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TOTAL SYNTHESIS OF (±) - PANICULIDE - A

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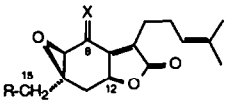
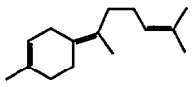
Abstract: An efficient synthesis of the paniculide A precursor **4** has been achieved beginning with 3-methylglutaric anhydride, and utilizing as the key step an intramolecular Diels-Alder reaction of an acetylenic oxazole to give a 2-methoxyfuran. Acid hydrolysis then provided the requisite butenolide ring characteristic of the paniculides.

Introduction

The paniculides (**1**) are a family of highly oxygenated sesquiterpenes isolated from callus cultures derived from the hypocotyl and stem tissues of *Andrographis paniculata*.[1] Paniculide A (**1a**, R = H, X = β - OH), isolated as the minor constituent under conditions of constant temperature and light, is also structurally the simplest, while



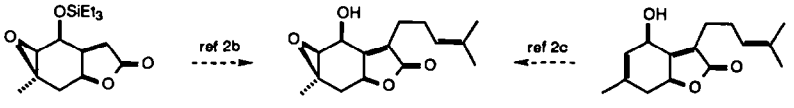
Paniculides A - D (1a - 1d)



Bisabolene (2)

paniculides B (**1b**, R = OH, X = β - OH) and C (**1c**, R = OH, X = O) differ in oxidation state at C-15, and C-8 and C-15, respectively. Paniculide D (**1d**, R = H, X = O), although not isolated from plant sources, has been suggested as a "likely, albeit as yet unknown natural product" on the basis of biosynthetic considerations.[2b] All of these materials are members of the bisabolane class of sesquiterpenes, being structurally related to γ-bisabolene (**2**), and the absolute configuration of **1b** has recently been shown to be as indicated by X-ray analysis.[3]

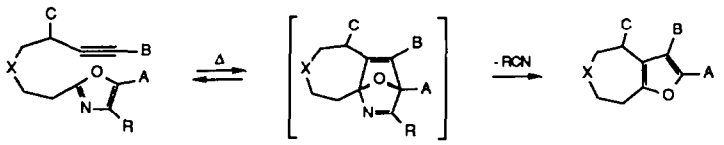
Not surprisingly, the paniculides have been the subject of considerable synthetic attention, including the first successful preparation of **1a** - **1d** by Smith *et al.*,[2a,b] and additional syntheses of **1a** by Yoshikoshi *et al.*,[2c] and ourselves.[2d] Also, formal syntheses of **1b** and **1c** have been reported by Baker *et al.*,[2e] and Taschner has described some preliminary results directed toward the synthesis of **1a**.[2f] By way of summary, in the Smith approach to **1a** the highly substituted lactone derivative **3** was prepared with good stereocontrol and subsequently elaborated to the desired target compound *via* a sequence of reactions involving alkylation, phenylselenation and selenoxide elimination.[2a,b] In the Yoshikoshi approach, a novel vinylfuranone annulation procedure was employed to prepare



3 1a 4

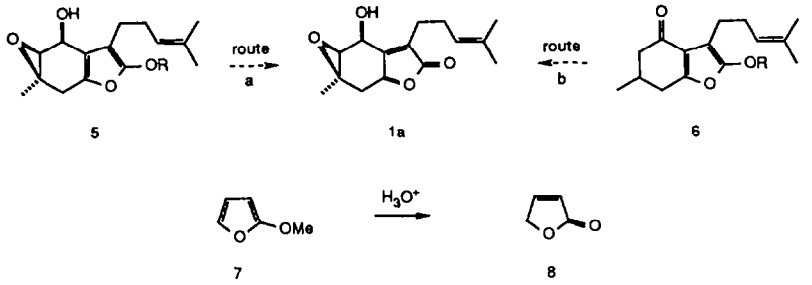
the allylic alcohol **4**, which was directly converted to **1a** *via* a metal catalyzed epoxidation.[2c] In this paper we provide experimental details for our independent synthesis of **4**,[2d] which can be carried out on gram scales and larger with excellent stereocontrol. Also, we describe preliminary efforts directed toward an enantiospecific synthesis of **1a**.

For some time now we have been developing a general synthetic approach to the furanosesquiterpenes, the most notable feature of which is the use of an intramolecular Diels-Alder reaction of an acetylenic oxazole to generate a fused furan ring (see below).[2d,4] This approach is of particular utility for the preparation of highly substituted



I II III

furans, since substituents of the type A, B, and C are transposed in a predictable fashion through intermediate II to the final adduct III. For the case in point, we expected that substrates of type **5** and **6** might be conveniently assembled by such a process, and subsequently converted to **1a** using standard methodology (Scheme 1). Thus, following *route a*, there was precedent to suggest that mild acid hydrolysis of **5** would lead directly to the requisite butenolide ring by protonation at C-12 and 1,4-addition of water (*cf.* **7** ---> **8**).[5] Alternatively, following



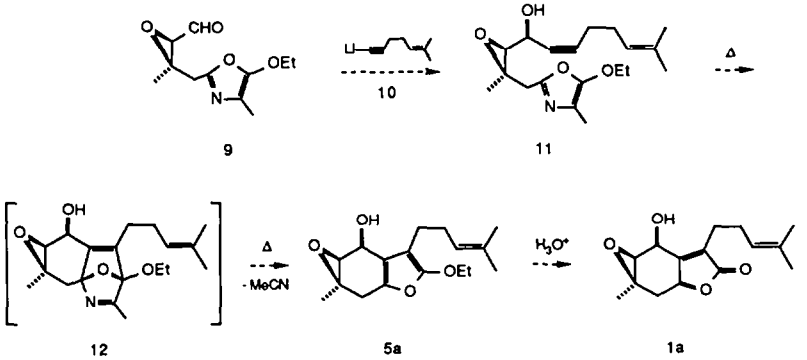
Scheme 1

route b, the furanoketone **6** appeared to be an ideal candidate for conversion to the Yoshikoshi precursor **4**, [2c] which had previously been converted to **1a** by epoxidation (*vide supra*). Each of these routes was explored in turn.

Results and Discussion

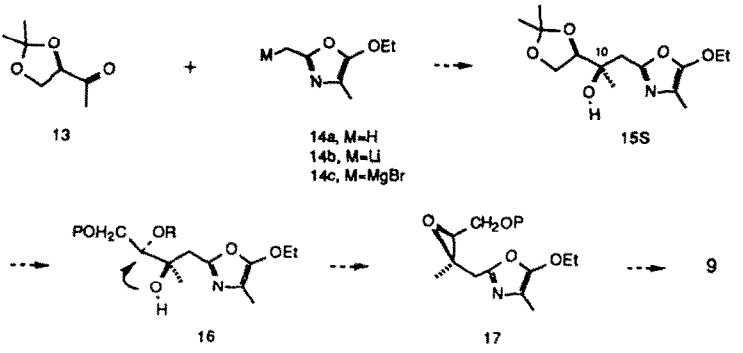
(a) Route a: An Enantiospecific Approach to the Synthesis of 1a.

