Registry No. 1, 53910-25-1; 4, 14003-66-8; 5, 6307-17-1; 6a, 72079-75-5; 6b, 72079-76-6; 7 (isomer 1), 69195-96-6; 7 (isomer 2), 82228-58-8; 8, 69195-97-7; 9, 69195-91-1; 10, 69195-92-2; 11, 71222-44-1; 12a, 72079-79-9; 12b, 72079-80-2; 12c, 69196-03-8; 13, 69196-04-9; (8*R*)-14, 82264-17-3; (8*S*)-14, 82264-18-4; 15a, 82228-59-9; 15b, 82228-60-2; benzaldehyde, 100-52-7; nitromethane, 75-52-5; triethyl orthoformate, 122-51-0; 2-deoxy-3,5-di-*O*-(*p*-toluoyl)-D-*erythro*-pentofuranosyl chloride, 3601-39-6.

Michael Reactions in Aprotic Media. An Effective Method of Construction of α,α,β-Trisubstituted Ketones and Application to Natural Product Synthesis

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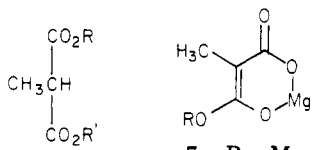
By proper selection of the reaction conditions, 1,4-additions of malonate and propionate anions to 2-(phenylthio)-2-cyclopentenone were accomplished. Subsequent trapping of the intermediate enolates with an electrophile in the aprotic media afforded α,α,β-trisubstituted ketones regiospecifically. The effects of the counterion, solvent, and temperature were examined. An application of this method to the formal synthesis of the pseudoguaianolides (±)-aromatin and (±)-confertin is described.

The Michael-type addition, defined as the nucleophilic addition of an anion to the carbon–carbon double bond of an α,β-unsaturated ketone, aldehyde, nitrile, or carboxylic acid derivative, has been extensively used as an effective method for carbon–carbon bond formation.[2] However, the conventional Michael reactions conducted in protic media exhibit several disadvantages[2a] such as the self-condensation of substrates, side reactions resulting from alkoxide anions, and the reversibility of reactions at high temperatures. These disadvantages can be circumvented by carrying out the addition reaction in an aprotic medium at low temperature[2b,c] with subsequent trapping of the intermediate enolate by an electrophile to form two new carbon–carbon bonds in a one-pot operation.

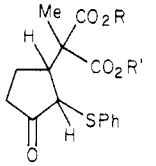
When an α,β-unsaturated ketone is employed in the reaction, the nucleophile can either add to the carbonyl center (1,2-addition) to provide alcohol products or add to the β-carbon (1,4-addition) to afford ketone products. It has been shown that the regioselectivity of addition is dependent upon reaction conditions such as temperature and solvent. For example, Schultz and Yee[3] have demonstrated that protonation of the reaction mixture of 2-cyclohexenone and the enolate of a 2-substituted propionate at −78 °C gives kinetic 1,2-adduct. However, stirring of the reaction mixture at 25 °C followed by protonation affords 1,4-adduct. Still[4] has shown that (trimethylstannyl)lithium adds to 2-cyclohexenone in the 1,2-fashion in diethyl ether but in the 1,4-fashion in tetrahydrofuran. Parallel results have been found in the addition of [(2-lithiophenyl)thio]acetonitrile to cyclic enones[5] and in the addition of [1,1-bis(methylseleno)-ethyl]lithium to 2-cyclohexenone.[6] The reactions[7] between (alkylthio)- or (phenylthio)allyl anions and 2-cyclopentenone have been shown to give predominantly 1,2-adducts in THF. However, generation of the anions in the presence of hexamethylphosphoric triamide (HMPA, 1 equiv) followed by the addition of 2-cyclopentenone furnishes exclusively 1,4-adducts. The preference of 1,4-ad-

Chart I

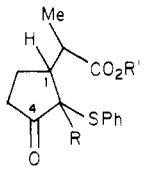


6a, R = R′ = Me
b, R = R′ = Et
c, R = Et; R′ = *t*-Bu

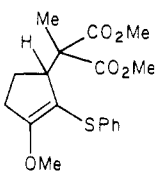
7a, R = Me
b, R = Et



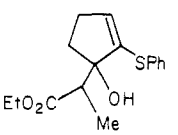
8a, R = R′ = Me
b, R = R′ = Et
c, R = Et; R′ = *t*-Bu
d, R = Me; R′ = H
e, R = Et; R′ = H



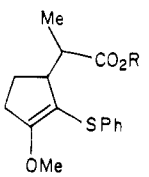
9, R = H; R′ = Me
10, R = H; R′ = Et
13, R = Me; R′ = Me
14, R = Me; R′ = Et



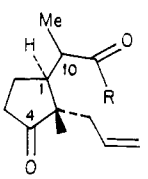
11



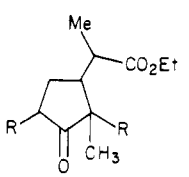
12



15a, R = Me
b, R = Et



16, R = OEt
17, R = OH
18, R = Cl
19, R = Me



20, R = H
21, R = CH_2CHCH_2

(1) Taken in part from the author's Ph.D. thesis, Yale University, 1981. Current address: Department of Chemistry, National Taiwan University, Taipei, Taiwan, Republic of China. The author is grateful to Professor Frederick E. Ziegler for his guidance throughout this work.

(2) (a) Bergmann, E. D.; Ginsburg, D.; Pappo, R. *Org. React.* **1959**, *10*, 179. (b) Boeckman, R. K., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 6179. (c) Stork, G.; Singh, J. *Ibid.* **1974**, *96*, 6181.

(3) Schultz, A. G.; Yee, Y. K. *J. Org. Chem.* **1976**, *41*, 4044.

(4) (a) Still, W. C.; Mitra, A. *Tetrahedron Lett.* **1978**, 2659. (b) Still, W. C. *J. Am. Chem. Soc.* **1977**, *99*, 4836.

(5) Wang, N. Y.; Su, S. S.; Tsai, L. Y. *Tetrahedron Lett.* **1979**, 1121.

(6) (a) Lucchetti, J.; Dumont, W.; Krief, A. *Tetrahedron Lett.* **1979**, 2695. (b) Lucchetti, J.; Krief, A. *Ibid.* **1978**, 2697.

(7) (a) Binns, M. R.; Haynes, R. K.; Houston, T. L.; Jackson, W. R. *Tetrahedron Lett.* **1980**, *21*, 573. (b) Binns, M. R.; Haynes, R. K. *J. Org. Chem.* **1981**, *46*, 3790.

