and concentrated. The residue was purified by PTLC (ethyl acetate–hexane, 1:10; $CHCl_3$ elution) to give **27** (82 mg, 90%) as a colorless syrup. **27**: TLC R_f 0.53 (ethyl acetate–hexane, 1:10); $[\alpha]^{21}_D$ -31.9° (*c* 1.19); IR $\nu_{max}^{CHCl_3}$ 2990, 2940, 2860, 2100, 1460, 1430, 1380, 1260, 1170, 1160, 1110 cm^{-1}; ^1H NMR δ 1.07 (9 H, s, $OSiC(CH_3)_3$), 1.23, 1.43 (3 H × 2, each s, $C(CH_3)_2$), 1.53–2.57 (3 H, m, H-1,5,5'), 3.63 (2 H, d, J = 7 Hz, CH_2OSi), 3.95 (1 H, dt, J = 3 and 8 Hz, H-4), 4.28 (1 H, dd, J = 3 and 7 Hz, H-3), 4.45 (1 H, dd, J = 2 and 7 Hz, H-2), 7.20–7.80 (10 H, m, $OSi(C_6H_5)_2$). Anal. Calcd for $C_{25}H_{33}N_3O_3Si$: C, 66.48; H, 7.36; N, 9.30. Found: C, 66.38; H, 7.47; N, 9.03.

(1*R*,2*R*,3*S*,4*R*)-4-Azido-1-(hydroxymethyl)-2,3-(isopropylidenedioxy)cyclopentane (28). Compound **27** (80 mg, 0.18 mmol) was desilylated with tetrabutylammonium fluoride (0.27 mL), and compound **28** (37 mg, 98%) was obtained after a silica gel column chromatography (ethyl acetate–hexane, 1:6). **28** as a colorless syrup: TLC R_f 0.53 (ethyl acetate–hexane, 1:1); $[\alpha]^{19}_D$ -35.2° (*c* 1.05); IR $\nu_{max}^{CHCl_3}$ 3610, 3470, 2990, 2930, 2880, 2100, 1450, 1435, 1385, 1310, 1255, 1200, 1160 cm^{-1}; ^1H NMR δ 1.30, 1.45 (3 H × 2, each s, $C(CH_3)_2$), 1.50–1.83, 2.00–2.50 (1 H, 3 H, each m, H-1,5,5', OH), 3.63 (2 H, d, J = 6 Hz, CH_2OH), 3.97 (1 H, dt, J = 2 and 6 Hz, H-4), 4.43 (1 H, dd, J = 2 and 6 Hz, H-2 or -3), 4.58 (1 H, dd, J = 2 and 6 Hz, H-3 or -2). Anal. Calcd for $C_9H_{15}N_3O_3$: C, 50.69; H, 7.09; N, 19.71. Found: C, 51.01; H, 6.91; N, 19.69.

(1*R*,2*S*,3*R*,4*R*)-2,3-Dihydroxy-4-(hydroxymethyl)-1-cyclopentanamine (7). A solution of **28** (13.4 mg, 0.06 mmol) in 80% aqueous acetic acid (3 mL) was heated at 60 °C for 2 h and concentrated. The residue was dissolved in methanol (3 mL), and the solution was hydrogenated in the presence of Raney nickel T-4 under atmospheric hydrogen pressure for 30 min. The catalyst was passed through a Celite pad and washed with methanol. The combined filtrate and washings were concentrated. The residue was charged on a coloumn of Amberlite CG-120 (H^+) (5 mL), and the column was eluted with 0.07 M aqueous ammonia. The ninhydrin positive fraction was concentrated to give **7** (8.7 mg, 94%) as a colorless syrup. **7**: TLC R_f 0.63 (methanol–water, 1:2); $[\alpha]^{23}_D$ -10.7° (*c* 0.44, water); ^1H NMR (400 MHz, CD_3OD) δ 1.07 (1 H, dt, $J_{1,5}$ = $J_{4,5}$ = 8.8 Hz, $J_{5,5'}$ = 12.7 Hz, H-5), 2.00–2.10 (1 H, m, H-4), 2.14 (1 H, ddd, $J_{1,5'}$ = 8.8 Hz, $J_{4,5'}$ = 7.3 Hz, $J_{5,5'}$ = 12.7 Hz, H-5'), 3.15 (1 H, dt, $J_{1,2}$ = 7.3 Hz, $J_{1,5}$ = $J_{1,5'}$ = 8.8 Hz, H-1), 3.51 (1 H, dd, $J_{1,2}$ = 7.3 Hz, $J_{2,3}$ = 5.4 Hz, H-2), 3.54 (2 H, dd, J = 1.5 and 5.9 Hz, CH_2OH), 3.83 (1 H, dd, $J_{2,3}$ = 5.4 Hz, $J_{3,4}$ = 4.4 Hz, H-3); ^{13}C NMR (CD_3OD) δ 31.86 (C-5), 46.74 (C-4), 56.79 (C-1), 64.59 (CH_2OH), 74.15 (C-3), 79.56 (C-2); high-resolution mass spectrum, calcd for $C_6H_{13}NO_3$ m/z 147.0894, found, M, 147.0886.

Acknowledgment. We thank to Mr. Akio Takahashi (Keio University) for performing elemental analyses.

An Approach to Pseudomonic Acids from D-Xylose[1]

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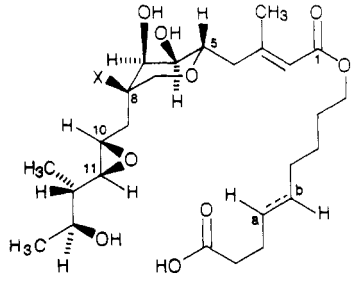
The four contiguous chiral centers present in pseudomonic acid C are constructed in an efficient way from D-xylose. The key steps involve a highly selective intermolecular radical reaction between benzyl 4-bromo-4-deoxy-2,3-di-*O*-benzoyl-β-L-lyxopyranoside (**9**) and phenyl vinyl sulfone for incorporating the lower appendage and a stereoselective intramolecular Michael addition to achieve the correct stereochemistry at the anomeric site.