We initially envisioned that the oxazole aldehyde **9** might be transformed to **1a** *via* a three step sequence of reactions involving *(a)* condensation of **9** with 1-lithio-6-methyl-5-hepten-1-yne (**10**) to afford the acetylenic alcohol **11**; *(b)* thermolysis of **11** to provide the ethoxyfuran **5a**; and *(c)* acid catalyzed hydrolysis of **5a** as described above (Scheme 2). Various approaches were considered for the synthesis of the oxazole aldehyde **9**. In particular,



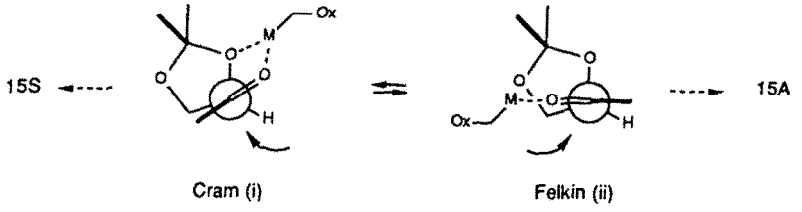
Scheme 2

however, it seemed feasible that condensation of (2R)-(+)-1,2-O-isopropylidene-3-butanone (**13**)[6] with a metallated derivative of 2,4-dimethyl-5-ethoxyoxazole (**14a**)[7] might produce the *syn*-alcohol **15S**, which upon suitable activation, and cyclization, would afford the Z-epoxy-alcohol **17** (Scheme 3).[8] The conversion of **17** to **9** should



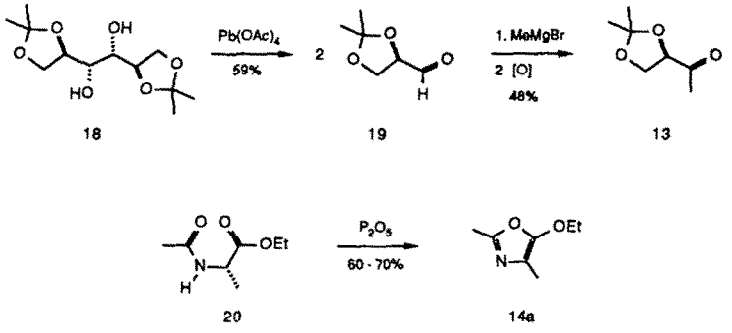
Scheme 3

then be straightforward. This route would have the advantage of proceeding in a highly convergent fashion with total control over relative and absolute stereochemistry. We recognized, however, that such an approach was also critically dependent upon the condensation of **14b/c** with **13** occurring *via* the Cram chelation model **i** to provide the



necessary R-configuration at C-10.[9] The alternative Felkin mode of addition,[10] proceeding *via* **ii**, would afford the epimeric *anti*-alcohol **15A**, thus leading eventually to the geometric isomer of the desired epoxide **17**.

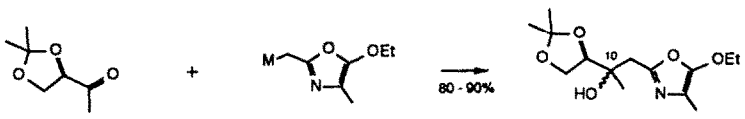
The requisite starting materials, **13** and **14a**, were prepared following slight modifications of published procedures (Scheme 4).[6,7] Thus, 1,2,5,6-di-O-isopropylidene-*D*-mannitol (**18**) was readily cleaved with lead tetraacetate to afford (R)-(+)-1,2-O-isopropylidene glyceraldehyde (**19**), which upon condensation with



Scheme 4

methylmagnesium bromide, and Swern oxidation,[11] gave the desired methyl ketone **13**. 2,4-Dimethyl-5-ethoxyoxazole (**14a**) was prepared in 60-70% yield by cyclodehydration of ethyl N-acetylalaninate (**20**).

After considerable experimentation, reproducible conditions were developed for the condensation of either **14b** or **14c** with **13** (*cf.* experimental section). In a typical run, **14b** gave a 5 : 1 mixture of products of Rf 0.42 and Rf 0.40 at -78° C in THF (~89% combined yield), decreasing to a ratio of 2.5 : 1 upon changing to hexane as solvent, employing either normal or inverse modes of addition (Table 1, entries 1 - 3). In similar fashion, **14c**



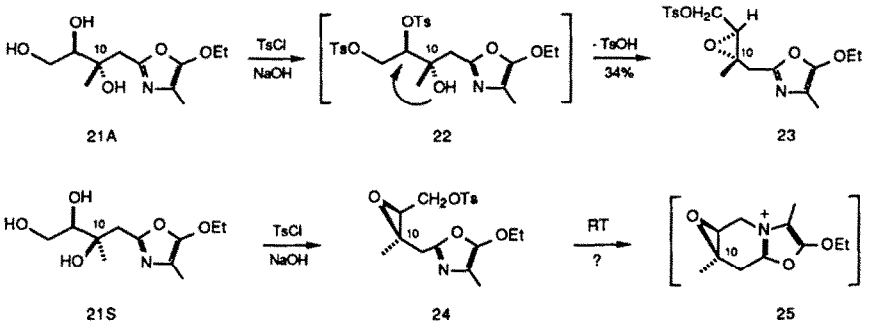
13 14b, M=Li 14c, M=MgBr 15S, A

Entry	Compound	Solvent	Conditions	R_f 0.42 : R_f 0.40
1	14b	THF	-78°	5:1
2	14b	hexane	-78°	2.5:1
3	14b	hexane	Inv. Add., -78°	2.5:1
4	14c	THF	-98°	5:1
5	14c	THF	X's $MgBr_2$	3:1

Table 1

afforded a 5 : 1 ratio of products in THF at -98° C, decreasing to 3 : 1 in the presence of excess $MgBr_2$ (entries 4 and 5). Unfortunately, it was not possible to unequivocally assign stereochemistry at C-10 by spectral means. Experiments 2,3, and 5, however, were revealing in that each of these reactions should have proceeded with enhanced chelation control,[12] resulting in an increased percentage of **15S**. On this basis we suspected that the major product, having Rf 0.42, was the undesired *anti*-alcohol **15A**. This suspicion was confirmed by the experiments described below.

Both **15A** and **15S** were routinely hydrolyzed to the respective triols **21A** and **21S** (1 : 1 HOAc/H2O, 50-65%), which we expected could be converted to the corresponding internal epoxides for additional characterization. Various approaches for carrying out this latter transformation involving selective protection and/or activation were pursued with little success. Eventually, however, we found that the material presumed to be **21A** reacted with excess TsCl in NaOH/glyme to afford a 34% yield of the E-epoxide **23**,[13] most likely *via* the di-tosylate **22** (Scheme 5).[14] The structure of **23** was securely established by extensive decoupling and NOE experiments,



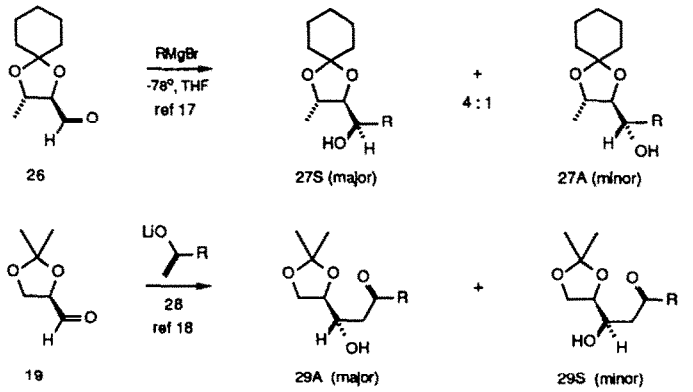
21A 22 23

21S 24 25

Scheme 5

thereby confirming our original assignment for **15A**. Using this same methodology, **21S** gave the Z-epoxide **24**, which in addition to having the expected spectral properties,[15] slowly decomposed to a compound tentatively identified as the oxazolium salt **25** upon standing in solution at ambient temperature. Intermolecular examples of such alkylations are well known.[16]

The reasons for the disappointing stereochemical outcome in the condensation of **13** with **14b** and **14c** remain unclear, particularly in view of the fact that closely related systems such as **26** show good *syn*-stereoselectivity with simple Grignard reagents (Scheme 6).[17] Interestingly, however, during the course of this work Heathcock *et al.* described results similar to our own dealing with the aldol condensation of various lithium enolates **28** with the glyceraldehyde acetonide **19**.[18] In this work the *anti*-isomer **29A** predominated by ratios of 2 : 1 to > 95 : 1, depending on the size of R. Heathcock rationalized these results in terms of two competing transition



