Stereocontrol in Horner-Wadsworth-Emmons Condensations of a *gem*-Dimethylcyclopropyl Aldehyde with α-Substituted Phosphono Acetates

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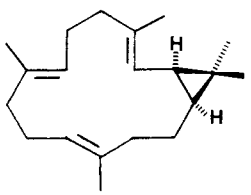
Oxidative cleavage of 2-carene provides a keto aldehyde attractive as a synthon for terpenoids containing *gem*-dimethylcyclopropyl rings. However, the sensitivity of this keto aldehyde to intramolecular aldol condensations proscribes the use of many standard conditions for Wadsworth-Horner-Emmons condensations that might be used to extend this carbon skeleton. Through use of dioxolane-containing phosphono acetates and lithium bases, it is possible to obtain olefin derivatives of this keto aldehyde with reasonable selectivity for either *E* or *Z* stereochemistry depending on the choice of phosphonate esters.

gem-Dimethylcyclopropyl rings are common features in many natural products, including (-)-casbene (**1**),[2] (-)-bertyadionol (**2**),[3] and (-)-taylorione (**3**).[4] Several compounds in these families have been prepared by total synthesis,[5] with chrysanthemic acid derivatives often serving as the ultimate source of the chirality of the cyclopropanoid systems. However, it might be argued that chiral cyclopropyl-containing synthons can be more readily derived from carenes (bicyclo[4.1.0]heptenes), especially because carenes of both enantiomeric series are readily available.[6,7] For example, oxidative cleavage of (+)-2-carene (**4**) gives the keto aldehyde **6**,[6] and ozonolysis of the (-)-2-carene acetate (**5**)[7] gives the analogous aldehyde **7**.



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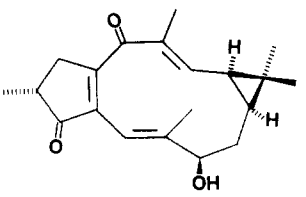

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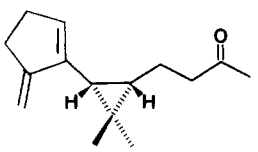

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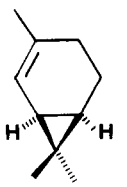

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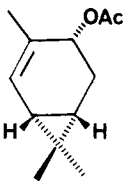

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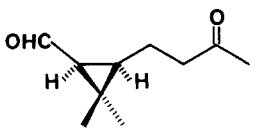

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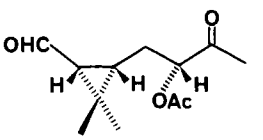

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The cyclopropyl keto aldehydes **6** and **7** are appropriately functionalized for assembly into many terpenoid structures, especially through aldol-type condensations. One major barrier to such use of these compounds is the uncertainty of stereochemical control in the olefin-forming reactions. Related problems include the possibility of self-condensation through intramolecular aldol condensation and the risk of epimerization of the cyclopropyl stereochemistry. To begin to resolve these issues, we have studied different conditions for Horner-Wadsworth-Emmons condensations with various phosphonates, the cyclopropyl aldehyde **6**, and the ketal derivative of this aldehyde (**12**).

While compound **6** is readily obtained by ozonolysis of (+)-2-carene, it is a rather sensitive compound. Upon treatment with base it readily condenses to cyclopentene **8**,[6] and it readily undergoes air oxidation to the keto acid **9** at room temperature. In an effort to circumvent these problems and yet retain the functional handle provided by the ketone carbonyl, compound **6** was converted to the protected aldehyde **12** by the straightforward sequence of Scheme I. Material prepared in this manner gave data identical with that previously reported for the enantiomeric series, prepared via a seven-step sequence from (1*R*,3*S*)-(+)-*cis*-chrysanthemic acid,[5a] but was more readily available. However, while compound **12** is undoubtedly more stable to base than the parent aldehyde **6**, it is sensitive to air oxidation and thus must be handled with care.

To study expansion of the cyclopropyl aldehyde **6** (or its dioxolane derivative **12**) into larger terpenoid fragments, we prepared several Horner-Wadsworth-Emmons reagents that can be viewed as potential terpenoid synthons. For example, compound **15** was readily prepared from the commercially available phosphono ester **13**, through formation of the phosphonate anion in THF followed by alkylation with 1-bromo-3-chloropropane. However, when this phosphonate was allowed to react with aldehyde **6** (LDA, THF, -78 °C to room temperature), the condensation product **18** was obtained as a 52:48 mixture of *E* and *Z* isomers. When the ketal aldehyde **12** was treated under