Pseudomonic acids A (**1a**), B (**1b**), C (**1c**), and D (**1d**) are members of a small group of metabolites with antimicrobial and antimycoplasmal activity, produced by submerged fermentations of a strain of *Pseudomonas flourescens* NCIB 10586.[2] The detailed studies of structural and chemical characterizations of the major component pseudomonic acid A and the lesser components B, C, and D have been reported in a series of papers.[3] The pseudomonic acids display no cross resistance with other antibiotics due to their novel mechanism of action, namely, interference with bacterial protein synthesis by inhibition of isoleucyl-tRNA sythetase. The therapeutic value of these antibiotics has been clinically developed in the Beecham laboratories.[4]

In recent years, different strategies for the total synthesis of pseudomonic acid C and numerous approaches have been reported.[5] Herein, we detail our approach to (+)-pseudomonic acid C from D-xylose, the least expensive among all pentoses.



pseudomonic acids A–D

1a: X = H; C_a–C_b = C_2H_4
1b: X = OH; C_a–C_b = C_2H_4
1c: X = H; C_{10}–C_{11} no epoxide, double bond; C_a–C_b = C_2H_4
1d: X = H; C_a–C_b = (*E*)-CH=CH

A retrosynthetic analysis for the synthesis of pseudomonic acid C was arrived at as shown in Scheme I. It indicates that the most convenient locations for bond disconnections are at the two olefinic linkages leading to

(1) Taken in part from the Ph.D. Thesis of M.V.R., University of Hyderabad, 1987.

(2) (a) Fuller, A. T.; Mellows, G.; Woolford, M.; Banks, G. T.; Barrow, K. D.; Chain, E. B. *Nature (London)* **1971**, *234*, 416. (b) Chain, E. B.; Mellows, G. *J. Chem. Soc., Chem. Commun.* **1974**, 847.

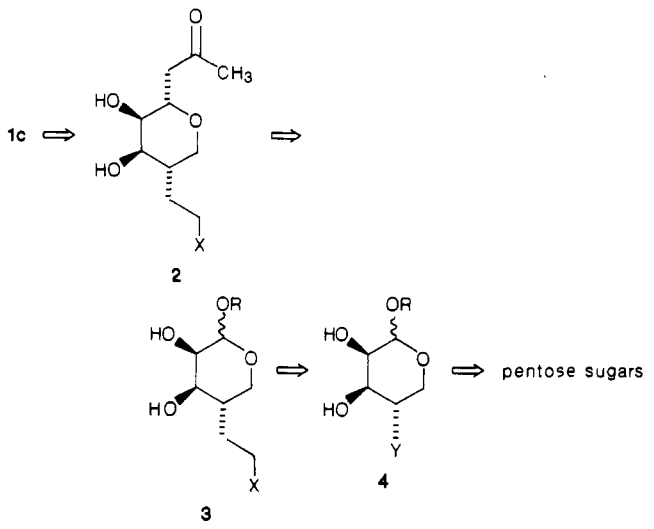
(3) (a) Alexander, R. G.; Clayton, J. P.; Luk, K.; Rogers, N. H.; King, T. J. *J. Chem. Soc., Perkin Trans 1* **1978**, 561. (b) Chain, E. B.; Mellows, G. *J. Chem. Soc., Perkin Trans. 1* **1977**, 294. (c) O-Hanlon, P. J.; Rogers, N. H.; Tyler, J. W. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2655. (d) Clayton, J. P.; O-Hanlon, P. J.; Rogers, N. H.; King, T. J. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2827 and references cited therein.

(4) The approved generic name for pseudomonic acid is Mupirocin. For recent structure–activity studies: Crimmin, M. J.; O-Hanlon, P. J.; Rogers, N. H. *J. Chem. Soc., Perkin Trans. 1* **1985**, 549.

(5) (a) Kozikowski, A. P.; Schmiesing, R. J.; Sorgi, K. L. *J. Am. Chem. Soc.* **1980**, *102*, 6577. (b) Bean, J. M.; Aburaki, S.; Pougny, J. R.; Sinay, P. *J. Am. Chem. Soc.* **1983**, *105*, 621. (c) Fleet, G. W. J.; Gough, M. J.; Shing, T. K. M. *Tetrahedron Lett.* **1983**, 24, 3661. (d) Keck, G. E.; Kachensky, D. F.; Enholm, E. J.; *J. Org. Chem.* **1985**, *50*, 4317. (e) Williams, D. R.; Moore, J. L.; Yamada, M. *J. Org. Chem.* **1986**, *51*, 3916. (f) Bates, H. A.; Farina, J.; Tong, M. *J. Org. Chem.* **1986**, *51*, 2637. See ref 5f for additional citations of synthetic approaches.

0022-3263/88/1953-1432$01.50/0

Scheme I



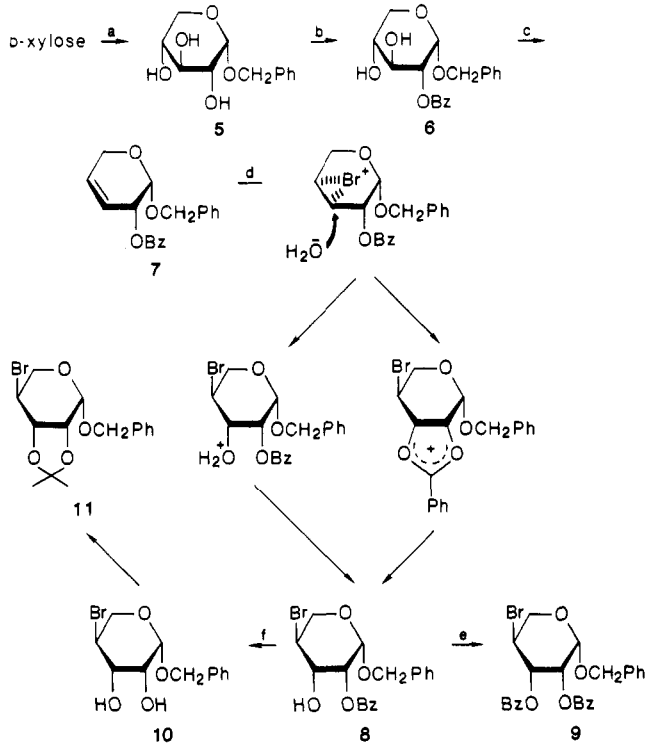
an advanced intermediate **2**, which contains the four contiguous chiral centers on a tetrahydropyran ring present in **1c**. The orientation of the two hydroxyl groups at C-6 and C-7 is cis (D-*erythro*), as is that of the two C-branch points. The top appendage can be introduced by methodologies known for the preparation of *C*-glycosyl compounds. The introduction of the lower appendage would require a stereoselective C-branching with a two-carbon unit, capable of elaboration to the C_{10}–C_{11} double bond (pseudomonic acid numbering), at C-4 of **4**. X in **3** should thus be capable of elaboration into the desired trans-olefinic linkage at C_{10}–C_{11} in **1c**. We anticipated that incorporation of the two-carbon unit at C-4 (sugar numbering) could be accomplished by an intermolecular free radical reaction. Thus the prime objective was to synthesize the radical precursor **4** from a pentose sugar.