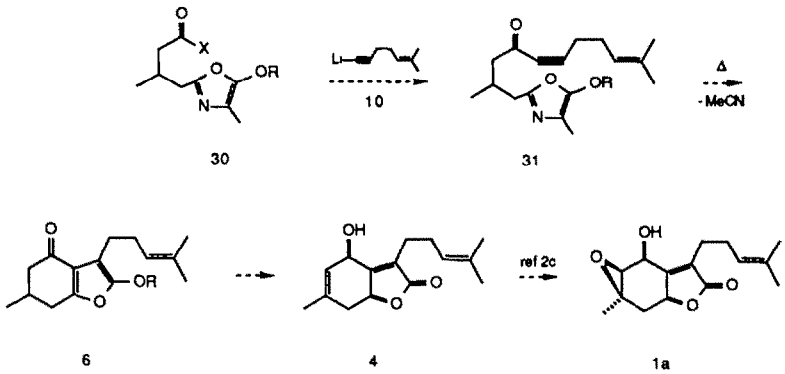
Scheme 6

states, one of which is oriented in accordance with Cram-chelation control, while the other conforms to the Felkin model. In both of our studies, the low percentages of *syn*-isomers **15S** and **29S** may be due to unfavorable complexation of the isopropylidene oxygen with the metal cation because of its decreased basicity.[12]

In principle, at least, the desired isomer **15S** might predominate if one were to reverse the order of addition of organometallic reagents to the glyceraldehyde acetonide **19** (*cf.* Scheme 4 and Table 1). However, in view of the modest stereoselectivities thus far observed, there was little reason to believe that a dramatic increase in isomer ratios would be realized. Therefore, we devoted an increasing proportion of our efforts to the pursuit of *route b*, and as described below, these efforts culminated in the formal total synthesis of **1a**.

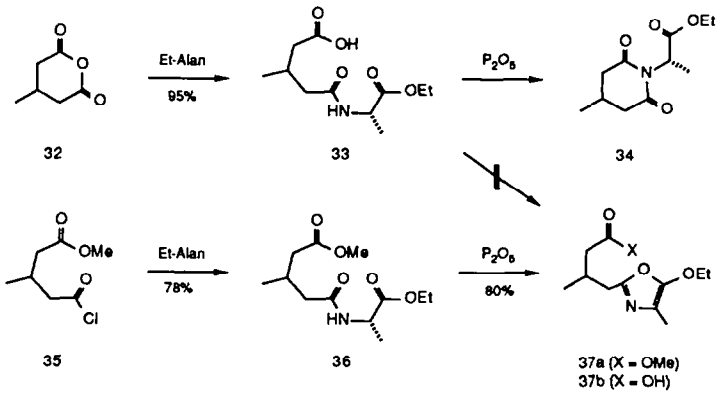
(b) Route b: A Highly Efficient Synthesis of the Yoshikoshi Precursor 4.

We have previously noted that furanoketones of type **6** were attractive intermediates for the synthesis of the Yoshikoshi precursor **4** (*route b*, above, R = Et, Me),[2c] and efforts to prepare such compounds were well underway concurrent with the work described above. As the key step, we were confident that **6** could be derived in a single step by thermolysis of the acetylenic oxazole **31**, in close analogy with our related work in this area (Scheme 7).[4]



Scheme 7

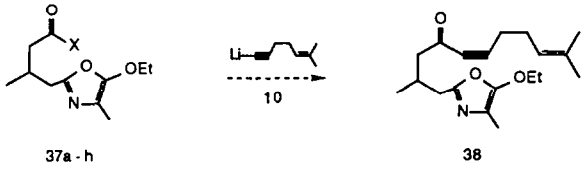
Also, it appeared likely that **31** might be available *via* coupling of the lithium acetylide **10** with an active ester of general structure **30**, and finally, we expected that **30** could be prepared using standard methodology. This last presumption turned out to be correct, although not without an unexpected diversion (Scheme 8). Thus, ring



Scheme 8

opening of 3-methylglutaric anhydride (**32**) with ethyl alaninate proceeded normally to afford the glutaric amide **33**, but **33**, upon cyclodehydration, gave the glutarimide derivative **34** to the complete exclusion of the oxazole acid **37b**. Fortunately, however, the analogous methyl ester **36**, obtained by acylation of ethyl alaninate with the readily available acid chloride **35**,[19] was cleanly dehydrated to the oxazole ester **37a** with P_2O_5 (80%).[20] Ester **37a** could then be hydrolyzed to the acid **37b** in virtually quantitative yield with hot methanolic KOH.

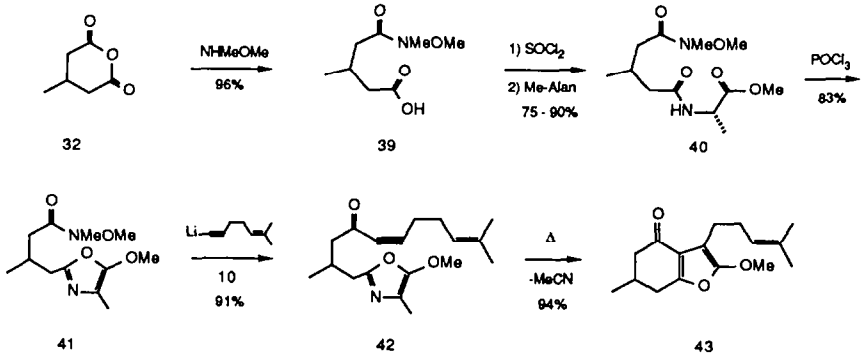
Various active esters **37c** - **37h** were prepared in fair to moderate yields from **37b** following literature procedures,[21c-h] and each was subjected to condensation with the lithium acetylide **10**. For **37c** - **37g** the major



a) X = OMe; b) X = OH; c) X = Cl; d) X = OTFA; e) X = 1-Imidazolo; f) X = 2-pyridylthio; g) X = OCO_2Et; h) X = NMeOMe

products obtained were those resulting from either bis-addition or proton abstraction, with only trace amounts of **38** observable by TLC. In contrast, however, the results obtained with the "Weinreb amide" **37h** (X = NMeOMe)[21h] were gratifying in that **38** was produced as the only identifiable product (> 90% yield). It remained now only to modify these procedures for greater efficiency, and this was accomplished as outlined in Scheme 9.

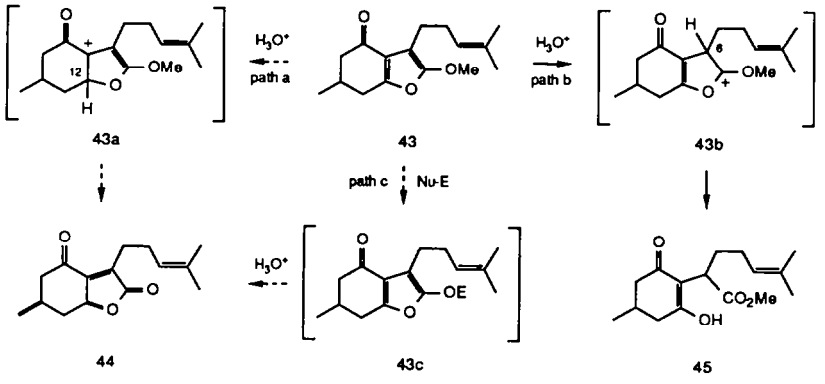
Thus, **32** was readily opened with N, O-dimethylhydroxylamine to give the amide derivative **39** (96%), which was cleanly converted to the oxazole amide **41** by initial coupling with methyl alaninate followed by