(1) Fellow of the Alfred P. Sloan Foundation, 1985-1989.
(2) Robinson, D. R.; West, C. A. *Biochemistry* **1970**, *9*, 70, 80. Sitton, D.; West, C. A. *Phytochemistry* **1975**, *14*, 1921.
(3) Ghisalberti, E. L.; Jefferies, P. R.; Payne, T. G.; Worth, G. K. *Tetrahedron* **1973**, *29*, 403.
(4) Matsuo, A.; Sato, S.; Nakayama, M.; Hayashi, S. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2652.
(5) Such syntheses include: (a) (-)-Casbene: Crombie, L.; Kneen, G.; Pattenden, G.; Whybrow, D. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1711. (b) (-)-Bertyadionol: Smith, A. B., III; Dorsey, B. D.; Visnick, M.; Maeda, T.; Malamas, M. S. *J. Am. Chem. Soc.* **1986**, *108*, 3110. (c) (-)-Taylorione: Nakayama, M.; Ohira, S.; Shinke, S.; Matsushita, Y. *Chem. Lett.* **1979**, 1245.
(6) (+)-2-Carene is commercially available, while the (-)-enantiomer is readily prepared, and its oxidative cleavage into the enantiomer of aldehyde **6** has been reported: Taylor, M. D.; Minaskanian, G.; Winzenberg, K. N.; Santone, P.; Smith, A. B., III *J. Org. Chem.* **1982**, *47*, 3960.
(7) For syntheses of carenones of both enantiomeric series, cf.: Maas, D.; Blagg, M.; Wiemer, D. F. *J. Org. Chem.* **1984**, *49*, 853. ApSimon, J. *Total Synthesis of Natural Products*; Wiley: New York, 1988; Vol. 7, p 412.

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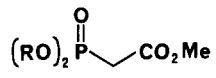
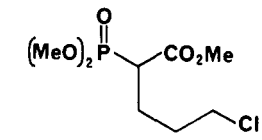


13 R=Me

14 R=CF_3CH_2



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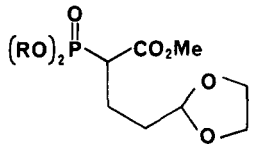
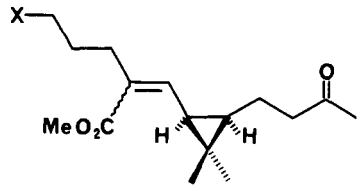


16 R=Me

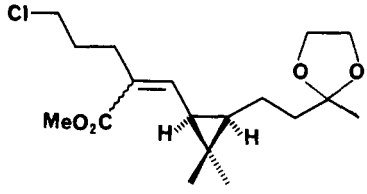
17 R=CF_3CH_2

the same conditions, another discouraging 1:1 mixture of the two stereoisomers **20** was obtained.



18 X=Cl

19 X=I



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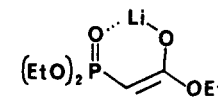
Marshall and co-workers[8] have studied the stereochemistry of trisubstituted olefins formed through condensation of some α-substituted phosphono esters with various aldehydes. In their study, a reasonable preference for the *E* stereoisomer could be obtained under several different conditions, but conditions that favored *Z* stereochemistry in previous studies[9,10] had diminished effectiveness with α-substituents larger than a methyl group. Marshall's work, together with the few previous studies on phosphono derivatives of esters larger than propionate,[11] suggest that stereocontrol in such systems can be difficult to obtain. In this context, the product mixtures obtained with phosphonate **15** can be rationalized but not made attractive.

In their studies of Horner–Wadsworth–Emmons reactions in base-sensitive systems, Masamune, Roush, and co-workers[12] postulated that lithium bases gave favorable results due to the intermediacy of a tight ion pair, such as structure **21**. If the α-substituent provided an alternative site of complexation, it appeared possible to modify the reactivity of such a phosphonate anion while still retaining the use of a lithium base. One model for such a



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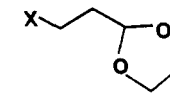
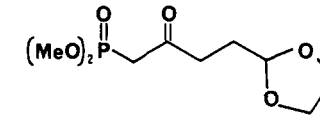


22 X=MgBr

23 X=Br



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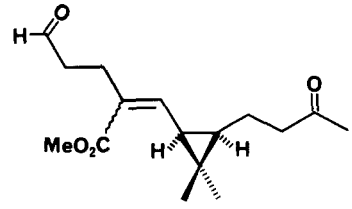
substituent was found in the Grignard reagent **22**, where internal complexation has been reported to moderate the reactivity of the organometallic compound.[13] In addition, the lithium salt of phosphonate **24** has been reported to react with a sensitive cyclohexanecarboxaldehyde to give an *E*-disubstituted olefin product in very good yield.[14] Accordingly, to test the extent of stereocontrol available with an α-substituent capable of complexation, we prepared the phosphonate **16** by reaction of bromo acetal **23** with phosphonate **13** (NaH, DMF).[15]

When the Horner–Wadsworth–Emmons reaction of phosphonate **16** and aldehyde **6** was attempted using $LiN(TMS)_2$ in DME (Scheme II) at low temperature and long reaction time, the desired condensation product **25** was obtained in essentially quantitative yield. An *E*:*Z* ratio of 86:14 was noted by GC MS of the reaction mixture, and there was no detectable formation of the intramolecular aldol product **8**. While the *E* and *Z* isomers could be separated by column chromatography, this was accompanied by considerable loss of material.[5a] Other standard conditions for the condensation, such as NaH/THF or $KN(TMS)_2$/THF with 18-crown-6,[9] gave only the aldol product **8** if any reaction was observed.