0022-3263/82/1947-3464$01.25/0

Table I. Conjugate Addition of 2-Methylmalonates to 2-(Phenylthio)-2-cyclopentenone

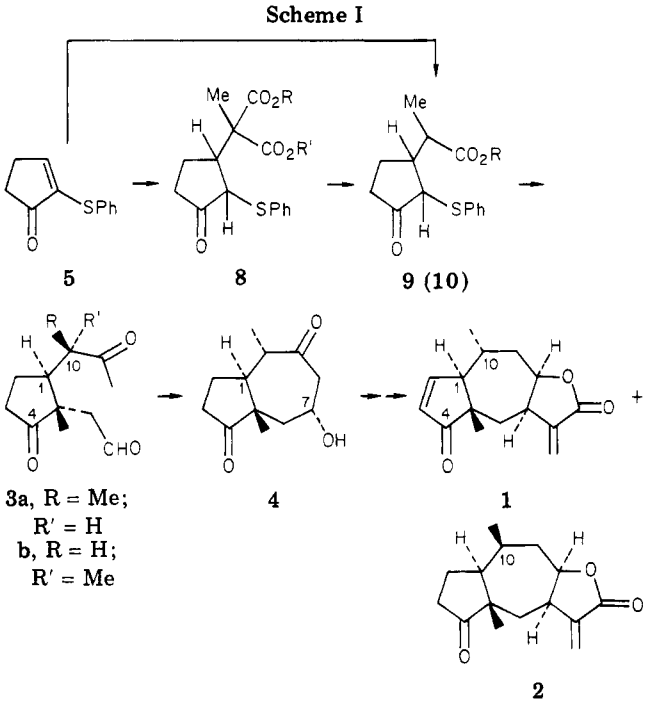
malonate	base	solv	equiv of HMPA	temp, °C	time, h	% addition[a]	% yield[b]
6b	NaOEt	EtOH	0	0	2	80	57
6b	*n*-BuLi	THF	0	−78	2	90	
6a	NaH	THF	0	−78	2	95	78
6a	NaH	THF	3	−78	4	95	
6a	KH	THF	0	−78	3	50	
6a	KH	THF	3	−78	3	70	
6a	KH	THF	0	0	1	16	
6c	NaH	THF	0	−78	2	99	80
7a		DMF	0	−45	7	99	
7b		DMF	0	−45	7	99	
7b		DMF	0	−25	7	75	
7b		DMF	0	0	7	50	
7b		DMF	0	25	7	10	
7b		THF	0	−45	7	0	
7b		THF	2	−45	7	5	

[a] The percentage of 1,4-addition was determined by the analysis of the NMR spectrum of the workup reaction mixture. [b] Crystallization yield.

dition in the presence of HMPA has been reported by other groups.[8]

Organocuprates[9] and certain functional group stabilized carbanions[10] are defined as good Michael donors, for these nucleophiles add regioselectively to α,β-unsaturated ketones in a 1,4-fashion. In contrast, nucleophiles such as ester enolate[11] and cyclic dithiane anions[12] are defined as poor Michael donors, for they prefer 1,2-additions to enones. Due to the limited number of established good Michael donors, the use of the conventional poor Michael donors to achieve 1,4-addition to enones would be most desirable. In this context, the details of the addition of the anions of 2-methylmalonate and propionate (**6** and **7**, Chart I), both potential equivalents of methyl ethyl ketone, to 2-(phenylthio)-2-cyclopentenone (**5**) under a variety of conditions were examined. As a matter of paramount importance, the possibility of effecting 1,4-addition of the propionate enolate, a conventional poor Michael donor, to α,β-unsaturated ketones was explored. An application of this methodology is demonstrated by the construction of diketo aldehyde **3** as a key intermediate[13] (Scheme I) for the synthesis of the pseudoguaianolides aromatin (**1**) and confertin (**2**). The selection of 2-(phenylthio)-2-cyclopentenone as a Michael acceptor was designed to induce 1,4-addition with the assistance of the α-phenylthio group,[14] as well as to stabilize the resulting enolate to ensure regiospecificity in the subsequent alkylation.[15] Furthermore, geminate alkylation could be accomplished by removal of the phenylthio group with dissolving metal and subsequent trapping of the resulting enolate with an electrophile.[15]

Scheme I



Results and Discussion

Preparation of 2-(phenylthio)-2-cyclopentenone was carried out by Monteiro's method[13] or by bromination of 2-(phenylthio)cyclopentanone[16] with *N*-bromosuccinimide in the presence of trifluoroacetic acid as a catalyst. Treatment of 2-(phenylthio)-2-cyclopentenone with dialkyl methylmalonates **6** under a variety of conditions (entries 1–8, Table I) afforded 1,4-adducts **8**. It appeared that the additions were complete in the presence of lithium or sodium ion but not with the potassium counterion. A parallel reaction (entries 9 and 10, Table I) of 2-(phenylthio)-2-cyclopentenone and the magnesium salt of monoalkyl methylmalonate **7**[17] also resulted in complete conjugate addition in dimethylformamide (DMF) at −45 °C, giving adduct **8d** (or **8e**). Adduct **8** was composed of a mixture

(8) (a) Ostrowski, P. C.; Kane, V. V. *Tetrahedron Lett.* **1977**, 3549. (b) Dolak, T. M.; Bryson, T. A. *Ibid.* **1977**, 1961. (c) Brown, C. A.; Yamaichi, A. *J. Chem. Soc., Chem Commun.* **1979**, 100. (d) Wartski, L.; Bouz, E. M.; Seyden-Penne, J. *Tetrahedron Lett.* **1979**, 1543. (e) Cossentini, M.; Deschamps, B.; Anh, N. T.; Seyden-Penne, J. *Tetrahedron* **1977**, *33*, 409, 413.

(9) (a) Posner, G. H. *Org. React.* **1972**, *19*, 1. (b) Posner, G. H. "An Introduction to Syntheses Using Organocopper Reagents"; Wiley: New York, 1980.

(10) For example: (a) Hermann, J. L.; Richman, J. E.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 3271. (b) Stork, G.; Maldonado, L. *J. Am. Chem. Soc.* **1974**, *96*, 5272. (c) Seebach, D.; Bustinghaus, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 57. (d) Grieco, P. A.; Yokoyama, Y. *J. Am. Chem. Soc.* **1977**, *99*, 5210. (e) Stowell, J. C. "Carbanions in Organic Synthesis"; Wiley: New York, 1979; pp 192–198.

(11) Ravid, U.; Ikan, R. *J. Org. Chem.* **1974**, *39*, 2637.

(12) (a) Corey, E. J.; Crouse, D. *J. Org. Chem.* **1968**, *33*, 298. (b) Seebach, D.; Grobel, B.-T.; Beck, A. K.; Braun, M.; Geiss, K.-H. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 443. (c) Carey, F. A.; Court, A. S. *J. Org. Chem.* **1972**, *37*, 1926. (d) Seebach, D.; Kolb, M.; Grobel, B.-T. *Chem. Ber.* **1973**, *106*, 2277.

(13) Ziegler, F. E.; Fang, J. M. *J. Org. Chem.* **1981**, *46*, 825.

(14) Monteiro, H. J. *J. Org. Chem.* **1977**, *42*, 2324.

(15) (a) Coates, R. M.; Pigott, H. D.; Ollinger, J. *Tetrahedron Lett.* **1974**, 3955. (b) Kamata, S.; Uyeo, S.; Haga, N.; Nagata, W. *Synth. Commun.* **1973**, 265.

(16) Held, P.; Gross, M.; Jumar, A. *Z. Chem.* **1970**, *10*, 187.

(17) (a) McMurry, J. E.; Andrus, W. A.; Musser, J. H. *Synth. Commun.* **1978**, 53. (b) Bram, G.; Vilkes, M. *Bull. Soc. Chim. Fr.* **1964**, 945.