Scheme 9

cyclodehydration with $POCl_3$ in pyridine (83%).[22] Compound **41**, upon reaction with 1-lithio-6-methyl-5-heptene-1-yne (**10**),[23] then gave a 91% yield of the acetylenic ketone **42**, which upon brief thermolysis in ethyl benzene afforded the methoxyfuran **43** (**6**, R = Me) in 94% yield (> 60% overall yield from **32** on a 5 g scale).[24]

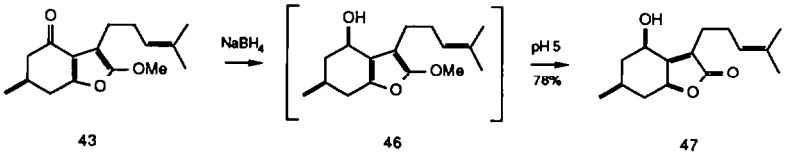
With ample quantities of **43** now in hand, we expected that the remaining steps necessary for the conversion of **43** to the key butenolide alcohol **4** would be straightforward (*cf.* Scheme 7, above). In preliminary studies, however, we were disappointed to find that **43** could not be converted to the butenolide ketone **44** by acid catalyzed hydrolysis (Scheme 10, *path a*). At pH 1-5, for example, **43** appeared to be indefinitely stable at ambient



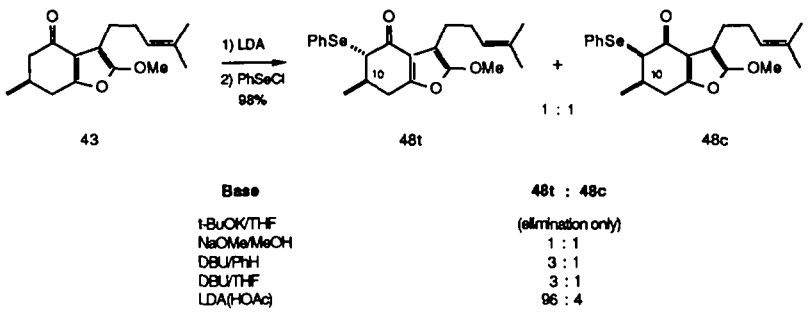
Scheme 10

temperature, while under more forcing conditions (1 N H_2SO_4, 50° C) the only product isolated was the ester derivative **45** resulting from ring opening (*path b*). These results are best rationalized by the fact that the desired protonation at C-12 is rendered highly unfavorable by the inductive influence of the C-8 carbonyl group (*cf.* intermediate **43a**), while protonation at C-6 produces the relatively stable cation **43b**. Various non-hydrolytic procedures for cleaving the O-Me bond were also investigated, most of these having their origins in HSAB theory (*cf. path c*).[25] Of the many reagents of general structure Nu-E examined, only trimethylsilyl iodide (TMSI) exhibited some degree of promise,[26] providing in one instance a 41% yield of **44**. Unfortunately, however, this result was not reproducible and depended in a complex fashion on the purity and source of TMSI.

In a fortuitous discovery, we eventually found that the furanoalcohol **46**, obtained by $NaBH_4$ reduction of **43**, was rapidly hydrolyzed to the single butenolide **47** upon attempted chromatographic purification, or upon exposure to dilute acetic acid (78% overall yield from **43**). This divergence in hydrolytic stability is in full accord

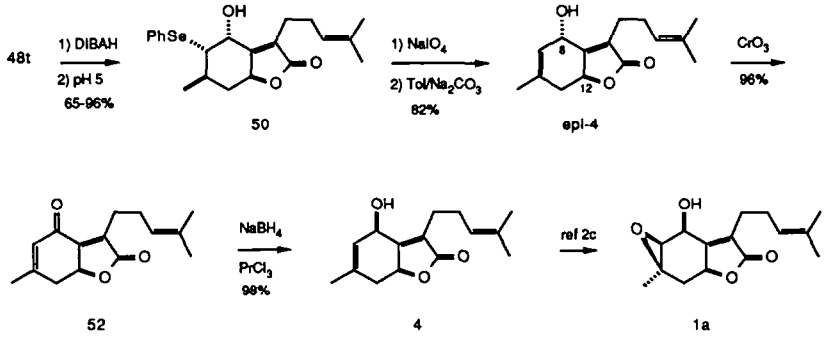


with the rationale provided above, since protonation at C-12 will be energetically favorable in **46**. Of more immediate interest, however, we were now in position to extrapolate this observation to the synthesis of **4** by simple adjustment of oxidation state. Thus, **43** was first alkylated with LDA/PhSeCl to provide a 1 : 1 mixture of the phenylselenides **48t** and **48c** (98%, Scheme 11, following page), which upon kinetic deprotonation (LDA) - protonation (HOAc) afforded the desired isomer **48t** in a 96 : 4 ratio.[27] As indicated, several attempts to equilibrate **48t** and **48c** under thermodynamic control provided only modest improvements in the **48t** : **48c** ratio, or were complicated by elimination of PhSeH to give the corresponding furanophenol (*t*-BuOK/THF).



Scheme 11

Compound **48t**, in turn, was smoothly reduced to the phenylselenide alcohol **49α** (DIBAH, -78°),[28] which, without isolation, was directly hydrolyzed at pH 5 to give **50** in 65-96% overall yield from **48t** (Scheme 12). Oxidation of **50** to the corresponding selenoxide **51** was then cleanly accomplished with saturated aqueous $NaIO_4$ in THF (1 : 1, ~ 100%), but we experienced initial difficulties in the elimination of PhSeOH from **51**. Thus, only trace amounts of the desired allylic alcohol *epi*-**4** were obtained under the usual conditions for this conversion,[29] the major product being that derived from deoxygenation of **51** to return **50**. Furthermore, all efforts at applying the standard remedies for this situation were unsuccessful.[30] Eventually, however, we found that the desired transformation could be accomplished in 82% overall yield from **50** when the elimination was carried out in a two phase system consisting of 1 : 1 toluene/saturated Na_2CO_3 at reflux. Under these conditions we believe that PhSeOH is rapidly extracted from the reaction medium before it can initiate deoxygenation or cause other complications.



Scheme 12

Finally, epimerization at either C-8 or C-12 in racemic *epi*-**4** could in principle produce the desired target compound (±)-**4**, and, in fact, we have obtained trace amounts of this material both by equilibration at C-12 (*t*-BuOK/THF),[31] and by direct inversion at C-8.[2c] By far the most efficient procedure, however, involved an initial oxidation of *epi*-**4** to give the enone **52** (CrO_3/pyr, 96%), followed by reduction with the reagent system $NaBH_4/PrCl_3 \cdot 6\,H_2O$ (98%) to afford (±)-**4** as the exclusive stereoisomer in 94% overall yield.[32] Significantly, in the absence of $PrCl_3 \cdot 6\,H_2O$ this same reduction gave a 1 : 1 mixture of **4** and *epi*-**4**, as well as products derived from conjugate addition.