For maximum flexibility in application of the keto aldehyde **6**, a route favoring *Z*-olefin products also would be desirable. To explore one route to a *Z* olefin, the bis(trifluoroethyl) phosphonate **17** was prepared by alkylation of compound **14** with bromo acetal **23**. Although potassium bases are usually paired with such fluoroalkyl phosphonates to obtain maximum *Z* selectivity,[9] such conditions were not useful in this case because aldehyde **6** is so prone to aldol condensation. For example, treatment of aldehyde **6** with phosphonate **17** and potassium hexamethyldisilazide in the presence of 18-crown-6 gave only the aldol product **8**. However, with phosphonate **17** and conditions (DBU, LiCl, CH_3CN) that allow Horner–Wadsworth–Emmons reactions with base-sensitive compounds,[12] a 75:25 ratio of *Z*:*E* products (**25**) was obtained in 80% isolated yield.

To complete this phase of our study, the acetal (*E*)-**25** was treated with aqueous HCl and ether in a two-phase reaction, to obtain the aldehyde **26**. The same compound



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(9) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.
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(12) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.
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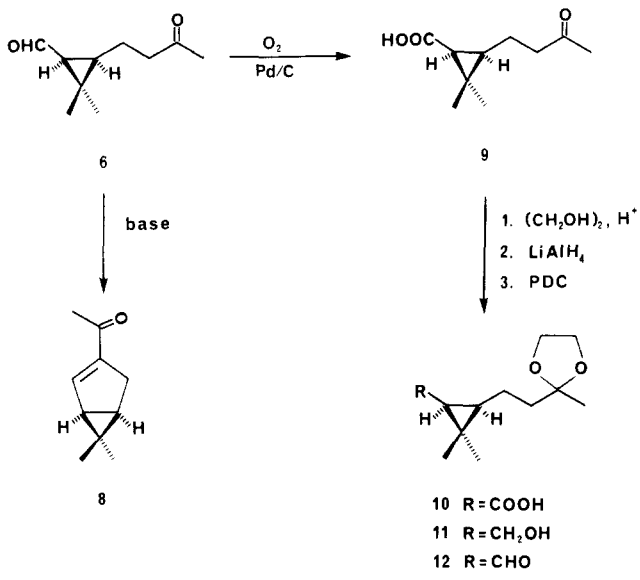
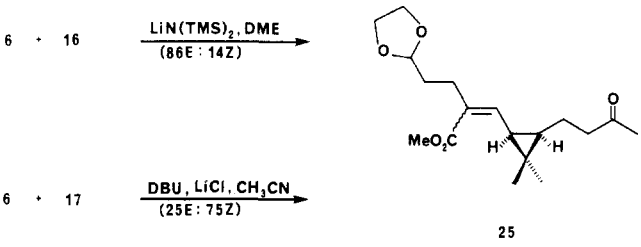
(14) Overman, L. E.; Lesuisse, D.; Hashimoto, M. *J. Am. Chem. Soc.* **1983**, *105*, 5373.
(15) Tius, M. A.; Fauq, A. H. *J. Am. Chem. Soc.* **1986**, *108*, 1035.

Scheme I



Scheme II



was prepared from the chlorides (*E*)- and (*Z*)-**18**, by treatment with NaI[16] to obtain the analogous alkyl iodides ((*E*)- and (*Z*)-**19**), followed by oxidation with DMSO[17] and separation of the olefin isomers by chromatography. Because the products of these sequences are identical, there is no evident loss of stereochemistry at the cyclopropyl group during the transformations following the Horner–Wadsworth–Emmons condensation or at the olefin during acetal hydrolysis. The new keto aldehydes (*E*)- and (*Z*)-**26** contain functionality appropriate for further elaboration into various terpenoid skeletons.

The results of this study of Horner–Wadsworth–Emmons reactions suggest that it is possible to employ the base-sensitive keto aldehyde **6** in this condensation, making compound **6** a valuable chiral synthon for *gem*-dimethylcyclopropyl-substituted compounds. Furthermore, by utilizing an α-substituent on the phosphono ester that is capable of complexing with a Li counterion, it is possible to obtain condensation products in good yields, with reasonable stereocontrol for either the *E* or *Z* isomer. While more extensive studies must be conducted to establish the generality of this effect, these results suggest that competitive internal complexation is a new factor that can affect stereocontrol in the Horner–Wadsworth–Emmons reaction. This factor may be of more widespread applicability in appropriately designed phosphonates.

Experimental Section

Tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately prior to use, and all reactions in this solvent were conducted under a positive pressure of an inert gas. Column chromatography was done on Merck grade 62 silica gel (60–200 mesh), while radial chromatography was performed with a Chromatotron apparatus and Merck PF254 silica gel with $CaSO_4 \cdot 0.5H_2O$. NMR spectra (^1H and ^{13}C) were recorded with $CDCl_3$ as both solvent and internal standard. Electron impact (EI) mass spectra were recorded at 70 eV; only selected ions are reported here.

