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A SYNTHESIS OF (+)-PEDERIN. THE METALLATED DIHYDROPYRAN APPROACH.

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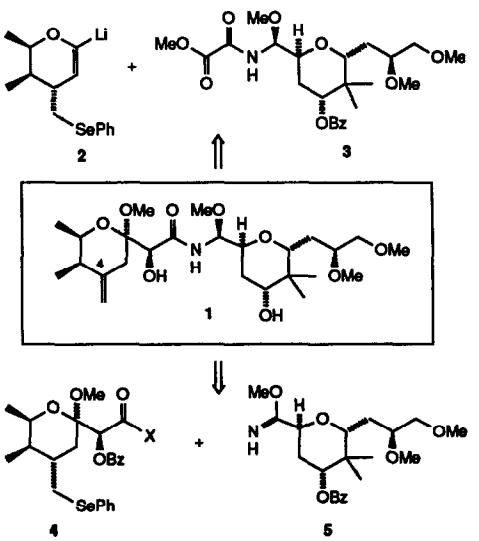
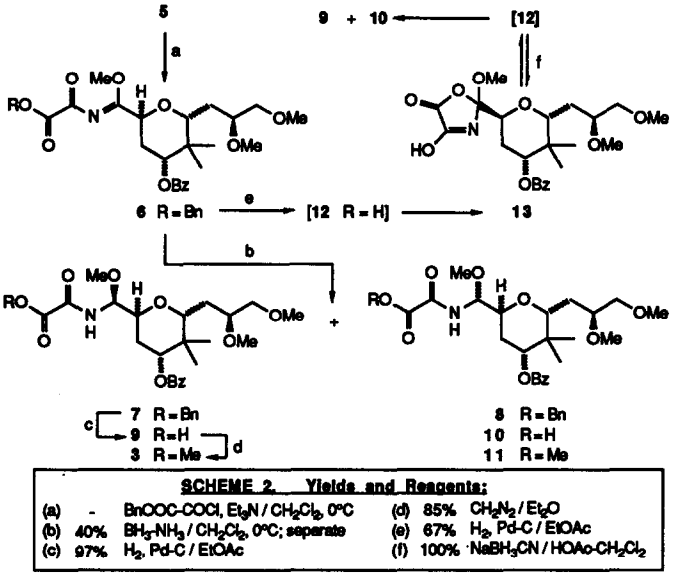
Summary: The addition of a 6-lithio-3,4-dihydro-2*H*-pyran to a methyl oxamate ester in the presence of TMEDA is a key step in the synthesis of a masked 1,2,3-tricarbonyl moiety used to construct the N-(1-alkoxy-1-alkyl)-amide bridge of the potent cytotoxic agent pederin. A Pd(0)-catalysed stannylation of an O-trifluoromethylsulfonyl ketene acetal provides an efficient synthesis of the 6-(trimethylstannyl)-3,4-dihydro-2*H*-pyran which transmetallates to the lithium derivative on treatment with *n*-BuLi.

Pederin (**1**) is a highly cytotoxic substance isolated from the beetle *Paederus fuscipes*. All three successful syntheses of pederin reported to date[1-3] grappled with the acid-lability of the N-(1-alkoxy-1-alkyl)-amide and homoallylic acetal groups by delaying their introduction until the latest possible stage in the synthesis. For example, in our first synthesis of pederin[3], we constructed the N-(1-alkoxy-1-alkyl)-amide bridge by the union of the imidate ester **5** (Scheme 1) with the activated carboxylic acid fragment **4** using a modification of the pioneering methodology of Matsumoto and co-workers[1]. The sensitive homoallylic acetal ensemble was then completed in the penultimate step of the synthesis by a selenoxide elimination to generate the requisite exocyclic methylene group at C4. Unfortunately the strategic advantages of this approach were vitiated to some extent by the instability of the carboxyl fragments **4** (X = OH, Cl). We now report a new strategy for the synthesis of pederin based on the synthesis of a masked 1,2,3-tricarbonyl intermediate by reaction of the oxamate ester **3** with the metallated dihydropyran **2** serving as an acyl anion equivalent[4]. A prime advantage of this strategy is the circumvention of problems of intermediate instability encountered in our previous synthesis. The protocol devised for the synthesis of the metallated dihydropyran in the presence of the phenylselenyl moiety is particularly noteworthy.



