Approaches Towards the Synthesis of Papulacandin D: Preparation and Structural Elucidation of the Acyl Side Chain

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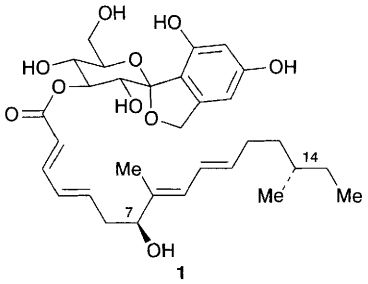
Both degradation and total synthesis from L-(+)-isoleucine are used to establish the absolute stereochemistry of the *O*-3′-acyl side chain of papulacandin D.

The papulacandins are a group of antifungal agents extracted from the fermentation broth of *Papularia spherosperma*.[1] These compounds are strongly active against *Candida albicans* and several other yeasts.[1–3] Their mode of action involves the inhibition of β-1,3-glucan synthase, an enzyme vital in the construction of fungal cell walls.[2] Papulacandin D **1** consists of a *C*-arylglycosidic spiroketal esterified at the *O*-3 hydroxy by a tetra-unsaturated fatty acyl side chain. Although the gross structure of papulacandin D is well established, neither the relative nor absolute stereochemistries of the C-7 hydroxy group or the C-14 methyl residue of the acyl side chain are known.[1] We now report the determination of the absolute configuration and synthesis of the papulacandin D acyl side chain.[4]

Following a known method,[5] L-(+)-isoleucine was transformed into (*S*)-2-methylpentanol **2**. Toluene 4-sulfonation of **2** and subsequent displacement with potassium cyanide yielded the nitrile **3** (Scheme 1).† Reduction of **3** (DIBAL-H) and Wittig homologation gave the α,β-unsaturated ester **4** (*E*:*Z*, 98:2). Subsequent reduction of **4** (DIBAL-H), reoxidation to the aldehyde (PCC) and further Wittig homologation yielded the diene ester **5** (*E*:*Z*, 92:8). The two geometric isomers were easily separated by chromatography. The *E*,*E*-ester **5** was converted into the aldehyde **6** *via* a reduction (DIBAL-H)/oxidation (MnO_2) sequence. Homologation of **6**, with prop-2-ynyl zinc bromide,[6] yielded alcohol **7** as a inseparable mixture of diastereoisomers (1:1). After protection as the triethylsilyl ether, the delicate tetraene ester **8** was elaborated *via* hydrozirconation followed by direct palladium(0) coupling of the derived vinyl zirconium intermediate with methyl 3-bromo-(*E*)-acrylate.[7] No traces of the fully conjugated pentaene **9**, produced by the elimination of water, were detected.

With a route to the side chain secure, attention was directed to solving the stereochemical ambiguities. We considered that the C-7 stereochemistry could be defined *via* an asymmetric propynylation of aldehyde **6** (Scheme 1), but this approach was unsuccessful. Thus, a method of kinetic resolution was pursued. Sharpless asymmetric epoxidation[8] of the allylic alcohol **7** resulted in recovery of alcohol **10** (45%) and isolation of the corresponding epoxide **11** (14%) (Scheme 2). Mosher ester analysis of the derived alcohol **19** (*vide infra*) revealed a diastereoisomeric excess of 96% (HPLC)‡. It is clear from this result that any of the four diastereoisomers of the acyl side chain should be accessible *via* the reactions in Schemes 1 and 2.



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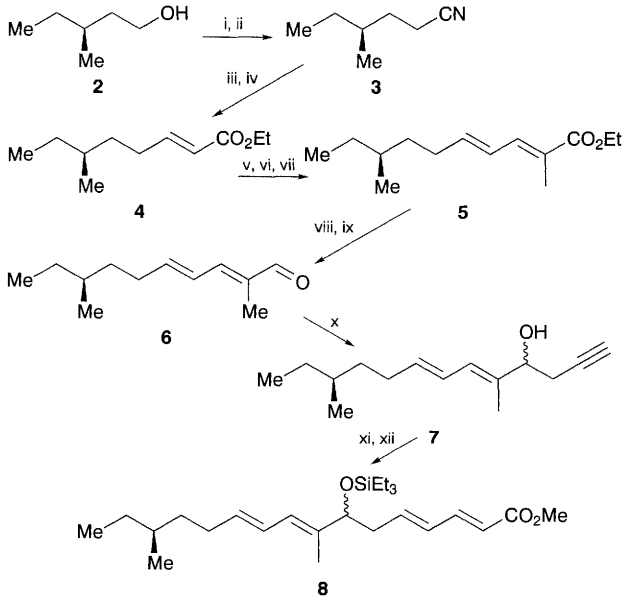
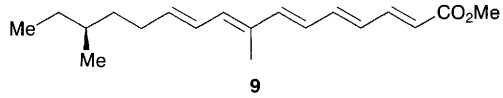
Papulacandin D