On the basis of the retrosynthetic analysis depicted in Scheme I, D-xylose was chosen as the starting material. A comparison of the structure of the intermediate **3** with that of D-xylose reveals that the stereochemistry of the C-3 hydroxyl group in D-xylose has to be inverted and that C-branching at C-4, with inversion of the present configuration, has to be introduced. Thus, the first task was to differentiate the C-1, C-2 hydroxyls of D-xylose from the C-3, C-4 pair and also to differentiate C-1 and C-2 from one another.

Results and Discussion

The aforementioned hydroxyl differentiation in D-xylose was achieved by converting it to benzyl α-D-xylopyranoside (**5**) and selective protection of the 2-hydroxyl group in **5**, as its benzoate, to give benzyl 2-*O*-benzoyl-α-D-xylopyranoside (**6**).[6] In order to execute the other steps in a planned sequence, it was decided to destroy the two centers viz., C-3 and C-4 in **6**, by elimination of two hydroxyl groups and then to recreate them in the desired fashion. Dehydroxylation of the monobenzoate **6** was achieved by using a combination of triphenylphosphine, iodoform, and imidazole to give **7**. Treatment of the allylic benzoate **7** with *N*-bromosuccinimide in aqueous DMSO gave bromohydrin **8**, as a single product, as shown in Scheme II. The spectral data support the structure of benzyl 4-bromo-4-deoxy-2-*O*-benzoyl-β-L-lyxopyranoside (**8**). Benzoylation of **8** gave the dibenzoate **9**. The confirmation of the regio- and stereochemical relationship between the

Scheme II[a]



[a] (a) $PhCH_2OH$, H^+; (b) PhCOCl, Py, −40 °C; (c) TPP, CHI_3, imidazole, toluene, reflux; (d) NBS, aqueous DMSO, room temperature; (e) PhCOCl, Py, room temperature; (f) MeOH:H_2O:triethylamine, 5:2:1; (g) Me_2CO, H^+, anhydrous $CuSO_4$.

two hydroxyl groups in **8** was based on decoupling experiments on both **8** and its dibenzoate **9**, in addition to the formation of the isopropylidene derivative **11** from benzyl 4-bromo-4-deoxy-β-L-lyxopyranoside (**10**). Additionally, the appearance of H-2 in **9** at δ 5.88 as a triplet (J = 4 Hz) requires that the H-2 proton has two equatorial–axial or two axial–equatorial couplings, thereby proving that the two hydroxyl groups are cis to each other. The appearance of H-3 as a doublet of doublet at δ 5.40 (J = 4, 11 Hz) establishes the trans stereochemical relationship between the bromine at C-4 and the benzoate at C-3.

The bromohydrin dibenzoate **9** was considered as the radical precursor to construct a part of the lower side chain of **1c**. It is reported that the newly formed C–C bonds in C-branched sugars using radical reactions are predominantly equatorial when the neighboring substituents are also equatorial. Axial attack predominates only when both the neighboring substituents are axial.[7] These observations suggest that the use of **9** as the radical precursor would lead to the formation of a C–C bond at C-8 from the α-face (pseudomonic acid numbering and stereochemistry), especially in view of the presence of the two benzoate groups at C-6 and C-7, which would build in sufficient steric bias on the β-face.

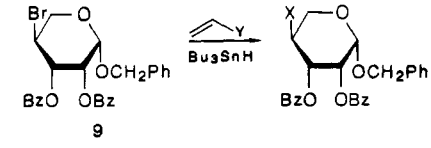


Table I lists the reactions of **9** with different alkenes having electron-withdrawing or radical-stabilizing sub-

(6) Friedman, N.; Cohen, S.; Bergmann, E. D. *Isr. J. Chem.* **1970**, *80*, 663. (b) Jones, J. K. N.; Sivakumaran, T. *Can. J. Chem.* **1967**, *45*, 2493.

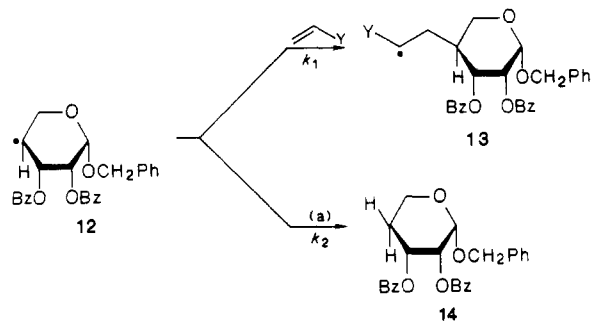
(7) Giese, B.; Groninger, K. *Tetrahedron Lett.* **1984**, *25*, 2743.

Table I. Reactions of 9 with Different Alkenes

run	Y =	solvent	mode of initiation[a]	isolated product X =	product number	yield, %
1	CN	benzene	A or B	H	14	50–60
2	CN	toluene	A	H	14	45
3	CN	*t*-BuOH	A or B	H	14	58
4	CO_2Me	toluene	A	H	14	40
5[b]	SO_2Ph	*t*-BuOH	A	$CH_2CH_2SO_2Ph$	15	77–80

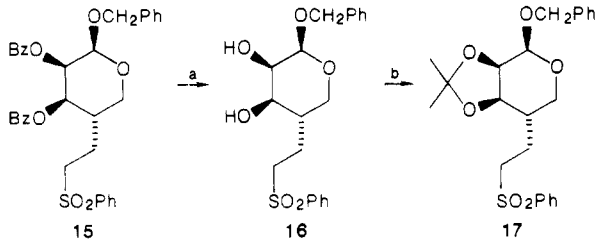
[a] A = thermal initiation using AIBN. B = photochemical initiation at room temperature using a 450-W Hanovia lamp with Pyrex filter. [b] Bu_3SnH is generated in situ by using a catalytic amount of Bu_3SnCl and $NaCNBH_3$.

Scheme III[a]



[a] (a) Bu_3SnH.

Scheme IV[a]

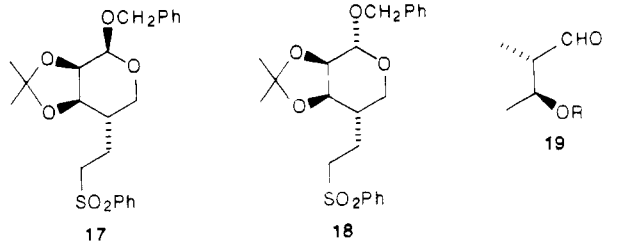


[a] (a) MeOH/H_2O/TEA, 5:2:1, room temperature; (b) Me_2CO, H^+, $CuSO_4$, room temperature.

stituents and tributyltin hydride. In runs 1–4, when the reactions of **9** with alkenes like acrylonitrile and methyl acrylate were carried out, either photochemically at room temperature or thermally with AIBN as the radical initiator, only the reduced product benzyl 4-deoxy-2,3-di-*O*-benzoyl-β-L-lyxopyranoside (**14**) was isolated.

