1→6. Figure 2A contains all three characteristic ions for each linkage indicating a 1→6, 1→6, 1→6 pattern.

Investigations into using the dilithiated precursor as a method for determining linkage position in larger oligomers are currently underway. Semiempirical calculations on both mono- and dilithiated disaccharides and metastable decomposition studies are also underway in order to better access the position of lithium coordination to the molecule.

Supplementary Material Available: CID spectra of mono- and dilithiated species for the five isomeric disaccharides discussed as well as CID of mono- and dilithiated precursors for three trimers, two tetramers, and two trimers with furanose reducing ends (11 pages). Ordering information is given on any current masthead page.

The Olefination of Functionalized Alkylidenemalonates by 1,1-Dimetalloalkanes: A New Chemo- and Stereoselective Preparation of Functionalized Olefins

Charles E. Tucker, S. Achyutha Rao, and Paul Knochel*

The Willard H. Dow Laboratories, Department of Chemistry, The University of Michigan, Ann Arbor, Michigan 48109

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Summary: The polyfunctional alkylidenemalonates **1**, readily prepared by an addition–elimination reaction of FG-RCu(CN)ZnI to [(phenylsulfonyl)methylidene]-malonates of type **7**, were found to undergo a highly chemoselective and stereoselective olefination reaction with 1,1-dimetalloalkanes of zinc and magnesium. An application to the stereospecific preparation of an insect pheromone **8** is reported.

The reaction of aldehydes and ketones with phosphorus reagents,[1] arsenic and tellurium ylides,[2] α-metalated boranes and silanes,[3] various 1,1-dimetallic reagents, and transition metal carbenes[4] has proven to be one of the best methods for the preparation of olefins. We report herein a new stereoselective olefination of polyfunctional alkylidenemalonates **1** by 1-magnesio-1-zincioalkanes of type **2** leading to functionalized olefins **3**. The reaction proceeds under very mild conditions (−78 °C to −20 °C, 10 min),[5] shows a remarkable chemoselectivity, and gives excellent yields (76–91%; Scheme I and Table I). It can be formulated as being a Michael addition affording a γ-metalated enolate **4**, followed by a fragmentation of **4** furnishing the olefin **3** and a magnesium and zinc dienolate **5**. The starting 1,1-dimetalloalkanes **2** are readily obtained by the allylzincation of alkenylmagnesium bromides[6] (THF, 0–35 °C, 40 min; >90% yield), whereas the polyfunctional alkylidenemalonates **1a–j** were prepared[5] in high yields by the addition of copper–zinc organometallics[7] RCu(CN)ZnI **6a–f,h** and $PhMe_2SiCu(CN)Li$ **6g**[8] to the new reagents[9] [(phenylsulfonyl)methylidene]malonates **7a–c** (THF, −78 °C to −30 °C, 1 h, 40–90%; Scheme II and Table II). The fast rate of the reaction allows the successful olefination of alkylidenemalonates having ester, nitrile, chloride, or thioether functionalities (Table I). Even a function highly susceptible to olefination reactions[1-4] such as an aromatic aldehyde survives our mild reaction conditions, demonstrating clearly the *exceptional chemoselectivity* of this reaction (entry 14 of Table I). Thus diethyl (4-formylbenzylidene)malonate **1k** furnishes the desired alkyliden-

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(5) **Typical Procedure: (a) Formation of Functionalized Alkylidenemalonates 1.** To a solution of 11 mmol of the copper reagent FG-R-Cu(CN)ZnI, prepared according to ref 7, in 11 mL of THF, cooled to −78 °C was added dropwise a solution of 10 mmol of [(phenylsulfonyl)methylidene]malonate **7** in 3 mL THF. The reaction mixture was allowed to warm to −30 °C and was stirred until completion (1–2 h). The reaction was then quenched by addition to 100 mL of saturated aqueous NH_4Cl, diluted with 100 mL of ether and worked up as usual. The residual crude product was purified by flash chromatography, yielding colorless oils in 40–90% yields. **(b) Formation of Functionalized Olefins 3.** To a solution of 12 mmol of the 1-magnesio-1-zincioalkane **2** (prepared according to ref 6e) cooled to −78 °C, was added dropwise a solution of 10 mmol of the functionalized alkylidenemalonate **1** in 3 mL of THF. The solution was then warmed quickly to −20 °C and stirred for 10 min. The reaction was quenched in 100 mL of a saturated aqueous NH_4Cl solution and diluted with 100 mL of ether. The resulting organic layer was then washed with 100 mL of aqueous NH_4Cl, washed with 100 mL of water, and dried over $MgSO_4$, and the solvents removed by evaporation. The residual oils were then purified by flash column chromatography giving the functionalized olefins of type **3** in 72–91% yields.