The synthetic (±)-**4** thus obtained, in 11 steps, and ~ 24-42% overall yield from 3-methylglutaric anhydride (**32**), had identical spectral data as that of an authentic sample and was readily converted to (±)-paniculide-A (**1a**) following the published procedure.[2c]

Experimental

(2R, 3R)-1,2-O-Isopropylidene-3-methyl-4-[2'-(4'-methyl-5'-ethoxyoxazolyl)]-3-butanol (15S), and **(2R, 3S)-1,2-O-Isopropylidene-3-methyl-4-[2'-(4'-methyl-5'-ethoxyoxazolyl)]-3-butanol (15A)**. A solution of 750 mg (5.32 mmol, 1.1 eq) of **14a** in 53 ml of dry THF was cooled under nitrogen to -78° C in a 3-necked flask, and treated in a dropwise fashion over 12 min, with vigorous stirring, with 3.85 ml (4.97 mmol, 1.05 eq) of a 1.29 M solution of *n*-BuLi/hexane. The resulting clear gold solution was then allowed to warm slowly to -27° over a period of 40 min before cooling once again to -78°. A solution of 703 mg (4.84 mmol, 1.0 eq) of **13** in 4 ml of THF was then added dropwise over 8 min, maintaining a temperature between -78° and -65°, and the reaction was stirred for an additional 1 h at -60° before cooling to -78° and quenching with 0.28 ml (1.0 eq) of glacial HOAc. After warming to RT, the brown reaction mixture was diluted with 60 ml of pH 7 phosphate buffer and extracted with 3 x 60 ml of CH_2Cl_2. The combined organic extracts were then dried over anhydrous Na_2SO_4, concentrated, and chromatographed (silica gel, 1 : 1 EtOAc/hexane) to afford 1.21 g (89%) of a 1 : 5 mixture of **15S** (Rf 0.40) and **15A** (Rf 0.42) as a yellow oil. The isomers could be separated by repeated chromatography. **15S** : Mass spectrum, m/e 284 (M-1); IR(CH_2Cl_2) 3532, 1672, 1567, 1377, 1327, 1225, 1162 cm^{-1}; NMR($CDCl_3$) δ 1.16 (s, 3H), 1.33 (s, 3H), 1.40 (s, 3H), 1.33 (t, 3H), 1.99 (s, 3H), 2.73 (d, 1H, J = 15 Hz), 2.88 (d, 1H, J = 15 Hz), 3.27 (s, 1H), 3.86-4.03 (m, 3H), 4.10 (q, 2H). **15A** : NMR($CDCl_3$) δ 1.18 (s, 3H), 1.30 (s, 3H), 1.40 (s, 3H), 1.31 (t, 3H), 1.97 (s, 3H), 2.69 (d, 1H, J = 15 Hz), 2.85 (d, 1H, J = 15 Hz), 3.79 (s, 1H), 3.91-4.01 (m, 3H), 4.08 (q, 2H). **Anal.** Calcd for $C_{14}H_{23}NO_5$ (**15S**): C, 58.93; H, 8.12; N, 4.91. Found: C, 58.74; H, 8.27; N, 5.26.

(2R, 3R)-1,2-Dihydroxy-3-methyl-4-[2'-(4'-methyl-5'-ethoxyoxazolyl)]-3-butanol (21S). A solution of 82.1 mg (0.29 mmol) of isopropylidene **15S** in 2.0 ml of 1 : 1 HOAc/H_2O was stirred for 16 h at RT and then concentrated under reduced pressure to dryness. The resulting orange gum was taken up in 10 ml of 10% aqueous $NaHCO_3$ and extracted continuously for a period of 24 h with CH_2Cl_2. The organic extract was then dried over anhydrous Na_2SO_4 and chromatographed (silica gel, 5% MeOH/CH_2Cl_2) to afford 44.8 mg (64%) of **21S** as a very viscous oil, Rf 0.16 . Mass spectrum, m/e 245 (M^+); IR(CH_2Cl_2) 3380 (v br), 1674, 1566, 1230, 1088, 1028 cm^{-1}; NMR($CDCl_3$) δ 1.16 (s, 3H), 1.29 (t, 3H), 1.94 (s, 3H), 2.79 (d, 1H, J = 15 Hz), 2.95 (d, 1H, J = 15 Hz), 3.51 (m, 2H), 3.60-3.87 (m, 3H), 4.10 (q, 2H).

(2R, 3S)-1,2-Dihydroxy-3-methyl-4-[2'-(4'-methyl-5'-ethoxyoxazolyl)]-3-butanol (21A). In identical fashion to that described above for **21S**, 225.2 mg (0.79 mmol) of **15A** afforded 102.6 mg (53%) of **21A** as a very viscous oil, Rf 0.16 (silica gel, 5% MeOH/CH_2Cl_2). Mass spectrum, m/e 245 (M^+); IR(CH_2Cl_2) 3380 (v br), 1674, 1566, 1230, 1088, 1028 cm^{-1}; NMR($CDCl_3$) δ 1.19 (s, 3H), 1.30 (t, 3H), 1.95 (s, 3H), 2.69 (d, 1H, J = 14 Hz), 2.95 (d, 1H, J = 14 Hz), 3.51-3.85 (m, 5H), 4.09 (q, 2H). **Anal.** Calcd for $C_{11}H_{19}NO_5$: C, 53.87; H, 7.81; N, 5.72. Found: C, 53.89; H, 8.24; N, 5.90.

(2S, 3S)-2,3-Epoxy-3-methyl-1-(O-*p*-toluenesulfonyl)-4-[2'-(4'-methyl-5'-ethoxyoxazolyl)]-butane (23). A well stirred suspension of 15.8 mg (0.396 mmol, 6 eq) of powdered NaOH in 0.3 ml of freshly distilled (Na) glyme was treated in one portion with a solution consisting of 16.2 mg (0.066 mmol) of triol **21A** and 50.5 mg (0.264 mmol, 4 eq) of recrystallized ($CHCl_3$/pet ether) TsCl in 0.4 ml of glyme. The resulting mixture was then stirred for a period of 22 h before pouring into 4 ml of pH 7 buffer and extracting with 3 x 10 ml of CH_2Cl_2. The combined organic extracts were dried over anhydrous Na_2SO_4, concentrated, and chromatographed to afford 8.4 mg (34%) of E-epoxide **23** as a pale yellow oil, Rf 0.20 (silica gel, 1 : 1 EtOAc/hexane). Mass spectrum, m/e 381 (M^+); IR(CH_2Cl_2) 3041, 2966, 2911, 1671, 1372, 1198, 1186 cm^{-1}; NMR($CDCl_3$) δ 1.23 (s, 3H), 1.31 (t, 3H), 1.96 (s, 3H), 2.42 (s, 3H), 2.67 (d, 1H, J = 15 Hz), 2.87 (d, 1H, J = 15 Hz), 3.12 (t, 1H), 4.11 (q, 2H), 4.00-4.11 (m, 2H), 7.34 (d, 2H), 7.79 (d, 2H). **Anal.** Calcd for $C_{18}H_{23}NO_6S$: C, 56.68; H, 6.08; N, 3.67. Found: C, 56.89; H, 6.26; N, 4.19.

Ethyl-N-(4-carbomethoxy-3-methylbutyryl)-L-alaninate (36). A mechanically stirred solution of 29.0 g (0.19 mol) of ethyl L-alaninate hydrochloride in 136 ml of freshly distilled (CaH_2) pyridine was cooled to 0° C and treated in dropwise fashion with 34.7 g (0.19 mol, 1.03 eq) of acid chloride **35**,[19] maintaining a temperature between 0 and 5°. The resulting thick yellow suspension was stirred overnight at RT before concentrating under reduced pressure to remove most of the pyridine. The residue was then diluted with 200 ml of CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered, and concentrated to an orange oil, which upon short path distillation afforded 38.0 g (78%) of **36**

as a yellow, viscous oil, bp 140-143° (0.3-0.35 mm). IR($CHCl_3$) 1725, 1665 cm^{-1}; NMR($CDCl_3$) δ 0.92 (d, 3H, J = 5 Hz), 1.17 (t, 3H, J = 7.5 Hz), 1.30 (d, 3H), 1.99-2.42 (m, 5H), 3.58 (s, 3H), 4.11 (q, 2H, J = 7.5Hz), 4.49 (m, 1H), 6.28 (br s, 1H).