It is evident from these runs that the radical **12** is abstracting a hydrogen atom from tributyltin hydride to give **14** instead of adding to the alkene to give **13**, Scheme III. In other words, $k_1/k_2 \ll 1$. The same reduced product **14** was obtained even with high $H_2C{=}CHCN/Bu_3SnH$ concentration ratios and with slow addition of tributyltin hydride over a period of half an hour.

In an attempt to add the radical **12** to the alkene, the substitution on the alkene was changed from Y = CN or CO_2Me to SO_2Ph. It was also decided to work with low concentrations of tributyltin hydride by generating it in situ from tributyltin chloride and sodium cyanoborohydride.[8] In run 5 of table I, the reaction of **9** with 10 equiv of phenyl vinyl sulfone, in refluxing *tert*-butyl alcohol, using a combination of tributyltin chloride and sodium cyanoborohydride gave benzyl 4-[2-(phenylsulfonyl)ethyl]-4-deoxy-2,3-di-*O*-benzoyl-β-L-lyxopyranoside (**15**). The structure of **15** was assigned unambiguously from its spectral data. The trans relationship between the substituents at C-3 and C-4 in **15** is evident from the appearance of H-3 as a doublet of doublet at δ 5.17 with coupling constants of 4 and 7 Hz. The exclusive formation of **15** is in keeping with the observations of Giese[7] regarding the formation of carbon–carbon bonds in branched-chain sugars through intermolecular radical reactions and highlights the utility of the method for this purpose. Additionally, hydrolysis of **15** using a solution of methanol, water and triethylamine gave the *cis*-diol **16**, Scheme IV. Treatment of **16** with a catalytic amount of sulfuric acid and anhydrous copper sulfate in acetone gave benzyl 4-[2-(phenylsulfonyl)ethyl]-4-deoxy-2,3-*O*-isopropylidene-β-L-lyxopyranoside (**17**). The acetonide derivative **17** was different from the similar intermediate **18**,



prepared from L-lyxose as the major product by Keck and co-workers.[5d] Both **17** and **18** are alike, the only difference being at the anomeric carbon of the pyran nucleus wherein **17** has the *O*-benzyl group in the β-configuration and **18** has it in the α-configuration. As the chiral center at C-5 (pseudomonic acid numbering) has to be destroyed and regenerated while incorporating the acetonyl side chain, the stereochemistry at the anomeric carbon in **17** or **18** is not of significance.

At this stage of the synthesis, the choice exists between condensing the sulfone **15** with the requisite aldehyde **19** to complete the lower appendage or introducing the acetonyl appendage at C-5. In the former method, although the condensation of sulfone **15** with aldehyde **19** is a straightforward process, the reductive elimination (Julia reaction)[9] of the resulting β-hydroxy sulfone to introduce the C_{10}–C_{11} alkene and concomitant cleavage of the benzyl glycoside at C-5 give poor yields.[10] To circumvent this problem, it was decided to incorporate the acetonyl appendage at C-5 of **15** first. Protection of the acetonyl group, condensation of the sulfone with the aldehyde **19**, and reductive elimination appeared to be a straightforward process. Hence the viability of this strategy was investigated.

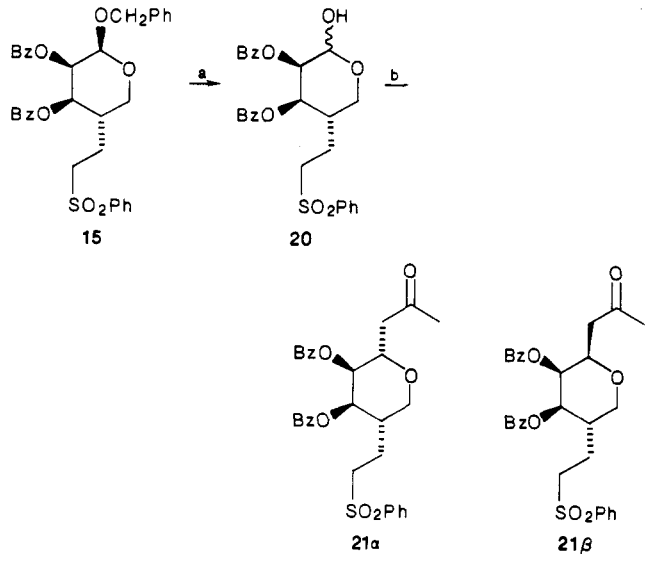
In the first instance, transfer hydrogenolysis of the benzyl glycoside **15** was accomplished by using cyclohexene and 10% palladium on carbon in refluxing methanol to give the lactol **20**, Scheme V. Reaction of **20** with an excess of (acetylmethylene)triphenylphosphorane in acetonitrile at 70 °C, followed by treatment of the crude product with DBU at 0 °C gave a mixture of ketones **21α** and **21β** in a ratio of 5:1. The structure of 1-[5-[2-(phenylsulfonyl)ethyl]-2α,3β,4β,5α-tetrahydro-3,4-di-*O*-benzoyl-2*H*-pyran-2-yl]-2-propanone (**21α**) was supported

(8) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303.

(9) Julia, M.; Paris, J. M. *Tetrahedron Lett.* **1973**, *14*, 4833.

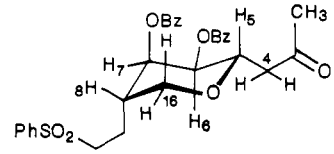
(10) While the work reported here was in progress, Keck and coworkers have reported the synthesis of pseudomonic acid C employing a similar strategy.[5d]

Scheme V[a]

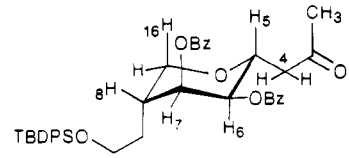


[a] (a) cyclohexene, Pd/C, methanol, reflux; (b) $Ph_3P{=}CHCOCH_3$, CH_3CN; DBU, 0 °C.

by its spectral data. ^1H NMR of **21α** [δ 5.48 (br t, 1 H, H-7), 5.04 (dd, 1 H, H-6, J = 3, 10), 4.46 (oct, 1 H, H-5, J = 9, 8, 3), 4.02 (dd, 1 H, H-16, J = 2, 12), 3.64 (dd, 1 H, H-16′, J = 2, 12), 2.28–2.92 (m, 3 H, H-8, -CH_2CO)] showed a very strong similarity to the spectrum of 1-[5-[2-(*tert*-butyldiphenylsilyl)oxy]ethyl]-2α,3β,4β,5α-tetrahydro-3,4-di-*O*-benzoyl-2*H*-pyran-2-yl]-2-propanone (**22**) reported by Kozikowski and co-workers.[5a]



21α



22

Transformation of **21α** into pseudomonic acid C can be readily accomplished through well-established processes. Thus, all the chiral centers present in the tetrahydropyran ring of **1c** have been constructed in an efficient way. This synthetic approach toward **1c**, starting from a readily available and an exceedingly inexpensive D-xylose, is comparable to the other methods reported in the literature. The correlation of **17** with the minor intermediate in Kecks' synthesis[5d] makes this a formal total synthesis of **1c**.