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(9) [(Phenylsulfonyl)methylidene]malonates **7** have been prepared by the oxidation of the corresponding (*S*)-(phenylmethylidene)malonate (Husinec, S.; Porter, A. E. A.; Strachan, C. H. *Collect. Czech. Chem. Commun.* **1987**, *52*, 207) in 95% yield; MCPBA (2.3 equiv); CH_2Cl_2, 0 °C, 10 h (see the supplementary material). Diethyl (chloromethylidene)- and (ethoxymethylidene)malonate were found to be unreactive with RCu(CN)ZnI; compare with: Cahiez, G.; Alami, M. *Tetrahedron* **1989**, *45*, 4163.

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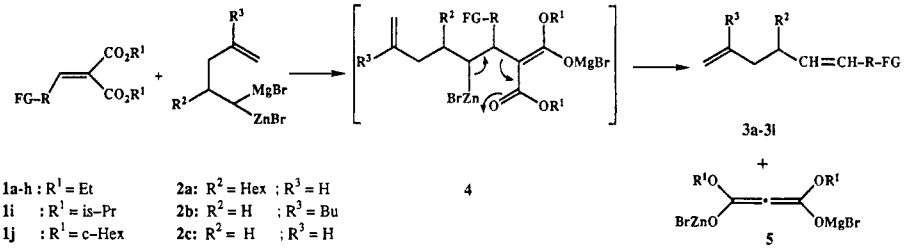
Table I. Functionalized Olefins 3a–l Obtained by the Reaction of the 1-Magnesio-1-zincioalkanes 2a or 2b with Polyfunctional Alkylidenemalonate 1a–k[a]

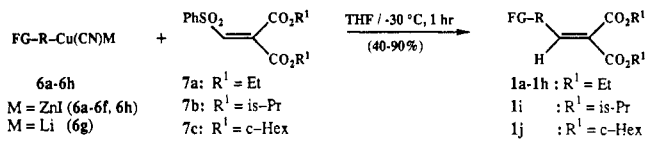
entry	alkylidene-malonate of type 1[b]	1,1-dimetallo-alkane of type 2[d]	products of type 3[d]	FG-R	R^2	R^3	Z/E	yield, %
1	**1a**	**2a**	**3a**	$(CH_2)_3CO_2Et$	Hex	H	82:18	83
2	**1b**	**2a**	**3b**	$(CH_2)_3OAc$	Hex	H	79:21	79
3	**1c**	**2a**	**3c**	$(CH_2)_3CN$	Hex	H	83:17	88
4	**1d**	**2a**	**3d**	$(CH_2)_4Cl$	Hex	H	88:12	75
5	**1e**	**2a**	**3e**	c-Hex	Hex	H	78:22	79
6	**1f**	**2a**	**3f**	$(CH_2)_3SPh$	Hex	H	70:30	91
7	**1g**	**2a**	**3g**	$SiMe_2Ph$	Hex	H	14:86	83
8	**1a**	**2b**	**3h**	$(CH_2)_3CO_2Et$	H	Bu	45:55	81
9	**1c**	**2b**	**3i**	$(CH_2)_3CN$	H	Bu	7:93	79
10	**1d**	**2b**	**3j**	$(CH_2)_4Cl$	H	Bu	100:0	86
11	**1e**	**2b**	**3k**	c-Hex	H	Bu	77:23	76
12	**1i**	**2a**	**3a**	$(CH_2)_3CO_2Et$	Hex	H	84:16	60
13	**1j**	**2a**	**3a**	$(CH_2)_3CO_2Et$	Hex	H	91:9	91
14	**1k**[c]	**2a**	**3l**	4-PhCHO	Hex	H	20:80	72

[a] See Table II. [b] See Scheme II. [c] Diethyl (4-formylbenzylidene)malonate (**1k**) has been prepared from diethylmalonate and terephthaldicarboxaldehyde according to ref 10 (44% yield). [d] See Scheme I.

Scheme I



Scheme II



ated aldehyde **3l** in 72%. Malonates such as **1e** and **1g** bearing a bulky substituent (FG-R: c-Hex or Me_2PhSi) are smoothly converted to the corresponding olefins (entries 5, 7, 11 of Table I); furthermore, the reagent **1g** allows a new stereoselective approach to (*E*)-vinylsilanes. Although the stereochemistry of the newly formed double bond has predominatly the *Z* configuration (*Z*/*E*: ca. 80/20), a dependence with the substituents R^2,R^3 of the 1,1-dimetalloalkane **2** and FG-R,R^1 of the alkylidenemalonate **1** has been observed. Thus, the chloro-substituted alkylidenemalonate **1d** gives very high *Z*/*E* ratios (88/12 and 100/0; entries 4 and 10), whereas the reaction of the cyano-substituted alkylidenemalonate **1c** with **2b** affords mostly the *E* isomer (*Z*/*E*: 7/93). Malonates bearing phenyl or silyl substituents furnish mainly *E* olefins (entries 7 and 14).

