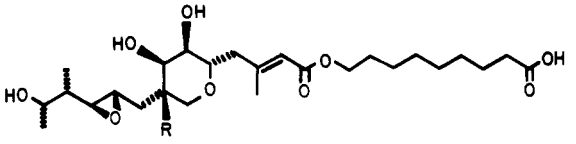
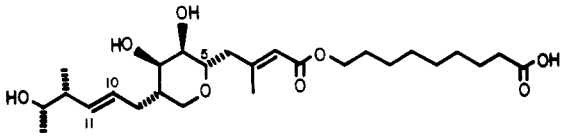
Total Synthesis of Pseudomonic Acid C

Summary: A convergent total synthesis of pseudomonic acid C from L-lyxose is described in which a highly stereoselective free-radical C–C bond construction plays a key role.

Sir: The pseudomonic acids **1a–c** are a unique family of potent and promising antibiotics whose chemistry and pharmacology is the subject of intensive investigation.[1] These materials have also attracted considerable interest with respect to total synthesis.[2] Herein we record an especially direct approach to the title compound (**1c**).



1a R=H
1b R=OH



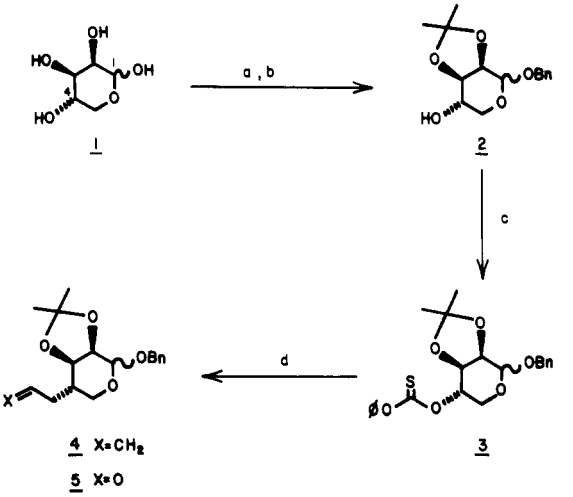
1c

A key element of the synthetic strategy detailed below is recognition of the structure of (+)-pseudomonic acid C as that of a highly modified L-lyxose, a commercially available sugar. Thus the synthetic planning may be reduced to the synthesis of the requisite "upper" and "lower" appendages for incorporation at C_1 and C_4, respectively, coupled with appropriate means for their stereocontrolled introduction. In this context, it should be noted that the C_5 or "upper" appendage (pseudomonic acid numbering) is potentially vulnerable to equilibration via a retro-Michael-Michael sequence, which, unfortunately, affords the undesired stereochemistry at this center,[2a] and that obvious disconnections at both olefinic units [(C_2–C_3) and (C_{10}–C_{11})] can, in principle, be utilized to enhance the convergence of the approach and its potential to provide ready access to a large number of analogues.

Our synthesis thus begins with L-lyxose. Differentiation of the C_1,C_4 pair of hydroxyls, which must be replaced, from the C_2, C_3 pair, which must be retained, with simultaneous differentiation of C_1 from C_4, was readily achieved in two steps by treatment of L-lyxose with benzyl alcohol (excess, taken as solvent) containing a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH), followed by exposure of the resultant *O*-benzylglycoside to dimethoxypropane and *p*-TsOH in acetone (23 °C) to afford **2** (85% from lyxose). Incorporation of the "lower" (C_4, lyxose numbering) side chain was then initiated by treatment of **2** with 1.1 equiv of methyllithium in THF at −78 °C followed by quenching with 1.1 equiv of phenyl chlorothioformate to afford **3** (Scheme I). Reaction of **3** with 2.0 equiv of allyltri-*n*-butylstannane with photochemical initiation[3] then yielded, after purification by flash[4] chromatography, the desired **4** in 72% isolated yield from **2**.[5]