2-(3-Carbomethoxy-2-methylpropyl)-5-ethoxy-4-methyloxazole (37a). Following the general procedure of Kondrat'eva *et al.*,[20] a mixture of 50.0 g (0.13 mol) of **36** and 109.0 g (0.18 mol, ~4 eq) of P_2O_5 in 410 ml of $CHCl_3$ was heated at reflux, with mechanical stirring, for a period of 18 h. After cooling to RT, the residual P_2O_5 was carefuly crushed, and the resulting thick suspension was slowly added, in small portions, to ice-cold saturated $NaHCO_3$ maintaining a pH of 6-7. The organic layer was separated, and the aqueous layer was extracted with 4 x 75 ml of CH_2Cl_2. The combined extracts were then washed with brine, dried over anhydrous Na_2SO_4, concentrated and distilled to afford 37.0 g (80%) of **37a** as a nearly colorless oil, bp 85° C (0.1 mm). Mass spectrum, m/e 241 (M^+); IR($CHCl_3$) 1740, 1670, 1575 cm^{-1}; NMR($CDCl_3$) δ 1.01 (d, 3H, J = 5 Hz), 1.34 (t, 3H, J = 8 Hz), 2.00 (s, 3H), 2.33 (m, 3H), 2.56 (m, 2H), 3.67 (s, 3H), 4.11 (q, 2H, J = 8 Hz).

2-(3-Carboxy-2-methylpropyl)-5-ethoxy-4-methyloxazole (37b). A solution consisting of 45.1 g (0.19 mol) of ester **37a** and 31.0 g (0.56 mol, 3 eq) of KOH in 700 ml of MeOH was heated at reflux for a period of 20 h. After cooling to 0° C, the reaction was diluted with 140 ml of H_2O, acidified to pH ~3 with 400 ml of cold 1 M HCl, and extracted thoroughly with 5 x 100 ml of CH_2Cl_2. The combined extracts were then dried over anhydrous Na_2SO_4 and concentrated to afford 41.0 g (96%) of **37b** as a golden yellow oil. IR($CHCl_3$) 3000, 1725, 1675, 1570 cm^{-1}; NMR($CDCl_3$) δ 1.01 (d, 3H, J = 5 Hz), 1.33 (t, 3H, J = 8 Hz), 2.00 (s, 3H), 2.33 (br, 2H), 2.51 (br, 1H), 2.66 (br, 2H), 4.13 (q, 2H, J = 8 Hz), 11.99 (s, 1H).

5-(Methoxymethylamino)-3-methyl-5-oxo-pentanoic acid (39). An ice cold suspension of 21.6 g (0.169 mol) of 3-methylglutaric anhydride (**32**) and 18.09 g (0.185 mol, 1.1 eq) of N,O-dimethylhydroxylamine hydrochloride in 200 ml of freshly distilled (P_2O_5) $CHCl_3$ was treated in dropwise fashion, with vigorous stirring, with 30.0 ml (0.371 mol, 2.2 eq) of dry pyridine while maintaining a temperature between 0 - 5° C. After addition was complete, the resulting pale yellow solution was stirred for an additional 10 min at 5°, and then for 7 h at RT, before concentrating under reduced pressure. The semi-solid residue obtained was partitioned between 100 ml of 1 : 1 CH_2Cl_2/Et_2O and 150 ml of brine, and the aqueous layer was extracted with an additional 3 x 75 ml of CH_2Cl_2. The combined organic extracts were then washed with brine, dried over anhydrous Na_2SO_4, and concentrated to afford 30.6 g (96%) of **39** as a viscous yellow oil which was used without further purification. IR($CHCl_3$) 3000 (br), 1711, 1653 cm^{-1}; NMR($CDCl_3$) δ 1.06 (d, 3H, J = 5 Hz), 2.45 (m, 5H), 3.20 (s, 3H), 3.70 (s, 3H), 11.55 (s, 1H).

N-[5-(Methoxymethylamino)-3-methyl-1,5-dioxopentyl]-L-alanine (40). 26.9 g (0.143 mol) of monoamide **39**, obtained as described above, was cooled to 0° C and treated in dropwise fashion, with vigorous stirring, with 16.97 g (0.143 mol, 1 eq) of freshly distilled $SOCl_2$ while maintaining a temperature between 0 - 5°. After addition was complete, the ice bath was removed and the reaction temperature was allowed to rise to RT over a period of 30 min. The crude acid chloride thus obtained was extremely unstable and was immediately coupled with methyl L-alaninate hydrochloride, following an identical procedure as that described above for **36**, to afford 30.0 g (76%) of **40** as colorless crystals (from Et_2O), mp 104 - 106°. Overall yields as high as 90% from **39** were obtained on smaller scales (~ 5 g). Mass spectrum, m/e 274 (M^+); IR($CHCl_3$) 3431, 1739, 1675, 1633 cm^{-1}; NMR($CDCl_3$) δ 1.10 (d, 3H, J = 5 Hz), 1.40 (d, 3H, J = 7 Hz), 2.15 - 2.50 (m, 5H), 3.20 (s, 3H), 3.71 (s, 3H), 3.75 (s, 3H), 4.60 (q, 1H, J = 7Hz), 6.80 (br s, 1H). **Anal.** Calcd for $C_{12}H_{22}N_2O_5$: C, 52.54; H, 8.08; N, 10.21. Found: C, 53.87; H, 9.02; N, 10.27.

N,5-Dimethoxy-N,β,4-trimethyl-2-oxazolebutanamide (41). A solution of 6.0 g (0.022 mol) of diamide ester **40** in 27 ml of dry pyridine was cooled to 0° C, and treated in dropwise fashion, with vigorous stirring, with 4.0 ml (0.043 mol, 2 eq) of freshly distilled $POCl_3$. After addition was complete, the resulting brown mixture was allowed to slowly warm to RT and stirring was continued for an additional 18 h. The reaction was then concentrated under reduced pressure, and the residual brown gum was diluted with 100 ml of CH_2Cl_2 and neutralized by the slow addition of ~ 100 ml of ice cold saturated $NaHCO_3$ with vigorous stirring. The aqueous layer was extracted with an additional 4 x 50 ml of CH_2Cl_2, and the combined extracts were washed with 50 ml of saturated $NaHCO_3$ and 50 ml of brine before drying over anhydrous Na_2SO_4 and concentrating under reduced pressure. Chromatography

over silica gel (75 : 25 hexanes/acetone) then afforded 4.6 g (83%) of **41** as a light orange oil. Mass spectrum, m/e 256 (M^+); IR($CHCl_3$) 1690, 1683, 1667, 1560 cm^{-1}; NMR($CDCl_3$) δ 0.90 (d, 3H, J = 6.5 Hz), 1.85 (s, 3H), 2.05 - 2.56 (m, 5H), 3.04 (s, 3H), 3.54 (s, 3H), 3.76 (s, 3H). **Anal.** Calcd for $C_{12}H_{20}N_2O_4$: C, 56.24; H, 7.87; N, 10.93. Found: C, 56.03; H, 8.09; N, 10.75.

1-Lithio-6-methyl-5-hepten-1-yne (10). Following the general procedure of Smith *et al.*,[23] 20.0 g (0.123 mol) of 1-bromo-4-methyl-3-pentene [33] was added in a dropwise fashion, over a period of 30 min, and with vigorous stirring, to a cold (5 - 8° C) suspension of 1.90 g (0.129 mol, 1.05 eq) of lithium acetylide/ethylenediamine complex in 64 ml of dry DMSO. After addition was complete, the reaction mixture was allowed to warm to RT over a period of ~ 1 h, and maintained at this temperature for an additional 1 h before cooling to 15°, and quenching by the slow addition of 25 ml of H_2O (T < 15°). Extraction with 4 x 100 ml of hexane, followed by careful distillation, then afforded 8.36 g (63%) of 6-methyl-5-heptene-1-yne as a clear, colorless oil, bp 115 - 122°. Mass spectrum, m/e 108 (M^+); IR($CHCl_3$) 3225, 2100 cm^{-1}; NMR($CDCl_3$) δ 1.68 (s, 3H), 1.75 (s, 3H), 1.88 (m, 1H), 2.16 (m, 4H), 5.10 (m, 1H). The acetylide anion **10** was readily generated from this material by dropwise addition of an equimolar quantity of *n*-butyllithium/hexane at -78° as described below.