(1*S*,3*R*)-*cis*-2,2-Dimethyl-3-(3-oxobutyl)cyclopropanecarboxylic Acid (9). Oxygen was bubbled through a mixture of 5% Pd/C and keto aldehyde **6**[7] (2.08 g, 12.4 mmol) in methanol (65 mL) at room temperature, and the reaction volume was kept constant by periodic addition of methanol. After 24 h, complete oxidation was indicated by GC analysis. The mixture was filtered through a Celite pad and concentrated in vacuo, and the crude product was dissolved in 1 M NaOH (60 mL). After extraction with ether (2 × 40 mL), the aqueous layer was acidified with 3 M HCl (30 mL) and extracted with ether (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and then concentrated in vacuo to obtain compound **9** as a pale yellow oil (1.91 g, 84%; >95% pure by GC): ^1H NMR identical with literature data for the opposite enantiomer;[18] IR 3150, 1715, 1692 cm^{-1}; EIMS, *m/z* (rel intensity) 184 (M^+, 0.1), 169 (2), 166 (2), 138 (5), 126 (100), 95 (44), 83 (34), 43 (81).

(1*S*,3*R*)-*cis*-2,2-Dimethyl-3-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]cyclopropanecarboxylic Acid (10). A catalytic amount of *p*-toluenesulfonic acid was added to a solution of keto acid **9** (1.90 g, 10.3 mmol) and ethylene glycol (2.2 mL) in benzene (75 mL), and the reaction mixture was heated at reflux for ca. 8 h with continuous removal of water (Dean–Stark trap). The resulting solution was diluted with ether, washed with water, dried ($MgSO_4$), and finally concentrated in vacuo to yield ketal acid **10** as a pale oil (2.22 g, 95%): ^1H NMR δ 4.03–3.7 (m, 4 H), 2.0–1.3 (m, 6 H), 1.32 (s, 3 H), 1.24 (s, 3 H), 1.16 (s, 3 H); EIMS, *m/z* (rel intensity) 228 (M^+, 1), 213 (2), 185 (3), 123 (8), 87 (100), 43 (37); HRMS calcd for $C_{12}H_{20}O_4$ 228.1361, found 228.1368.

(1*S*,3*R*)-*cis*-2,2-Dimethyl-3-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]cyclopropanecarboxaldehyde (12). Lithium aluminum hydride (0.988 g) was added to a solution of acid **10** (2.22 g, 9.74 mmol) in THF (90 mL) at 0 °C. The mixture was allowed to warm to room temperature overnight, and then excess hydride was quenched by successive addition of water (1 mL), 3 M NaOH (1 mL), and water (3 mL). The resulting precipitate was removed by filtration through a Florisil pad, and the filtrate was concentrated in vacuo to give the corresponding alcohol **11** (1.88 g, 90%) as a colorless liquid (EIMS, *m/z* (rel intensity) 214 (M^+, 0.4), 183 (3), 152 (2), 134 (2), 121 (8), 99 (5), 87 (100), 79 (9), 59 (11), 43 (38)). Without further purification, this alcohol was immediately oxidized to the analogous aldehyde.

Pyridinium dichromate (PDC, 2.38 g, 6.2 mmol) was added to a solution of the alcohol **11** (0.70 g, 3.3 mmol) in dichloromethane (30 mL) at 0 °C, and the mixture was stirred for 1.5 h. The reaction mixture was allowed to warm to room temperature, and stirring was continued for 2.5 h. The resulting mixture was filtered through a Florisil pad, which was washed with additional CH_2Cl_2 (ca. 20 mL). Concentration of the filtrate gave crude aldehyde **12** (0.39 g, 56%) as an unstable yellow liquid: ^1H NMR identical with data reported for the opposite enantiomer;[5a] EIMS, *m/z* (rel intensity) 197 ($M^+ - 15$, 5), 183 (1), 121 (6), 110 (48), 99 (14), 95 (22), 87 (100), 43 (43).

2-(Dimethoxyphosphinyl)-5-chloropentanoic Acid, Methyl Ester (15). Sodium hydride (60% dispersion in mineral oil; 640 mg, 16 mmol) was washed with pentane to remove mineral oil and then suspended in THF. A solution of trimethyl phosphonoacetate (2.4 mL, 14.9 mmol) in THF (40 mL) was added dropwise over a period of 20 min. After evolution of hydrogen had ceased, the solution was stirred for an additional 1.75 h at room temperature, 1-bromo-3-chloropropane (3 mL, 30 mmol) was added, and the resulting mixture was heated at reflux overnight. The reaction mixture was quenched by addition of saturated ammonium chloride and extracted with ether, and the combined organic extracts were washed with brine. After drying ($MgSO_4$) and concentration in vacuo, the desired phosphonate

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(18) Matsuo, A.; Nozaki, H.; Kubota, N.; Uto, S.; Nakayama, M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 203.