Fermentation of *Papularia spherosperma* followed by isolation of the crude mixture of papulacandins,[1] saponification and methylation[1,9] (CH_2N_2) gave the natural fatty ester **12**. Reaction with (*S*)-α-methoxy-α-trifluoromethylphenylacetyl chloride gave the ester **13** (Scheme 3) which on analysis was shown to consist of one diastereoisomer (^1H and ^{13}C NMR and HPLC). Additionally, this diastereoisomer was also shown to match (^1H



Scheme 1 *Reagents and conditions*: i, TsCl, py, ii, KCN, 18-crown-6, THF, 80% (both steps); iii, DIBAL-H, Et_2O, −78 °C; iv, $Ph_3P{=}CHCO_2Et$, CH_2Cl_2 85% (both steps); v, DIBAL-H, Et_2O, −78 °C, 95%; vi, PCC, CH_2Cl_2, 80%; vii, $Ph_3P{=}C(Me)CO_2Et$, CH_2Cl_2, 85%; viii, DIBAL-H, Et_2O, −78 °C, 94%; ix, MnO_2, CH_2Cl_2, 95%; x, Zn dust, prop-2-ynyl bromide, THF, 95%; xi, Et_3SiCl, imidazole, DMAP, CH_2Cl_2, 88%; xii, (η^5-$C_5H_5)_2Zr(Cl)H$, methyl 3-bromo-(*E*)-acrylate, [$(Ph_3P)_2PdCl_2$ + DIBAL-H], THF, 82%



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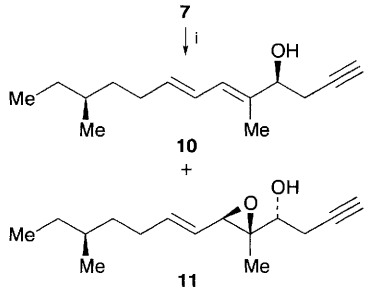
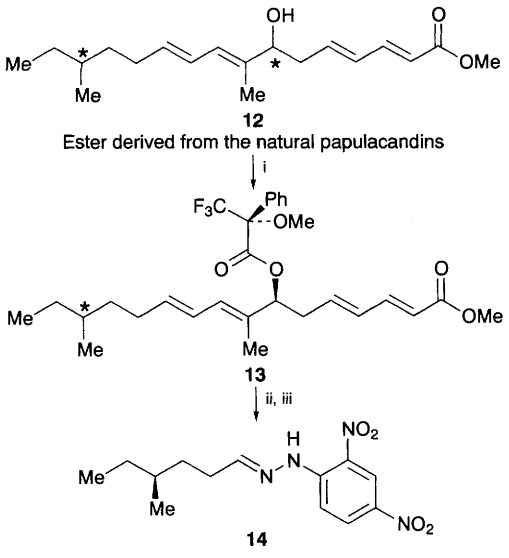
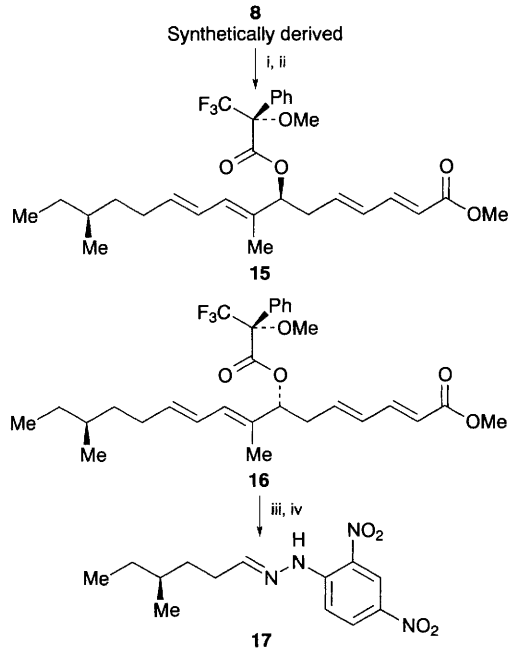


