Pergamon

*Tetrahedron Letters*, Vol. 38, No. 30, pp. 5367-5370, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01174-X

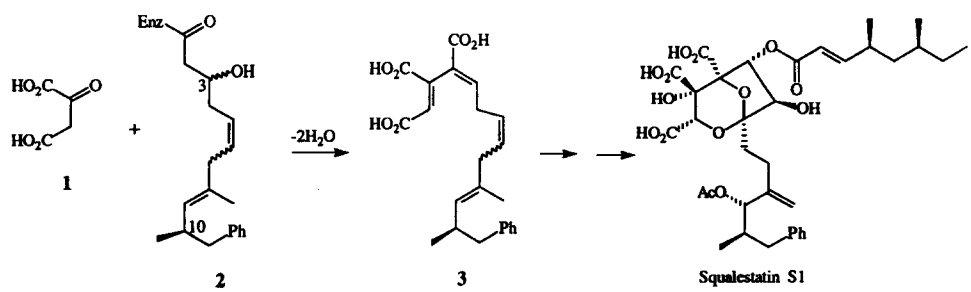
# Enantioselective Synthesis of a Putative Hexaketide Intermediate in the Biosynthesis of the Squalestatins

**Thomas J. Simpson, Robert W. Smith, Susan M. Westaway, Christine L.Willis***
School of Chemistry, University of Bristol, Cantock's Close, Bristol BS8 1TS, UK.

**Antony D. Buss, Richard J. P. Cannell, Michael J. Dawson, Brian A. M. Rudd.**
Glaxo Wellcome, Research and Development, Medicines Research Centre, Gunnels Wood Road, Stevenage SG1 2NY, UK.

*Abstract* A convergent synthesis of (3*R*, 5*Z*, 8*E*, 10*R*)-3-hydroxy-8,10-dimethyl-11-phenylundec-5,8-dienoic acid **4**, a putative hexaketide intermediate in the biosynthesis of the squalestatins, is described. A key step in the assembly of the carbon framework is the coupling of alkyne **19** with allylic bromide **13** giving, after further functional group manipulations, the target compound as a single diastereomer. The approach may be adapted for the preparation of the corresponding (3*S*, 5*Z*, 8*E*, 10*R*)-isomer as well as for the incorporation of carbon-13 labels required for biosynthetic studies.


The squalestatins (or zaragozic acids) e.g S1 are a group of natural products originally isolated from a *Phoma* species and more recently from further fungal species and filamentous *Ascomycetes*.[1] They are potent inhibitors of squalene synthase and hence, of cholesterol biosynthesis. From the results of feeding labelled precursors to the squalestatin producer *Phoma* sp C2932, it has been proposed that squalestatins are derived via a mixed biosynthetic pathway involving a Krebs' cycle intermediate **1** and a polyketide intermediate **2** to give the tricarboxylic acid **3** (Scheme 1).[2] The stereochemistry at the 10-position of **2** is known to be *R* since this centre is retained in the final squalestatin structure and it is assumed that the 8,9-double bond adopts *E* geometry since a minor metabolite, squalestatin V5, with this structural feature has been isolated.[3] The 3-hydroxyl group and the 5,6-olefin are required in order to rationalise the formation of the 2,8-dioxabicyclo[3.2.1]octane core of the squalestatins,[2] but the stereochemistries of these latter groups are not known. Hence, a flexible approach to the synthesis of the possible isomers of the hexaketide intermediate is required which may be adapted for the incorporation of a

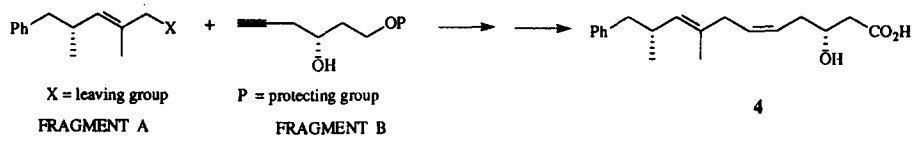



**Scheme 1**

suitable isotopic label e.g. carbon-13 for biosynthetic studies. We now describe the enantioselective synthesis of (3*R*,5*Z*,8*E*,10*R*)-hexaketide **4** using an approach which may be simply adapted for the incorporation of carbon-13 labels as well as for the preparation of the (3*S*, 5*Z*,8*E*,10*R*)-isomer.