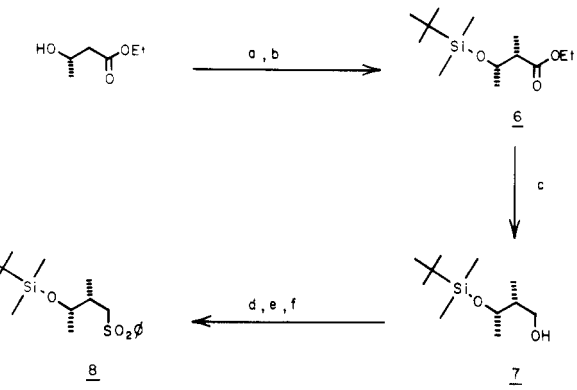
Elaboration of carbons 11–14 of pseudomonic acid C was achieved by alkylation of the ethyl ester of commercially available (*R*)-β-hydroxybutyric acid via the protocol of Frater[6] to afford **6** in 89% yield after silation[7] with *tert*-

Scheme I[a]



[a] Reagents: (a) $PhCH_2OH$, *p*-TsOH; (b) $CH_3C(OMe)_2CH_3$, acetone, *p*-TsOH; (c) MeLi; PhOCSCl; (d) $CH_2{=}CHCH_2SnBu_3$, toluene, *hν*.

Scheme II[a]



[a] Reagents: (a) LDA; CH_3I, THF; (b) *t*-BuSi$(CH_3)_2$Cl, imidazole, DMF; (c) $(i\text{-Bu})_2AlH$, CH_2Cl_2; (d) MsCl, pyr; (e) NaSPh, DMF; (f) *m*-CPBA, CH_2Cl_2.

(1) (a) Fuller, A. T.; Mellows, G.; Woolford, M.; Banks, G. T.; Barrow, K. D.; Chain, E. B. *Nature (London)* **1971**, *234*, 416–417. (b) Chain, E. B.; Mellows, G. *J. Chem. Soc., Chem. Commun.* **1974**, 847–848. (c) Alexander, R. G.; Clayton, J. P.; Luk, K.; Rogers, N. H.; King, T. J. *J. Chem. Soc., Perkin Trans. 1* **1978**, 561–565. (d) Clayton, J. P.; Luk, K.; Rogers, N. H. *Ibid.* **1979**, 308–313. (e) Clayton, J. P.; Oliver, R. S.; Rogers, N. H.; Kins, T. J. *Ibid.* **1979**, 838–846. (f) Coulton, S.; O-Hanlon, P. J.; Rogers, N. H. *Ibid.* **1982**, 729–734. (g) Clayton, J. P.; O-Hanlon, P. J.; Rogers, N. H. *Tetrahedron Lett.* **1980**, *21*, 881–884. (h) Clayton, J. P.; O-Hanlon, P. J.; Rogers, N. H.; King, T. J. *J. Chem. Soc., Perkin Trans 1* **1982**, 2827–2833. (i) Chain, E. B.; Mellows, G. *Ibid.* **1977**, 318–322. (j) Chain, E. B.; Mellows, G. *Ibid.* **1977**, 294–309. (k) Hughes, J.; Mellows, G. *J. Antibiot.* **1978**, *31*, 330–335. (l) Hughes, J.; Mellows, G. *Biochem. J.* **1978**, *176*, 305–318. (m) Hughes, J.; Mellows, G. *Ibid.* **1980**, *191*, 209–219.

(2) (a) Kozikowski, A. P.; Schmiesing, R. J.; Sorgi, K. L. *J. Am. Chem. Soc.* **1980**, *102*, 6577–6580. (b) Snider, B. B.; Phillips, G. B. *Ibid.* **1982**, *104*, 1113–1114. (c) Schoenenberger, B.; Summermatter, W.; Ganter, C. *Helv. Chim. Acta* **1982**, *65*, 2333–2337. (d) Fleet, G. W. J.; Spensley, C. R. C. *Tetrahedron Lett.* **1982**, *23*, 109–112. (e) Fleet, G. W. J.; Goush, M. J. *Ibid.* **1982**, *23*, 4509–4512. (f) Raphael, R. A.; Stibbard, J. H. A.; Tidbury, R. *Ibid.* **1982**, *23*, 2407–2410. (g) Curran, D. P. *Ibid.* **1982**, *23*, 4309–4310. (h) Fleet, G. W. J.; Shing, T. K. M. *Ibid.* **1983**, *24*, 3665–3668. (i) Fleet, G. W. J.; Gough, M. J.; Shing, T. K. M. *Ibid.* **1983**, *24*, 3661–3664.

