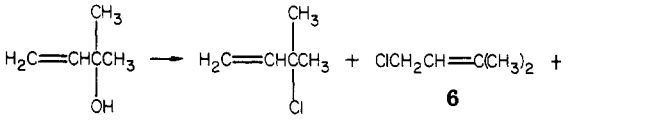
Table I. Reactions of Alcohols with HCA/Ph_3P[a]

run	alcohol	molar quantities × 10^2			molar ratio of HCA/ alcohol	volume of sulfolane, mL	yield of chloride, %[b,c]
		alcohol	HCA	Ph_3P			
1	1	3.40	10.7	2.70	3.15	30	93.7
2	1	2.73	5.23	2.83	1.92	20	85.3
3	1	13.9	13.9	14.5	1.00	40	95.7
4[d]	1	2.37	2.57	2.78	1.08	20	84.3
5[e]	1	2.34	2.52	2.82	1.08	30	93.0
6	1	2.83	2.21	3.02	0.78	20	80.4
7	1	2.30	1.37	2.31	0.60	18	80.1
8	1	2.45	0.967	2.50	0.39	18	76.2
9	1	3.40	1.37	3.66	0.40	20	76.3
10	1	2.50	0.544	2.55	0.22	18	49.5[f]
11	1	3.74	0.718	3.80	0.17	18	36.8[g]
12	2	3.74	3.69	3.79	0.99	20	78.6
13	2	3.14	1.56	3.21	0.50	18	77.7
14	3	3.82	3.81	3.87	1.00	21	72.1
15	4	3.31	3.31	3.34	1.00	18	59[h]

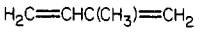
[a] HCA in sulfolane was added to alcohol and Ph_3P in sulfolane at 10 °C, except for runs 4 and 5. [b] Isolated yield based on alcohol, except for run 1 in which Ph_3P was the limiting reagent. [c] The distilled product is cleanly 3-chloro-2-methyl-1-propene (runs 1-11), 1-chlorobutane (runs 12, 13), or 2-chlorobutane (run 14), except where noted. [d] Alcohol 1 added to HCA/Ph_3P in sulfolane. [e] Ph_3P added to alcohol 1/HCA in sulfolane. [f] Distilled product, by NMR and VPC, is ca. 95% chloride and 5% unreacted alcohol. [g] Along with 0.0138 mol of chloride, the distillate contains 0.0056 mol of unreacted alcohol; the pot residue, by NMR, contains both unreacted Ph_3P and alcohol 1. [h] The distilled product, by VPC and NMR, is a mixture (% yield) of chlorides **5** (37%) and **6** (22%) and diene **7** (27%).

tion of CCl_4 in our original procedure[3b] is not a problem in the improved method.

Saturated alcohols 1-butanol (**2**) and 2-butanol (**3**) also react readily and in high yield under the same conditions (runs 12-14); as above, 0.5 equiv of HCA suffices. Especially gratifying is the behavior of tertiary allylic alcohol 2-methyl-3-buten-2-ol (**4**). When HCA was used as both



4 **5** **6**



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reagent and solvent, the yields of products **5**-**7** were 21.2%, 43.2%, and 17.7%, respectively.[3b] Although elimination is still a problem in sulfolane (run 15), the major allylic chloride is now the unrearranged **5**.

(3) (a) R. M. Magid, O. S. Fruchey, and W. L. Johnson, *Tetrahedron Lett.*, 2999 (1977); (b) R. M. Magid, O. S. Fruchey, W. L. Johnson, and T. G. Allen, *J. Org. Chem.*, 44, 359 (1979).

Experimental Section

All ^1H NMR spectra were obtained with a Varian T-60 spectrometer; tetramethylsilane was used as an internal standard. VPC analyses were performed by using a Varian Aerograph Model 920 gas chromatograph with a 9 ft × $^1/_4$ in. column of SE-30 (5%) on 80/100 Chromosorb W. Sulfolane and hexachloroacetone were stored over 4-Å molecular sieves.