15 was obtained as a pale yellow oil (3.52 g, 91%; >95% purity by GC). An aliquot was further purified by preparative GC to obtain the analytical sample: ^{1}H NMR δ 3.81 (d, 6 H, J_{HP} = 10.9 Hz[19]), 3.77 (s, 3 H), 3.54 (t, 2 H, J = 6.4 Hz), 3.03 (ddd, 1 H, J_{HP} = 23.1, J = 10.1, 4.7 Hz), 2.14–1.99 (m, 2 H), 1.91–1.77 (m, 2 H); ^{13}C NMR 169.1, 53.4 (2), 52.6, 44.3, 44.0, 31.1, 24.6; EIMS, *m/z* (rel intensity) 229 (M^+ – OMe, 8), 227 (24), 223 (92), 199 (23), 195 (38), 191 (83), 163 (54), 109 (100). Anal. Calcd for $C_8H_{16}ClO_5P$: C, 37.15; H, 6.23. Found: C, 37.38; H, 6.35.

(1*R*,3*R*)-*cis*-2-(3-Chloropropyl)-3-[2,2-dimethyl-3-(3-oxobutyl)cyclopropyl]-2-propenoic Acid, Methyl Ester (18). Phosphonate **15** (4.06 g, 15.7 mmol in 5 mL THF) was added dropwise to a freshly prepared solution of LDA (16 mmol; prepared in situ from 1 M *n*-BuLi (16 mL) and diisopropylamine (2.4 mL)) in THF (25 mL), and the reaction mixture was stirred at –78 °C for 2 h. Keto aldehyde **6** (2.50 g, 15 mmol) was added; the reaction mixture was allowed to warm to 0 °C and then stirred at room temperature overnight. Water (20 mL) was added, the resulting layers were separated, and the aqueous layer was extracted with ether (3×). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo yielding 4.46 g (94%) crude product in a 52:48 ratio based on GC MS. Further purification by MPLC (silica gel, 5% ethyl acetate in hexane) afforded both *E* and *Z* isomers.

(*E*)-**18**: ^{1}H NMR (90 MHz) δ 6.63 (d, 1 H, J = 10.3 Hz), 3.71 (s, 3 H), 3.54 (t, 2 H, J = 6.2 Hz), 2.48 (t, 4 H, J = 7 Hz), 2.1–1.4 (m, 6 H), 2.12 (s, 3 H), 1.16 (s, 3 H), 1.09 (s, 3 H); ^{13}C NMR δ 207.6 (s), 167.2 (s), 141.3 (d), 130.6 (s), 51.0 (q), 44.1 (t), 43.0 (t), 32.3, 31.8, 29.5, 28.6, 27.0 (d), 23.7 (d), 22.2, 19.1 (t), 15.2 (q); EIMS, *m/z* (rel intensity) 270 (M^+ – 32, 5), 268 (13), 259 (4), 257 (10), 227 (6), 225 (16), 174 (16), 119 (48), 105 (65), 91 (84), 43 (100).

(*Z*)-**18**: ^{1}H NMR (90 MHz) δ 5.78 (d, 1 H, J = 10.6 Hz), 3.74 (s, 3 H), 3.51 (t, 2 H, J = 6 Hz), 2.47 (m, 4 H), 2.13 (s, 3 H), 2.1–1.4 (m, 8 H), 1.14 s, 3 H), 1.06 (s, 3 H); ^{13}C NMR δ 207.6 (s), 167.5 (s), 141.6 (d), 129.8 (s), 50.6 (q), 43.6 (t), 42.9 (t), 31.5 (2, t), 29.4, 28.5, 27.3, 23.7 (t), 22.2, 18.9 (t), 14.9 (q); EIMS, *m/z* (rel intensity) 270 (M^+ – 32, 8), 268 (21), 259 (7), 257 (20), 227 (12), 225 (30), 174 (79), 119 (70), 105 (86), 91 (93), 43 (100). Anal. Calcd for $C_{16}H_{25}O_3Cl$: C, 63.88; H, 8.38. Found: C, 63.86; H, 8.10.