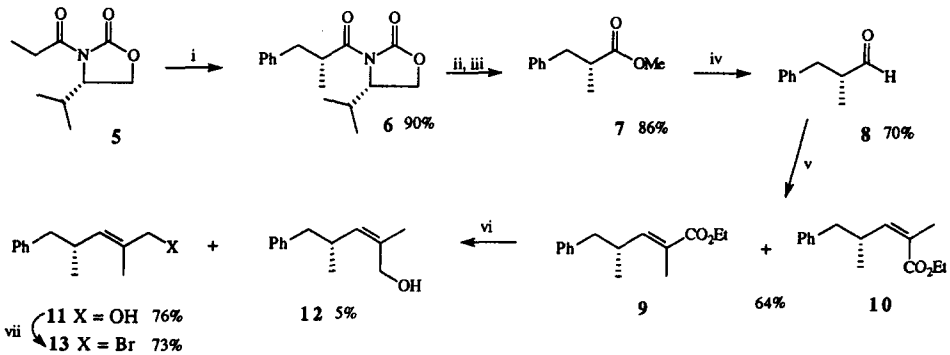
## Results and Discussion

The basic strategy for the synthesis of hexaketide **4** is shown in Scheme 2 and involves coupling an allylic halide or sulfonate ester (Fragment A) with an alkyne (Fragment B) to establish the carbon skeleton followed by a series of functional group manipulations to give the carboxylic acid.



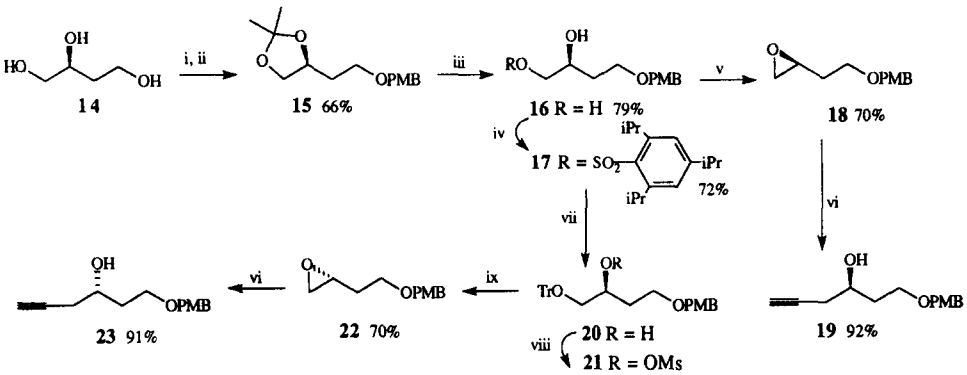

**Scheme 2**

Synthesis of Fragment A The *R* stereochemistry at the site which will become C-10 in the target molecule was established using a chiral auxiliary as shown in Scheme 3. Evans[4] has reported that oxazolidinone **5** may be converted to benzylpropionyl oxazolidinone **6** in 92% yield by generating the enolate with LDA at -78°C followed by treatment with benzyl bromide at 0°C, but on repeating this reaction the best yield of **6** was 44%. However, we found that the sodium enolate of **5** reacted smoothly with benzyl bromide to give the required benzylpropionyl oxazolidinone **6** in a reproducible 90% yield. Hydrolysis of **6** with lithium hydroperoxide[5] followed by esterification of the resultant acid with diazomethane gave ester **7**. Reduction of **7** with DIBALH in toluene at -78°C proceeded smoothly to give aldehyde **8** which was coupled with the commercially available (carbethoxyethylidene)triphenylphosphorane to give a mixture of (*E*)- and (*Z*)-α,β-unsaturated esters **9** and **10** which proved inseparable by either flash chromatography or medium pressure chromatography (MPLC). Reduction of the mixture of **9** and **10** with DIBALH gave the corresponding allylic alcohols **11** and **12** in 81% yield and in the ratio 15:1. The allylic alcohols were separated by MPLC and the geometry of the olefins was determined by nOe studies. Signal enhancement was observed for the olefinic proton on irradiation of the allylic methyl protons in the (*Z*)-isomer **12**, but not in the (*E*)-isomer **11**, confirming that the required (*E*)-isomer was the major product.[6] Reaction of **11** with bromine and triphenylphosphine gave solely the (*E*)-allylic bromide **13** in 73% yield.