General Procedure for Reactions. In a 100-mL, round-bottomed flask equipped with magnetic stirrer were placed ca. 0.03 mol of the alcohol and (usually) a slight excess of Ph_3P in 10-15 mL of sulfolane. To the cooled (10 °C) stirred solution was added HCA in ca. 10 mL of sulfolane dropwise; after an initial temperature rise and formation of a precipitate, the temperature gradually dropped to ambient as the rest of the HCA solution was added. The reaction mixture was allowed to come to room temperature. Immediate flash distillation at 4-5 torr into a dry ice-acetone-cooled receiver gave product which was analyzed by VPC and ^1H NMR; in most instances, the material was exclusively the allylic or saturated chloride.

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Communications

Regiochemical Control in the Conjugate Addition of Dithianylidene Anions: Total Syntheses of (±)-Aromatin and (±)-Confertin

Summary: The lithium anion of the dithiane of (*E*)-2-methyl-2-butenal has been shown to undergo a highly regioselective Michael addition-alkylation sequence. Subsequent stereoselective transformations of the derived adduct have culminated in syntheses of the pseudoguaianolides (±)-aromatin and (±)-confertin.

Sir: Aromatin (**12b**)[1] and confertin (**15**)[2] are representatives of the class of physiologically active pseudoguaianolide sesquiterpenes.[3] The former substance (helenanolide) stereochemically differs from the latter (am-

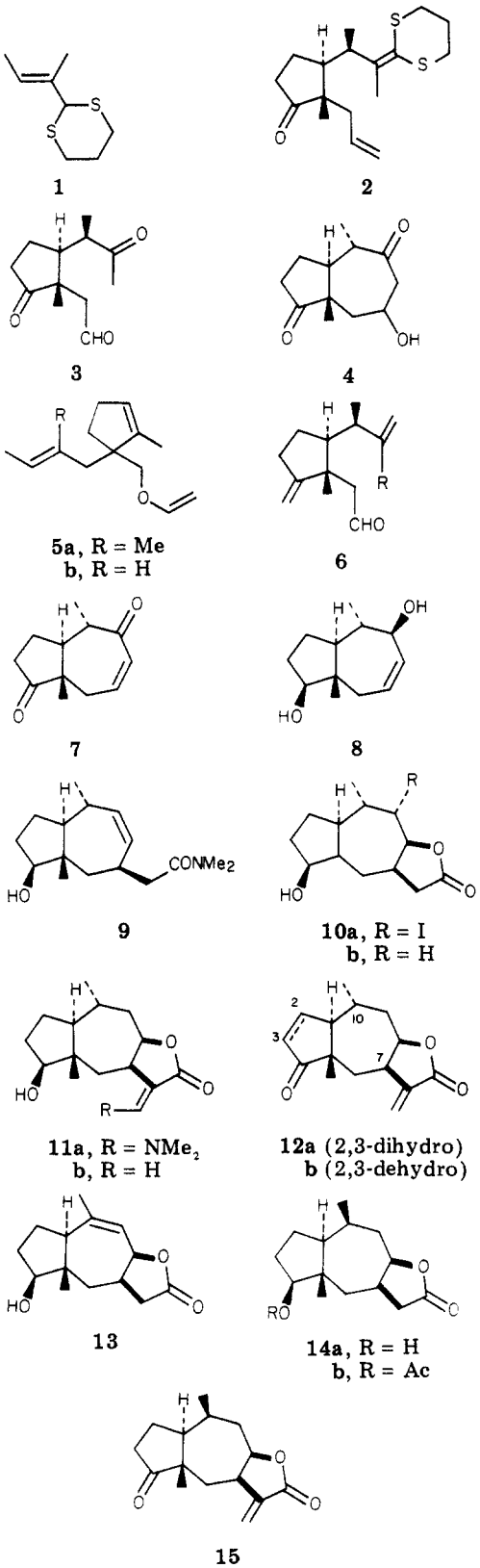
(1) For a recent synthesis of (±)-aromatin see: Lansbury, P. T.; Hangauer, D. G.; Vacca, J. P. *J. Am. Chem. Soc.* **1980**, *102*, 3964.