(3) Keck, G. E.; Yates, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 5829–5831.

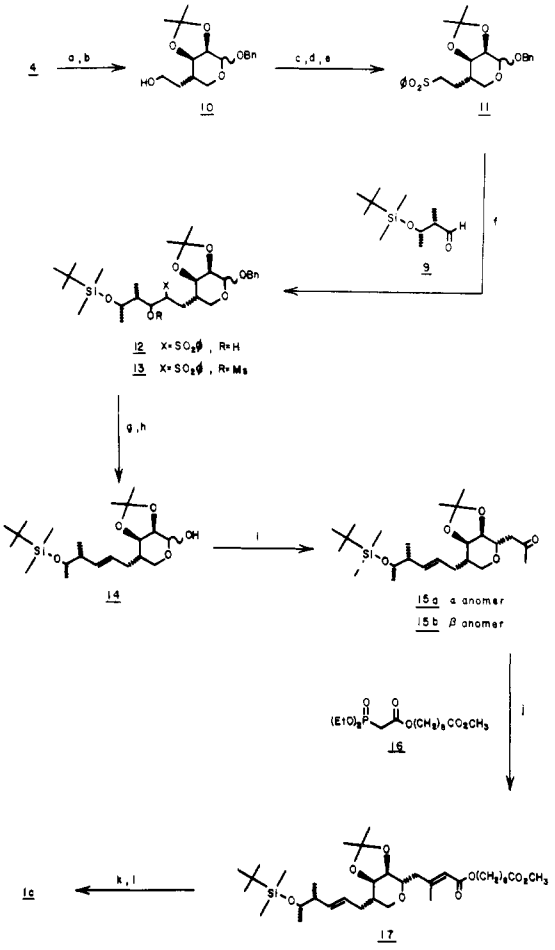
(4) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

(5) (a) The stereoisomeric product was not isolated, although the anomeric mixture of benzylglycosides complicates unambigous establishment of the stereoselectivity here. Stereochemistry was confirmed by correlation with materials previously characterized by high-field NMR in the Kozikowski[2a] route. (b) This substance returned a correct C, H combustion analysis. (c) Full experimental details for this and other transformations described will be given in our full paper.

(6) Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2825–2829, 2829–2833.

0022-3263/84/1949-1462$01.50/0

Scheme III[a]



[a] Reagents: (a) OsO_4, $NaIO_4$, aqueous THF; (b) $NaBH_4$, EtOH; (c) MsCl, pyr; (d) NaSPh, DMF; (e) CH_3CO_3H, $NaHCO_3$, CH_2Cl_2; (f) LDA, THF; 9; (g) MsCl, pyr, 12; (h) Li, NH_3 (l), THF; (i) $(Ph)_3PCH{=}CHCOCH_3$, 1,2-dichloroethane; (j) $LiN(SiMe_3)_2$, dioxane; (k) 80% HOAc; (l) Na_2CO_3, KOH, EtOH, THF.

butyldimethylchlorosilane (Scheme II). Reduction with diisobutylaluminum hydride (2.1 equiv) in CH_2Cl_2 at −20 °C for 1 h, followed by workup with Rochelle salt, yielded alcohol **7**, which was subjected, without purification, to the following sequence of reactions to yield sulfone **8** (90% from **6**): (1) mesylation (MsCl–pyr, 23 °C), (2) sulfide formation (NaSPh, DMF, 0 °C), and (3) oxidation (*m*-CPBA, CH_2Cl_2, 23 °C).