1-(5-methoxy-4-methyl-2-oxazolyl)-2,10-dimethyl-9-undecen-5-yn-4-one (42). The acetylide anion **10** was prepared by cooling a solution of 3.17 g (29.3 mmol, 1.56 eq) of 6-methyl-5-heptene-1-yne (see above) in 60 ml of dry THF to -78° C under nitrogen, and then treating this solution in a dropwise fashion, with vigorous stirring, with 10.9 ml of 2.70 M *n*-butyllithium/hexane (0.029 mol, 1.56 eq) over a period of 1.25 h. After addition was complete, the resulting pale yellow solution of **10** was stirred for an additional 3 h at -78°.

In a separate 1000 ml, 3-necked flask, a solution of 4.80 g (18.73 mmol, 1 eq) of **41** in 490 ml of dry THF was cooled to -15° under nitrogen. This solution was then treated in a dropwise fashion, over a period of 1.5 h, with the pre-cooled solution of **10** prepared as described above. Transfer was accomplished *via* a double tipped needle using positive nitrogen pressure, and the reaction temperature was maintained between -15° and - 10° throughout. After addition was complete, the resulting yellow solution was stirred for an additional 30 min at -15° before cooling to -78° and quenching with 1.7 ml (1.56 eq) of glacial HOAc. Upon warming to RT, the reaction was partitioned between 200 ml of 1 : 1 CH_2Cl_2/Et_2O and 150 ml of brine, and the aqueous layer was extracted with an additional 3 x 100 ml of 1 : 1 CH_2Cl_2/Et_2O. The combined organic extracts were then washed with brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and chromatographed over silica gel (85 : 15 hexanes/acetone) to afford 5.1 g (91%) of **42** as a yellow oil. Mass spectrum, m/e 303 (M^+); IR($CHCl_3$) 2215, 1675, 1575 cm^{-1}; NMR($CDCl_3$) δ 0.93 (d, 3H, J = 6.5 Hz), 1.55 (s, 3H), 1.63 (s, 3H), 1.93 (s, 3H), 2.16 - 2.36 (m, 5H), 2.43 - 2.66 (m, 4H), 3.80 (s, 3H), 5.09 (m, 1H). **Anal.** Calcd for $C_{18}H_{25}NO_3$: C, 71.25; H, 8.31; N, 4.62. Found: C, 70.89; H, 8.59; N, 4.50.

6,7-Dihydro-2-methoxy-6-methyl-3-(4-methyl-3-pentenyl)-4(5H)-benzofuranone (43). A mixture of 4.80 g (15.82 mmol) of acetylenic oxazole **42** and 0.087 g (0.79 mmol, 5 mol %) of hydroquinone in 400 ml of freshly distilled (Na) ethylbenzene was heated at reflux under a nitrogen atmosphere, and with protection from light and moisture, for a period of 11 h. The resulting bright yellow solution was then concentrated under reduced pressure to an orange oil, which upon chromatography over silica gel (96 : 4 hexanes/acetone) afforded 3.91 g (94%) of **43** as a yellow oil. Mass spectrum, m/e 262 (M^+); IR($CHCl_3$) 1670, 1650, 1580 cm^{-1}; NMR($CDCl_3$) δ 1.05 (d, 3H, J = 5 Hz), 1.48 (s, 3H), 1.57 (s, 3H), 2.15 (m, 3H), 2.40 (m, 5H), 2.78 (q, 1H, J = 10 Hz), 3.80 (s, 3H), 5.08 (m, 1H).

***(trans)*-6,7-Dihydro-2-methoxy-6-methyl-3-(4-methyl-3-pentenyl)-5-(phenylseleno)-4(5H)-benzofuranone (48t).** A solution of 0.20 ml (1.45 mmol, 1.6 eq) of freshly distilled (CaH_2) diisopropylamine in 3.0 ml of dry THF was cooled to -78° C under an atmosphere of nitrogen in a 25 ml 3-necked flask equipped with a thermometer and nitrogen inlet. A total of 0.45 ml (1.3 eq) of 2.63 M *n*-BuLi/hexane was then added in a dropwise fashion, with vigorous stirring, over a period of 15 min, and stirring was continued for an additional 20 min at -78°. While maintaining a temperature of -78°, a solution of 0.24 g (1.0 eq) of the methoxyfuran **43** in 1.6 ml of dry THF was added during a period of 30 min. The resulting yellow solution was stirred for 1.5 h at -78° and was then treated with 0.50 ml (10% by volume) of freshly distilled (CaH_2) HMPA. After stirring an additional 10 min, a solution of 0.31 g (1.62 mmol, 1.8 eq) of PhSeCl in 0.5 ml of THF was added in one portion (slight exotherm), and the reaction mixture was allowed to warm to -30° over a period of 2 h before cooling to -78° and quenching with 0.083

ml (1.6 eq) of glacial HOAc. After warming to RT, the reaction was diluted with 20 ml of pH 7 phosphate buffer and extracted with 2 x 15 ml of Et_2O. The combined organic extracts were then dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and chromatographed over silica gel (3 : 1 hexanes/Et_2O) to give 0.37 g (98%) of red-orange **48t** and **48c** as a 1 : 1 mixture. For characterization purposes, **48t** and **48c** could be separated by repeated preparative TLC (silica gel, 96 : 4 hexanes/acetone). ***Trans*-phenylselenide 48t**: NMR($CDCl_3$) δ 1.10 (d, 3H, J = 8 Hz), 1.49 (s, 3H), 1.59 (s, 3H), 2.14 (m, 2H), 2.40 (m, 3H), 2.60 (m, 1H), 3.16 (dd, 1H, J = 16.9, 5 Hz), 3.67 (d, 1H, J = 4 Hz), 3.84 (s, 3H), 5.08 (m, 1H), 7.23 (m, 3H), 7.56 (m, 2H). ***Cis*-phenylselenide 48c**: NMR($CDCl_3$) δ 1.29 (d, 3H, J = 5 Hz), 1.53 (s, 3H), 1.61 (s, 3H), 2.17 (m, 2H), 2.41 (m, 3H), 2.64 (br s, 2H), 3.75 (d, 1H, J = 3.9 Hz), 3.86 (s, 3H), 5.13 (m, 1H), 7.24 (m, 3H), 7.61 (m, 2H).

A 1 : 1 mixture of 0.36 g of **48t/48c** was dissolved in 2.5 ml of dry THF, and the resulting solution was added in a dropwise fashion, over a period of 1 h, to a well-stirred solution of lithium diisopropylamide in THF maintained at -78° (LDA was prepared as described above from 0.41 ml [2.92 mmol, 3.3 eq] of diisopropylamine and 1.04 ml [2.76 mmol, 3.1 eq] of 2.65 M *n*-BuLi/hexane in 6.0 ml of dry THF). After stirring for an additional 2.5 h at -78°, the bright yellow solution was quenched with 0.17 ml (3.3 eq) of glacial HOAc and worked up as described above to afford 0.36 g (~ 100%) of **48t** and **48c**, which by nmr analysis was 96% **48t** (~ 94% overall yield from **43**).