2-(Dimethoxyphosphinyl)-4-(1,3-dioxolan-2-yl)butanoic Acid, Methyl Ester (16). Sodium hydride (60% dispersion in mineral oil; 1.32 g, 33 mmol) was washed with pentane, and suspended in anhydrous DMF (39 mL).[14] Trimethyl phosphonoacetate (**13**, 4.45 mL, 27.5 mmol) was added dropwise via syringe pump to the vigorously stirred suspension, and the resulting mixture was stirred for 1.5 h. After addition of alkyl bromide **23** (3.9 mL, 33 mmol), the reaction mixture was heated at reflux for 19 h and then quenched by addition of saturated ammonium chloride (40 mL). The aqueous layer was extracted with ether (33 mL) and then extracted with CH_2Cl_2 in a Soxhlet apparatus. The combined organic extracts were dried ($MgSO_4$) and concentrated at high vacuum for 24 h at room temperature to remove residual DMF. This procedure yielded phosphonate **16** (3.1 g, 40%) as a 3/1 mixture of mono and dialkylated materials. While this mixture could be used in Horner–Wadsworth–Emmons reactions, an analytical sample was obtained by preparative GC: ^{1}H NMR (90 MHz) δ 3.79 (d, 6 H, J = 11 Hz), 3.77 (s, 3 H), 3.9–3.1 (m, 6 H), 1.5 (m, 4 H); IR 1734 cm^{-1}; EIMS, *m/z* (rel intensity) 281 (M^+ – 1, 1), 251 (5), 196 (17), 183 (32), 165 (15), 151 (24), 109 (48), 73 (100). Anal. Calcd for $C_{10}H_{19}O_7P{\cdot}1.5H_2O$: C, 38.84; H, 7.17. Found: C, 38.85; H, 6.89.

(1*R*,3*R*)-*cis*-3-[2,2-Dimethyl-3-(3-oxobutyl)cyclopropyl]-2-[2-(1,3-dioxolan-2-yl)ethyl]-2-propenoic Acid, Methyl Ester (25). A solution of $LiN(TMS)_2$ (3.6 mmol in 25 mL DME), was prepared at –50 °C from hexamethyldisilazane (0.76 mL) and *n*-BuLi (2.3 mL, 1.55 M in hexane). A solution of phosphonate **16** (1.42 g, 5.05 mmol) in DME (15 mL) was added dropwise via syringe, and, after 45 min, a solution of keto aldehyde **6** (0.61 g, 3.6 mmol) in DME (10 mL) was added. The resulting mixture was stirred at –50 °C, with temperature maintained by a cryostat bath, until GC analysis indicated complete reaction (56 h). The solvents were removed at reduced pressure, leaving a pale yellow gummy oil. This oil was dissolved in water (60 mL) and extracted with dichloromethane (3 × 30 mL). The combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$), and concentrated in vacuo, yielding a pale yellow liquid consisting of a mixture of *E* and *Z* isomers of the unstable olefin **25** (1.1 g, 94%) in an 86:14 ratio. Purification of an aliquot via radial chromatography (silica gel, toluene (97%), EtOAc (2.7%), AcOH (0.3%) to toluene (90%), EtOAc (9%), AcOH (1%)) yielded (*E*)-**25**: ^{1}H NMR δ 6.57 (d, 1 H, J = 10.7 Hz), 4.87 (t, 1 H, J = 4.7 Hz), 4.0–3.8 (m, 4 H), 3.72 (s, 3 H), 2.6–2.4 (m, 4 H), 2.14 (s, 3 H), 1.85–1.60 (m, 4 H), 1.25–1.00 (m, 2 H), 1.15 (s, 3 H), 1.08 (s, 3 H); EIMS, *m/z* (rel intensity) 324 (M^+, 1), 292 (5), 198 (30), 165 (40), 133 (40), 99 (60), 73 (100), 43 (40); HRMS calcd for $C_{18}H_{28}O_5$ 324.1937, found 324.1951.

2-[Bis(2,2,2-trifluoroethoxy)phosphinyl]-4-(1,3-dioxolan-2-yl)butanoic Acid, Methyl Ester (17). According to the procedure described with compound **15** above, phosphonate **14** (1.8 mL, 8.56 mmol) was treated with NaH (460 mg, 11.5 mmol) and bromide **23** (1.14 mL, 9.4 mmol) in DMF (24 mL). After addition of water (100 mL) and extraction with ether (4 × 25 mL), the aqueous layer was saturated with solid NaCl and extracted again with ether (2 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to obtain the desired product **17** (2.48 g, 69%), accompanied by its dialkylated analogue (6:1 ratio). An aliquot was further purified by vacuum distillation (135–138 °C/0.6 mmHg): ^{1}H NMR δ 4.88 (t, 1 H, J = 4.2 Hz), 4.5–4.3 (m, 4 H), 4.0–3.8 (m, 4 H), 3.78 (s, 3 H), 3.29 (ddd, 1 H, J_{HP} = 22.5 Hz, J = 10.5, 5.0 Hz), 2.2–2.0 (m, 2 H), 1.9–1.6 (m, 2 H); EIMS, *m/z* (rel intensity) 417 (M^+ – 1, 22), 387 (18), 343 (55), 318 (29), 287 (58), 257 (100), 219 (20), 163 (31). Anal. Calcd for $C_{12}H_{17}O_7F_6P$: C, 34.46; H, 4.10. Found: C, 34.31; H, 4.29.

