solvent; dissolution was effected by swirling. A 10-mg portion of DMAP was added and the test tube was shaken. The time necessary for complete dissipation of color was recorded and the appearance of any precipitate noted.

Isolation of the 2-10 Ion Pair. To a 50-mL, three-necked flask, fitted with a magnetic stirring bar, rubber septum, and nitrogen inlet, was charged 400 mg (1.50 mmol) of carbonic acid, methyl 3-phenylbenzofur-2-yl ester (**4a**) and 30 mL of hexane. To the stirring solution was added 183 mg (1.50 mmol) of 4-(dimethylamino)pyridine, resulting in the immediate precipitation of a purple, highly crystalline solid (the hexane supernatant remained clear and colorless). The hexane was removed via syringe while maintaining a nitrogen atmosphere, leaving 550 mg (94%) of the purple product. Exposure of this material to air resulted in immediate decolorization, deliquescence, and consequential decomposition to an unidentifiable product mixture.

The above experiment was repeated, except that after aspiration of the hexane, 30 mL of chloroform was added via syringe with stirring. A deep blue color formed immediately which dissipated after ca. 30 s. TLC analysis indicated the presence of DMAP and the C-acylated isomer **3a**. The clear, pale yellow solution was worked up as in the general procedure for rearrangement reactions (see above) to afford 364 mg (94%) of 2,3-dihydro-2-oxo-3-phenyl-3-benzofurancarboxylic acid, methyl ester (**3a**), exhibiting identical physical and spectral characteristics as material prepared in earlier experiments.

Acknowledgment. The donors of the Petroleum Research Fund, administered by the American Chemical Society, are gratefully acknowledged for partial support of this project. Additionally, we thank the Council for Faculty Research and Eastern Illinois University for partial financial support. Summer support for two of us (S.M.A. and J.S.S.) was generously provided by the Dow Chemical Company.

Registry No. 1, 3117-37-1; **3a**, 108139-61-3; **3b**, 108139-62-4; **3c**, 108139-63-5; **3d**, 108139-64-6; **3e**, 110745-15-8; **3f**, 110745-16-9; **3g**, 110745-17-0; **3h**, 110745-18-1; **3i**, 110745-19-2; **4a**, 108139-58-8; **4b**, 108139-57-7; **4c**, 108139-59-9; **4d**, 108139-60-2; **4e**, 110745-20-5; **4f**, 110745-21-6; **4g**, 110745-22-7; **4h**, 110745-23-8; DMAP, 1122-58-3; ethyl chloroformate, 541-41-3; propyl chloroformate, 109-61-5; butyl chloroformate, 592-34-7; *sec*-butyl chloroformate, 17462-58-7; benzyl chloroformate, 501-53-1; allyl chloroformate, 2937-50-0; vinyl chloroformate, 5130-24-5; methyl chloroformate, 79-22-1; phenyl chloroformate, 1885-14-9.

Stereoselective Synthesis of Vinylcyclopropanes via Palladium-Catalyzed Reactions

J. E. Bäckvall,*[1a,c] J. O. Vågberg,[1a] C. Zercher,[1a] J. P. Genêt,*[1b] and A. Denis[1b]

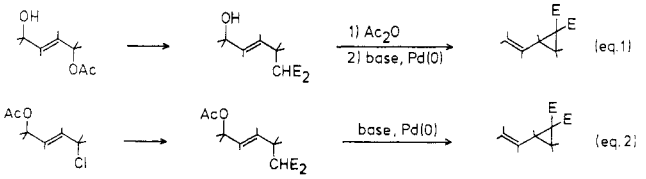
Department of Organic Chemistry, Royal Institute of Technology, S-100 44 Stockholm, Sweden, and Laboratoire de Synthèse Organique et Organometallique Associé au CNRS, Université Pierre et Marie Curie, 75005 Paris, France

Received April 1, 1987

Vinylcyclopropanes were synthesized in a stereocontrolled manner from 1-acetoxy-4-chloro-2-alkenes. A stereospecific palladium-catalyzed substitution of the chloro group by dimethyl malonate anion and subsequent palladium-catalyzed cyclization afforded the vinylcyclopropanes in about 70% overall yield. In the cyclization $Pd(dppe)_2$, $Pd(dba)_2$/dppe, or $Pd(OAc)_2$/dppe was used as catalyst. The best result was obtained with $Pd(OAc)_2$/dppe. It was found that the cyclization to vinylcyclopropane is reversible and under prolonged reaction time dienylmalonates are formed.

Vinylcyclopropanes are a class of compounds that has attracted considerable interest among organic chemists. There are many naturally occuring vinylic cyclopropanes, e.g., carenes, sesquicarenes, sirenine, dictyopterenes, pyrethroids, etc.[2] In addition, vinylcyclopropanes are important synthetic intermediates.[3] As a consequence a number of methods for their preparation have been developed.[2c,d,4]

One of us has recently developed a method for the preparation vinylcyclopropanes from 2-alkene-1,4-diol monoacetates utilizing palladium catalysis (eq 1).[4] We would now like to extend this methodolgy by utilizing 1-acetoxy-4-chloro-2-alkenes[5] as starting materials (eq 2).



This allows control of the relative stereochemistry between the cyclopropane ring and the double bond. In addition, bicyclic vinylcyclopropanes are available by this approach.

In the original approach (eq 1)[4] the starting material was obtained either from hydrogenation of a 2-alkyne-1,4-diol or from condensation of an 1-alkyn-3-ol derivative with an aldehyde (or ketone) and subsequent hydrogenation. Thus, when both carbons bearing the oxygen atoms are chiral, a mixture of two diastereomers is formed. By the use of chloro acetates as starting materials (eq 2) this problem can be overcome. These chloro acetates are prepared from the appropriate conjugated diene in a ste-

(1) (a) Royal Institute of Technology. (b) Université Pierre et Marie Curie. (c) Present address: Department of Chemistry, University of Uppsala, Box 531, 751 21 Uppsala.