Scheme 2 *Reagents and conditions*: i, $Ti(OPr^i)_4$. D-(−)-DIPT, Bu^tOOH, CH_2Cl_2, 4 Å mol. sieves, **10** 45%, 96% de and **11** 14%



Scheme 3 *Reagents and conditions*: i, *S*-(+)PhC(OMe)(CF_3)COCl, DMAP, CH_2Cl_2, 93%; ii, O_3, −78 °C, MeOH; Me_2S, −78 to 25 °C; iii, 2,4-dinitrophenylhydrazine, H_2SO_4, 63% (both steps)

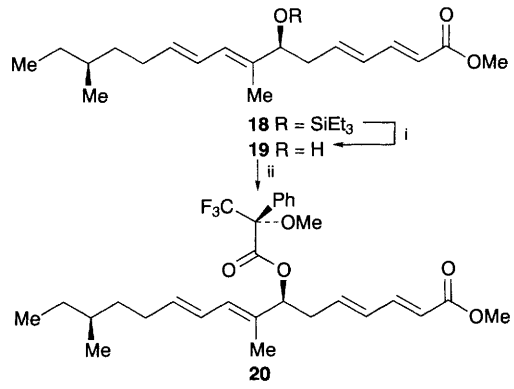


Scheme 4 *Reagents and conditions*: i, TBAF, THF, 0 °C; ii, (+)-*S*-MTPA-Cl, DMAP, CH_2Cl_2, 89%; iii, O_3, −78 °C, MeOH; Me_2S, −78 to 25 °C; iv, 2,4-dinitrophenylhydrazine, H_2SO_4, EtOH, 65% (both steps)

and ^{13}C NMR and HPLC) one of the synthetic diastereoisomers in the mixture of **15** and **16** (Scheme 4).

The allylic alcohol **10** is predicted to have the 7S configuration according to the model proposed by Sharpless and co-workers.[10] Conversion of alcohol **10** into the corresponding Mosher ester and ^1H NMR analysis[11] gave additional proof of this stereochemical assignment. Protection of **10** as its triethylsilyl ether and chain extension gave tetraene ester **18** (Scheme 5). Deprotection with *tert*-butylammonium fluoride revealed the alcohol **19** and this was transformed into ester **20**. Again Mosher analysis of diester **20** was consistent with the stereochemistry of the C-7 hydroxy being *S*. Ester **20** also matched (^1H and ^{13}C NMR and HPLC) the natural ester **13**. With all of this evidence the stereochemistry about the C-7 hydroxy can unequivocally be assigned as *S*.

Ozonolysis of the natural ester **13** (Scheme 3) gave the corresponding aldehyde which was isolated as its 2,4-dinitrophenyl hydrazone derivative **14**. Comparison of the optical rotation of **14** {$[\alpha]_D^{25}$ = +13.2 (*c* = 0.29 in $CHCl_3$)} with the synthetic material derived directly from L-isoleucine **17** {$[\alpha]_D^{25}$ = +12.6 (*c* = 0.30 in $CHCl_3$)} (Scheme 4) was fully consistent with the configuration about the C-14 methyl group being *S*. We therefore conclude that papulacandin D has the structure **1** in which the acyl side chain has the 7*S*,14*S* configuration. Compounds **12** and **19** were also shown to be identical by their circular dichroic spectra.



Scheme 5 *Reagents and conditions*: i, TBAF, THF, 0 °C 98%; ii, (+)-*S*-MTPA-Cl, DMAP, CH_2Cl_2, 93%

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Footnotes

† All new compounds were fully characterised by spectroscopic data and microanalysis and/or HRMS.

‡ Apex silica 5U (25 cm × 4.6 mm), eluted with 2.5% ethyl acetate in hexanes at 1.0 cm^3 min^{-1} on a ATI Unican crystal 200 HPLC system with diode array detection from 220 to 360 nm.

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