A significant improvement on the stereoselectivity can be achieved by using alkylidenemalonates bearing bulky alkoxy groups (**1i** and **1j**). Thus, the reaction of diisopropyl alkylidenemalonate **1i** with the dimetallic reagent **2a** afforded the diene **3a** with a *Z*:*E* ratio of 84:16 (entry 12 of Table I). Furthermore, the *dicyclohexyl* alkylidenemalonate **1j** furnished the same diene **3a** with a *Z*:*E* ratio of 91:9 (entry 13) compared to the ratio of 82:18 obtained with the *diethyl* alkylidenemalonate **1a** (entry 1).

As an application of this methodology, we prepared the cabbage looper moth pheromone (*Z*)-1-acetoxy-7-dodecene (**8**)[11] in two steps from commercially available vinylmagnesium bromide and alkylidenemalonate **1h** in 70% overall yield and in >99.9% stereoisomeric purity (Scheme III). The addition of vinylmagnesium bromide to allylzinc bromide[12] gives the dimetallic reagent **2c** in quantitative yield (THF, 0 °C, 1 h). The reaction of **2c** with the diethyl (7-acetoxyheptylidene)malonate **1h** prepared under our standard conditions from **7a** (THF, −30 °C, 2 h, 88% yield) provided the stereochemically pure (*Z*)-1-acetoxy-7,11-dodecadiene (**3m**) in 80% yield (THF, −20 °C, 0.5 h). A selective reduction of the terminal double bond using 9-borabicyclo[3.3.1]nonane (9-BBN)[13] furnished the desired pheromone **8** in 87% yield and >99.9% stereoisomeric purity ((i) 9-BBN (1 equiv), THF, 25 °C, 3.5 h; (ii) AcOH (7 equiv), THF, 25 °C, 2 h).

Table II. Polyfunctionalized Alkylidenemalonates 1a–j Obtained by the Reaction of Polyfunctionalized Copper–Zinc Reagents (RCu(CN)ZnI) with the [(Phenylsulfonyl)methylidene]malonates 7a–c

entry	FG-R	R^1	product 1	yield,[a] %
1	$(CH_2)_3CO_2Et$	Et	**1a**	90
2	$(CH_2)_3OAc$	Et	**1b**	88
3	$(CH_2)_3CN$	Et	**1c**	83
4	$(CH_2)_4Cl$	Et	**1d**	84
5	c-Hex	Et	**1e**	80
6	$(CH_2)_3SPh$	Et	**1f**	74
7	$SiMe_2Ph$	Et	**1g**	40
6	$(CH_2)_6OAc$	Et	**1h**	88
9	$(CH_2)_3CO_2Et$	i-Pr	**1i**	82
10	$(CH_2)_3CO_2Et$	c-Hex	**1j**	74

[a] Isolated yields of analytically pure products. Satisfactory spectral data (IR, ^1H, and ^{13}C NMR, high-resolution mass spectra) were obtained for all compounds.

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(12) Gaudemar, M. *Bull. Soc. Chim. Fr.* **1962**, 974.

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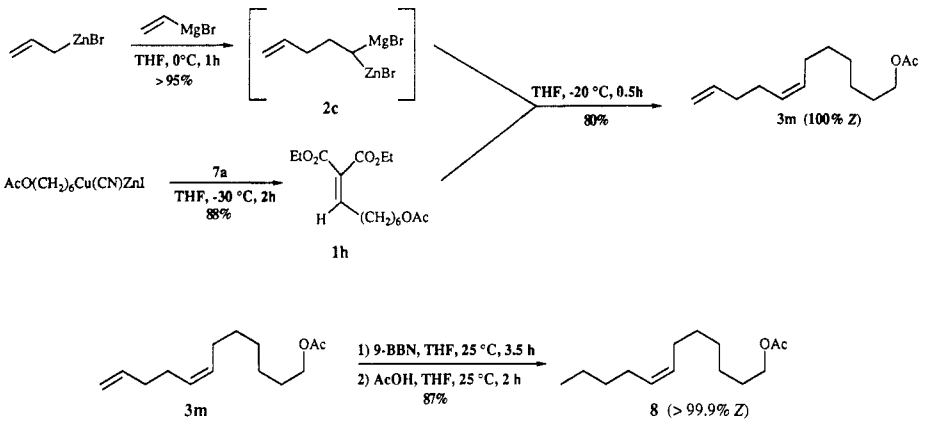
Scheme III



In conclusion, we have shown that the olefination of alkylidenemalonates **1** by 1,1-dimetalloalkanes **2** can accommodate a variety of functional groups and afford polyfunctional olefins **3** with fair to excellent *Z* stereoselectivities. Further studies are currently underway in our laboratories.