(2) (a) *Handbook of Terpenoids*; Dev, S., Ed.; CRC: Boca Raton, FL, 1982; Vol. 2. (b) Otha, Y.; Hirose, Y. *Tetrahedron Lett.* **1968**, 1251. Nutting, W. H.; Rapoport, H.; Machlis, L. *J. Am. Chem. Soc.* **1968**, *90*, 6434. (c) Moore, R. E. *Acc. Chem. Res.* **1977**, *10*, 40. (d) Elliot, M.; Janes, N. F. *Pyrethrum: the Natural Insecticides*; Casida, J. E., Ed.; Academic: New York, 1973; p 56. (e) Elliot, M.; Janes, N. F. *Chem. Soc. Rev.* **1978**, *7*, 473. (f) Arlt, D.; Jautelat, M.; Lantzsch, R. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 703.

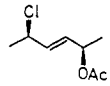
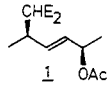
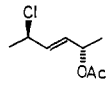
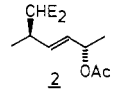
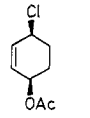
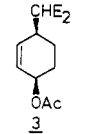
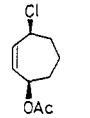
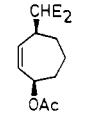
(3) Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66.

(4) (a) Genêt, J. P.; Piau, F.; Ficini, J. *Tetrahedron Lett.* **1980**, *21*, 3183. (b) Genêt, J. P.; Piau, F. *J. Org. Chem.* **1981**, *46*, 2414. (c) Genêt, J. P.; Balabane, M.; Charbonnier, F. *Tetrahedron Lett.* **1982**, *23*, 5027. (d) Colobert, F.; Genêt, J. P. *Tetrahedron Lett.* **1985**, *26*, 2779. (e) Genêt, J. P.; Denis, A.; Charbonnier, F. *Bull. Soc. Chim. Fr.* **1986**, 793. (f) Genêt, J. P. Gaudin, J. M., submitted for publication.

(5) Bäckvall, J. E.; Nyström, J.-E.; Nordberg, R. E. *J. Am. Chem. Soc.* **1985**, *107*, 3676.

0022-3263/87/1952-5430$01.50/0

Table I. Preparation of Compounds 1–4[a,b]

chloro acetate	product	% yield[c]	characterztn
	 1	96[d]	ref 5
	 2	94[e]	ref 5
	 3	99[f]	ref 5
	 4	95[f]	g

[a] E = COOMe. [b] The chloro acetate was reacted with 1.1–1.5 equiv of dimethyl malonate in the presence of 2 mol % of $Pd(OAc)_2$ and 8 mol % of PPh_3 (THF, 20 °C, 1 h). [c] Yield of pure product after Kugelrohr distillation. [d] >95% *R*R**. [e] >95% *R*S**. [f] >98% cis. [g] IR, ^1H NMR, ^{13}C NMR, elemental analysis.

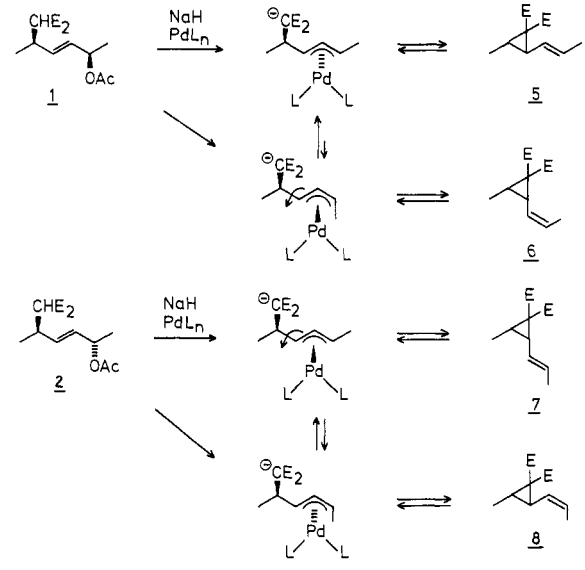
reospecific reaction with control of the 1,4-relative stereochemistry.[5] Thus a control of the stereochemistry of the vinylcyclopropane should be possible, since the 1,3-chirality transfer in the cyclization step is known to be high.[4d,f]

The compounds **1–4** were prepared from the corresponding chloro acetates via a stereoselective palladium-catalyzed nucleophilic substitution of the chloro group (Table I).[5] The reaction is rapid (10–30 min, 20 °C) and utilizes 2 mol % of $Pd(OAc)_2$ as catalyst together with triphenylphosphine.[6] The diastereomeric purity of compounds **1–4** was determined by ^1H NMR and found to be in the range of 95–98%.

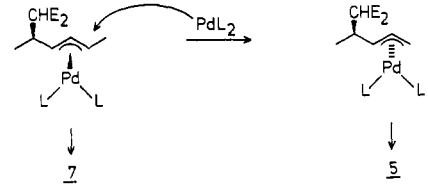
Reaction of compound **1** with NaH in THF followed by addition of the palladium(0) catalyst resulted in a formal S_N' cyclization and formation of vinylcyclopropane **5** (entries 1–2, Table II). The reaction proceeds via a π-allylpalladium intermediate followed by an intramolecular attack by the carbanion (Scheme I). Since formation of the π-allyl complex occurs with inversion of configuration at carbon[7] and the attack by the carbanion takes place with another inversion at carbon[8] the two possible products would be **5** and **6**.[9] Since formation of **6** would have to proceed through a rather strained transition state leading to the cis-*E* product, the expected product from **1** would be **5**. This is also observed. Compound **6** could not be detected (<1%). However, small amounts of the other possible isomers **7** and **8** were present. It was concluded from the ^1H NMR that **5** was 93% trans-*E* when $Pd(dppe)_2$ was used as catalyst (entry 1) and >95% trans-*E* when $Pd(OAc)_2$/dppe was used as catalyst (entry 2). When corrected for a diastereomeric purity of 95% for **1**, the stereospecificities of the reactions are 98% and 100% respectively.