Experimental Section

Melting points were determined on a Buchi 510 capillary point apparatus and are uncorrected. Optical rotations were measured with an Autopol II automatic polarimeter at 25 °C. IR spectra were recorded on Perkin-Elmer Model 1310 or 297 spectrophotometers. Solid samples were prepared as KBr wafers and liquid samples as films between NaCl plates. ^1H NMR (100 MHz) and ^{13}C NMR (25 MHz) spectra were obtained on a Jeol-FX-100 spectrometer. All spectra were measured in chloroform-*d* solutions with tetramethylsilane as internal standard unless otherwise stated. Spectral assignments are as follows: (1) chemical shift on the δ scale (TMS = δ 0.00); (2) multiplicity; (3) number of hydrogens integrated for by the signal; (4) assignment of the signal; and (5) coupling constant in hertz (Hz). Decoupling experiments were carried out by irradiating the frequency of the signal concerned with high power (6–8 W) and observing the affected signals. Elemental analyses were performed on a Perkin-Elmer 240 C CHN analyzer.

HPLC analysis was done on an LKB instrument fitted with a Merck μ-Porasil column and UV detector. Analytical TLC was performed on (10 × 5 cm) glass plates coated with (250 μm) with Acmes' silica gel G or GF 254 containing 13% calcium sulfate as binder. Column chromatography was performed on Acmes' silica gel (100–200 mesh) and usually eluted with 20–30% ethyl acetate–hexane, unless otherwise mentioned. All moisture-sensitive reactions were carried out under dry nitrogen and all solvents were distilled from appropriate drying agents just before use. Petroleum ether refers to the fraction boiling between 60 and 80 °C. The purity of all new compounds without analytical data was checked and found to be satisfactory by HPLC.

Benzyl 2-*O*-Benzoyl-α-D-*erythro*-pent-3-enopyranoside (7). Triphenylphosphine (15.2 g, 58.0 mmol), iodoform (11.3 g, 29.0 mmol) and imidazole (1.97 g, 29.0 mmol) were added to a stirred solution of **6**[6] (5 g, 14.5 mmol) in dry toluene (100 mL), and the resulting mixture was refluxed for 21 h. The reaction mixture after attaining room temperature was washed with aqueous $NaHCO_3$ (100 mL). The aqueous layer was extracted with toluene (2 × 25 mL). The combined organic phase was washed with aqueous $Na_2S_2O_3$ and water and dried. The solvent was evaporated and the crude material chromatographed on a column of silica gel (200 g) to give a syrupy **7** (3.8 g, 85%): $[\alpha]_D$ +37.5° (*c* 1.3, $CHCl_3$); IR (film) 1720, 875, 845, and 820 cm^{-1}; ^1H NMR δ 7.28–7.81 (m, 10 H, Ar), 5.84 (dq, 2 H, *HC*=C*H*), 5.50 (br t, 1 H, H-2), 5.16 (d, 1 H, H-1, J = 4), 4.68 (center of AB q, 2 H, OCH_2Ph, J = 12), 3.80–4.40 (m, 2 H, H-5, H-5′).

Benzyl 4-Bromo-4-deoxy-2-*O*-benzoyl-β-L-lyxopyranoside (8). To a stirred solution of **7** (1.28 g, 3.87 mmol) in 8:2 DMSO–water (10 mL) was added *N*-bromosuccinimide (0.90 g, 5.0 mmol) in small portions. After stirring the reaction mixture at room temperature for 10 h, another lot of *N*-bromosuccinimide (0.45 g, 2.50 mmol) in small portions was added and the stirring continued for 20 h. The reaction mixture was diluted with water (20 mL) and extracted with ether (3 × 25 mL). The combined organic phase was repeatedly washed with water, dried, and concentrated. The residue was subjected to column chromatography to give a syrupy **8** (1.25 g, 80%): $[\alpha]_D$ +103° (*c* 0.68, $CHCl_3$); IR (film) 3500 and 1720 cm^{-1}; ^1H NMR δ 7.28–8.18 (m, 10 H, Ar), 5.68 (t, 1 H, H-2), 5.20 (d, 1 H, H-1, J = 4), 4.72 (center of AB q, 2 H, OCH_2Ph, J = 12), 3.60–4.50 (m, 4 H, H-3, H-4, H-5, H-5′), 2.46 (br s, 1 H, OH).

Benzyl 4-Bromo-4-deoxy-2,3-di-*O*-benzoyl-β-L-lyxopyranoside (9). Benzoyl chloride (0.255 mL, 2.2 mmol) was slowly added to a stirred solution of **8** (0.814 g, 2.0 mmol) in dry pyridine (10 mL) at 0 °C. The reaction mixture was stirred for 15 h at room temperature and then poured into chilled aqueous K_2CO_3 (15 mL). After stirring for 1 h, the product was extracted with dichloromethane (3 × 25 mL). The combined organic phase was washed with aqueous $NaHCO_3$, dried, and evaporated. To remove the residual pyridine, toluene (2 × 10 mL) was added and then evaporated from the residue. The crude material was chromatographed to give a syrupy **9** (0.93 g, 91%) which solidified on long standing to a waxy solid whose melting point could not be determined: $[\alpha]_D$ +118° (*c* 0.935, $CHCl_3$); IR (film) 1720 cm^{-1}; ^1H NMR δ 7.28–8.20 (m, 15 H, Ar), 5.88 (t, 1 H, H-2, J = 4), 5.40 (dd, 1 H, H-3, J = 4, 11), 5.10 (d, 1 H, H-1, J = 4), 4.70 (center of AB q, 2 H, OCH_2Ph, J = 12), 3.60–4.50 (m, 3 H, H-4, H-5, H-5′). Anal. Calcd for $C_{26}H_{23}O_6Br$: C, 61.06; H, 4.53; Found: C, 61.10; H, 4.46.