SCHEME 1

Methyl O-benzoylmeropederoate **3**, a crucial advanced intermediate in our synthetic plan, was synthesised from the imidate ester **5** by two routes as shown in Scheme 2. In the first route, the N-oxalyl imidate ester **6** underwent metal hydride reduction (step b) to give a 1:1 mixture of the benzyl oxamate esters **7** and **8** which were readily separated by column chromatography on silica gel eluting with EtOAc in hexane. Hydrogenolysis of the more polar diastereoisomer afforded O-benzoylmeropederoic acid **9**[5] which was converted to methyl ester **3** in good yield. The preparation of **3** from **5** by using methyl oxalyl chloride in place of the benzyl derivative is an obvious abbreviation which was thwarted by the chromatographic inseparability of the methyl esters **3** and **11**.



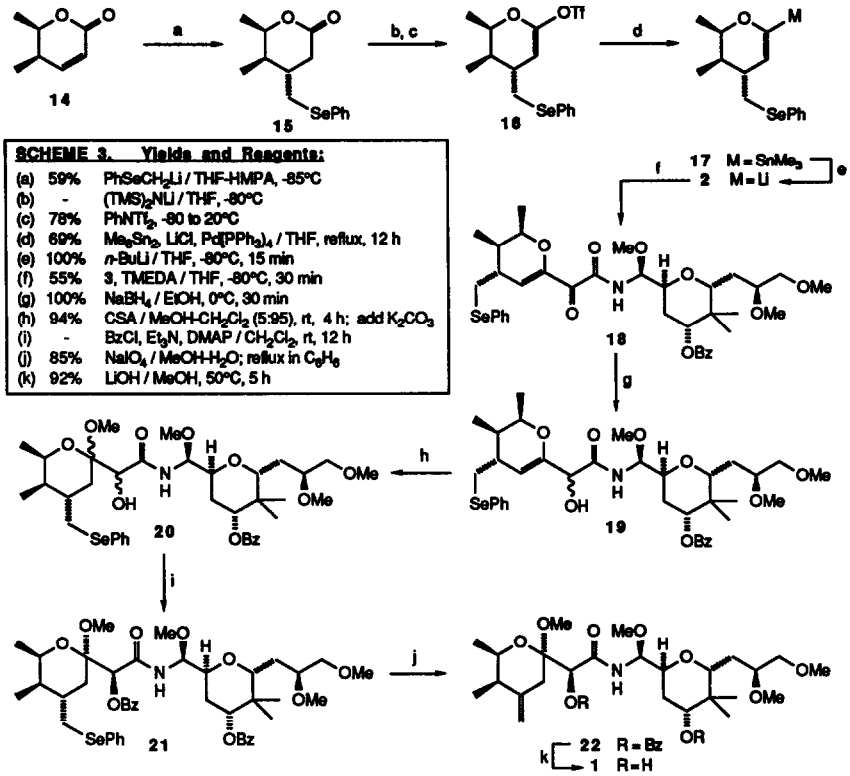
SCHEME 2. Yields and Reagents:

(a) - $BnOOC\text{-}COCl$, Et_3N / CH_2Cl_2, 0°C
(b) 40% $BH_3\text{-}NH_3$ / CH_2Cl_2, 0°C; separate
(c) 97% H_2, Pd-C / EtOAc
(d) 85% CH_2N_2 / Et_2O
(e) 67% H_2, Pd-C / EtOAc
(f) 100% $NaBH_3CN$ / HOAc-CH_2Cl_2

In the second route, an attempt to produce meropederoic acid derivative **9** directly by catalytic reduction of the N-oxalyl imidate function in **6** gave instead the oxazolidindione **13** owing to rapid hydrogenolysis of the benzyl ester followed by cyclisation of the resultant carboxylic acid **12**. However, the cyclisation was reversible: by treating **13** with $NaBH_3CN$ in acetic acid-CH_2Cl_2, O-benzoylmeropederoic acid and its diastereoisomer **10** were obtained in quantitative yield.