Reaction of compound **2** under the same conditions as in entry 1 ($Pd(dppe)_2$) was nonstereospecific and led to a mixture of isomers **5**, **7**, and **8** in a ratio of 45:11:44 (entry 4). Interestingly the isomer distribution varied with the

Scheme I



Scheme II



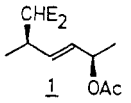
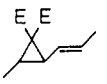
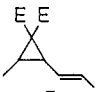
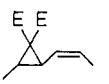
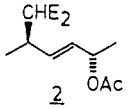
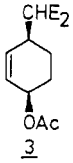
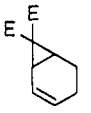
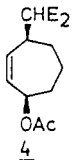
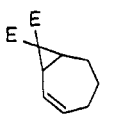
reaction conditions. Thus, with a shorter reaction time and lower concentration (0.25 M) and with $Pd(OAc)_2$/dppe as catalyst the ratio **5**/**7**/**8** was 6:70:24 (entry 5). Since the isomers **7** and **8** are those expected from a stereospecific reaction (cf. Scheme I), the relative yield of product from a stereospecific reaction is 94%. This corresponds to a stereoselectivity of 99% when corrected for a 95% diastereomeric purity for **2**. Contrary to entry 4, the major product is **7** in entry 5. It was generally found that if the reaction was run for a long time or with less ligand the ratio **7**/**8** decreased, indicating that **7** is the kinetic product and **8** the thermodynamic product of the two. This is consistent with an equilibrium between the vinylcyclopropane and the π-allylpalladium complex (vide infra).

Interestingly, the reaction of **1** and **2** using a ratio of Pd/dppe of 1/1 resulted in a less stereospecific reaction in both cases. Thus, under these conditions **1** and **2** afforded **5**, **7**, and **8** in an approximate ratio of 7:1:2 and 6:1:3, respectively.

The reason for the loss of stereospecificity in some of the cyclizations of **1** and **2** is not clear. Isomerization in palladium(0)-catalyzed reactions is sometimes caused by a cis migration of acetate in the π-allylpalladium intermediate,[10,11] leading to isomerization of the starting material.[11] We therefore isolated the starting material after approximately 70–80% conversion of **1** and **2** for those cases where a considerable loss of stereospecificity took place. ^1H NMR analysis of the recovered starting materials showed that no isomerization had occurred. This indicates that the loss of stereospecificity is not caused by the isomerization of the starting material. Furthermore, the addition of chloride ligands (from LiCl or $Bu_4N^+Cl^-$), which

(6) This generates a palladium(0)–phosphine catalyst in situ.
(7) Hayashi, T.; Hagihara, T.; Konishi, M.; Kumada, M. *J. Am. Chem. Soc.* **1983**, *105*, 7767.
(8) (a) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4730. (b) Hayashi, T.; Konishi, M.; Kumada, M. *J. Chem. Soc., Chem. Commun.* **1984**, 107.
(9) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385.
(10) Bäckvall, J. E.; Nordberg, R. E.; Björkman, E. E.; Moberg, C. *J. Chem. Soc., Chem. Commun.* **1980**, 943. Bäckvall, J. E.; Nordberg, R. E.; Wilhelm, D. *J. Am. Chem. Soc.* **1985**, *107*, 6892.
(11) Trost, B. M.; Verhoeven, T. R.; Fortunak, J. M. *Tetrahedron Lett.* **1979**, 2301.

Table II. Cyclization of 1-4 to Vinylcyclopropanes[a,b]

entry	start materl	catalyst (method)	reacn time/temp (substrate conc)	product(s)[d] 5	7	8	% yield[e]
	 1						
1		$Pd(dppe)_2$ (A)	18 h/25 °C (0.5 M)	93	3	4	70
2		$Pd(OAc)_2$ + 2.4 dppe (B)	1 h, 25 min/50 °C (0.25 M)	>95	4	<1	72
3		none	21 h/80 °C[c] (0.25 M)	89	5	6	(71)[f]
	 2						
4		$Pd(dppe)_2$ (A)	18 h/25 °C (0.5 M)	45	11	44	70
5		$Pd(OAc)_2$ + 2.4 dppe (B)	1 h/50 °C (0.25 M)	6	70	24	70
6		$Pd/(dba)_2$ + 2 dppe (C)	22 h/50 °C (0.25 M)	8	74	18	54
7		none	16 h/80 °C[c] (0.25 M)	9	74	17	37 (65)[f]
	 3				 9		
8		$Pd(dppe)_2$ (A)	25 min/40 °C (0.5 M)		>98		71
9		$Pd(OAc)$ + 2.4 dppe (B)	45 min/50 °C (0.17 M)		>98		68
	 4				 10		
10		$Pd(OAc)_2$ + 2.4 dppe (B)	45 min/50 °C (0.17 M)		>98		77
11		$Pd(dba)_2$ + 2 dppe (C)	6 h/50 °C (0.17 M)		>98		69

[a] E = COOMe. [b] The palladium-catalyzed reactions were performed in THF. The amount of palladium catalyst was 5 mol %. [c] The noncatalyzed reactions were run in dimethoxyethane (DME). [d] The product ratio was determined by ^1H NMR in the isolated products. [e] Unless otherwise noted: isolated yields after flash chromatography or Kugelrohr distillation. The isomer distribution was the same before and after purification. [f] Yields determined from the ^1H NMR of the crude products.

is known to strongly inhibit migration of acetate by blocking its coordination,[12,13] did not improve the stereoselectivity.

A likely explanation for the loss of stereospecificity observed here would be that the palladium(0) phosphine complex is attacking the π-allylpalladium intermediate according to Scheme II. Recent results indicate that such a mechanism accounts for the isomerization of optically active π-allylpalladium complexes in the presence of palladium(0) phosphine complexes.[14] Also, the fact that a lower stereospecificity was obtained when the ratio Pd/dppe was 1:1 compared to 1:2 is consistent with such a mechanism.

Reaction of compound **3** under analogous conditions afforded vinylcyclopropane **9** in 71% yield (entry 8, Table II). Also the seven-membered ring compound **4** gave the corresponding bicyclic vinylcyclopropane **10**. The latter reaction was very sensitive to the reaction conditions and the use of less ligand gave only a 4:1 mixture of the dienes **11** and **12** in 67% isolated yield. By carefully monitoring

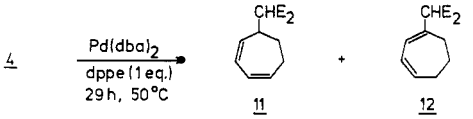
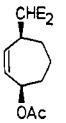
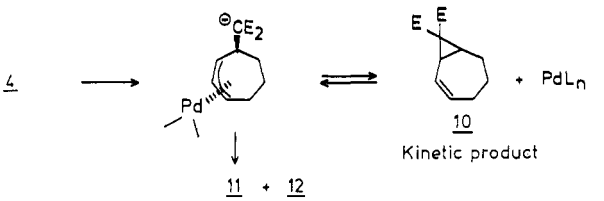


Table III. Pd-Catalyzed Reaction of 4[a,b]

reacn time, h	 4	 10	 11	 12	ratio 11/12
0	100				
2		96.5	2.3	1.2	2
3.5		93.6	4.1	2.2	2
12		72.0	19.8	8.2	2.4
15		62.1	26.7	11.2	2.4
18.5		50.5	34.9	14.6	2.4
40		7.8	65.1	27.2	2.4
46		3.9	68.4	27.7	2.5

[a] The reaction was performed at 80 °C in dimethoxyethane with 0.1 equiv each of $Pd(dba)_2$ and dppe. [b] The reaction was monitored by gas chromatography.