Table II. Reaction of Ethyl Propionate and 2-(Phenythio)-2-cyclopentenone

entry	base	additive (equiv)	temp, °C	time	% addition[a] 1,4	% addition[a] 1,2	total yield, %
1	LICA		−78	5.5 h	0	100[b]	77
2	LICA		−78 (3 h) → 0 (1 h)		7	93	51
3	LICA	CuI (1)	−78	4.5 h	100	0	64
4	LICA	HMPA (2)	−78	2 h	76	24	
5	LICA	HMPA (2)	−78 (2 h) → 0 (0.5 h)		100	0	81
6	LICA	HMPA (2)	−78	4 min	30[c]	3[c]	
7	LTMP[d]	HMPA (2)	−78 (2 h) → 0 (0.5 h)		100	0	83
8	LHMS[d]		−78	4 h	100	0	45
9	LHMS		−78 (4 h) → 0 (0.5 h)		100	0	48
10	LHMS	HMPA (2)	−78	2 h	100	0	50
11	LHMS	HMPA (2)	−78 (2 h) → 0 (0.5 h)		100	0	45

[a] The ratio of addition products was determined by GC analysis. [b] Followed by addition of 1 equiv of HMPA and stirring for 2 h at −78 °C, the product mixture contained 10% of 1,4-adduct. After being stirred for additional 0.5 h at 0 °C, it then gave exclusively 1,4-adduct. [c] Incomplete reaction with 60% recovery of 2-(phenylthio)-2-cyclopentenone. [d] LTMP represents lithium 2,2,6,6-tetramethylpiperidide, and LHMS represents lithium 1,1,1,3,3,3-hexamethyldisilazide.

of cis and trans isomers[18] as evidenced by its subsequent transformation into ester **9** (or **10**), which consisted of a mixture of diastereomers as revealed by the NMR analysis.

Attempted trapping the enolate of adducts **8a–c** with methyl iodide resulted in no methylation at −78 °C. The process was retarded, presumably as it would introduce severe steric interaction between the phenylthio group and the malonate group. Attempts to induce methylation by elevating the temperature (0 °C) resulted in the retro-Michael reaction as evidenced by the formation of dialkyl dimethylmalonate at the expense of adducts **8a–c**. However, treatment of the enolate of adduct **8a** with methyl fluorosulfate ("magic methyl", −78 °C, 0.5 h) provided methyl enol ether **11**[19] in 78% yield.

Pyrolysis of monomalonate adduct **8d** (or **8e**) at 160 °C afforded decarboxylation to give ester **9** (or **10**) as a mixture of four diastereomers (**a–d**, due to three asymmetric centers at C_1, C_5, and C_{10}) in a ratio of 3:15:62:20 as determined by the NMR spectrum. Isomers **c** and **d** displayed the C_5 proton resonance (δ 3.41 and 3.20, respectively) as doublets with the coupling constants of 9–10 Hz, whereas isomers **a** and **b** exhibited coupling constants of 6.7 Hz for the corresponding doublets at δ 3.71 and 3.51, respectively. According to precedent,[18,20] **c** and **d** (82%) were assigned at trans isomers with large coupling constants, while **a** and **b** (18%) were assigned at cis isomers with small coupling constants.

Simultaneous hydrolysis and decarboxylation of adduct **8a** (or **8b**) under acidic conditions (AcOH–HCl(aq), 135 °C),[13] followed by esterification in methanol, afforded ester **9** in 40% yield. Acid-catalyzed cleavage of *tert*-butyl ester[21] from **8c** provided intermediate acid **8e** for pyrolysis to ester **10** (73% overall yield).

Since 2-methylmalonates obviously function as propionate equivalents, the possibility of employing propionate anion as a Michael donor was investigated (Table II). The enolate of ethyl propionate was generated by Rathke's method[22] by using lithium isopropylcyclohexylamide (LICA) in THF at −78 °C. Treatment of the enolate with 2-(phenylthio)-2-cyclopentenone at −78 °C provided exclusively 1,2-adduct **12**.[23] The different addition courses of the malonate and propionate anions to 2-(phenylthio)-2-cyclopentenone can be interpreted by the hard and soft acids and bases principle.[24] Thus, the relatively soft malonate anion added to the relatively soft β-carbon of the enone (1,4-addition), while the relatively hard propionate anion added to the relatively hard carbonyl center (1,2-addition).

Although the lithium enolate of ethyl propionate generated by using the base 1,1,1,3,3,3-hexamethyldisilazide (entries 8 and 9, Table II) did add to 2-(phenylthio)-2-cyclopentenone in the 1,4-fashion, the modest yields could not be improved. Presumably, deprotonation of the propionate ester was sluggish with this bulky and mild base, and self-condensation of the ester became competitive in consuming the resulting enolates.[22a]

On the other hand, addition of 1 equiv of CuI·$P(OMe)_3$ complex[25] to the lithium enolate of ethyl propionate, followed by treatment with 2-(phenylthio)-2-cyclopentenone in THF at −78 °C, gave exclusively 1,4-adduct **10** in 64% yield. Adduct **10** was composed of four diastereomers (**a**/**b**/**c**/**d** ratio of 18:2:9:71) as revealed by analysis of the NMR spectrum. While the lithium enolate gave carbon–carbon bond formation in a single step,[26] the addition of the Cu(I) enolate could proceed stepwise via a Cu(III) intermediate, as proposed for the reaction involving cuprates,[27] to effect the 1,4-addition to the α,β-unsaturated ketone. Trapping the resulting enolate of 1,4-adduct **10** with methyl iodide (−78 to 25 °C, 9 h) afforded only 20% of methylated product **13** and 80% of unmethylated adduct **10**. The poor alkylation was presumed to be a consequence of the increased covalent nature of the copper–oxygen bond.[28]

(18) (a) Pappo, R.; Collins, P. W. *Tetrahedron Lett.* **1972**, 2627. (b) Kurozumi, S.; Toru, T.; Tanaka, T.; Kobayashi, M.; Miura, S.; Ishimoto, S. *Ibid.* **1976**, 4091.

(19) Methyl enol ether **11**: IR (neat) 1725, 1625, 1425, 1330, 1250, 1090, 710 cm^{-1}; NMR (270 MHz, $CDCl_3$) δ 7.48–6.94 (5 H), 3.79 (3 H, s), 3.66 (3 H, s), 3.48 (3 H, s), 3.88–3.63 (1 H, m, H-1), 2.61–2.54 (2 H), 2.29 (1 H, m), 1.80 (1 H, m), 1.39 (3 H, s). Anal. Calcd for $C_{18}H_{22}O_5S$: C, 61.71; H, 6.29. Found: C, 61.76; H, 6.35.

(20) (a) Posner, G. H.; Sterling, J. J.; Whitten, C. E.; Lentz, C. M.; Brunelle, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 107. (b) Posner, G. H.; Whitten, C. E.; Sterling, J. J.; Brunelle, D. J. *Tetrahedron Lett.* **1974**, 2591.

(21) Fonken, G. S.; Johnson, W. S. *J. Am. Chem. Soc.* **1952**, *74*, 831.

(22) (a) Rathke, M. W.; Lindert, A. *J. Am. Chem. Soc.* **1971**, *93*, 2318. (b) Rathke, M. W. *Ibid.* **1970**, *92*, 3222. (c) Rathke, M. W.; Sullivan, D. F. *Ibid.* **1973**, *95*, 3050.

(23) Alcohol **12**: NMR (90 MHz, $CDCl_3$) δ 7.60–7.20 (5 H), 5.60 (1 H, t, J = 2 Hz, vinyl proton), 4.20 (2 H, q, J = 7 Hz), 3.56 (1 H, br s), 2.98 (1 H, q, J = 7 Hz), 2.50–1.80 (4 H), 1.28 (3 H, t, J = 7 Hz), 1.14 (3 H, d, J = 7 Hz); IR (neat) 3500, 2890, 1730, 1475, 1375, 1188, 1050 cm^{-1}; MS, m/e (relative intensity) 292 (7, M^+), 274 (14, $M^+ - H_2O$), 191 (48), 190 (100), 149 (99), 134 (37).

(24) (a) Ho, T. L. "Hard and Soft Acids and Bases Principle in Organic Chemistry"; Academic Press: New York, 1977. (b) Ho, T. L. *J. Chem. Educ.* **1978**, *55*, 355. (c) Pearson, R. G. *J. Chem. Educ.* **1968**, *45*, 581, 643.