(2) For syntheses of confertin see: (a) Marshall, J. A.; Ellison, R. H. *J. Am. Chem. Soc.* **1976**, *98*, 4312. (b) Semmelhack, M. F.; Yamashita, A.; Tomesch, J. C.; Hirotsu, K. *Ibid.* **1978**, *100*, 5565. (c) Wender, P. A.; Eissenstat, M. A.; Filosa, M. P. *Ibid.* **1979**, *101*, 2196. (d) Quallich, G. J.; Schlessinger, R. H. *Ibid.* **1979**, *101*, 7627.

(3) (a) Kupchan, S. M.; Eakin, M. A.; Thomas, A. M. *J. Med. Chem.* **1971**, *14*, 1147. (b) Lee, K. H.; Huang, E. S.; Piantadosi, C.; Pagano, J. S.; Geissman, T. A. *Cancer Res.* **1971**, *31*, 1649. (c) Rodriguez, E.; Towers, G. H. N.; Mitchell, J. C. *Phytochemistry* **1976**, *15*, 1573. (d) Hall, I. H.; Lee, K. H.; Mar, E. C.; Starnes, C. O. *J. Med. Chem.* **1977**, *20*, 333.

0022-3263/81/1946-0825$01.00/0

Chart I



brosanolide) by the configuration of the C_{10} methyl group. We have developed, in the context of our previous work with ketene dithioacetals,[4] a dithiane-derived synthon which is the functional equivalent of the thermodynamic enolate of methyl ethyl ketone in an aprotic Michael addition. This new methodology is exemplified by the stereoselective total synthesis of (±)-aromatin and the formal total synthesis of (±)-confertin.

The dithiane of (*E*)-2-methyl-2-butenal (**1**; see Chart I) was metalated (*n*-BuLi, THF, 0 °C, 1 h, N_2) to provide the dithianylidene derivative of **1**.[5,6] Treatment of the resulting yellow solution with 2-methyl-2-cyclopentenone[7] (0.25 h, −78 °C; −78 to +25 °C, 3 h; 25 °C, 1 h) followed by alkylation of the resultant ketone enolate as its cuprous salt (−78 °C, $CuI\cdot(CH_3O)_3P$, 5 min; $CH_2{=}CHCH_2Br$, 2.5 h) provided, after chromatography, ketene dithioacetal **2** [NMR (270 MHz, $CDCl_3$) δ 1.01 (3 H, s, R_3CCH_3), 1.08 (3 H, d, J = 6.6 Hz, R_2CHCH_3), 1.82 (3 H, s, $=CRCH_3$); IR (neat, FT) 1735 cm^{-1}][8,9] in 50% yield. When the intermediates from the Michael addition step were subjected to protonation as opposed to allylation, VPC and 270-MHz NMR analyses indicated a ratio of 27:2:71 of 1,2/1,4-α/1,4-γ for the addition products. The alkylation products were present as **2** (87%), unallylated **2** (9%) and diallylated **2** (4%). The use of the cuprous counterion repressed the formation of undesired (Li exchange) monoallylated isomers. This sequential operation establishes these stereocenters and controls the ambident reactivity of the donor and acceptor in a highly selective fashion. Liberation of the methyl ethyl ketone equivalent and the required aldehyde was readily achieved by ozonolysis[10] (O_3, CH_2Cl_2, MeOH, −78 °C; DMS) with subsequent hydrolysis (3/1 HOAc–H_2O, 25 °C, 4 h) to provide the tricarbonyl compound **3** [NMR ($CDCl_3$, 270 MHz) δ 0.96 (3 H, s, C_5 CH_3), 1.16 (3 H, d, J = 6.6 Hz, C_{10} CH_3), 2.17 (3 H, s, $COCH_3$), 9.61 (1 H, br s, $W_{1/2}$ = 3 Hz, CHO); IR ($CHCl_3$, FT) 1738, 1722, 1713 cm^{-1}] in 65% yield. This intermediate was also accessible through the Cope–Claisen rearrangement. Thermolysis of **5a** (311 °C, 50 min) provided a 3/1 mixture of **6a** and its C_5 isomer, respectively. Ozonolysis of **6a** provided **3**, identical (270-MHz NMR) with **3** derived from the previous route. The assignment of the stereochemistry at C_{10}, although irrelevant to subsequent transformations, is based upon analogy with the known sterochemistry of the rearrangement of **5b** to **6b** and its C_5 isomer.[11]