Scheme III



the reaction by GLC it was shown that the vinylcyclopropane **10** is an intermediate in the transformation of **4** to **11** and **12** (Table III). This requires that the vinylcyclopropane is opened by palladium(0) and in equilibrium

(12) Nordberg, R. E.; Bäckvall, J. E. *J. Organomet. Chem.* **1985**, *C24*, 285.
(13) Bäckvall, J. E.; Nordberg, R. E. *J. Am. Chem. Soc.* **1981**, *103*, 4959.
(14) Mackenzie, P. B.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2046.

with the π-allylpalladium complex (Scheme III). The kinetic product of the system is **10**, which on prolonged reaction time will be transformed to **11** and **12**. Palladium(0)-catalyzed ring cleavage of vinylcyclopropanes to generate an intermediate π-allylpalladium complex has been observed previously.[15]

The equilibrium between the vinylcyclopropane and the π-allyl complex cannot in itself account for the loss of stereospecificity discussed above, provided the ring opening is stereospecific and occurs with inversion.[16] However, the equilibrium can facilitate the isomerization by generating the π-allyl intermediate (cf. Scheme II).

The corresponding noncatalyzed reaction of **1** and **2** (NaH, DME, 80 °C) resulted in a predominant syn S_N' displacement (entries 2 and 5, Table II).[17] The relative yield of syn product from **1** and **2** is 89% and 91%, respectively, which corresponds to a stereoselectivity of 94% and 96%, respectively, when corrected for a diasteromeric purity of 95% for **1** and **2**. The noncatalyzed reaction was considerably slower and required elevated temperature. Attempts to run a noncatalyzed reaction on substrates **3** and **4** under the same conditions were unsuccessful and gave only traces of product (<3%).

It is interesting to compare the catalysts used in the different procedures: $Pd(dppe)_2$ (A), $Pd(OAc)_2$/dppe (B), and $Pd(dba)_2$/dppe (C). In all cases tried the catalyst used in procedure B was the most efficient one. It is also by far the most convenient system to use since palladium acetate is a readily available compound that is completely stable toward air. The catalyst used in procedure C was considerably slower than those used in procedures A and B, indicating that dba to some extent acts as a ligand during the reaction.

Experimental Section

General. Infrared spectra were obtained on a Perkin-Elmer 257 spectrophotometer. NMR spectra were recorded with a Bruker WP 200 FT spectrometer (^1H NMR at 200 MHz and ^{13}C NMR at 50.3 MHz) or a Bruker AM 400 FT spectrometer (^1H NMR at 400 MHz and ^{13}C NMR at 100.6 MHz). Chemical shifts are reported in δ units, parts per million (ppm) downfield from tetramethylsilane, unless otherwise noted. All NMR spectra were obtained in $CDCl_3$ solutions. Resolution enhancement was used to determine the coupling constants. DEPT (distortionless enhancement by polarization transfer) spectra were determined to assign carbon multiplicities (s, C; d, CH; t, CH_2; q, CH_3). Analytical GLC was performed on a Varian Model 3700 gas chromatograph with a FID detector, connected to a computing integrator. A 25-m DB-1 (methylsilicone) capillary column was used. Preparative HPLC was performed on a Waters M-45 instrument with a μ-Porasil column (silica, 10-μm packing, 30 × 0.4 cm) and a differential refractometer as detector. Kugelrohr distillations were performed with a Büchi Kugelrohr apparatus. Melting points were obtained on a Büchi 510 melting point apparatus, and are uncorrected. Thin-layer chromatography (TLC) was performed on 0.2-mm Merck precoated silica gel plates (60 F 254). Flash chromatography separations were performed on Merck silica gel 60 (230–400 mesh), as described by Still.[18] All chromatography solvents were distilled prior to use. Elemental analyses were performed by Analytical Laboratories, Engelskirchen, Germany.

Bis(dibenzylideneacetone)palladium(0), ($Pd(dba)_2$) was prepared according to a described procedure.[19] Palladium acetate was purchased from Fluka AG. 1,2-Bis(diphenylphosphino)ethane, (dppe) was purchased from the Aldrich Chemical Co. and was recrystallized from ethanol prior to use. Dimethyl malonate was obtained from the Aldrich Chemical Co. and was distilled prior to use. Sodium hydride (80% in oil, Merck) was washed with two or three portions of distilled *n*-hexane before use. Tosyl azide was prepared by the literature procedure.[20] Tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME) were distilled from deep blue solutions of potassium/benzophenone under nitrogen. All reactions were conducted under an atmosphere of dry nitrogen in oven-dried (120 °C) or flame-dried glassware.