(25) (a) Dane, V.; Warnoff, E. W. *Org. React.* **1970**, *18*, 217. (b) Cf. ref. 9b.

(26) Kharasch, M. S.; Towney, P. O. *J. Am. Chem. Soc.* **1941**, *63*, 2308.

(27) House, H. O.; Chu, C. Y.; Phillips, W. V.; Sayer, T. S. B.; Yau, C. C. *J. Org. Chem.* **1977**, *42*, 1709.

(28) Coates, R. M.; Sandefur, L. O. *J. Org. Chem.* **1974**, *39*, 275.

Table III. Reaction of Ethyl Propionate and 2-Methyl-2-cyclopentenone

base	additive (equiv)	temp °C	time, h	% addition[a] 1,4	% addition[a] 1,2	total yield, %
LICA		−78	3	0	100	63
LICA	HMPA (2)	−78	4	0	100	70
LICA	CuI (1)	−78	6	55	45	59
LICA	CuI (2)	−78	5	67	33	62
LICA	CuI (1) + HMPA (2)	−78	4	35	65	51
LICA	HMPA (1)	−78 (2 h) → −10 (0.5 h)			[b]	
LHMS	HMPA (1)	−78	4		[b]	

[a] The ratio of additions was determined by GC analysis. [b] A messy mixture due to the polymerization of 2-methyl-2-cyclopentenone.

The preference of 1,4-addition was also effected by treating the lithium enolate with 2 equiv of HMPA prior to the addition of enone **5**. The reaction was performed at −78 °C followed by warming to 0 °C to give 1,4-adduct in high yield. The solvent effect on the selectivity of 1,4- vs. 1,2-addition has been interpreted by the generalized perturbation theory.[29] Accordingly, the reaction in the presence of HMPA undergoes the orbital-controlled process, which favors 1,4-addition for the relative atomic coefficient of C_4 (β-carbon), is greater than that of C_2 (carbonyl) in the LUMO of enone. However, the cation coordination of the carbonyl oxygen in the absence of HMPA inverts the atomic coefficients, giving a high percentage of 1,2-addition.

In a parallel reaction of ethyl propionate and 2-methyl-2-cyclopentenone (Table III), the regioselectivity was not effectively reversed by treating the lithium enolate with cuprous salt or HMPA. The presence of the α-phenylthio group induced 1,4-addition (Table II), while the α-methyl group gave no prominent assistance to the 1,4-addition.

Trapping the lithium enolate of adduct **10** with methyl iodide resulted in partial methylation. Presumably, the amine produced in situ competitively reacted with methyl iodide to form an ammonium salt which then protonated the adduct enolate.[30] The complete methylation was accomplished by treatment of the sodium enolate of adduct **10** (Table IV) with 3 equiv of methyl iodide, thus giving **14** (C-methylation) and **15b** (O-methylation) in a ratio of 82:18 as determined by the GC analysis. Methyl enol ether **15b** was unstable and upon acid treatment gave ester **10**, which was recycled.

Ester **14** underwent reductive cleavage of the phenylthio group by treatment with lithium/ammonia.[14] The resulting enolate was trapped with allyl bromide (2.5 equiv, −33 °C) to provide the desired *gem*-alkylated ester **16** regioselectively. The yield (41%) of **16** was rather suppressed due to incomplete desulfenylation and overalkylation. Ester **16** was composed of a mixture of two diastereomers in a ratio of 45:55 as determined by the NMR spectrum. Since the alkylation conceivably occurred at the less hindered face of cyclopentane ring to give predominantly trans isomer,[31] the close ratio of two products most likely indicated *R* and *S* diastereomers differing at C_{10}. This conclusion was supported by subsequent transformations of **16** into a 4:6 mixture of diketo aldehydes **3a** and **3b**.

Table IV. Methylation of the Enolate of 10 with Methyl Iodide

base	additive (equiv)	% methylation[a]	products 14[b]	products 15b[c]
NaH		100	75	17
LDA		28	25	0
LDA	HMPA (1)	32	30	0
LDA	HMPA (3)	70	55	10
LICA	CuI (1)	20	20	0
LICA	HMPA (2)	45	39	1
LTMP	HMPA (2)	70	61	3
LHMS		38	35	0
LHMS	HMPA (2)	38	34	2

[a] Determined by the analysis of NMR spectrum of the worked up reaction mixture. [b] Isolated yield (percent) of the C-methylation product after chromatography. [c] Relative ratio of the O-methylation to the C-methylation product as determined by GC analysis. The O-methylation product partially decomposed upon chromatography.

Elaboration of ester **16** to methyl ketone **19** was accomplished by Posner's method.[32] Subsequent ozonolysis[33] of **19** in a mixture of dichloromethane and acetic acid, instead of the more conventional solvent of methanol, prevented the resultant aldehyde **3** from forming an acetal. Diketo aldehyde **3** (77%) was obtained as a mixture of two diastereomers in a ratio of 4:6 as determined by GC and NMR analyses. The assignment of two diastereomers **3a** and **3b** was confirmed by comparison with the authentic samples previously prepared.[12] Treatment of the diastereomeric mixture of aldehyde **3** in alkali[34] (25 °C, 4 h) gave 92% yield of aldol **4**[12], which has been transformed into (±)-aromatin and (±)-confertin.

Conclusion

Present study demonstrated that additions of nucleophiles to α,β-unsaturated ketones are dependent upon the reaction conditions. The addition course (1,4- vs. 1,2-addition) is effected by selections of the Michael acceptor [2-(phenylthio)-2-cyclopentenone vs. 2-methyl-2-cyclopentenone], the Michael donor (malonate vs. propionate anion), the countercation (Li, Na, K, Mg, or Cu), the solvent (THF vs. THF–HMPA), the base, and the reaction temperature. The discovery of employing propionate anion as an effective Michael donor in the presence of cuprous iodide or HMPA is extremely useful. Although the Michael reactions in aprotic media afforded both cis and trans isomers, the trans isomer usually predominated. The use of these reactions for construction of α,α,β-trisubstituted

(29) (a) Lefour, J. M.; Loupy, A. *Tetrahedron* **1978**, *34*, 2597. (b) Klopman, G. "Chemical Reactivity and Reaction Paths"; Wiley: New York, 1974; pp 55–81. (c) Klopman, G. *J. Am. Chem. Soc.* **1968**, *90*, 223. (d) Deschamps, B.; Anh, N. T.; Seyden-Penne, J. *Tetrahedron Lett.* **1973**, 527. (e) O'Sullivan, W. I.; Swamer, F. W.; Humphlett, W. J.; Hauser, C. R. *J. Org. Chem.* **1961**, *26*, 2306.

(30) Scott, L. T.; Brunsvold, W. R.; Kirms, M. A.; Erden, I. *J. Am. Chem. Soc.* **1981**, *103*, 5216.

(31) (a) Fank, R. L.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1977**, *99*, 5483. (b) Posner, G. H.; Lentz, C. M. *Ibid.* **1979**, *101*, 934.

(32) (a) Posner, G. H.; Whitten, C. E. *Tetrahedron Lett.* **1970**, 4647. (b) Posner, G. H.; Whitten, C. E.; McFarland, P. E. *J. Am. Chem. Soc.* **1972**, *94*, 5106.

(33) Pappas, J. J.; Keaveney, W. P. *Tetrahedron Lett.* **1966**, 4273.

(34) Ohfune, Y.; Grieco, P. A.; Wang, C.-L. J.; Majetich, G. *J. Am. Chem. Soc.* **1978**, *100*, 5946.

ketones is applicable to natural product synthesis.

Experimental Section

Microanalyses were performed by Atlantic Microlabs (Atlanta, GA) or the Olin Corp (New Haven, CT). Melting points were determined on a Fisher-Johns or Thomas-Hoover (open capillaries) apparatus and are corrected.