Exposure of **3** to alkali (2% KOH–aqueous CH_3OH (1/5), 25 °C, 4 h, N_2) gave rise (83% yield) to a single aldol product **4**[12] [NMR ($CDCl_3$, 270 MHz) δ 0.78 (3 H, s), 1.22 (3 H, d, J = 7 Hz), 4.00 (1 H, tdd, J = 11.2, 4.4, 2.6 Hz, C_7 H); IR ($CHCl_3$, FT) 3458, 1739, 1700 cm^{-1}], which was reluctant to eliminate under alkaline ($NaOCH_3$, $HOCH_3$) conditions, lending credence to the trans ring fusion.

(4) Ziegler, F. E.; Tam, C. C. *Tetrahedron Lett.* **1979**, 4717.

(5) Approximately 10% of the (*Z*)-dithiane was formed from pure (*E*)-aldehyde by using modified (BF_3-Et_2O, HOAc, CH_2Cl_2, −20 °C) Fieser conditions: Heymann, H.; Fieser, L. F. *J. Am. Chem. Soc.* **1951**, *73*, 5252. The (*E*)-dithiane was selectively metalated in preference to the *Z* isomer.

(6) All new compounds gave correct combustion analyses and/or spectral data.

(7) Gaddis, A. M.; Butz, L. W. *J. Am. Chem. Soc.* **1947**, *69*, 1203.

(8) Compound **2** (90%) was contaminated (270-MHz NMR) with 5% each of two isomers, whose structures were not determined.

(9) Cf. ref 2b.

(10) Cf.: Chaussin, R.; Leriverend, P.; Paquer, D. *J. Chem. Soc., Chem. Commun.* **1978**, 1032; Strobel, M.-P.; Morin, L.; Paquer, D. *Tetrahedron Lett.* **1980**, 523.

(11) Ziegler, F. E.; Piwinski, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 880, 6576; **1979**, *101*, 1611. The stereochemistries of **6b** and its C_5 epimer were rigorously demonstrated in the most recent of these communications. The stereochemistries of **6a** and its C_5 epimer were based on the following spectroscopic data. For **6a**: NMR ($CDCl_3$, 270 MHz) δ 9.67 (1 H, t, J = 3 Hz, CHO), 1.09 (3 H, d, J = 7 Hz, $C_{10}CH_3$), 1.08 (3 H, s, C_5 CH_3). For **6b**: δ 9.67 (1 H, t, J = 3 Hz, CHO), 1.07 (3 H, d, C_{10} CH_3), 1.06 (3 H, s, C_6-CH_3). For the C_5 epimer of **6a**: δ 9.72 (1 H, t, J = 3 Hz, CHO), 1.13 (3 H, d, J = 7 Hz, C_{10} CH_3), 1.36 (3 H, s, C_5 CH_3). For the C_5 epimer of **6b**: δ 9.72 (1 H, t, J = 3 Hz, CHO), 1.10 (3 H, d, J = 7 Hz, C_{10} CH_3), 1.31 (3 H, s, C_5 CH_3).

(12) Epimerization at C_{10} occurs during the aldol; see: Ohfune, Y.; Grieco, P. A.; Wang, C.-L.; Majetich, G. *J. Am. Chem. Soc.* **1978**, *100*, 5946.