**Scheme 3** *Reagents:* i) NaHMDS, BnBr; ii) LiOH, $H_2O_2$; iii) $CH_2N_2$; iv) DIBALH, toluene, -78°C; v) $Ph_3PCHCO_2Et$, $CH_3CN$; vi) DIBALH, toluene, 0°C; vii) $Ph_3P$, $Br_2$.

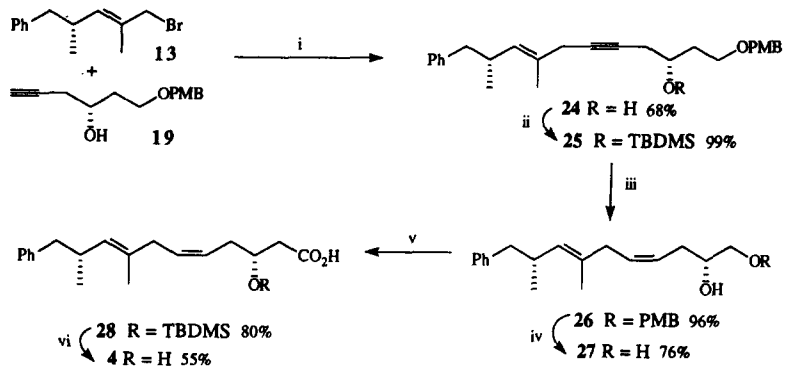
Enantioselective Synthesis of (+)- and (-)-Fragment B We envisaged assembly of the carbon skeleton of Fragment B *via* nucleophilic attack of an acetylide anion or equivalent on epoxide **18** which, in turn, could be derived from commercially available (*S*)-butane-1,2,4-triol **14** (Scheme 4). In the later stages of the synthesis of hexaketide **4** it would be necessary to have different protecting groups for the primary alcohol in **14** (to become C-1 in **4**) and the secondary alcohol (to become C-3 in **4**) such that the primary alcohol could be selectively deprotected and oxidised to a carboxylic acid. Hence the 1,2-diol of **14** was transiently protected as the acetonide whilst the remaining primary alcohol was protected as the *p*-methoxybenzyl (PMB) ether **15**. Removal of the acetonide was followed by selective conversion of the primary alcohol of diol **16** to a sulfonate ester. The required monotosylate was formed in only 59% yield whereas an improved yield (72%) of a monosulfonate **17** was achieved using the more bulky reagent, 2,4,6-triisopropylbenzenesulfonyl chloride.[7] Treatment of **17** with base, benzylammonium hydroxide (TRITON B) gave the desired (*S*)-epoxide **18** which was converted to the required (*R*)-alkynol **19**[8] in 92% yield using lithium acetylide-ethylenediamine complex[9] in DMSO.




**Scheme 4** *Reagents*: i) $Me_2CO$, TsOH; ii) $MeO(C_6H_4)CH_2Cl$, NaH, THF; iii) AcOH; iv) $[(CH_3)_2CH]_3C_6H_2SO_2Cl$ $Et_3N$; v) TRITON B, MeOH; vi) $HCCLi.NH_2CH_2CH_2NH_2$, DMSO; vii) $Ph_3CCl$, $Et_3N$, DMAP; viii) MsCl, $Et_3N$; ix) TsOH, MeOH, TRITON B.

The enantiomer **23** was also prepared via diol **16** as shown in Scheme 4. Treatment of **16** with triphenylmethyl chloride in the presence of base led to selective protection of the primary alcohol as the trityl ether **20**. The secondary alcohol was activated as the mesylate **21** and then converted to epoxide **22** in a single pot reaction using catalytic toluene-*p*-sulfonic acid followed by addition of benzylammonium hydroxide giving **22** in 70% yield from **20**. Treatment of epoxide **22** with lithium acetylide-ethylenediamine complex[9] gave the (*S*)-alkynol **23**[8] in excellent yield.