Infrared spectra were recorded on a Beckmann Model 4250, Perkin-Elmer 727, or Nicolet Series 7000 Fourier transform (FT) spectrometer and are reported in wave numbers (cm^{-1}). Proton magnetic resonance spectra (NMR) were obtained on a Bruker HX-270 (270 MHz) or Perkin-Elmer R-32 (90 MHz) spectrometer and are reported in parts per million (δ) downfield from tetramethylsilane. Mass spectra were obtained on a Hitachi RMU-6E or Hewlett-Packard 5985 GC/MS (3% OV-101 on Chromosorb W, 3 ft × 0.25 in.) spectrometer operating at 70 eV. Gas chromatography (GC) was performed on a Perkin-Elmer Series 1400 thermal or a Series 3920 flame-ionization chromatograph by using a column of 1.5% OV-101 on Chromosorb GHP 100/120 (5 ft × $^1/_8$ in.).

Analytical thin-layer chromatography (TLC) was performed by using Baker-flex silica gel IB-F plates; preparative TLC employed Analtech 20 cm × 20 cm (2000 μm) plates. Column chromatography was conducted with Grace silica gel (100/200 mesh). Flash chromatography was performed as described by Still.[35] High-pressure liquid chromatography was carried out on a Waters LC 500 with silica gel cartridges.

Ozonization was performed on a Welsbach T-23 laboratory ozonator.

Reactions requiring anhydrous conditions were performed in flame-dried glassware under an inert atmosphere. Chemicals and solvents were purified and dried before use according to the standard procedure. Commercial *n*-BuLi (Alfa-Ventron) was standardized by the method of Kofron.[36]

Adduct 8a. A solution of dimethyl methylmalonate (6.42 g, 44 mmol) in anhydrous THF (40 mL) was added at 0 °C to a suspension of sodium hydride (43 mmol, prewashed with pentane to remove the mineral oil) in THF (40 mL). The evolution of hydrogen was apparent. After being stirred for 40 min, the mixture was cooled to −78 °C, and a solution of 2-(phenylthio)-2-cyclopentenone (7.60 g, 40 mmol) in THF (60 mL) was added dropwise over a period of 50 min. After 2 h, the reaction mixture was quenched at −78 °C with a solution of acetic acid (7.2 mL, 120 mmol) in THF (10 mL) and allowed to warm to room temperature. The mixture was concentrated, taken up in ether, and washed with dilute aqueous sodium bicarbonate and brine. After drying ($MgSO_4$) and removal of solvent, adduct **8a** (mp 84.5–85.5 °C) was obtained after crystallization (ether–hexane): 10.4 g (78% yield); IR ($CHCl_3$) 1740–1725 cm^{-1}; NMR (270 MHz, $CDCl_3$) δ 7.51–7.26 (5 H), 3.75 (3 H, s), 3.74 (3 H, s), 3.57 (1 H, d, J = 6.6 Hz, H-5), 2.76 (1 H, td, J = 8.0, 6.6 Hz, H-1), 2.27–1.71 (4 H), 1.50 (3 H, s).

Anal. Calcd for $C_{17}H_{20}O_5S$: C, 60.69; H, 5.99; S, 9.53. Found: C, 60.60; H, 6.01; S, 9.45.

Adduct 8e (or 8d) and Its Decarboxylation Product 10 (or 9). At −45 °C, a solution of 2-(phenylthio)-2-cyclopentenone (2.85 g, 15 mmol) in anhydrous dimethylformamide (15 mL) was added dropwise to a solution of the magnesium salt of monoethyl methylmalonate[17] (3.42 g, 20.4 mmol) over a 10-min period. After being stirred for 7 h, the mixture was quenched with a solution of acetic acid (2.7 mL, 45 mmol) in THF (3 mL) and allowed to warm to room temperature. The mixture was taken up in water, acidified to pH 2 with 37% hydrochloric acid, and extracted with ether. The combined extracts were washed several times with cold 4% aqueous sodium bicarbonate. The washings were combined, acidified (pH 2) and extracted with ether again. After the mixture was dried ($MgSO_4$) and concentrated, 4.32 g of a crude oil, containing predominantly **8e** and a small amount of monoethyl methylmanolate (removed by subsequent decarboxylation), was obtained: NMR (90 MHz, $CDCl_3$) δ 7.58–7.16 (5 H), 4.20 (2 H, q, J = 7.0 Hz), 3.50 (1 H, d, J = 6.6 Hz, H-5), 2.78 (1 H, m, H-1), 2.40–1.66 (4 H), 1.50 (3 H, s), 1.25 (3 H, t, J = 7.0 Hz).

Decarboxylation was executed by heating the vigorously stirred and degassed crude oil under a nitrogen atmosphere. At 125 °C, the gas evolution was apparent. The temperature was raised to 160 °C over a 10-min period, and the decarboxylation was complete after 30 min of stirring at 160 °C. The brown residue was cooled, taken up in ether, and washed successively with cold 4% aqueous sodium bicarbonate followed by brine. After the mixture was dried ($MgSO_4$) and the ether removed, 3.04 g (69% yield) of compound **10** was obtained as a colorless oil via Kugelrohr distillation [140 °C (0.01 mmHg)]. The NMR spectrum revealed that **10** was composed of a mixture of diastereomers: NMR (90 MHz, $CDCl_3$, major isomer) δ 7.58–7.12 (5 H), 4.12 (2 H, q, J = 7 Hz), 3.42 (1 H, d, J = 9 Hz), 2.96–2.10 (6 H), 1.46–1.12 (6 H, mixed methyl groups); IR (neat) 1735 cm^{-1}.

Anal. Calcd for $C_{16}H_{20}O_3S$: C, 65.72; H, 6.89; S, 10.97. Found: C, 65.57; H, 6.90; S, 11.00.

Adduct **8d** was prepared from the addition of the magnesium salt of monomethyl methylmalonate to 2-(phenylthio)-2-cyclopentenone by using a procedure similar to that for its ethyl analogue **8e**. Decarboxylation of **8d** was effected at 160 °C to afford ester **9**, which was composed of four diastereomers (**a–d**) in a ratio of 3:15:62:20 as determined by its NMR spectrum: NMR (270 MHz, $CDCl_3$, major diastereomer **c**) δ 7.51–7.26 (5 H), 3.65 (3 H, s, CO_2CH_3), 3.41 (1 H, d, J = 8.9 Hz, H-5), 2.90 (1 H, m, H-1), 2.35–1.58 (5 H), 1.27 (3 H, d, J = 6.8 Hz, Me-10). Diastereomer **a** exhibited methyl ester resonance at δ 3.70 (s). Diastereomer **b** exhibited resonances at δ 3.73 (s, CO_2CH_3), 3.51 (d, J = 6.6 Hz, H-5), and 1.35 (d, J = 6.8 Hz, Me-10). Diastereomer **d** displayed resonances at δ 3.72 (s, CO_2CH_3), 3.20 (d, J = 9.9 Hz, H-5), 1.18 (d, J = 6.8 Hz, Me-10). IR ($CHCl_3$) 1740–1720 cm^{-1}; MS, m/e (relative intensity) 278 (31, M^+), 192 (19), 191 (100), 190 (26), 169 (30), 163 (28), 136 (22), 135 (20), 110 (22), 109 (32).