Preparation of Starting Materials. Dimethyl ((*E*)-(*R,*R**)-5-Acetoxyhex-3-en-2-yl)malonate (1).** A solution of sodium dimethyl malonate in THF (96 mL of a 0.125 M solution, 12.0 mmol; prepared from 1.05 equiv of dimethyl malonate and 1.00 equiv of sodium hydride) was added to a mixture of (*E*)-(*R**,*R**)-2-acetoxy-5-chloro-3-hexene[5] (1.41 g, 8.0 mmol), palladium acetate (36 mg, 0.16 mmol), and triphenylphosphine (168 mg, 0.64 mmol) under an atmosphere of nitrogen at 20 °C. After the mixture was stirred for 1 h at room temperature, saturated aqueous sodium hydrogen carbonate (30 mL), water (15 mL), and ether (60 mL) were added. The layers were separated, and the aqueous phase was extractd with ether (3 × 75 mL). The combined organic phases were washed with brine (50 mL) and dried ($MgSO_4$). The solvents were removed on a rotary evaporator, and the resulting oil was eluted through a short column (4.5 × 5 cm) of silica gel with ether. Drying ($MgSO_4$) and evaporation of the solvent gave 3.03 g of crude material. Excess dimethyl malonate was removed by Kugelrohr distillation [80 °C (0.5 mm)]. Further distillation [170 °C (0.4 mm)] gave 2.08 g (96%) of pure **1** as a colorless oil. (>95% *R**,*R** according to ^1H NMR[5]): ^{13}C NMR (100.6 MHz)[21] δ 169.6 (s, CO in AcO), 168.1 (s, CO in CO_2Me), 168.0 (s, CO in CO_2Me), 133.0 (d), 130.6 (d), 70.0 (d, *C*HOAc), 57.1 (d, *C*H($CO_2Me)_2$), 52.0 (q, OMe), 51.8 (q, OMe), 36.5 (d, *C*HCH($CO_2Me)_2$), 20.9 (q), 19.9 (q), 17.7 (q).

Dimethyl ((*E*)-(*R,*S**)-5-Acetoxyhex-3-en-2-yl)malonate (2).** **2** was prepared by using the same procedure as for the preparation of **1**. (*E*)-(*R**,*S**)-2-acetoxy-5-chloro-3-hexene[5] (1.41 g, 8.0 mmol) gave 2.05 g (94%) of **2** as a colorless oil after Kugelrohr distillation [165 °C (0.4 mm)]: >95% *R**,*S** according to ^1H NMR,[5] ^{13}C NMR (100.6 MHz)[21] δ 169.7 (s, CO in AcO), 168.10 (s, CO in CO_2Me), 168.05 (s, CO in CO_2Me), 132.9 (d), 130.6 (d), 70.1 (d, *C*HOAc), 57.2 (d, *C*H($CO_2Me)_2$), 52.0 (q, OMe), 51.8 (q, OMe), 36.6 (d, *C*HCH($CO_2Me)_2$), 20.9 (q), 20.0 (q), 17.8 (q).

Dimethyl (*cis*-4-Acetoxycyclohex-2-en-1-yl)malonate (3). Reaction of sodium dimethyl malonate (220 mL of a 0.125 M solution in THF, 27.5 mmol), palladium acetate (124 mg, 0.55 mmol), triphenylphosphine (593 mg, 2.26 mmol), and *cis*-1-acetoxy-4-chloro-2-cyclohexene[5] (4.37 g, 25.0 mmol) for 45 min according to the procedure for the preparation of **1** gave 6.69 g (99%) of **3** as a colorless oil after Kugelrohr distillation [200 °C (1 mm)]: >98% cis according to ^1H NMR;[5] ^{13}C NMR (100.6 MHz)[21] δ 170.2 (s, CO in AcO), 168.3 (s, CO in CO_2Me), 168.2 (s, CO in CO_2Me), 133.1 (d), 126.7 (d), 66.0 (d, *C*HOAc), 55.7 (d, *C*H($CO_2Me)_2$), 52.25 (q, OMe), 52.22 (q, OMe), 35.1 (d, *C*HCH($CO_2Me)_2$), 26.7 (t), 22.0 (d), 21.0 (q, CH_3 in AcO).

Dimethyl (*cis*-4-Acetoxycyclohept-2-en-1-yl)malonate (4). Essentially the same procedure as for the preparation of **1**, except that a 0.2 M solution of sodium dimethyl malonate in THF (94.5 mL, 18.9 mmol) was used for *cis*-1-acetoxy-4-chloro-2-cycloheptene[5] (2.97 g, 15.75 mmol). After the usual workup and Kugelrohr distillation [175 °C (0.2 mm)], 4.25 g (95%) of **4** was obtained as a slightly yellow oil (>98% cis): ^1H NMR (200 MHz) δ 5.76–5.59 (m, 2 H, olefinic), 5.49–5.39 (m, 1 H, C*H*OAc), 3.74 (s, 3 H, one of CO_2Me), 3.73 (s, 3 H, one of CO_2Me), 3.46 (d, *J* = 7.9 Hz, 1 H, C*H*($CO_2Me)_2$), 3.05–2.92 (m, 1 H, C*H*CH($CO_2Me)_2$), 2.05 (s, 3 H, OAc), 2.1–1.2 (m, 6 H, CH_2); ^{13}C NMR (100.6 MHz)[21] δ 170.0 (s, CO in AcO), 168.6 (s, CO in CO_2Me), 168.5 (s, CO in CO_2Me), 134.3 (d), 131.2 (d), 73.7 (d, *C*HOAc), 56.4 (d, *C*H($CO_2Me)_2$), 52.30 (q, OMe), 52.25 (q, OMe), 39.4 (d, *C*HCH($CO_2Me)_2$), 32.0 (t), 30.4 (t), 26.2 (t), 21.1 (q, CH_3 in AcO); IR (neat) 2955, 2935, 1740, 1440, 1375, 1250, 1155, 1030 cm^{-1}. Anal. Calcd

(15) Burgess, K. *Tetrahedron Lett.* **1985**, *26*, 3049 and references cited therein.

(16) All reported examples on formation of π-allylpalladium complexes from allylic derivatives follow an inversion mechanism (For example, see ref 5, 7–9, and 14).

(17) Bäckvall, J. E.; Vågberg, J. O.; Genêt, J. P. *J. Chem. Soc., Chem. Commun.* **1987**, 159.

(18) Still, W. C.; Kahn, M.; Mita, A. *J. Org. Chem.* **1978**, *43*, 2923.

(19) Rettig, M. F.; Maitlis, P. M. *Inorg. Synth.* **1977**, *17*, 135.

(20) Regitz, M.; Hocker, J.; Liedhegener, A.; *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. 5, p 179.

(21) Chemical shifts are reported with the middle peak of $CDCl_3$ (77.00 ppm) as internal standard.

for $C_{14}H_{20}O_6$: C, 59.15; H, 7.09. Found: C, 59.31; H, 6.98.