Synthesis of Hexaketide 4 With synthetic routes to both Fragments A and B established, the synthesis of the hexaketide **4** was completed as shown in Scheme 5. A range of conditions were investigated for the coupling reaction and the optimum involved generation of the acetylide anion of **19** with a 1,8-diazabicyclo[5.4.0]undec-7-ene/ copper (I) iodide complex[10] followed by reaction with 1.2 equivalents of bromide **13** in the presence of 2,6-di-*tert*-butyl-4-methylphenol as a radical scavenger giving the required hydroxy-alkyne **24** in 68% yield.[11]



**Scheme 5** *Reagents*: i) DBU, CuI; ii) TBDMSOTf, $Et_3N$; iii) $H_2$, Lindlars catalyst, quinoline, EtOH; iv) DDQ, $CH_2Cl_2$, $H_2O$; v) PDC, DMF; vi) AcOH, THF, $H_2O$.

Protection of the 3-hydroxyl group as the TBDMS ether **25** followed by partial hydrogenation of the alkyne with Lindlar's catalyst gave the (5*Z*)-alkene **26** in 96% yield over the two steps.The PMB group was oxidatively cleaved using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and the resultant primary alcohol **27** oxidised with PDC in DMF giving the acid **28**. Finally, deprotection of the secondary alcohol with acetic acid gave the target (3*R*, 5*Z*, 8*E*, 10*R*)-hexaketide **4** {$[\alpha]_D^{20}$ -25.0 (*c* 0.24 in $CHCl_3$)}.

This convergent approach to the synthesis of the hexaketide is flexible and may be simply adapted for the preparation of the analogous (3*S*, 5*Z*, 8*E*, 10*R*)-isomer from the (*S*)-alkynol **23**. In addition, using established procedures,[12] this approach may be modified for the incorporation of carbon-13 labels at various sites within the target molecule, for example at C-9 and C-10 of **4** using sodium [1,2-$^{13}C_2$]-acetate and at the 10-methyl group using [$^{13}$C]-methyl iodide, thus giving access to valuable compounds for biosynthetic studies.

*Acknowledgements* We are grateful to Glaxo Wellcome for financial support for RWS and SMW.

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11. Hydroxy-alkyne **24**: gum, $[\alpha]_D^{20}$ -27.1° (*c* 0.7 in $CHCl_3$), [Found:M$^+$, 406.2497 $C_{27}H_{34}O_3$ requires M,406.2508]; $\upsilon_{max}/cm^{-1}$ 3422, 3060, 3030, 2960, 2919, 2864, 1611, 1588, 1513; $\delta_H$ (300MHz, $CDCl_3$) 0.94 (d, *J* 6.4, 10-$CH_3$), 1.46 (s, 8-$CH_3$), 1.85 (m, 2-$H_2$), 2.40 (m, 4-$H_2$), 2.62 (m, 10-H and 11-$H_2$), 2.79 (s, 7-$H_2$), 3.01 (s, OH), 3.67 (m, 1-$H_2$), 3.80 (s, $OCH_3$), 3.95 (m, 3-H), 4.46 (s, $PhCH_2O$), 5.23 (d, *J* 7.7, 9-H), 6.87 (d, *J* 8.6, aromatic-$H_2$), 7.18 (m, Ar); $\delta_C$ (75MHz,$CDCl_3$) 16.1 (10-$CH_3$), 20.5 (8-$CH_3$), 27.6 and 28.8 (C-4 and C-7), 34.6 (C-10), 35.4 (C-2), 43.8 (C-11), 55.3 ($OCH_3$), 69.9 (C-3), 68.4 and 73.0 (C-1 and $ArCH_2O$), 78.5 and 80.1 (C-5 and C-6), 113.8, 125.6, 128.0, 129.3, 129.5, 130.0, 131.2, 140.9 and 159.3 (C-8, C-9 and aromatics).
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(*Received in UK* 19 *May* 1997; *revised* 12 *June* 1997; *accepted* 13 *June* 1997)