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Supplementary Material Available: Typical procedures for the preparation of compounds **1**, **3**, and **7** as well as characterization data for compounds **1a–j**, **3a–m**, and **7a–c** (9 pages). Ordering information is given on any current masthead page.

Synthesis of the Novel Sarcosine and Proline (FK-525) Analogues of FK-506: Rearrangement of the Allylic Ester System

D. Askin,* R. A. Reamer,* Daisy Joe, R. P. Volante, and I. Shinkai

Department of Process Research, Merck Sharp & Dohme Research Laboratories, P.O. Box 2000, Rahway, New Jersey 07065

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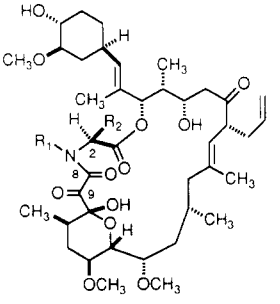
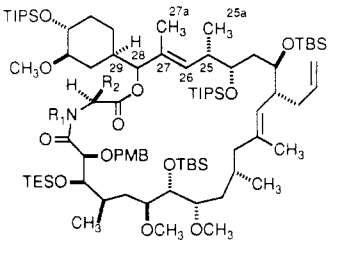
Summary: The novel sarcosine **2** and proline **3** (FK-525) analogues of FK-506 have been synthesized. Allylic rearranged products not observed in the pipecolinic acid series have been isolated from the amino acid formation/macrocyclization step.

The promising data now emerging from clinical studies in transplantation patients with the potent immunosuppressant FK-506[1] has resulted in intense interest in the search for analogues with enhanced efficacy. A systematic study of homologues modified at the tricarbonyl–amino acid linkage, while leaving the remainder of functionality about the macrocyclic array unperturbed, would provide valuable pharmacological information. In the accompanying article, we describe an efficient degradation of natural FK-506 to the selectively protected C_{10}–C_{34} synthetic intermediate **1**.[2] Herein, we demonstrate the use of **1** for the rapid entry into FK-506 amino acid homologues: the novel sarcosine derivative **2** and the proline derivative **3**, the latter isolated[3] from the same culture that produces FK-506. In addition, we report a striking dissimilarity in the amino acid formation/macrocyclization chemistry of the two analogues as compared to the pipecolinic acid (FK-506) series, i.e., the production of allylic rearranged macrocycles **15** and **17** (vide infra).



2 $R_1 = CH_3$, $R_2 = H$
3 R_1, $R_2 = (CH_2)_3$
FK-506 R_1, $R_2 = (CH_2)_4$



15 $R_1 = CH_3$, $R_2 = H$
17 R_1, $R_2 = (CH_2)_3$

Acylation of **1** with *N*-Boc-sarcosine (**4**, $R_1 = CH_3$, $R_2 = H$) and *N*-Boc-(*S*)-proline (**4**, R_1, $R_2 = (CH_2)_3$) under our previously established conditions[4] gave the esters **5**[5a,b] and **6**[5b] (Scheme I). Acetal hydrolysis then afforded the aldehydes **7** and **8** in 98% and 93% overall yields, respectively. Aldol condensation with **9** afforded the adducts **10**[5b]

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(2) Askin, D.; Joe, D.; Reamer, R. A.; Volante, R. P.; Shinkai, I. *J. Org. Chem.*, following paper in this issue. See following article for references to FK-506 isolation and biological activity.

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(4) (a) Jones, T. K.; Mills, S. G.; Reamer, R. A.; Askin, D.; Desmond, R.; Volante, R. P.; Shinkai, I. *J. Am. Chem. Soc.* **1989**, *111*, 1157–1159. (b) End game experimental procedures: Jones, T. K.; Reamer, R. A.; Desmond, R.; Mills, S. G. *J. Am. Chem. Soc.* **1990**, *112*, 2998–3017.

(5) (a) Satisfactory ^1H NMR, ^{13}C NMR, and IR spectral data were obtained for all new compounds. NMR spectral assignments were made using COSY-45 and HETCOR 2-D experiments.[10,11] (b) Satisfactory combustion analysis (C, H, N to within 0.4% of theory) was obtained for this compound. (c) Satisfactory combustion analysis was obtained on the corresponding diol prior to Swern oxidation (Scheme III).

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