Ester 10 via the Michael Reaction with the Copper Salt of Ethyl Propionate. To a solution of *N*-isopropylcyclohexylamine (0.181 mL, 1.1 mmol) in anhydrous THF (2 mL) was added *n*-butyllithium (0.441 mL, 1.05 mmol, 2.38 M solution in hexane) at 0 °C. After 20 min, the resulting LICA solution was cooled to −78 °C, and ethyl propionate (108 mg, 1.05 mmol) in THF (1 mL) was added dropwise. After 1 h, a solution of $CuI{\cdot}P(OMe)_3$ (330.2 mg, 1.05 mmol) in THF (0.5 mL) was added when the resulting solution turned brown. After 15 min, a solution of 2-(phenylthio)-2-cyclopentenone in THF (1 mL) was added dropwise at −78 °C over a period of 3 min. After being stirred for 4.5 h at −78 °C, the mixture was quenched with a solution of acetic acid (0.18 mL, 3 mmol) in THF (0.25 mL), warmed to room temperature, taken up in ether, and successively washed with 10% aqueous sodium cyanide, water, and brine. After drying ($MgSO_4$) of the mixture, removal of solvent, and distillation [Kugelrohr, 140 °C (0.01 mmHg)], ester **10** (187 mg, 0.64 mmol, 64% yield) was obtained, which was composed of four diastereomers (**a–d**) in a ratio of 18:2:9:71 as determined by the NMR spectrum: NMR (270 MHz, $CDCl_3$, major diastereomer **d**) δ 7.55–7.24 (5 H), 4.19 (2 H, q, J = 7.0 Hz), 3.20 (1 H, d, J = 9.9 Hz, H-5), 2.78 (1 H, m, H-1), 2.70–1.60 (5 H), 1.26 (3 H, t, J = 7.0 Hz), 1.18 (3 H, d, J = 7.0 Hz, Me-10); diastereomer **a** exhibited a C_5 proton resonance at δ 3.71 (d, J = 6.6 Hz), diastereomer **b** at δ 3.51 (d, J = 6.6 Hz), and diastereomer **c** at δ 3.41 (d, J = 8.9 Hz); IR (neat, mixture of diastereomers) 3050, 2980, 1750–1720, 1590 cm^{-1}; MS, m/e (relative intensity) 292 (30, M^+), 191 (100), 190 (26), 183 (25), 163 (27), 149 (38), 137 (20), 136 (25), 135 (22), 110 (27), 109 (46).

Ester 10 via the Michael Reaction with the Lithium Enolate of Ethyl Propionate in the Presence of HMPA. The LICA solution was prepared from *N*-isopropylcyclohexylamine (60 mmol), *n*-butyllithium (55 mmol), and THF (10 mL) at 0 °C and then cooled to −78 °C. To it was added a solution of ethyl propionate (5.61 g, 55 mmol) in THF (5 mL) dropwise over a 25-min period. The reaction mixture was stirred at −78 °C for 1 h, and a solution of hexamethylphosphoric triamide (19.3 mL, 111 mmol) in THF (10 mL) was added. After 20 min, a solution of 2-(phenylthio)-2-cyclopentenone (9.4 g, 49.5 mmol) in THF (50 mL) was added dropwise over a period of 30 min. The reaction mixture was stirred at −78 °C for 2.5 h, warmed to 0 °C, and stirred at that temperature for an additional 30 min. The reaction mixture was quenched with water (50 mL) and extracted with ether. The combined extracts were washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. After

(35) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(36) Kofron, W. C.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.

distillation [Kugelrohr, 140 °C (0.01 mmHg)], ester **10** (11.7 g, 40.1 mmol, 81% yield) was obtained as a mixture of four diastereomers (10:40:5:45 **a**/**b**/**c**/**d**) as determined by the NMR spectrum (90 MHz).

Compound 13 (or 14) via Methylation of 9 (or 10). A solution of compound **10** (11.7 g, 40.1 mmol) in THF (20 mL) was added to a suspension of sodium hydride (40.1 mmol, prewashed with hexane to remove the mineral oil) in THF (100 mL) at 0 °C. Gas evolution was apparent. After the mixture was stirred for 3 h, gas evolution subsided, and iodomethane (7.52 mL, 120 mmol) was added in one portion. The mixture was stirred overnight at 25 °C, quenched with water, and extracted with ether. The combined extracts were washed successively with dilute hydrochloric acid, aqueous sodium thiosulfate, and brine. After the mixture was dried ($MgSO_4$) and the solvents removed, the residual oil was found to be composed of compounds **14** (C-methylation) and **15b** (O-methylation) in a ratio of 82:18 as determined by GC analysis. Separation of these components on a Waters LC-500 (1:5 ethyl acetate–hexane) afforded 1.2 g (4.0 mmol, 10%) of methyl enol ether (**15b**, 9.2 g (30.1 mmol, 75% yield) of the desired compound **14**, and 0.7 g of starting material **10**, presumably derived from the decomposition of **15b** on the silica gel column.

The NMR spectrum revealed that **14** was composed of diastereomers: NMR (270 MHz, $CDCl_3$) δ 7.53–7.14 (5 H), 4.25 (mixed quartets of CO_2CH_2Me), 3.06–1.54 (6 H), 1.29 (mixed triplets of $CO_2CH_2CH_3$ and doublets of Me-10), 1.13 (mixed singlets of Me-5); IR (neat) 2980, 1740–1720 cm^{-1}; MS, m/e (relative intensity) 306 (15, M^+), 197 (100), 177 (46), 169 (21), 123 (90), 110 (74), 109 (45).

The methylation of **9** by using the above procedure provided **13**, which was composed of three diastereomers (5:7:2 **a**/**b**/**c**) as shown by the NMR spectrum: NMR (270 MHz, $CDCl_3$, diastereomer **b**) δ 7.46–7.25 (5 H), 3.73 (3 H, s, CO_2CH_3), 2.77 (1 H, m, H-10), 2.56–1.60 (5 H), 1.45 (3 H, d, J = 7.0 Hz, Me-10), 1.35 (3 H, s, Me-5); diastereomer **a** δ 3.77 (s, CO_2CH_3), 1.27 (d, J = 7.3 Hz, Me-10), 1.11 (s, Me-5); diastereomer **c** δ 3.61 (s, CO_2CH_3); MS, m/e (relative intensity) 292 (33, M^+), 183 (100), 177 (59), 155 (22), 127 (21), 123 (50), 110 (41), 109 (24).

Anal. Calcd for $C_{16}H_{20}O_3S$: C, 65.75; H, 6.85; S, 10.96. Found: C, 65.58; H, 6.95; S, 10.90.

Ester 16. Liquid ammonia (70 mL) was collected in a flask with a 2-propanol–dry ice condenser and dried over lithium metal. In a second flask were placed 202.6 mg (29.2 mmol) of lithium metal (freshly cut and rinsed with hexane) and 70 mL of anhydrous diethyl ether. The collected dry ammonia was allowed to slowly warm and distill into the second flask. The lithium bronze was formed, and an excess of ammonia (ca. 25 mL) was collected. The bronze suspension was cooled to −40 °C (acetonitrile–dry ice bath), and a solution of compound **14** (4.25 g, 13.9 mmol) in ether (15 mL) was added in one portion. After vigorous stirring for 3 h, a yellow suspension resulted, and allyl bromide (3.06 mL, 35.4 mmol) was added all at once at −40 °C. After being stirred for 2.8 h, the mixture was quenched with granular ammonium chloride (4.2 g, 77 mmol) at −40 °C.

The mixture was allowed to warm with evaporation of the excess ammonia. The residue was washed with brine, dried ($MgSO_4$), and concentrated to give a crude oil (5.05 g), which consisted of allyl phenyl sulfide and compounds **16**, **20**, and **21** (74:15:11 by GC). These components were separated on a Waters LC-500 (1:6 ethyl acetate–hexane) to give 1.25 g of allyl phenyl sulfide (R_f 0.48), 0.22 g of **21** (R_f 0.35), 1.39 g (5.84 mmol, 42% yield) of **16** (R_f 0.24), and 0.23 g of **20** (R_f 0.14).