Procedures for the Palladium-Catalyzed Cyclizations of Compounds 1-4 to Vinylcyclopropanes. Method A. Dimethyl *trans*-2-(*E*)-prop-1-enyl-3-methylcyclopropane-1,1-dicarboxylate (5). To a solution of 1 (272 mg, 1.0 mmol) in THF (2 mL) was added NaH (44 mg, 1.1 mmol) as a 60% suspension in oil. After the mixture was stirred for 1 h at 20 °C, $Pd(dppe)_2$ (45 mg, 0.05 mmol) was added. The mixture was then stirred at 25 °C for 18 h under an atmosphere of nitrogen. The reaction mixture was cooled to 15 °C, and then a 10% HCl solution (1 mL) together with ether (10 mL) was added. The organic phase was collected, washed with water (2 mL), and dried ($MgSO_4$). Evaporation of the solvents and purification of the crude product by flash chromatography (ether/hexane = 1:2) afforded 149 mg (70%) of a colorless oil. The product consisted of **5** (93%), dimethyl *cis*-2-(*E*)-prop-1-enyl-3-methylcyclopropane-1,1-dicarboxylate (**7**) (3%), and dimethyl *trans*-2-(*Z*)-prop-1-enyl-3-methylcyclopropane-1,1-dicarboxylate (**8**) (4%) according to ^1H NMR analysis. **5**: ^1H NMR (200 MHz) δ 5.72 (dq, J = 15.0, 6.5 Hz, 1 H, MeC*H*=C), 5.10 (ddq, J = 15.0, 8.5, 1.7 Hz, 1 H, MeC=C*H*), 3.74 (s, 3 H, one of CO_2Me), 3.72 (s, 3 H, one of CO_2Me), 2.36 (dd, J = 8.5, 7.5 Hz, 1 H, allylic cyclopropyl proton), 2.04 (dq, J = 7.5, 6.5 Hz, 1 H, other cyclopropyl proton), 1.66 (dd, J = 6.5, 1.7 Hz, 3 H, CH_3C=C), 1.12 (d, J = 6.5 Hz, 3 H, CH_3); ^{13}C NMR (100.6 MHz)[21] δ 168.6 (CO), 168.4 (CO), 129.4 (C=*C*-CH_3), 125.6 (*C*=CCH_3), 52.5 (2 C, OMe), 41.6 (C-1), 36.5 (C-2), 27.1 (C-3), 17.9 (C=*C*CH_3), 12.4 (CH_3); IR (neat) (on the mixture of **5**, **7**, and **8**) 2960, 1730, 1440, 1300, 1250, 1205 (broad), 1140, 1070 cm^{-1}. Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found (for the mixture of **5**, **7**, and **8**): C, 62.13; H, 7.49.

Method B. Mixture of Dimethyl *cis*-2-(*E*)-Prop-1-enyl-3-methylcyclopropane-1,1-dicarboxylate (7) and Dimethyl *trans*-2-(*Z*)-Prop-1-enyl-3-methylcyclopropane-1,1-dicarboxylate (8). To NaH (33 mg, 1.1 mmol) as a 80% suspension in oil was added a solution of **2** (272 mg, 1.0 mmol) in THF (4 mL). The mixture was stirred for 45 min at 20 °C, and then $Pd(OAc)_2$ (11 mg, 0.05 mmol) and dppe (48 mg, 0.12 mmol) were added. The reaction mixture was warmed to 50 °C and stirred for 1 h at this temperature, under an atmosphere of dry nitrogen. The original green color of the mixture had now turned to yellow. The solution was allowed to cool to room temperature, and then saturated aqueous $NaHCO_3$ (4 mL) and ether (10 mL) were added. The phases were separated, and the aqueous phase was extracted with ether (2 × 10 mL). The combined organic phases were washed with brine (5 mL) and dried ($MgSO_4$). The solvents were removed, and the resulting oil was eluted through a short column (5 × 2 cm) of silica gel with hexane/EtOAc (8:2). Rotary evaporation of the solvents and purification of the crude product by Kugelrohr distillation [130 °C (0.15 mm)] afforded 149 mg (70%) of a colorless oil. According to ^1H NMR analysis the product consisted of **7** (70%), **8** (24%), and **5** (6%). For analytical purposes **7** was separated from **5** and **8** by preparative HPLC.

7: ^1H NMR (200 MHz) δ 5.78 (dq, J = 15.0, 6.5 Hz, 1 H, MeC*H*=C), 5.23 (ddq, J = 15.0, 9.5, 1.7 Hz, 1 H, MeC=C*H*), 3.77 (s, 3 H, one of CO_2Me), 3.72 (s, 3 H, one of CO_2Me), 2.38 (dd, J = 9.7, 9.5 Hz, 1 H, allylic cyclopropyl proton), 1.93 (dq, J = 9.7, 6.8 Hz, 1 H, other cyclopropyl proton), 1.73 (dd, J = 6.5, 1.7 Hz, 3 H, CH_3C=C), 1.18 (d, J = 6.8 Hz, 3 H, CH_3); ^{13}C NMR (100.6 MHz)[21] δ 170.9 (CO), 167.3 (CO), 130.3 (C=*C*CH_3), 123.3 (*C*=CCH_3), 52.7 (OMe), 52.2 (OMe), 38.3 (C-1), 34.7 (C-2), 26.4 (C-3), 18.3 (C=CCH_3), 9.9 (CH_3); ^{13}C NMR assignments are based on a 2D proton–carbon correlation spectrum.

8: ^1H NMR (200 MHz) δ 5.58 (dq, J = 11.0, 7.0 Hz, 1 H, MeC*H*=C), 5.01 (ddq, J = 11.0, 8.5, 1.7 Hz, 1 H, MeC=C*H*), 3.76 (s, 3 H, one of CO_2Me), 3.71 (s, 3 H, one of CO_2Me), 2.55 (dd, J = 8.5, 7.5 Hz, 1 H, allylic cyclopropyl proton), 2.05 (dq, J = 7.5, 6.5 Hz, 1 H, other cyclopropyl proton), 1.74 (dd, J = 7.0, 1.7 Hz, 3 H, CH_3C=C), 1.15 (d, J = 6.5 Hz, 3 H, CH_3); ^{13}C NMR (100.6 MHz)[21] δ 168.6 (CO), 168.5 (CO), 128.7 (C=*C*CH_3), 125.2 (*C*=CCH_3), 52.4 (2 C, OMe), 41.9 (C-1), 31.9 (C-2), 27.9 (C-3), 13.4 (C=CCH_3), 12.5 (CH_3).