The next stage of the route was initially envisioned to proceed via the method of Julia,[8] i.e., coupling of sulfone **8** with aldehyde **5** (readily accessible by oxidative cleavage of **4**) followed by reductive elimination. However, despite extensive experimental investigation and highly successful condensations of sulfone **8** with a variety of simpler aldehydes, only very modest yields of coupled products could be obtained from reaction of the lithio derivative of sulfone **8** with aldehyde **5**. Fortunately, however, the requisite condensation could be readily achieved by reversing the roles of nucleophilic and electrophilic partners. To this end, ester **6** was reduced [$(i\text{-Bu})_2AlH$, CH_2Cl_2, −78 °C, 87%] to aldehyde **9**, and **4** (Scheme III) was converted (OsO_4, $NaIO_4$, aqueous THF, followed by reduction with $NaBH_4$ in ethanol, 85%) to alcohol **10**, from which sulfone **11** was prepared by a process parallelling that delineated above.[9] Coupling of the lithio derivative of **11** (LDA, 0 °C, 15 min) with aldehyde **9** (0 °C, THF) then proceeded very smoothly to afford β-hydroxy sulfone **12**, which, without purification, was converted (MsCl–pyr, 23 °C), to mesylate **13**. Reduction of crude **13** with lithium in liquid ammonia (−78 °C) then effected *both* the stereoselective introduction of the C_{10}–C_{11} trans olefin (pseudomonic acid numbering) *and* deprotection of the benzylglycoside to afford lactol **14** in 37% overall yield from **11** after purification by column chromatography over silica gel.

The stage was now set for introduction of the "upper" (C_1–C_5) side chain of pseudomonic acid C. Efforts concurrent with ours had provided "two-electron" approaches to this general problem,[10] and our own "one-electron" approach had been shown to be effective for the synthesis of C glycosides.[11a] Stereocontrol in the present endeavor could be envisioned by utilizing the same steric approach control element leading to the highly stereoselective introduction of the C_4 (lyxose numbering) appendage. However, in our hands, the "two-electron" approaches of Kishi and Kozikowski proved unsuitable for this case, as did a number of other "two-electron" approaches under investigation in our laboratories.[11a] Our "one-electron" methodology that was highly successful for the installation of an allyl moiety at C_4 of lyxose was compromised by a facile free-radical cyclization process in this case.[11b]

At this point we decided to reexamine the approach previously utilized[2a] in a *d,l* synthesis of pseudomonic acid C, that is, incorporation of the "upper" side chain via a Wittig–Michael sequence, as originally described for furanoses in the thorough and elegant studies of Moffatt and co-workers.[12] As initially employed[2a] this sequence yielded a 2.5:1 mixture of isomers at C_5 (pseudomonic acid numbering), but the conditions utilized (CH_3CN, 170 °C) seemed less than ideal for obtention of good stereocontrol. Moreover, we became intrigued by the question of the stereochemistry of the Michael reaction, in this case an intramolecular variant with an oxygen nucleophile, for acceptors with γ-oxygen substituents.[13]

To our delight, reaction of lactols **14** with excess acetylmethylene–triphenylphosphorane in dichloroethane (70 °C, 24 h) afforded largely a single (TLC) unsaturated ketone (in addition to small amounts of ring-closed materials), which was converted (catalytic K_2CO_3 in MeOH, 0 °C, using crude product) to a 6:1 mixture of the desired **15a** and **15b**. After chromatographic separation, the homogeneity of the major isomer (67% yield) was easily confirmed by standard chromatographic and spectroscopic techniques. Confirmation of structure was achieved unambigously by conversion to **7** (which was independently

(7) Corey, E. J.; Vankateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(8) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, 4833–4836.

(9) In this case, oxidation was best accomplished with peracetic acid in methylene chloride containing excess sodium bicarbonate.
(10) (a) Kozikowski, A. P.; Sorgi, K. L. *Tetrahedron Lett.* **1982**, *23*, 2281–2284. (b) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976–4978. (c) Kozikowski, A. P.; Sorgi, K. L.; Wang, B. C.; Zhang-bao, X. *Tetrahedron Lett.* **1983**, *24*, 1563–1566.
(11) (a) Keck, G. E.; Enholm, E. J.; Kachensky, D. F., unpublished results. (b) Reaction of the thiophenylglycoside derived from lactol **14** with methallylstannane was unsuccessful in simple model systems (lacking carbons 12 and 13) due to cyclization of the intermediate anomeric radical onto the C_{10}-C_{11} unsaturation (pseudomonic acid numbering) followed by capture of the resulting radical by methallyltri-*n*-butylstannane.
(12) Ohrui, H.; Jones, G. H.; Moffatt, J. J.; Maddox, M. L.; Christensen, A. T.; Bryon, S. K. *J. Am. Chem. Soc.* **1975**, *97*, 4602–4613.
(13) (a) Although a rationalization for the relative stability of products obtained in such processes has appeared,[13b] no explanation for the kinetic production of the less stable isomer has been advanced. However, almost without exception, the kinetic products are precisely those that one would predict for a Felkin–Anh[13c] addition antiperiplanar to the γ-oxygen substituent. (b) Ohrui, H.; Emoto, S. *J. Org. Chem.* **1977**, *42*, 1951–1957. (c) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61–70 and references therein.

