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# BIS HETEROANNULATION. 8. TOTAL SYNTHESIS OF (±)-PANICULIDE-A

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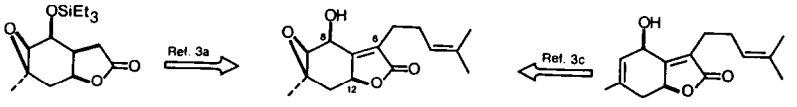
Abstract: An efficient synthesis of the title compound 1 has been achieved beginning with 3-methylglutaric anhydride.

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.[1] As a part of these studies we have also recently reported on the synthetic utility of highly substituted furan derivatives for the preparation of methylene acids, lactones, butenolides and related materials.[1b] In this paper we wish to elaborate on these results by describing a facile synthesis of (±)-paniculide-A (1), a novel sesquiterpene which was initially isolated from the hypocotyl and stem tissues of Andrographis paniculata,[2] and which has been the subject of considerable synthetic attention.[3] During the course of this work we have also developed useful new conditions for effecting phenylselenoxide eliminations, and we have uncovered an interesting example of a transition metal mediated $NaBH_4$ reduction providing exceptional stereochemical control.

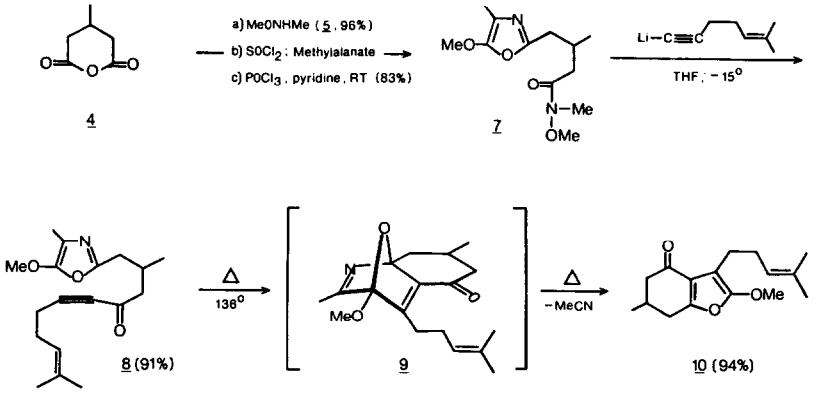



2 Paniculide - A (1) 3

Two approaches have previously been utilized for the synthesis of 1 (see above).[3] In the first of these the highly substituted lactone derivative 2 was prepared with good stereocontrol and subsequently elaborated to 1 via an alkylation-phenylselenation-selenoxide elimination sequence.[3a,b] In the second approach a novel vinylfuranone annulation procedure was

employed to prepare the allylic alcohol 3, which was directly converted to 1 via a metal catalyzed epoxidation.[3c] Although this latter route suffered from modest yields in the synthesis of 3, it has the potential advantage of allowing for a kinetic resolution in the conversion of 3 to 1,[4] with the added possibility of recycling the undesired enantiomer. In order to study these questions we have developed an extremely efficient procedure for the preparation of 3 in gram quantities and larger.

The key intermediate for our synthesis of 3 was the methoxyfuran 10, which was readily prepared from commercially available 3-methylglutaric anhydride (4) as follows (Scheme 1).[5]

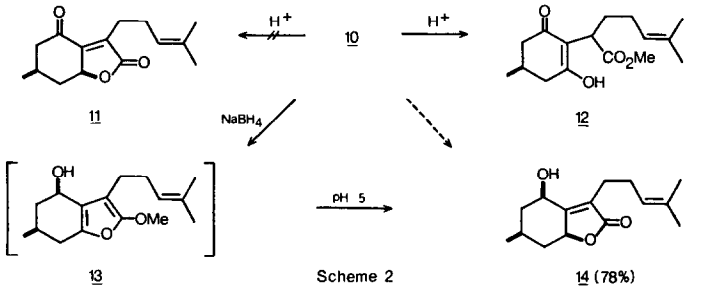



Scheme 1

Thus, 4 was readily opened with N,O-dimethylhydroxylamine to give the amide derivative 5 (96%) which was cleanly converted to the oxazole amide 7 by initial coupling with methyl alanate (90%) followed by cyclodehydration ($POCl_3$, pyridine, 83%).[6] This latter material, upon reaction with 1-lithio-6-methyl-5-heptene-1-yne,[7] then gave an excellent yield of the acetylenic ketone 8,[9] which upon brief thermolysis (ethyl benzene, 5% hydroquinone, 136° C, 11h) afforded the target compound 10 in 94% yield (61% overall yield from 4, 5 g scale).[1]