(1*R*,3*R*)-*cis*-3-[2,2-Dimethyl-3-(3-oxobutyl)cyclopropyl]-2-[2-(1,3-dioxolan-2-yl)ethyl]-2-propenoic Acid, Methyl Ester ((*Z*)-25). A mixture of phosphonate **17** (2.0 g, 4.8 mmol), anhydrous lithium chloride (0.21 g, 4.8 mmol), and DBU (0.62 mL, 4.15 mmol) in acetonitrile (50 mL) was stirred at room temperature, and a solution of keto aldehyde **6** (0.52 g, 3.1 mmol) in acetonitrile (5 mL) was added. After stirring overnight, the solution was concentrated in vacuo, and the remaining oil was partitioned between water (50 mL) and dichloromethane (25 mL). The aqueous layer was extracted with dichloromethane (2 × 25 mL), and the combined organic extracts were washed with brine (25 mL), dried ($MgSO_4$), and concentrated in vacuo to afford crude **25** (1.03 g, 100%) as an unstable mixture of *Z* and *E* isomers in a 75/25 ratio. Purification of an aliquot via radial chromatography (silica gel, toluene (99%), EtOAc (0.9%), AcOH (0.1%) to toluene (90%), EtOAc (9%), AcOH (1%)) yielded (*Z*)-**25**: ^{1}H NMR δ 5.72 (d, 1 H, J = 10.3 Hz), 4.87 (t, 1 H, J = 4.7 Hz), 4.0–3.8 (m, 4 H), 3.74 (s, 3 H), 2.6–2.4 (m, 4 H), 2.20 (s, 3 H), 1.85–1.60 (m, 4 H), 1.25–1.00 (m, 2 H), 1.12 (s, 3 H), 1.04 (s, 3 H); EIMS, *m/z* (rel intensity) 324 (M^+, 1), 292 (6), 267 (6), 198 (31), 189 (29), 165 (48), 133 (44), 119 (37), 99 (100), 73 (59), 43 (35); HRMS calcd for $C_{18}H_{28}O_5$ 324.1937, found 324.1937.

(1*R*,3*R*)-*cis*-3-[2,2-Dimethyl-3-(3-oxobutyl)cyclopropyl]-2-(3-oxopropyl)-2-propenoic Acid, Methyl Ester (26). A solution of acetal (*E*)-**25** (46 mg, 0.142 mmol) in ether (10 mL) was treated with aqueous HCl (3 M, 6 mL) at room temperature for 24 h. The ethereal layer was separated, and the aqueous layer was extracted with ether (10 mL). The combined organic extracts were washed with saturated $NaHCO_3$, dried ($MgSO_4$), and concentrated in vacuo to yield the desired aldehyde (*E*)-**26** as an unstable oil (33 mg, 84%): ^{1}H NMR δ 9.79 (d, 1 H, J = 1.5 Hz), 6.60 (d, 1 H, J = 10.8 Hz), 3.72 (s, 3 H), 2.71–2.68 (m, 2 H), 2.62–2.58 (m, 2 H), 2.46 (t, 2 H, J = 7.4 Hz), 2.15 (s, 3 H), 1.8–1.6 (m, 2 H), 1.44 (dd, 1 H, J = 10.8, 8.7 Hz), 1.16 (s, 3 H), 1.09 (s, 3 H), 1.15–1.06 (m, 1 H); ^{13}C NMR δ 208.2 (s), 201.7 (d), 167.3 (s), 141.8 (d), 130.4 (s), 51.6 (q), 43.3 (t), 43.2 (t), 32.8, 29.8, 28.9, 27.3, 25.2, 19.8, 19.4 (q), 15.5 (q); EIMS, *m/z* (rel intensity) 262 (M^+ – 18, 2), 248 (M^+ – 32, 30), 237 (27), 205 (45), 161 (56), 133 (62), 119 (85), 105 (81), 91 (100), 79 (47), 43 (53); HRMS calcd

(19) The relationship of the –OMe signals, a minor point of some confusion in phosphono acetates in the past,[8,20] was established by heteronuclear decoupling experiments (^{31}P irradiated; ^{1}H observed).

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for $C_{15}H_{20}O_3$ (M^+ - MeOH) 248.1412, found 248.1411. Anal. Calcd for $C_{16}H_{24}O_4 \cdot H_2O$: C, 64.41; H, 8.78. Found: C, 64.06; H, 8.20.

(1*R*,3*R*)-*cis*-2-(3-Iodopropyl)-3-[2,2-dimethyl-3-(3-oxobutyl)cyclopropyl]-2-propenoic Acid, Methyl Ester (19). A mixture of the chlorides (*E*/*Z*)-**18** (203 mg, 0.675 mmol) and sodium iodide (0.7 g) was allowed to react in refluxing acetone (16 mL) for 28 h,[16] yielding the desired iodide **19** (216 mg, 81%). Purification of an aliquot by column chromatography (silica gel, gradient elution ethyl acetate in hexane) gave an analytical sample of (*E*)-**19**: ^{1}H NMR (90 MHz) δ 6.61 (d, 1 H, J = 10 Hz), 3.72 (s, 3 H), 3.20 (t, 2 H, J = 7 Hz), 2.6-2.4 (m, 4 H), 2.1-1.4 (m, 6 H), 2.15 (s, 3 H), 1.18 (s, 3 H), 1.08 (s, 3 H); ^{13}C NMR δ 208.0, 167.5, 141.5, 130.6, 65.6, 51.4, 43.1, 33.0, 32.6, 29.8, 28.9, 27.3, 25.2, 24.9, 19.3, 15.4; EIMS, m/z (rel intensity) 374 (M^+ - 18, 2), 360 (18), 349 (14), 317 (11), 266 (29), 155 (47), 147 (37), 119 (68), 105 (68), 91 (100), 43 (61). Anal. Calcd for $C_{16}H_{25}O_3I \cdot 4H_2O$: C, 41.39; H, 7.16. Found: C, 41.36; H, 6.92.