prepared from natural material) via chain extension with the phosphonate **16**[14] in dioxane (75% isolated yield). Natural and synthetic materials so obtained proved spectroscopically (300 MHz ^1H NMR, ^{13}C NMR) and chromatographically (TLC, HPLC) identical. Protecting-group removal (80% aqueous acetic acid) then afforded methyl pseudomonate C, indistinguishable from naturally derived material by high-field NMR and TLC analysis, which upon hydrolysis[2a] yields the title compound.

Acknowledgment. Support of this research through Grant No. GM-28961 from the National Institutes of Health, by the Alfred P. Sloan Foundation, and by Eli Lilly & Co. is gratefully acknowledged, as is funding for the purchase of the VG Micromass 7070 mass spectrometer utilized in this work, which was provided by the National Science Foundation and the University of Utah Institutional Funds committee. We thank Dr. Norman Rogers of Beecham Pharmaceutical Co. for samples of pseudomonic acids A and C as well as unpublished experimental procedures for the conversion of pseudomonic acid A to pseudomonic acid C.

(14) This material is readily accessible via esterification (dicyclohexylcarbodiimide, 4-(dimethylamino)pyridine) of bromoacetic acid with methyl 9-hydroxynonanoate, followed by Arbuzov reaction with trimethyl phosphite.[5c]

(15) Fellow of the Alfred P. Sloan Foundation, 1981-1985.

Gary E. Keck,*[15] David F. Kachensky
Eric J. Enholm
Department of Chemistry
University of Utah
Salt Lake City, Utah 84112
Received January 18, 1984

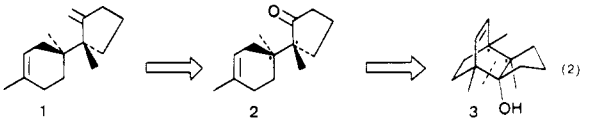
Stereoselective Synthesis of (±)-Trichodiene

Summary: A stereoselective synthesis of (±)-trichodiene (**1**) is described whose key step is the conversion of the tricyclic, homoallylic alcohol **3**, via β-fragmentation of its potassium alkoxide **3a**, to cyclopentanone **2**.

Sir: The naturally occurring bicyclic sesquiterpene hydrocarbon trichodiene (**1**), the biogenetic precursor of the biologically active trichothecanes, was first isolated in 1970 from the fungus *Trichothecium roseum* and its structure determined by degradation and spectroscopy.[1] Up to now, relatively few syntheses of **1** have been reported,[2] reflecting the general difficulty of controlling the stereochemistry of two adjacent chiral centres where there is free rotation about the common carbon-carbon bond. We present herein an effective solution to this problem in the context of a short, stereoselective synthesis of racemic trichodiene.

Recently, as a synthetic application of the β-fragmentation of potassium homoallylic alkoxides,[3] we reported the regioselective preparation of 1-(3-cyclohexenyl)-2-alkanones from 2-substituted bicyclo[2.2.2]oct-5-en-2-ols (eq 1).[4] Retrosynthetic analysis (eq 2) thus indicated that cyclopentanone **2**, a direct synthetic precursor of tri-

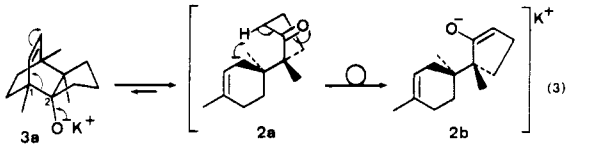
chodiene,[2a,c] would be formed analogously from the tri-



cyclic, homoallylic alcohol **3** in which the correct relative stereochemistry of the two relevant quaternary centers is already set up. An efficient preparation of **3** from 1,4-dimethyl-1,3-cyclohexadiene (**4**)[5] and the successful realisation of this synthetic strategy are outlined in Scheme I.

