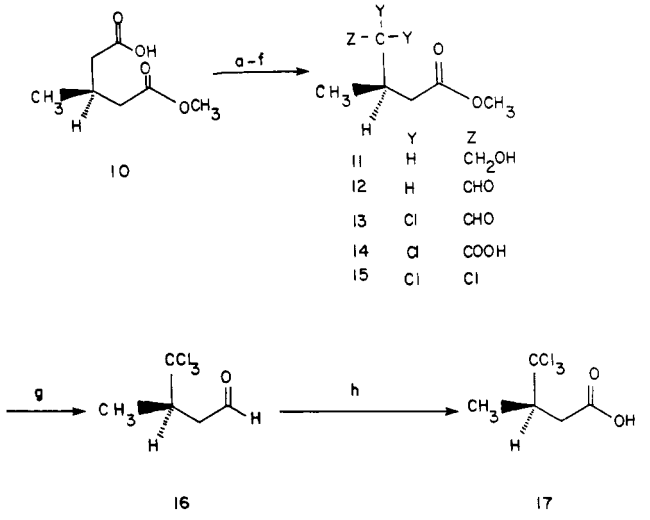
Abstract: The total synthesis of (+)-(2*R*,4*R*)-5,5,5-trichloro-4-methyl-2-[(*R*)-methyl(4,4,4-trichloro-3-methylbutanoyl)-amino]-*N*-[1-(thiazol-2-yl)methyl]pentanamide (**3**), trivial name demethyldysidenin, along with a diastereomer, (−)-demethylisodysidenin (**4**), is described. These compounds 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

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.

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]

(1) Kazlauskas, R.; Lidgard, R. O.; Wells, R. J. *Tetrahedron Lett.* **1977**, 3183.
(2) (a) Charles, C.; Braekman, J. C.; Daloze, D.; Tursch, B.; Karlsson, R. *Tetrahedron Lett.* **1978**, 1519. (b) Charles, C.; Braekman, J. C.; Daloze, D.; Tursch, B. *Tetrahedron* **1980**, *36*, 2133.
(3) The numbering system for these compunds was adopted to conform to the existing literature.
(4) Biskupiak, J. E.; Ireland, C. M. *Tetrahedron Lett.* **1984**, 2935.
(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.

0002-7863/85/1507-0199$01.50/0