Benzyl 4-Bromo-4-deoxy-β-L-lyxopyranoside (10). The bromohydrin **8** (1.35 g, 3.30 mmol) was added to a mixture of methanol/water/triethylamine in the ratio of 5:2:1 (110 mL) and stirred at room temperature for 24 h. The reaction mixture was concentrated at room temperature under vacuum to a thick syrup and was extracted with ether (3 × 40 mL). The combined organic phase was washed with water and concentrated, and the residue was filtered through a column of silica gel to give **10** (0.96 g, 96%): mp (ethanol) 55–56 °C; $[\alpha]_D$ +72 ° (*c* 0.47, $CHCl_3$); IR 3450 cm^{-1}; ^1H NMR δ 7.28 (s, 5 H, Ar), 4.62 (center of AB q, 2 H, OCH_2Ph),

4.60 (d, 1 H, H-1, J = 4), 3.80–4.20 (m, 2 H, H-5, H-5′), 2.90–3.50 (m, 5 H, H-2, H-3, H-4, 2 O*H*); ^{13}C NMR 137.3, 128.2, 127.9, 127.8, 96.7, 70.0, 65.0, 59.7, 53.2, and 51.79 ppm.

Benzyl 4-Bromo-4-deoxy-2,3-*O*-isopropylidene-β-L-lyxopyranoside (11). To a stirred solution of **10** (0.030 g, 0.10 mmol) in dry acetone (5 mL) was added anhydrous $CuSO_4$ (0.050 g) followed by a catalytic amount of sulfuric acid. The resulting mixture was stirred for 10 h at room temperature, neutralized with $NaHCO_3$, and filtered. The residue was washed with dichloromethane (2 × 10 mL) and the combined organic phase was evaporated. The resulting material was chromatographed over silica gel to yield syrupy **11** (0.028 g, 85%): IR (film) 1110, 1090, and 820 cm^{-1}; ^{1}H NMR δ 7.28 (s, 5 H, Ar), 4.80 (d, 1 H, H-1, J = 3), 4.72 (center of AB q, 2 H, OCH_2Ph, J = 12), 3.50–4.30 (m, 5 H, H-2, H-3, H-4, H-5, H-5′), 1.40 (s, 3 H), 1.29 (s, 3 H).

Intermolecular Radical Reaction of 9 with Olefins. General Procedure for Photochemical Initiation. A solution of **9** (0.127 g, 0.25 mmol), the appropriate olefin (2.50 mmol), and tributyltin hydride (0.08 mL, 0.30 mmol) in the appropriate solvent (5 mL) was placed in a Hanovia photolysis apparatus. After thoroughly degassing the solution with dry nitrogen, it was irradiated for 6 h at room temperature with a 450-W Hanovia lamp equipped with a Pyrex filter. After adding dichloromethane (10 mL), the mixture was vigorously shaken with aqueous potassium fluoride and the organic phase was separated. The aqueous phase was extracted with dichloromethane (2 × 15 mL), the combined organic phase was washed with water, dried, and concentrated, and the residue was chromatographed.

General Procedure for Thermal Initiation. A thoroughly degassed solution of **9** (0.127 g, 0.25 mmol), the requisite olefin (2.50 mmol), AIBN (0.004 g), and tributyltin hydride (0.08 mL, 0.30 mmol) in the appropriate solvent (5 mL) was prepared and immediately refluxed for 5–6 h. The workup and purification was identical with that for the photochemical initiation.

Reaction of 9 with Acrylonitrile (Photochemical Initiation). A solution of **9** (0.127 g, 0.25 mmol), acrylonitrile (0.162 mL, 2.50 mmol), and tributyltin hydride (0.08 mL, 0.30 mmol) in benzene was irradiated following the general procedure. After workup, the residue was chromatographed over silica gel to give a major syrupy component (0.064 g): IR (film) 1720 cm^{-1}; ^{1}H NMR δ 7.28–8.16 (m, 15 H, Ar), 5.30–5.60 (m, 2 H, H-2, H-3), 5.20 (d, 1 H, H-1, J = 4), 4.84 (center of AB q, 2 H, OCH_2Ph), 4.24–4.56 (m, 1 H, H-5), 3.56–3.96 (m, 1 H, H-5′), 2.60–3.30 (m, 2 H, CH_2). Anal. Calcd for $C_{26}H_{24}O_6$: C, 72.210; H, 5.59. Found: C, 72.10; H, 5.36. This data corresponds to that of benzyl 4-deoxy-2,3-di-*O*-benzoyl-β-L-lyxopyranoside (**14**).

Reaction of 9 with Acrylonitrile (Thermal Initiation). A solution of **9** (0.127 g, 0.25 mmol), acrylonitrile (0.162 mL, 2.50 mmol), tributyltin hydride (0.08 mL, 0.30 mmol), and AIBN (0.004 g) in benzene was prepared and refluxed for 6 h following the general procedure. After workup, the residue was chromatographed to give **14** (0.053 g, 50%) identical with that obtained earlier.

A thoroughly degassed solution of **9** (0.127 g, 0.25 mmol), acrylonitrile (0.32 mL, 5.0 mmol), and AIBN (0.004 g) in toluene (5 mL) was prepared and tributyltin hydride (0.08 mL, 0.30 mmol) in toluene (2 mL) was slowly added over a period of 30 min at 60 °C, and then the solution was refluxed for 5 h. After the standard workup, the residue was chromatographed to give a major component (0.48 g), which corresponded to **14**.[11]

Reaction of 9 with Methyl Acrylate. A thoroughly degassed solution of **9** (0.127 g, 0.25 mmol), methyl acrylate (0.225 g, 2.50 mmol), and AIBN (0.004 g) in toluene (5 mL) was prepared. Tributyltin hydride (0.08 mL, 0.30 mmol) in toluene (2 mL) was slowly injected over a period of 30 min at 80 °C and then the solution was refluxed for 6 h. The resulting residue, after appropriate workup, was chromatographed to give **14** (0.042 g).