Diels-Alder reaction between **4** and 2-chloroacrylonitrile (1.5 equiv) in toluene containing hydroquinone at 90 °C during 60 h followed by hydrolysis[6] of the intermediate cycloadducts gave bicyclo[2.2.2]enone **5** (57%, bp 68-70 °C (10 mmHg)).[7] With lithium diisopropylamide (LDA) as base, two successive low temperature alkylations, methylation and then allylation, afforded dienone **6** (84%, bp 53-55 °C (0.05 mmHg)) with high stereoselectivity (≥95%[8]). The stereochemistry at C(3) is controlled by the second alkylation in which allyl iodide reacts exclusively at the less hindered face of the tetrasubstituted lithium enolate. Chemoselective and regioselective hydroboration of the monosubstituted alkenyl double bond in **6** with 9-borabicyclo[3.3.1]nonane (9-BBN) (1.1 equiv in tetrahydrofuran (THF) at 25 °C), oxidation with aqueous basic hydrogen peroxide, tosylation of the resulting keto alcohol, and treatment with lithium bromide (2.6 equiv) in acetone at reflux during 1.5 h then afforded bromo ketone **7** (77% from **6**, bp 88-90 °C (0.05 mmHg)). An intramolecular Barbier reaction[9] using lithium in THF at 0 °C in a sonicator[10] completed the synthesis of **3** (54%, bp 70-72 °C (0.05 mmHg)).[11]

With **3** in hand the key step was effected by treatment with potassium hydride (1.1 equiv) in hexamethylphosphoric triamide (HMPA) at 25 °C and then heating the thus formed potassium alkoxide **3a** at 140 °C during 1 h. Quenching (20% aqueous NH_4Cl) followed by an extractive workup led to the isolation of stereochemically pure **2** in 32% yield.[12,13] In analogy with previous work[4]



(1) (a) Nozoe, S; Machida, Y. *Tetrahedron Lett.* **1970**, 2671-2674. (b) *Tetrahedron* **1972**, *28*, 5105-5117.

(2) (a) Welch, S. C.; Prakaso Rao, A. S. C.; Wong, R. Y. *J. Org. Chem.* **1980**, *45*, 4077-4085. (b) Suda, M. *Tetrahedron Lett.* **1982**, *23*, 427-428. (c) Schlessinger, R. H.; Schultz, J. A. *J. Org. Chem.* **1983**, *48*, 407-408.

(3) For other synthetic applications, see: (a) Snowden, R. L.; Muller, B. L.; Schulte-Elte, K. H. *Tetrahedron Lett.* **1982**, *23*, 335-338. (b) Snowden, R. L. *Helv. Chim. Acta* **1983**, *66*, 1031-1038.

(4) Snowden, R. L.; Schulte-Elte, K. H. *Helv. Chim. Acta* **1981**, *64*, 2193-2202.

(5) Ruttimann, A; Wick, A.; Eschenmoser, A. *Helv. Chim. Acta* **1975**, *58*, 1450-1455.

(6) Evans, D. A.; Scott, W. L.; Truesdale, L. K. *Tetrahedron Lett.* **1972**, 121-124.

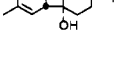
(7) Reactions involving air-sensitive reagents or substances were conducted under a N_2 atmosphere. Satisfactory spectroscopic data (IR, ^1H NMR, and MS) were obtained for each synthetic intermediate by using chromatographically purified and homogeneous samples.

(8) This lower stereoselectivity limit was determined by ^{13}C NMR spectral comparison of the crude reaction mixture with the C(3) epimer of **6**, independently prepared from **5**, with a similar high stereoselectivity, by inversion of the alkylation sequence.

(9) Blomberg, C.; Hartog, F. A. *Synthesis* **1977**, 18-30.

(10) Luche, J.-L.; Damiano, J.-C. *J. Am. Chem. Soc.* **1980**, *102*, 7926-7927.

(11) Another tertiary alcohol, tentatively assigned the tricyclic-[5.4.0.0^{2,6}] structure i, was also isolated in 11% yield.



0022-3263/84/1949-1464$01.50/0