Aldehydes (*E*)- and (*Z*)-26 from iodides 19. A solution of sodium bicarbonate (12 g) in DMSO (90 mL)[17] was heated to 150 °C, and the iodides **19** (55:45 *E*:*Z*; 7.9 g, 20 mmol) were added in one portion. After 10 min at 150 °C, the reaction mixture was poured into ice (100 g). The water-DMSO mixture was extracted with ether (5 × 50 mL), and the combined ether extracts were dried ($MgSO_4$) and concentrated in vacuo to give aldehyde **26** (5.5 g, 98%). Separation of the isomers was achieved via column chromatography (silica gel, gradient elution of ether in chloroform). (*E*)-**26**: identical with material prepared above. (*Z*)-**26**: ^{1}H NMR δ 9.74 (d, 1 H, J = 1.5 Hz), 5.79 (d, 1 H, J = 10.4 Hz), 3.75 (s, 3 H), 2.47 (t, 2 H, J = 7.4 Hz) 2.3-2.1 (m, 4 H), 2.15 (s, 3 H), 1.8-1.6 (m, 2 H), 1.15-0.95 (m, 2 H), 1.13 (s, 3 H), 1.07 (s, 3 H); ^{13}C NMR δ 208.3 (s), 201.4 (d), 167.7 (s), 142.7 (d), 129.9 (s), 51.1 (q), 43.7 (t), 43.3 (t), 32.9, 29.9, 28.7, 27.6, 27.6, 24.3, 19.3 (q), 15.2 (q); EIMS, m/z (rel intensity) 262 (M^+ - 18, 2), 248 (24), 237 (23), 205 (38), 161 (47), 154 (49), 133 (54), 119 (81), 105 (76), 98 (67), 91 (100), 79 (49), 43 (55); HRMS calcd for $C_{15}H_{20}O_3$ (M^+ - MeOH) 248.1412, found 248.1432.

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Stereochemistry of the Michael Addition of N,N-Disubstituted Amide and Thioamide Enolates to α,β-Unsaturated Ketones[1]

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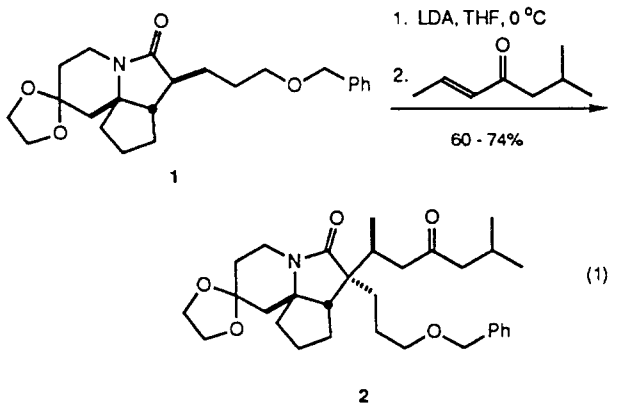
A systematic study of the regio- and diastereoselectivity of the kinetic Michael addition of amide and thioamide enolates to a series of α,β-unsaturated ketones has been carried out. Factors that influence the diastereo- and regiochemical outcome of the reaction include the substitution pattern of the enone and enolate, the enolate counterion, and the solvent. Numerous examples of high selectivity have been discovered. In a number of examples, either the syn or the anti addition products can be obtained by varying the nature of the solvent, donor atom, and/or counterion. These results have correlated in terms of a coherent transition-state model.

Background

The Michael addition reaction is a powerful and widely used method of synthesis.[2] Although the reaction was discovered[3] and developed as a general method[4] more than 100 years ago, its stereochemistry has been investigated only recently.[5] Several years ago, in the context of an alkaloid total synthesis,[6] we discovered that lactam **1** adds cleanly to 6-methylhept-2-en-4-one to provide keto lactam **2** as a 9:1 mixture of isomers (eq 1). Although the stereostructures of the products were not rigorously assigned, circumstantial evidence suggested that the major isomer has the relative configuration indicated at the exocyclic stereogenic center.



(1)

The foregoing observations stimulated us to further explore the stereochemistry of the addition of preformed amide enolates to enones. Although the simple diastereoselectivity of the addition of amide enolates to cinnam-

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