Method C. Dimethyl Bicyclo[5.1.0]oct-2-ene-8,8-dicarboxylate (10). A solution of **4** (226 mg, 1.5 mmol) in THF (9 mL) was added to an 80% suspension of NaH in oil (45 mg, 1.5 mmol). The mixture was stirred for 1 h at 20 °C and was then cannulated into a flask containing $Pd(dba)_2$ (43 mg, 0.075 mmol) and dppe (60 mg, 0.15 mmol). The mixture was warmed to 50 °C and stirred for 6 h at this temperature, under an atmosphere of dry nitrogen. The reaction mixture was allowed to cool to room temperature, and then saturated aqueous $NaHCO_3$ (5 mL) together with ether (10 mL) was added. The layers were separated, and the aqueous phase was extracted with ether (2 × 10 mL). The combined organic phases were washed with brine (5 mL) and dried ($MgSO_4$). The solvents were removed by rotary evaporation, and the crude product was eluted through a short column (5 × 2 cm) of silica gel with hexane/EtOAc (8:2). Evaporation of the solvents gave 310 mg of a yellow oil, which contained the product together with dibenzylideneacetone and dppe. Kugelrohr distillation [165 °C (0.2 mm)] gave 233 mg (69%) of **10** as a white crystalline solid: mp 59–60 °C: ^1H NMR (200 MHz) δ 5.75–5.52 (m, 2 H, olefinic), 3.73 (s, 3 H, one of CO_2Me), 3.72 (s, 3 H, one of CO_2Me), 2.55–2.34 (m, 1 H), 2.32–2.22 (m, 1 H), 2.18–1.94 (m, 3 H), 1.85–1.52 (m, 1 H); ^{13}C NMR (100.6 MHz)[21] δ 170.8 (s, CO), 167.0 (s, CO), 131.0 (d, CH_2*C*=C), 123.4 (d, C=*C*CH), 52.5 (q, OMe), 52.0 (q, OMe), 38.1 (s, C-8), 30.7 (d), 29.7 (d), 28.3 (t), 23.6 (t), 23.1 (t); IR (CCl_4) 2950, 1735, 1440, 1325, 1260, 1200 (broad), 1120 cm^{-1}. Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.43; H, 7.08.

Dimethyl Bicyclo[4.1.0]hept-2-ene-7,7-dicarboxylate (9). Reaction of **3** (270 mg, 1.0 mmol) in THF (6 mL) according to method B (45 min, 50 °C), gave 142 mg (68%) of pure **9** as a white crystalline solid, after the normal workup and Kugelrohr distillation [155 °C (0.2 mm)]: mp 38–39°C: ^1H NMR (200 MHz) δ 5.90 (m, 1 H, olefinic), 5.71 (ddd, J = 10.0, 5.0, 3.1 Hz, 1 H, olefinic), 3.73 (s, 3 H, one of CO_2Me), 3.71 (s, 3 H, one of CO_2Me), 2.28–1.83 (m, 5 H), 1.67 (dtt, J = 17.3, 9.0, 3.0 Hz, 1 H); ^{13}C NMR (100.6 MHz)[21] δ 170.0 (s, CO), 167.6 (s, CO), 127.7 (d, CH_2*C*=C), 121.7 (d, C=*C*CH), 52.5 (q, OMe), 52.4 (q, OMe), 40.7 (s, C-7), 26.5 (d), 24.4 (d), 20.4 (t), 15.9 (t); IR (neat) 3040, 2955, 1730, 1440, 1330, 1260, 1195 broad), 1110, 710, 690 cm^{-1}. Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.70; H, 6.63.

Procedure for the Noncatalyzed Reactions. Mixture of 5, 7, and 8. A solution of **2** (136 mg, 0.5 mmol) in DME (6 mL) was added to an 80% dispersion of NaH in oil (15 mg, 0.5 mmol). The mixture was stirred at 20 °C for 20 min and was then heated at reflux for 16 h. The reaction mixture was allowed to cool to room temperature, and then aqueous $NaHCO_3$ (5 mL) and ether (10 mL) were added. The organic phase was collected, and the aqueous phase was extracted with ether (2 × 10 mL). The combined organic phases were washed with brine (5 mL) and dried ($MgSO_4$). Evaporation of the solvents and purification of the crude product by flash chromatography (hexane/EtOAc = 8:2) gave 39 mg (37%) of a colorless oil. According to ^1H NMR analysis the mixture consisted of **5** (9%), **7** (74%), and **8** (17%).

Configurational Assignments of the Vinylcyclopropanes 5, 7, and 8. The products **5**, **7**, and **8** were unambigously assigned from their ^1H and ^{13}C NMR spectra. The J_{HH} of the cyclopropane in **5**, **7**, and **8** are 7.5, 9.7, and 7.5 Hz, respectively. The J_{HH} of the olefin in **5**, **7**, and **8** are 15.0, 15.0, and 11.0 Hz, respectively. All three carbon atoms of the cyclopropane in **7** appear at a higher field than in the trans isomer **5**.[22] Furthermore, an authentic sample of **5** was prepared by an other method.

Authentic Sample of 5. Dimethyl diazomalonate was prepared from dimethyl malonate and tosyl azide according to a procedure by Regitz.[23] The dimethyl diazomalonate was then reacted with an excess of (*E*,*E*)-2,4-hexadiene and a catalytic amount of finely divided activated copper powder, to produce **5** as the only product.[24] The ^1H NMR spectrum of this compound was identical with the one obtained from the major product in the palladium-catalyzed cyclization of **1**.

Mixture of Dimethyl Cyclohepta-2,4-dien-1-ylmalonate (11) and Dimethyl Cyclohepta-1,3-dien-1-ylmalonate (12). A solution of **4** (284 mg, 1.0 mmol) in DME (5 mL) was reacted with $Pd(dba)_2$ (58 mg, 0.1 mmol) and dppe (40 mg, 0.1 mmol) according to procedure C (50 °C, 29 h). Workup according to procedure C and purification by flash chromatography (hexane/EtOAc = 8:2) yielded 149 mg (67%) of a slightly yellow oil, which according

(22) *Stereochemistry*; Kagan, H. B., Ed.; Georg Thieme Verlag: Stuttgart 1977; pp 77–81.
(23) Regitz, M. *Synthesis* **1972**, 351.
(24) Mazzocchi, P. H.; Tamburin, H. J. *J. Org. Chem.* **1973**, *38*, 2221.

to ^{1}H NMR analysis consisted of **11** and **12** in a ratio of 4:1. The oil also contained a small amount (less than 6%) of dibenzylideneacetone as an impurity.