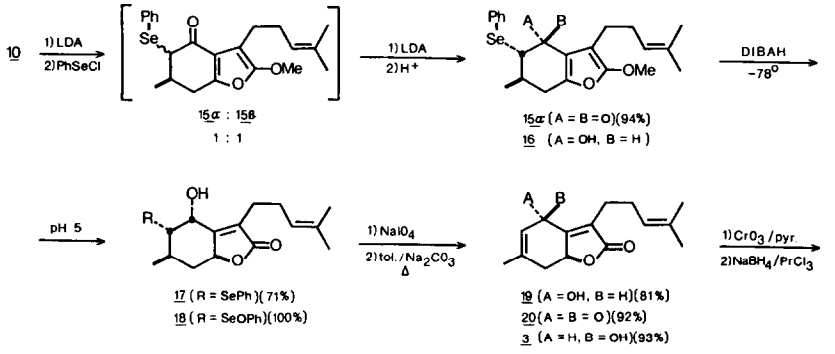
It was our intention, now, that a suitably functionalized derivative of 10 might serve as a convenient precursor for butenolides of type 3, but our initial experiments in this area were disappointing. In particular, we were surprised to find that 10 could not be converted to 11 under a variety of standard conditions (Scheme 2).[10] At pH 1 - 5, for example, 10 slowly decomposed to an intractable mixture, while under more forcing conditions (1 N $H_2SO_4$) the major product isolated was the ester derivative 12 corresponding to protonation at C-6. This hydrolytic behavior is best rationalized by the fact that the required protonation at C-12 is rendered highly unfavorable by the inductive influence of the 8-keto functionality. And in ac-

cordance with this hypothesis, we were pleased to find that the reduced species 13 was instantly transformed to the expected butenolide 14 upon aqueous workup at pH 5 (78% overall yield from 10).




13 Scheme 2 14 (78%)

Having thus established the viability of this route for the preparation of butenolides, the remaining steps necessary for the conversion of 10 to 3 followed in a straightforward fashion as diagrammed in Scheme 3. Thus, 10 was first alkylated with LDA / PhSeCl to provide a




Scheme 3

1 : 1 mixture of the phenylselenides 15α and 15β (-78° C, 5% HMPA / THF, 98%), [11] which upon kinetic deprotonation-protonation afforded the desired α-isomer in a 96 : 4 ratio (3.1 eq LDA, -78° C, THF; 3.2 eq HOAc; 94% overall yield from 10). Compound 15α, in turn, was smoothly converted to the selenide-alcohol 17 by initial reduction to the α-alcohol 16 (DIBAH, -78° C), which, without isolation, was directly hydrolyzed at pH 5 to give 17 in 71% overall yield from 15α (67% yield from 10). Oxidation of 17 to 18 was then cleanly accomplished with saturated aqueous $NaIO_4$ in THF (1 : 1, ~100%), but we experienced initial difficulties in the

conversion of 18 to 19. In particular, we obtained only trace yields of 19 under the usual conditions for this elimination, [11] the major product being that derived from deoxygenation of 18 to return 17. Furthermore, all efforts at applying the usual remedies for this situation met with failure. [12] Eventually, however, we found that the desired transformation could be carried out in 81% overall yield from 17 when this reaction was carried out in a two phase system consisting of 1 : 1 $PhCH_3$ / saturated $Na_2CO_3$ at reflux for 6 hours.

Finally, epimerization at either stereocenter in 19 was expected to produce the desired target compound, and, in fact, we have obtained trace amounts of (±)-3 both by equilibration at C-12 (t-BuOK / THF) [13] and by direct inversion at C-8. [3c] By far the most satisfactory procedure, however, involved an initial oxidation of 19 to give 20 ($CrO_3$ / pyridine, 92%) followed by reduction with the reagent system $NaBH_4$ / $PrCl_3$ (EtOH, RT, 93%) [14] to afford (±)-3 as the exclusive stereoisomer in 85% overall yield (in the absence of $PrCl_3$ this reduction gave a 1 : 1 mixture of 3 and 19, as well as products derived from conjugate addition). The material thus obtained had identical spectral data as that derived from authentic (±)-3 and was readily converted to (±)-paniculide-A (1) following the published procedure. [3c] The application of this route to the synthesis of (+)-1 will be the subject of a future publication.

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