Benzyl 4-[2-(Phenylsulfonyl)ethyl]-4-deoxy-2,3-di-*O*-benzoyl-β-L-lyxopyranoside (15). A mixture of **9** (0.110 g, 0.215 mmol), sodium cyanoborohydride (0.027 g, 0.43 mmol), AIBN (0.004 g), phenyl vinyl sulfone (0.36 g, 2.15 mmol) and tributyltin chloride (0.005 mL, 0.1 equiv) in thoroughly degassed *tert*-butyl alcohol (8 mL) was refluxed for 4 h. Dichloromethane (10 mL) was added and the solution was vigorously shaken with 3% aqueous ammonia (5 mL). After addition of brine, the organic phase was separated. The organic phase was washed with water, dried, and concentrated. The residue was chromatographed to give a solid which was recrystallized from dichloromethane–hexane to give **15** (0.103 g, 80%): mp 130–132 °C; $[\alpha]_D$ +46.8° (c 0.038, $CHCl_3$); IR 1720, 1300, and 1140 cm^{-1}; ^{1}H NMR δ 7.28–8.04 (m, 20 H, Ar), 5.36 (t, 1 H, H-2, J = 3), 5.14 (dd, 1 H, H-3, J = 4, 7), 4.82 (d, 1 H, H-1, J = 4), 4.64 (center of AB q, 2 H, OCH_2Ph, J = 12), 4.22 (dd, 1 H, H-5, J = 4, 12), 3.0–3.40 (m, 3 H, H-5′, CH_2SO$_2$Ph), 2.10–2.28 (m, 1 H, H-4), 1.80–2.04 (m, 2 H, CH_2CH$_2$SO$_2$Ph). Anal. Calcd for $C_{34}H_{32}O_8S$: C, 67.98; H, 5.37. Found: C, 66.96; H, 5.60.

Benzyl 4-[2-(Phenylsulfonyl)ethyl]-4-deoxy-β-L-lyxopyranoside (16). To **15** (0.060 g, 0.10 mmol) was added a mixture of methanol/water/triethylamine in a ratio of 5:2:1 (8 mL), and the solution was stirred at room temperature for 15 h. The reaction mixture was concentrated to a thick syrup at room temperature under vacuum. The resulting syrup was extracted with ether (2 × 20 mL) and concentrated. Purification by chromatography gave syrupy **16** (0.036 g, 93%): IR (film) 3500, 1640, 1320, 1140, and 740 cm^{-1}.

Benzyl 4-[2-(Phenylsulfonyl)ethyl]-4-deoxy-2,3-*O*-isopropylidene-β-L-lyxopyranoside (17). To a stirred solution of **16** (0.030 g, 0.069 mmol) in dry acetone (5 mL) was added anhydrous $CuSO_4$ (0.050 g) followed by a catalytic amount of sulfuric acid. The resulting mixture was stirred for 12 h at room temperature and then neutralized with $NaHCO_3$ and filtered. The residue was washed with dichloromethane (2 × 10 mL) and the combined organic phase was evaporated. The residue was chromatographed to give a solid, which was recrystallized from dichloromethane–hexane to give **17** (0.027 g, 82%): mp 121–122 °C; $[\alpha]_D$ +36° (c 0.041, $CHCl_3$); IR 1300, 1140, 1010, and 880 cm^{-1}; ^{1}H NMR δ 7.28–8.16 (m, 10 H, Ar), 4.84 (d, 1 H, H-1, J = 2), 4.72 (center of AB q, 2 H, OCH_2Ph, J = 12), 3.70–4.40 (m, 3 H, H-2, H-3, H-5), 3.04–3.60 (m, 3 H, H-5′, CH_2SO$_2$Ph), 1.60–1.90 (m, 3 H, H-4, CH_2CH$_2$SO$_2$Ph), 1.43 (s, 3 H), 1.30 (s, 3 H). Anal. Calcd for $C_{23}H_{28}O_6S$: C, 63.869; H, 6.524. Found: C, 63.99; H, 6.56.

Hydrogenolysis of Benzyl 4-[2-(Phenylsulfonyl)ethyl]-4-deoxy-2,3-di-*O*-benzoyl-β-L-lyxopyranoside (15). A mixture of **15** (0.060 g, 0.10 mmol), 10% Pd/C (0.080 g), cyclohexene (4 mL), and methanol (4 mL) was refluxed for 16 h. The catalyst was filtered and the solvent was evaporated to give a syrupy hemiacetal, which was filtered through a short column of silica gel to give syrupy **20** (0.038 g, 75%): $[\alpha]_D$ +21.6° (c 0.017, $CHCl_3$); IR (film) 3450, 1720, 1310, 1145, and 740 cm^{-1}; ^{1}H NMR δ 7.28–8.0 (m, 15 H, Ar), 5.0–5.80 (m, 3 H, H-1, H-2, H-3), 2.96–3.90 (m, 4 H, H-5, H-5′, CH_2SO$_2$Ph), 2.15–2.30 (m, 1 H, H-4), 1.50–2.0 (m, 2 H, H_2C-CH$_2$SO$_2$Ph).

1-[5-[2-(Phenylsulfonyl)ethyl]-2α,3β,4β,5α-tetrahydro-3,4-di-*O*-benzoyl-2*H*-pyran-2-yl]-2-propanone (21). A mixture of **20** (0.015 g, 0.029 mmol), (acetylmethylene)triphenylphosphorane (0.039 g, 0.12 mmol), and acetonitrile (2 mL) was refluxed for 48 h. TLC analysis indicated the consumption of starting material. The reaction mixture was cooled to 0 °C, a catalytic amount of DBU was injected, and the solution was stirred at 0 °C for 1 h. After evaporation of the solvent the residue was dissolved in ether (20 mL) and washed successively with chilled dilute HCl, water, and aqueous $NaHCO_3$, dried, and concentrated. The residue was chromatographed to give two components, in a ratio of 5:1. The faster moving spot was concentrated to a syrup (0.010 g, 70%) and had $[\alpha]$ +20.2° (c 0.018, $CHCl_3$): IR (film) 1720, 1620, 1310, and 1140 cm^{-1}; ^{1}H NMR δ 7.24–8.04 (m, 15 H, Ar), 5.48 (br t, 1 H, H-7), 5.04 (dd, 1 H, H-6, J = 3, 10), 4.46 (oct, 1 H, H-5, J = 9, 8, 3), 4.02 (dd, 1 H, H-16, J = 2, 12), 3.64 (dd, 1 H, H-16′, J = 2, 12), 3.0–3.38 (m, 2 H, CH_2SO$_2$Ph), 2.28–2.92 (m, 3 H, H-8, CH_2CO), 2.12 (s, 3 H, COCH_3), 1.88–2.24 (m, 2 H, CH_2CH$_2$SO$_2$Ph) in support of **21α**. Anal. Calcd for $C_{30}H_{30}O_8S$: C, 65.44; H, 5.49. Found: C, 65.10; H, 5.38. The slower moving spot (0.002 g), probably corresponding to **21β**, was not characterized.

(11) The same reduced product **14** was obtained when the reaction of **9** and acrylonitrile in *tert*-butyl alcohol was carried out by following both thermal and photochemical initiations.