Dehydration of 4 (P_2O_5–CH_3SO_3H, 25 °C, 1 h, N_2)[13] gave rise to enone 7 [NMR ($CDCl_3$, 270 MHz) δ 0.99 (3 H, s), 1.26 (3 H, d, J = 7.1 Hz), 6.01 (1 H, dd, J = 13.0, 2.7 Hz, C_8-H), 6.26 (1 H, ddd, J = 13.0, 5.6, 3.3 Hz, C_7 H); IR (CCl_4, FT) 1745, 1665 cm^{-1}], containing 10% of its β,γ isomer. Reduction ($LiAlH_4$, Et_2O, 25 °C) of the mixture proceeded stereoselectively (α attack) to provide diol 8 [mp 163–165 °C; NMR ($CDCl_3$, 270 MHz) δ 0.72 (3 H, s), 0.97 (3 H, d, J = 6.6 Hz), 1.70–1.51 (1 H, m, C_{10} H), 3.85 (1 H, ddd, J = 9.7, 3.0, 2.8 Hz, C_9 H), 5.77–5.57 (2 H, m, vinyl)] in 49% yield (from 4). Irradiation of the C_{10} CH_3 group (δ 0.97) revealed the C_{10} H multiplet as a triplet (J = 10.0 Hz), requiring the relative stereochemistry present at C_1, C_9, and C_{10}.

Introduction of the C_7 β-acetic acid residue was achieved by employing the Eschenmoser[14] variant of the Claisen rearrangement. Thus, diol 8 was converted [$(CH_3)_2NCCH_3(OCH_3)_2$, xylene, 138 °C, 7.5 h; 10% K_2CO_3 (1:1 aqueous CH_3OH), reflux, 2 h] to 9 [NMR ($CDCl_3$, 270 MHz) δ 2.95 (3 H, s, $N(CH_3)_2$), 3.00 (3 H, s, $N(CH_3)_2$), 5.27 (2 H, br s); IR ($CHCl_3$, FT) 3003, 1632 cm^{-1}] in 72% yield. The potassium carbonate treatment was necessary to expose the partially acetylated hydroxyl function. Direct iodolactonization of amide 9 (I_2, 50% aqueous THF, 25 °C, 10 h) yielded the iodo lactone 10a [89% yield; NMR ($CDCl_3$, 270 MHz) δ 3.64 (1 H, m, HCR_2OH), 4.67 (1 H, dd, J = 8.1, 3.1 Hz, C_9 H), 4.92 (1 H, dd, J = 8.1, 6.7 Hz, C_8 H); IR ($CHCl_3$, FT) 3607, 1787, 1771 cm^{-1}][15] as a pale yellow solid, which was directly submitted to reductive dehalogenation [$(n\text{-}Bu)_3SnH$, AIBN (catalyst), C_6H_6, 50 °C, 1 h, N_2], affording hydroxy lactone 10b [NMR ($CDCl_3$, 270 MHz) δ 0.84 (3 H, s), 0.98 (3 H, d, J = 7.3 Hz), 4.77 (1 H, ddd, J = 11.8, 8.0, 3.0 Hz, C_8H); IR ($CHCl_3$, FT) 3607, 3487, 1765 cm^{-1}].

Incorporation of the methylene group was accomplished by a new procedure. Treatment of lactone 10b with Bredereck's reagent[16] $[(CH_3)_2N]_2CHOCH_3$, 25–83 °C, 1.5 h; 83 °C, 8 h] yielded the crystalline vinylogous carbamate 11a [mp 178–180 °C dec; NMR ($CDCl_3$, 270 MHz) δ 3.03 (6 H, s, $N(CH_3)_2$), 4.58 (1 H, ddd, J = 11.8, 8.0, 2.9 Hz), 7.09 (1 H, s, vinyl H); IR ($CHCl_3$, FT) 3606, 3417, 1714, 1624 cm^{-1}] in nearly quantitative yield. Reduction[17] of 11a [DIBAL, THF (hexane), −78 to +25 °C, 2 h; saturated NH_4Cl, 25 °C, 8 h] provided methylene lactone 11b (97%) upon workup [NMR ($CDCl_3$, 270 MHz) δ 5.59 (1 H, d, J = 2.6 Hz, $=CH_2$), 6.26 (1 H, d, J = 2.6 Hz, $=CH_2$); IR ($CHCl_3$, FT) 3604, 3386, 1758, 1600 cm^{-1}]. Oxidation of 11b with pyridinium chlorochromate afforded quantitatively (±)-2,3-dihydroaromatin [12a, mp 118.5–120.5 °C (lit.[1] mp 113–114 °C)] whose 270-MHz NMR spectra and infrared spectrum were identical with those of an authentic sample. Finally, introduction of the 2,3 double bond was effected via selenylation–selenoxide elimination[1,18] to provide (±)-aromatin (52%), whose NMR spectral properties[19] were in accord with those of (−)-aromatin.