Ester **16** was composed of two diastereomers (45:55) as shown by the NMR spectrum: NMR (270 MHz, $CDCl_3$, major diastereomer) δ 5.60 (1 H, m), 5.04 (2 H, m), 4.15 (2 H, q, J = 7.0 Hz), 2.62–1.41 (8 H), 1.28 (3 H, t, J = 7.0 Hz, CH_2CH_3), 1.21 (3 H, d, J = 6.6 Hz, Me-10), 0.96 (3 H, s, Me-5); the minor diastereomer exhibited resonances at δ 1.30 (t, J = 7.0 Hz, CH_2CH_3), 1.28 (d, J = 6.6 Hz, Me-10), and 0.95 (s, Me-5); IR (neat, mixture of diastereomers) 3075, 1730, 1640, 1180, 995, 922 cm^{-1}; MS, m/e (relative intensity) 238 (9, M^+), 147 (33), 137 (87), 136 (100), 123 (39), 119 (36), 109 (80), 102 (89).

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.31; H, 9.20.

Compound **21**: MS, m/e (relative intensity) 278 (15, M^+), 237 (53), 177 (48), 163 (46), 145 (30), 135 (84), 121 (31), 109 (100), 108 (30), 107 (49), 102 (50). Compound **21** was a mixture of diastereomers as revealed by the NMR (270 MHz, $CDCl_3$): δ 5.79–5.50 (2 H, m, $RCH{=}CH_2$), 5.12–5.02 (4 H, m, $RCH{=}CH_2$), 4.21–4.11 (2 H, m, CO_2CH_2Me), 2.68–1.73 (9 H), 1.45–0.90 (9 H, mixed methyl groups). Compound **20**: MS, m/e (relative intensity) 198 (3, M^+), 149 (28), 102 (32), 97 (100).

Acid 17. Ester **16** (1.12 g, 4.71 mmol) was dissolved in absolute methanol (3.5 mL), and 5 mL of 45% aqueous potassium hydroxide was added. The mixture was refluxed (105 °C) for 4.5 h. The resulting brown solution was cooled, diluted with ice water, and washed with ether twice. The aqueous phase was acidified to pH 2 with 37% hydrochloric acid and extracted with ether three times. The combined extracts were washed with brine and dried over anhydrous magnesium sulfate. Removal of solvent in vacuo gave pure acid **17**: 0.98 g (4.67 mmol, 99% yield); IR (neat) 3600–3180 (OH), 1740, 1715 cm^{-1}; NMR (90 MHz, $CDCl_3$) δ 10.66 (1 H, br s, CO_2H), 5.61 (1 H, m), 5.03 (2 H, m), 2.72–1.44 (8 H), 1.36–1.22 (3 H, pseudo triplets of two doublets, J = 7 Hz, Me-10), 0.96 and 0.95 (3 H, 2 s of Me-5).

Acid Chloride 18 and Methyl Ketone 19. Acid **17** (0.98 g, 4.67 mmol; dried at 55 °C under 1 mmHg for 4 h) was placed in a round-bottomed flask, which was equipped with a glass-coated stirrer and a drying tube. Thionyl chloride (0.5 mL, 7 mmol) was added all at once, and the mixture was vigorously stirred. The evolution of gas was apparent. After 4.5 h, the complete formation of acid chloride was revealed by the IR spectrum of the product mixture, which exhibited an absorption at 1780 cm^{-1} for acid chlorides with the disappearance of acid absorption (1715 and 3600–3100 cm^{-1}). After removal of the excess of thionyl chloride by aspiration, the residue was distilled [Kugelrohr, 105 °C (0.02 mmHg)] to give acid chloride **18** (0.64 g) as a colorless fluid, which was used directly for the following cuprate reaction.

Under an atmosphere of nitrogen, anhydrous diethyl ether (40 mL) was added to flame-dried cuprous iodide (2.67 g, 14 mmol). The suspension was coolded to 0 °C, and a solution of methyllithium (21 mL, 27.9 mmol, 1.33 M ethereal solution complexed with lithium bromide) was added over a period of 3 min. After 5 min, the resulting pale yellow solution was cooled to −78 °C, the solution of freshly distilled acid chloride **18** (0.64 g) in ether (5 mL) was added dropwise over a period of 5 min. The mixture was vigorously stirred for 25 min, quenched with methanol (1.5 mL), and allowed to warm up to 25 °C. The mixture was poured into a solution of saturated ammonium chloride (50 mL) and 10% aqueous sodium cyanide (25 mL) and extracted with ether three times. The combined organic phase was successively washed with 10% aqueous sodium cyanide, water, and brine. After the mixture was dried and the solvent removed, the residue was distilled [Kugelrohr, 85 °C (0.02 mmHg)] to afford methyl ketone **19** (0.56 g, 2.69 mmol, 58% yield from acid **17**), which was composed of two diastereomers in a ratio of 6:4 as determined by the NMR spectrum: NMR (270 MHz, $CDCl_3$, major diastereomer) δ 5.60 (1 H, m), 5.07 (2 H, m), 2.74–1.37 (8 H), 2.20 (3 H, s, $COCH_3$), 1.12 (3 H, d, J = 6.6 Hz, Me-10), 0.92 (3 H, S, Me-5); minor diastereomer, δ 2.18 (s, $COCH_3$), 1.21 (d, J = 6.6 Hz), 0.94 (s); IR (neat) 3095, 2990, 1740, 1718 cm^{-1}; MS, m/e (relative intensity) 208 (5, M^+), 190 (39), 151 (29), 147 (26), 139 (63), 137 (47), 136 (43), 125 (33), 118 (48), 109 (82), 95 (100).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.84, H, 9.67.

Diketo Aldehyde 3. Ozone was bubbled through a solution of ketone **19** (197 mg, 0.95 mmol) dissolved in dichloromethane (1 mL) and glacial acetic acid (1 mL) at 0 °C. After 10–15 min, the uptake of ozone was complete, and the excess of ozone was detected by passing the effluent through a potassium iodide solution. The reaction mixture was purged with nitrogen for 10 min, and dimethyl sulfide[33] (2 mL) was added. The mixture was diluted with dichloromethane and stirred for 3 h at 25 °C. The mixture was then washed with sodium bicarbonate solution and water. After the mixture was dried and the solvent removed, the residue was distilled [Kugelrohr, 125 °C (0.03 mmHg)] to give diketo aldehyde **3**: 154 mg (0.73 mmol, 77% yield); TLC (1:1 ethyl acetate–hexane) R_f 0.21; IR ($CHCl_3$, FT) 2977, 2880, 1738, 1722, 1713 cm^{-1}.

Diketo aldehyde **3** was composed of two diastereomers (**a** and **b**) in a ratio of 4:6 as determined by GC and NMR analyses. Major diastereomer **3b** (1*S*,5*S*,10*S*): NMR (270 MHz, $CDCl_3$) δ 9.56 (1

H, br s, $W_{1/2}$ = 3 Hz, CHO), 3.03–1.93 (8 H), 2.20 (3 H, s, $COCH_3$), 1.17 (3 H, d, J = 6.6 Hz, Me-10), 0.86 (3 H, s, Me-5); GC/MS, m/e (relative intensity) 210 (3, M^+), 168 (61), 139 (16), 138 (25), 125 (22), 111 (21), 110 (53), 97 (100). Minor diastereomer **3a** (1*S*,5*S*,10*R*): NMR (270 MHz, $CDCl_3$) δ 9.61 (1 H, Br s, $W_{1/2}$ = 3 Hz, CHO), 3.02–1.22 (8 H), 2.17 (3 H, s, $COCH_3$), 1.16 (3 H, d, J = 6.6 Hz, Me-10), 0.96 (3 H, s, Me-5); GC/MS, m/e (relative intensity) 210 (1, M^+), 168 (57), 139 (20), 138 (9), 125 (13), 111 (21), 110 (95), 97 (100).