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Registry No. 1c, 71980-98-8; 6, 18403-20-8; 7, 112348-33-1; 8, 112348-34-2; 9, 112348-35-3; 10, 112348-36-4; 11, 112348-37-5; 14, 112348-38-6; 15, 112348-39-7; 16, 112348-40-0; 17, 89824-53-3; α-20, 112348-41-1; β-20, 112348-42-2; 21α, 112348-43-3; 21β, 112348-44-4; H_2C=CHCN, 107-13-1; H_2C=CHCOOMe, 96-33-3; H_2C=$CHSO_2Ph$, 5535-48-8; Ph_3P=$CHCOCH_3$, 1439-36-7; D-xylose, 58-86-6.

Synthesis of Macrocyclic Terpenoids by Intramolecular Cyclization. 12.[1] Total Synthesis of Methyl Ceriferate I, a 14-Membered Ring Sesterterpene from Scale Insects

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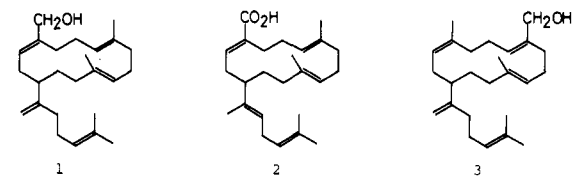
Total synthesis of (±)-methyl ceriferate I (6), the methyl ester of a cembrane-type sesterterpene isolated from the wax of scale insects, was achieved by means of Wadsworth–Emmons olefination as a key step. Three segments, 9, 10, and 11, were connected to yield, after some modifications, the allylic alcohol 22, which was converted into the phosphonoacetate 29 in nine steps including Claisen rearrangement of 22. Intramolecular Wadsworth–Emmons olefination of 29 afforded 6 and its geometrical isomer 30.

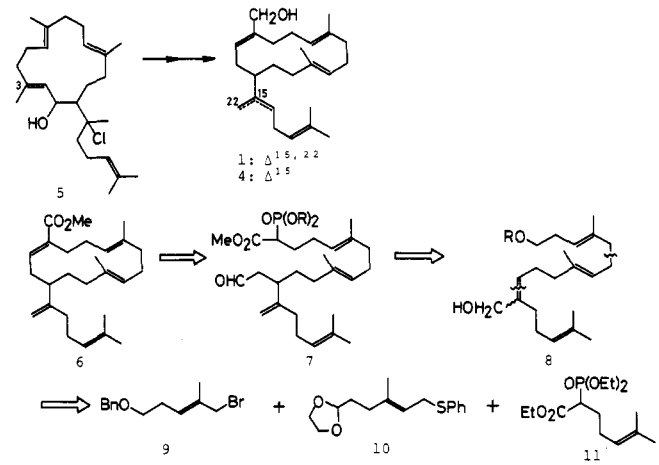
The wax secreted by the scale insect *Ceroplastes* sp. has been shown to contain various 14-membered ring sesterterpenes as exemplified by ceriferol I (1), ceriferic acid (2), and cericerol I (3).[2] To date 15 related substances have been isolated from the insect wax.[3]

Although the gross structure having a 14-membered ring with three annular double bonds (two trans and one cis) and an unsaturated side chain has been elucidated on the basis of spectroscopic analysis, the structural studies concerning the position of the annular cis double bond have been pursued with a somewhat complicated course. The common carbon framework with 2*Z*,6*E*,10*E* geometry was finally proposed by Naya et al.[3] on the basis of careful reexamination of NMR spectra and confirmed unequivocally by the synthesis of 1 and ceriferol (4).[4] In the first synthesis of cembrane sesterterpenes, namely 1 and 4, Kato et al.[4] employed a route involving functionalization of the C-3 methyl group of the preformed 14-membered ring compound 5. Considering the facts that one of the methyl groups on the ring is usually oxygenated into an allylic alcohol or unsaturated carboxylic acid in this class of sesterterpenes, intramolecular Wittig-type olefination should be a highly effective method since this route allows simultaneous construction of the macroring and an α,β-unsaturated ester moiety.[5] According to this methodology,

Chart I



Scheme I



we have recently achieved a total synthesis of (±)-methyl ceriferate I (6).[6] Our results demonstrate the usefulness

(1) Part 11 of this series: Kodama, M.; Shiobara, Y.; Sumitomo, H.; Mitani, K.; Ueno, K. *Chem. Pharm. Bull. (Tokyo)* **1987**, *35*, 4042.

(2) Miyamoto, F.; Naoki, H.; Takemoto, T.; Naya, Y. *Tetrahedron* **1979**, *35*, 1913. Kusumi, T.; Kinoshita, T.; Fujita, K.; Kakisawa, H. *Chem. Lett.* **1979**, 1129; Miyamoto, F.; Naoki, H.; Naya, Y.; Nakanishi, K. *Tetrahedron* **1980**, *36*, 3481. Naya, Y.; Miyamoto, F.; Kinoshita, K.; Kusumi, T.; Kakisawa, H.; Nakanishi, K. *Chem. Lett.* **1980**, 883.

(3) Pawlak, P. K.; Tempest, M. S.; Iwashita, T.; Nakanishi, K.; Naya, Y. *Chem. Lett.* **1983**, 1069.

(4) Fujiwara, S.; Aoki, M.; Uyehara, T.; Kato, T. *Tetrahedron Lett.* **1984**, *25*, 3003. See also: Ikeda, Y.; Aoki, M.; Uyehara, T.; Kato, T.; Yokoyama, T. *Chem. Lett.* **1983**, 1073.

(5) Wittig reaction approach to macroring formation: Masamune, S. *Angew, Chem.* **1977**, *89*, 602. Stork, G.; Nakamura, E. *J. Org. Chem.* **1979**, *44*, 4010. Nicolaou, K.; Seitz, S. P.; Pavia, M. R.; Petasis, N. A. *Ibid.* **1979**, *44*, 4011. Büchi, G.; Wuest, H. *Helv. Chim. Acta* **1979**, *62*, 2661. Aristoff, P. A. *J. Org. Chem.* **1981**, *46*, 1954. Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 2030. Tanaka, T.; Oikawa, Y.; Hamada, T.; Yonemitsu, O. *Tetrahedron Lett.* **1986**, *27*, 3651. Tanaka, T.; Oikawa, Y.; Nakajima, N.; Hamada, T.; Yonemitsu, O. *Chem. Pharm. Bull. (Tokyo)* **1987**, *35*, 2203. Tanaka, T.; Oikawa, Y.; Hamada, T.; Yonemitsu, O. *Ibid.* **1987**, *35*, 2219. Nakajima, N.; Tanaka, T.; Hamada, T.; Oikawa, Y.; Yonemitsu, O. *Ibid.* **1987**, *35*, 2228.

0022-3263/88/1953-1437$01.50/0