11: ^{1}H NMR (200 MHz) (assigned peaks in mixture with **12**) δ 5.9–5.6 (m, 4 H, olefinic), 3.75 (s, 3 H, one of CO_2Me), 3.74 (s, 3 H, one of CO_2Me), 3.51 (d, J = 8.8 Hz, 1 H, $CH(CO_2Me)_2$), 3.18 (m, 1 H, $CHCH(CO_2Me)_2$), 2.45–2.3 (m, 2 H, allylic CH_2), 1.95–1.75 (m, 2 H, CH_2).

12: ^{1}H NMR (200 MHz) (assigned peaks in mixture with **11**) δ 5.9–5.6 (m, 3 H, olefinic), 4.12 (s, 1 H, $CH(CO_2Me)_2$), 3.75 (s, 6 H, CO_2Me), 2.45–2.3 (m, 4 H, allylic CH_2), 1.95–1.75 (m, 2 H, CH_2).

Registry No. **1**, 96039-90-6; **2**, 96039-91-7; **3**, 82736-52-5; **4**, 110418-98-9; **5**, 39495-94-8; **7**, 110455-97-5; **8**, 110455-98-6; **9**, 15833-44-0; **10**, 110418-99-0; **11**, 91550-40-2; **12**, 110419-00-6; $Pd(dppe)_2$, 31277-98-2; $Pd(dba)_2$, 81141-80-2; dimethyl malonate, 108-59-8; (*E*)-(*R**,*R**)-2-acetoxy-5-chloro-3-hexene, 95177-49-4; (*E*)-(*R**,*S**)-2-acetoxy-5-chloro-3-hexene, 95177-50-7; sodium dimethyl malonate, 18424-76-5; *cis*-1-acetoxy-4-chloro-2-cyclohexene, 82736-39-8; *cis*-1-acetoxy-4-chloro-2-cycloheptene, 82736-40-1; dimethyl diazomalonate, 6773-29-1; (*E*,*E*)-2,4-hexadiene, 5194-51-4.

Stereochemistry of the Cyclic Tripeptide Antibiotic WS-43708A

Rajamoorthi Kannan and Dudley H. Williams*

University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K.

Received April 27, 1987

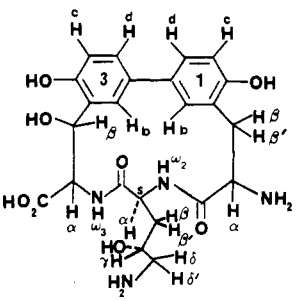
By the use of proton NMR spectroscopy, in particular of coupling constant and NOE data, it is shown that the cyclic tripeptide antibiotic WS-43708A has *S* stereochemistry at the α-carbon atom of all three amino acids and that the carbon atom at the benzylic position of residue 3 has *R* stereochemistry. The conformational preference of the biphenyl system has also been determined. Although WS-43708A appears to be the only reported antibiotic outside the vancomycin group to possess a biphenyl group, no evidence for binding of WS-43708A to the cell wall analogue N-Ac-D-Ala-D-Ala has been found. It is concluded therefore that WS-43708A exerts its antibacterial activity other than by binding to mucopeptide precursors terminating in D-Ala-D-Ala.

A covalent structure (**1**) for the cyclic tripeptide antibiotic WS-43708A has been reported by Hashimoto and co-workers.[1] The only stereochemical information which was available from their study was that residue 2 corresponds to *erythro*-γ-hydroxy-L-ornithine.[1] In view of a possible structural analogy between this structure and parts of the structures found for vancomycin group antibiotics,[2] we have fully determined and now report the stereochemistry of WS-43708A. Our interest in this stereochemistry was also initially aroused by the possibility that WS-43708A acts by inhibiting cell wall biosynthesis, as do also members of the vancomycin group.[2] We therefore wished to establish whether WS-43708A has a geometry suitable to bind mucopeptide precursors terminating in D-Ala-D-Ala.[2]

The earlier structural work on WS-43708A had been carried out in D_2O/DCl and CD_3OD/D_2O. Since we wished to utilize NOE and coupling data for the amide protons, it was desirable to work in DMSO-d_6 solution. As the dihydrochloride of the antibiotic (kindly provided by Dr. Hashimoto) was not soluble in DMSO-d_6, it was converted to the free base by dissolving in an aqueous solution of ammonium carbonate. The solution was then lyophilized several times to remove excess ammonium carbonate.

Proton NMR spectra of the above free base were obtained in DMSO-d_6 solution on a Bruker AM-400 spectrometer. Two and three bond proton–proton couplings were determined from a double quantum filtered phase-sensitive COSY spectrum. This spectrum also exposed the four bond couplings between benzylic protons and protons ortho to the benzylic position. Chemical shifts and coupling constants are summarized in Table I, by using the proton code given in **1**, and are in accord with the reported structure. Phase-sensitive NOESY and CAMELSPIN[3]

Table I. ^{1}H NMR Chemical Shifts and Coupling Constants for WS-437083A[a]



1

proton	chem shift, δ	J, Hz
ω_2	8.94	9.2
ω_3	8.40	9.7
3b	7.44	2.6
1d, 3d	7.18	m
1b	6.94	2.2
1c, 3c	6.9	7.5
β_3	5.72	s
α_2	5.04	m
α_3	4.52	9.7
α_1	4.14	m
γ_2	3.92	m
β_1	3.24	15, 6
β_1'	3.02	15, 3
δ_2	2.98	13, 3
δ_2'	2.78	13, 8
β_2, β_2'	1.84	m

[a] Spectrum of the free base in DMSO-d_6 at 330 K: m = multiplet: s = singlet. The amino acid residues are coded 1, 2, and 3 from the N- to the C-terminus.

(1) Uchida, I.; Ezaki, M.; Shigematsu, N.; Hashimoto, M. *J. Org. Chem.* **1985**, *50*, 1341–1342.
(2) Barna, J. C. J.; Williams, D. H. *Annu. Rev. Microbiol.* **1984**, *38*, 339–357.

0022-3263/87/1952-5435$01.50/0