Anal. Calcd for $C_{12}H_{18}O_3$ (mixture of diastereomers): C, 68.55; H, 8.63. Found: C, 68.27, H, 8.46.

Aldol 4. Diketo aldehyde **3** (154 mg, 0.73 mmol) was dissolved in 10 mL of absolute methanol, and 2 mL of 10% aqueous potassium hydroxide was added, while the mixture was allowed to stir for 4 h at 25 °C. The resulting brown solution was cooled in an ice bath and acidified to pH 2 with 37% hydrochloric acid (0.4 mL). The mixture was concentrated in vacuo, and the residue was extracted with ethyl acetate three times. The combined extracts were washed with saturated sodium chloride, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give a crude aldol **4**. Purification on a short silica gel column (ethyl acetate) resulted in 143 mg (0.68 mmol, 92%) of **4** (R_f 0.34) as a colorless oil: NMR (270 MHz, $CDCl_3$) δ 4.46 (1 H, br s, OH), 4.00 (1 H, tdd, J = 11.2, 4.4, 2.6 Hz, H-7), 3.01 (1 H, dd, J = 11.2, 10.0 Hz, H-8), 2.61 (1 H, dt, J = 10.0, 2.6 Hz, H-8), 2.59–1.32 (8 H), 1.22 (3 H, d, J = 7.0 Hz, Me-10), 0.78 (3 H, s, Me-5); IR (neat) 3460 (OH), 1739, 1700 cm^{-1}; MS, m/e (relative intensity) 210 (79, M^+), 192 (14), 97 (100).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.74; H, 8.72.

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Registry No. (±)-**1**, 74645-43-5; (±)-**2**, 60426-81-5; (±)-**3a**, 76156-83-7; (±)-**3b**, 81939-03-9; (±)-**4**, 81875-17-4; **5**, 34780-08-0; **6a**, 609-02-9; **6b**, 609-08-5; **6c**, 56834-42-5; **7a**, 69027-55-0; **7b**, 66446-63-7; **8a**, 81875-18-5; **8b**, 81875-19-6; **8c**, 81875-20-9; **8d**, 81875-21-0; **8e**, 81875-22-1; (±)-*cis*-**9** (isomer 1), 81875-23-2; (±)-*cis*-**9** (isomer 2), 81939-04-0; (±)-*trans*-**9** (isomer 1), 81939-05-1; (±)-*trans*-**9** (isomer 2), 81939-06-2; (±)-*cis*-**10** (isomer 1), 81875-24-3; (±)-*cis*-**10** (isomer 2), 81939-07-3; (±)-*trans*-**10** (isomer 1), 81939-08-4; (±)-*trans*-**10** (isomer 2), 81939-09-5; (±)-**11**, 81875-25-4; **12**, 81875-26-5; **13**, 81875-27-6; **14**, 81875-28-7; **15b**, 81875-29-8; (±)-**16** (isomer 1), 81875-30-1; (±)-**16** (isomer 2), 81939-10-8; (±)-**17** (isomer 1), 81875-31-2; (±)-**17** (isomer 2), 81939-11-9; (±)-**18** (isomer 1), 81875-32-3; (±)-**18** (isomer 2), 81939-12-0; (±)-**19** (isomer 1), 81875-33-4; (±)-**19** (isomer 2), 81939-13-1; **20**, 81875-34-5; **21**, 81875-35-6; ethyl propionate copper salt, 81875-36-7; ethyl propionate, 105-37-3; ethyl propionate lithium enolate, 81355-01-3; allyl bromide, 106-95-6; 2-methyl-2-cyclopentenone, 1120-73-6; ethyl 2-(1-hydroxy-2-methyl-2-cyclopenten-1-yl)propanoate, 81875-37-8.

Synthesis of the D_{2d}-Dinoradamantane Derivatives Having Two Coaxially Oriented Unsaturated Centers. 6-Methylene-D_{2d}-dinoradamantan-2-one and D_{2d}-Dinoradamantane-2,6-dione

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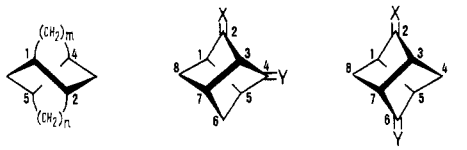
From the cyclopentadiene–maleic anhydride adduct was prepared the norbornenecarboxylic acid **22**. Treatment of the acid chloride **23** with triethylamine afforded the tetracyclic ketone **24** which was converted into the dinoradamantanecarboxylic acid **25** by a basic ring-opening reaction. The sequence of conversions involving the Cope elimination of the amine oxide derived from the amine **31** provided 6-methylene-D_{2d}-dinoradamantan-2-one (**6**) whose OsO_4–$NaIO_4$ oxidation eventually yielded D_{2d}-dinoradamantane-2,6-dione (**7**) of D_2 symmetry.

Bridging the 1,4 and 2,5 positions with CH_2 or CH_2CH_2 groups freezes cyclohexane's conformational mobility to make it assume a twist–boat conformation confined in the resulting tricyclic cage-shaped molecules.

Twistane (**1**) of D_2 symmetry and *twist*-brendane (**2**) of C_2 symmetry can be cited as examples (Chart I). They are both chiral, and their preparation in optically active modifications and determination of their absolute configuration have been reported from our laboratory.[1]

Bridging these positions with two CH_2 groups, however, provides an achiral tricyclic compound, D_{2d}-dinoradamantane (**3**), because introduction these CH_2 groups eventually creates another twist–boat cyclohexane moiety of opposite chirality interlocked with the original one. Since four CH_2 groups in D_{2d}-dinoradamantane (**3**) are a pair of enantiotopic molecular subunits, conversion of one

Chart I



(-) 1 D_2 m = n = 2 (-) 4 X=O, Y=H_2 6 X=O, Y=CH_2
(-) 2 C_2 m=1, n=2 (-) 5 X=O, Y=CH_2 7 X = Y = O
3 D_{2d} m = n = 1

of these CH_2 groups into carbonyl group desymmetrizes the D_{2d} symmetry inherent to **3**, leading to formation of D_{2d}-dinoradamantan-2-one (**4**) of C_2 symmetry. After having established the absolute configuration[2] of this interesting cage-shaped compound **4**, in which four among eight carbon atoms are asymmetric, we carried out its microbial[3] and horse liver alcohol dehydrogenase

(1) Adachi, K.; Naemura, K.; Nakazaki, M. *Tetrahedron Lett.* **1968**, 5467. Tichý, M.; Sicher, J. *Ibid.* **1969**, 4609. Tichý, M. *Ibid.* **1972**, 2001. Tichý, M.; Sicher, J. *Collect. Czech. Chem. Commun.* **1972**, *37*, 3106. Naemura, K.; Nakazaki, M. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 888. Nakazaki, M.; Naemura, K.; Harita, S. *Ibid.* **1975**, *48*, 1907.

(2) Nakazaki, M.; Naemura, K.; Arashiba, N. *J. Chem. Soc., Chem. Commun.* **1976**, 678. Nakazaki, M.; Naemura, K.; Arashiba, N. *J. Org. Chem.* **1978**, *43*, 888.

0022-3263/82/1947-3470$01.25/0