Entry into the ambrosanolide series was accomplished in the following way. Dehydrohalogenation of iodide 10a [DBN (30 equiv), THF, 53 °C, 10 h] provided olefin 13 as an oil in 94% yield. Crystallization afforded pure material [mp 120.5–121.5 °C; NMR ($CDCl_3$, 270 MHz) δ 1.74 (3 H, br s, C_{10} CH_3), 5.32 (1 H, br s, $W_{1/2}$ = 13 Hz, C_8 H), 5.41 (1 H, br s, $W_{1/2}$ = 6 Hz, C_9 H); IR ($CHCl_3$, FT) 3020, 1765, 1665 cm^{-1}]. Hydrogenation of 13 (PtO_2/H_2, EtOH, atomospheric press) occurred from the α face,[20] giving rise to 14a [NMR ($CDCl_3$) δ 0.91 (3 H, s), 1.02 (3 H, d, J = 7.0 Hz)] in 73% yield after chromatography. Acetylation of 14a (Ac_2O/pyr, 2 h) quantitatively provided acetoxy lactone 14b [mp 108.5–109.5 °C (lit.[2d] mp 110 °C), mmp 108.5–109.5 °C] identical (270-MHz NMR and IR) with a sample of 14b previously converted to (±)-confertin by Schlessinger.

The utility of sulfur-stabilized anions, as adumbrated in this communication, holds promise as an important technique for the synthesis of more highly oxygenated pseudoguaianolides and as a general method for the generation of enolate equivalents.

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(13) Eaton, P. E.; Carlson, G. R.; Lee, J. T. *J. Org. Chem.* **1973**, *38*, 4071.
(14) Felix, D.; Gschwend-Steen, K.; Wick, A. E.; Eschenmoser, A. *Helv. Chim. Acta* **1969**, *52*, 1030.
(15) The 1787-cm^{-1} band presumably arises from Fermi resonance. Removal of the iodine atom (10b) affords a single carbonyl absorption in the infrared spectrum.
(16) Bredereck, H.; Simchen, G.; Rebsdat, S.; Kantlehner, W.; Horn, P.; Wahl, R.; Hoffmann, H.; Grieshaber, P. *Chem. Ber.* **1968**, *101*, 41.
(17) We are indebted to Professor R. H. Mueller and Mr. M. Thompson for making this method available to us prior to publication.
(18) Grieco, P. A.; Ohfune, Y.; Majetich, G. *J. Am. Chem. Soc.* **1977**, *99*, 7393.
(19) The 60-MHz NMR spectrum of (−)-aromatin was supplied by Dr. A. Romo de Vivar.
(20) Examination of the crude reaction mixture (270-MHz NMR) indicated the absence of isomer 10b. Cf. ref 2d.

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Synthesis of 7β-Amido-7α-methoxy-3-methyl-1-oxacephalosporin[1]

Summary: The aldehyde disulfides 2 and 3 were prepared from 2α-methoxy-3-cephem 1 and subsequently reduced to the corresponding alcohols 4. Treatment of these alcohols with mercuric trifluoroacetate resulted in cyclization to 1-oxacepham 5. The epimerization of the 7α-amide and incorporation of the 7α-methoxy group in 5 were achieved with lithium methoxide and *tert*-butyl hypochlorite. The ester group was removed from the obtained compound 6 with trifluoroacetic acid, providing the biologically active 1-oxacepham acid 7.

Sir: The recent discovery that 1-oxacephalosporins are potent antibiotics prompted us to explore their synthesis.

(1) Azetidinone Antibiotics. 20. Paper 19: S. R. Lammert, A. I. Ellis, R. R. Chauvette, and S. Kukolja, *J. Org. Chem.*, **43**, 1243 (1978).

0022-3263/81/1946-0827$01.00/0