5,6,7,7a-Tetrahydro-4-hydroxy-6-methyl-3-(4-methyl-3-pentenyl)-5-(phenylseleno)-(4α,5α,6β,7aα)-2(4H)-Benzofuranone (50). A solution of 70.0 mg (0.17 mmol) of **48t** in 2.0 ml of freshly distilled (P_2O_5) CH_2Cl_2 was cooled to -78° C under a blanket of nitrogen, and treated in a dropwise fashion over a period of 20 min with 0.55 ml (3.3 eq) of 1.0 M DIBAH/CH_2Cl_2 with vigorous stirring. The reaction mixture was stirred for an additional 4 h at -78° before quenching with 0.30 ml of MeOH, followed by 0.09 ml of 50% aqueous HOAc. The resulting solution, of pH ~ 5, was then stirred for 17 h at RT before concentrating under reduced pressure and neutralizing with 2.1 ml of saturated aqueous $NaHCO_3$. The resulting gelatinous residue was filtered under suction and washed several times with CH_2Cl_2. The aqueous filtrate was extracted with 3 x 5 ml of CH_2Cl_2, and the combined extracts and washings were washed with 10 ml of brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatography over silica gel (4 : 1 hexanes/Et_2O) then afforded 62.7 mg (96%) of **50** as a pale yellow oil. The same material could be obtained in 65% yield on a 3 g scale following an identical procedure. IR($CHCl_3$) 3467, 1751 cm^{-1}; NMR($CDCl_3$) δ 0.88 (q, 1H, J = 12 Hz), 1.12 (d, 3H, J = 7 Hz), 1.36 (s, 3H), 1.50 (s, 3H), 2.06 (m, 5H), 2.54 (m, 1H), 2.82 (d, 1H, J = 12 Hz), 2.94 (m, 1H), 4.43 (m, 1H), 4.70 (m, 1H), 4.94 (dd, 1H, J = 12, 6 Hz), 7.30 (m, 3H), 7.56 (m, 2H). **Anal.** Calcd for $C_{21}H_{26}O_3Se$: C, 62.22; H, 6.46. Found: C, 62.16; H, 6.59.

***(trans)*-7,7a-Dihydro-4-hydoxy-6-methyl-3-(4-methyl-3-pentenyl)-2(4H)-benzofuranone (*epi*-4).** A solution of 2.00 g (4.93 mmol) of **50** in 16 ml of THF was cooled to 0° C and treated with 13.5 ml of saturated aqueous $NaIO_4$ with vigorous stirring over a period of 5 min. The ice bath was then removed and the milky suspension was stirred for an additional 35 min while slowly warming to RT. The reaction mixture was then partitioned between 50 ml of brine and 40 ml of Et_2O, and the aqueous layer was extracted with an additional 3 x 20 ml of Et_2O. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give ~ 2 g of crude selenoxide **51** as a semi-solid mass. Without purification, **51** was dissolved in a two phase system composed of 130 ml of toluene and 124 ml of saturated aqueous Na_2CO_3, and the reaction was heated at reflux, in an oil bath maintained at 115°, for a period of 6 h. After cooling to RT, most of the toluene was decanted and 100 ml of warm H_2O was added to dissolve precipitated Na_2CO_3. The aqueous layer was then extracted with 3 x 75 ml of Et_2O, and the combined Et_2O and toluene extracts were washed with 2 x 50 ml of H_2O, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was chromatographed over silica gel (94 : 6 CH_2Cl_2/Et_2O) to afford 1.00 g (82%) of ***epi*-4** as a pale yellow oil. Mass spectrum, m/e 248 (M^+); IR($CHCl_3$) 3500, 1755, 1445 cm^{-1}; NMR($CDCl_3$) δ 1.50 (s, 3H), 1.63 (s, 3H), 1.76 (s, 3H), 1.90 (m, 1H), 1.95 (dd, 1H, J = 16, 8 Hz), 2.12 - 2.30 (m, 4H), 2.76 (dd, 1H, J = 16, 8 Hz), 4.90 (br s, 1H), 5.07 (m, 2H), 5.63 (br s, 1H).

7,7a-Dihydro-6-methyl-3-(4-methyl-3-pentenyl)-2,4-benzofurandione (52). A solution of 1.60 g (6.44 mmol) of ***epi*-4** in 5.0 ml of freshly distilled (P_2O_5) CH_2Cl_2 was added in one portion to a vigorously stirring solution of CrO_3/pyr complex prepared from 3.86 g (6 eq) of CrO_3 and 6.26 ml of dry pryidine in 100 ml of CH_2Cl_2.[34] The reaction immediately precipitated a dark, tarry gum, and after stirring an additional 10 min the CH_2Cl_2 solution was decanted and the residue washed thoroughly with Et_2O. The combined organic washings were then concentrated and chromatographed over silica gel (95 : 5 CH_2Cl_2/Et_2O) to afford 1.39 g (88%) of **52** as a pale yellow oil. Yields

as high as 96% were obtained following an identical procedure on slightly smaller scales. Mass spectrum, m/e 246 (M^+); IR($CHCl_3$) 1760, 1675, 1655, 1629 cm^{-1}; NMR($CDCl_3$) δ 1.52 (s, 3H), 1.57 (s, 3H), 2.06 (s, 3H), 2.27 (m, 3H), 2.60 (m, 2H), 3.00 (dd, 1H, J = 16, 6 Hz), 5.04 (m, 1H), 5.18 (m, 1H), 6.10 (br s, 1H).

***(cis)*-7,7a-Dihydro-4-hydoxy-6-methyl-3-(4-methyl-3-pentenyl)-2(4H)-benzofuranone (4).** A solution of 1.24 g (4.87 mmol) of **52** and 1.79 g (1 eq) of $PrCl_3 \cdot 6\,H_2O$ in 37 ml of absolute EtOH was stirred at RT for 15 min, and was then cooled to 0° C and treated with 0.20 g (1.04 eq) of $NaBH_4$ in one portion. The reaction was stirred for an additional 1 h at RT before concentrating under reduced pressure to a dark residue which was partitioned between 60 ml of pH 7 phosphate buffer and 100 ml of Et_2O. The aqueous layer was extracted with an additional 4 x 30 ml of Et_2O, and the combined extracts were dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and chromatographed over silica gel (75 : 25 hexanes/acetone) to afford 1.23 g (98%) of **4** as a very pale yellow oil, Rf 0.65 (silica gel, 5 : 1 CH_2Cl_2/Et_2O). Mass spectrum, m/e 248 (M^+); IR($CHCl_3$) 3590, 3485, 3420, 1750, 1680 cm^{-1}; NMR($CDCl_3$) δ 1.48 (s, 3H), 1.62 (s, 3H), 1.74 (s, 3H), 2.00 (m, 1H), 2.16 (m, 3H), 2.52 (t, 2H, J = 7 Hz), 2.67 (dd, 1H, J = 16, 7 Hz), 4.81 (t, 1H, J = 7 Hz), 5.10 (m, 2H), 5.45 (br s, 1H). The synthetic **4** thus obtained had identical spectral data as that of an authentic sample, and was readily converted to (±)-paniculide-A (**1a**) following the published procedure.[2c]

References and Notes

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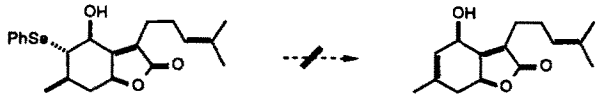
27. Interestingly, nmr studies showed that **48t** existed predominantly in the diaxial conformation **48t-A** in solution, presumably due to a strong gauche interaction between the PhSe and Me groups in the diequatorial conformer **48t-E**.

48t-E 48t-A

Of particular diagnostic value were the small coupling constants between H9 and H10 (J = 4.0 Hz) and the strongly deshielding influence of the PhSe group on H11 (δ 3.16, dd, J = 16.9, 5.0 Hz).

28. Other reducing reagents, such as $NaBH_4$ or LAH, afforded large amounts of the de-phenylselenated butenolide **47** upon reduction of **48t**. Furthermore, the isomeric alcohol **49ß**, which in principle could lead directly to the



49ß 4

desired Yoshikoshi precursor **4** by *in situ* oxidation and elimination, was a minor product with all reagents employed. Little effort was devoted to optimizing the yield of **49ß**, since all attempts at the direct conversion of **49ß** to **4** afforded only complex mixtures of products or returned unreacted starting material.

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