The next stage in the synthesis involved the bridging of the two tetrahydropyran rings by the N-(1-alkoxy-1-alkyl) moiety. It became apparent during the course of our studies that the phenylselenyl group, which allows the introduction of the labile exocyclic methylene group of pederin in the final stages of the synthesis, was best introduced before the bridge was constructed. Unfortunately this requirement jeopardised the dihydropyran strategy because all attempts to prepare the 6-lithiodihydropyran **2** in the usual way by metallation of the corresponding dihydropyran using alkyl-lithium reagents failed owing to preferential reaction of the lithium reagents with the selenium atom. A significant advance in our synthesis of pederin was the development of an efficient 4-step synthesis of the 6-(trimethylstannyl)-3,4-dihydropyran **17** (Scheme 3) *via* Pd(0)-catalysed stannylation[6] of the enol triflate intermediate **16**. Transmetallation of **17** to the 6-lithio derivative **2** followed by reaction with methyl oxamate ester **3** in the presence of TMEDA gave the stable keto amide **18** in 55% yield after flash chromatography. TMEDA was essential to the success of this reaction.

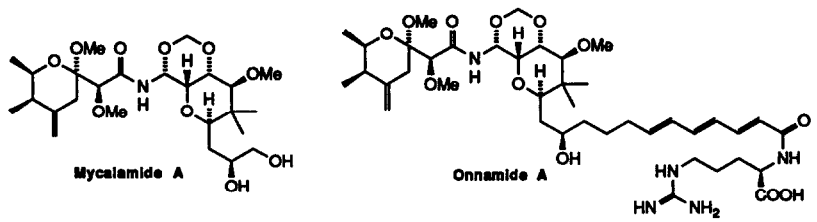
To complete the synthesis of pederin, the keto group was reduced to give a 2:1 mixture of diastereomeric alcohols which added methanol under acid catalysis to give the acetals **20** (4 diastereoisomers) which were separated by hplc after benzoylation. Conversion of diastereoisomer **21** (*ca.* 15-20% of the mixture) to (+)-pederin proceeded as described previously[3]. Our synthetic (+)-pederin was identical with an authentic sample of the natural product by tlc mobility, infra-red, nmr, and mass spectrometry.



SCHEME 3. Yields and Reagents:

(a)	59%	$PhSeCH_2Li$ / THF-HMPA, -85°C
(b)	-	$(TMS)_2NLi$ / THF, -80°C
(c)	78%	$PhNTf_2$, -80 to 20°C
(d)	69%	Me_3Sn_2, LiCl, $Pd[PPh_3]_4$ / THF, reflux, 12 h
(e)	100%	*n*-BuLi / THF, -80°C, 15 min
(f)	55%	**3**, TMEDA / THF, -80°C, 30 min
(g)	100%	$NaBH_4$ / EtOH, 0°C, 30 min
(h)	94%	CSA / MeOH-CH_2Cl_2 (5:95), rt, 4 h; add K_2CO_3
(i)	-	BzCl, Et_3N, DMAP / CH_2Cl_2, rt, 12 h
(j)	85%	$NaIO_4$ / MeOH-H_2O; reflux in C_6H_6
(k)	92%	LiOH / MeOH, 50°C, 5 h

In conclusion our second synthesis of pederin demonstrates a new protocol for the construction of a masked 1,2,3-tricarbonyl system which should be applicable to other demanding natural products of considerable biological significance such as the antiviral agents Onnamide A[7] and Mycalamide A[8] which are closely related to pederin and the immunosuppressant FK-506[9]. A vital feature of this protocol is the easy preparation of metallated enol ethers in the presence of heteroatom substituents which otherwise impede the metallation of enol ethers under the usual conditions[10].



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