

A CONCISE ENANTIOCONTROLLED ROUTE TO (+)-PATULOLIDE C†

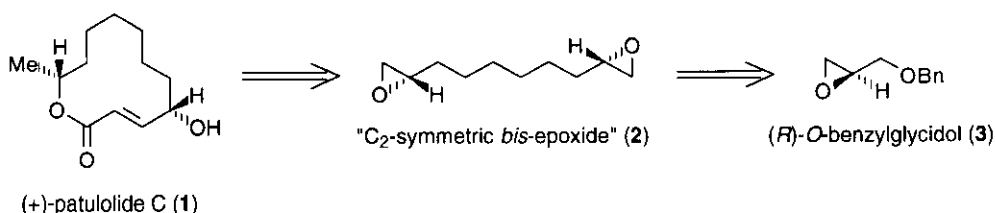
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Abstract — A naturally occurring antifungal macrolide (+)-patulolide C has been synthesized enantioselectively via the C₂-symmetric *bis*-epoxide by incorporation of two molecular units of (*R*)-*O*-benzylglycidol.

(+)-Patulolide C¹ (**1**) is an antifungal macrolide produced by *Penicillium urticae* S11R59.¹ Owing to its simple structure, several syntheses including chiral approaches have been reported to date by employing various strategies.² We wish to report herewith a new strategy enabling enantio- and diastereoselective construction of both of the two chiral centers of the macrolide (**1**) at the same time which could have only been attained by a non-selective or a sequential manner in the conventional syntheses.

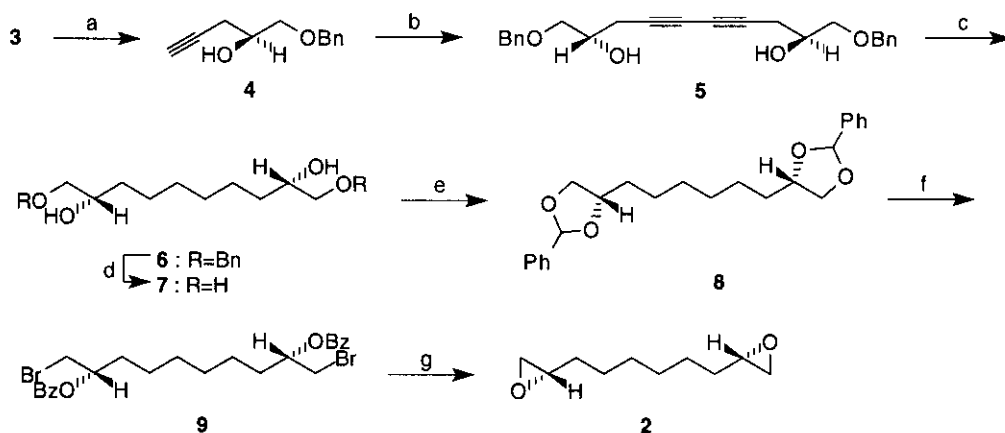
We first set the C₂-symmetric (*S,S*)-*bis*-epoxide (**2**) as the key intermediate for the synthesis of (+)-patulolide C (**1**) and we planned to construct this key *bis*-epoxide (**2**) by connecting two (*R*)-*O*-benzylglycidol³ (**3**) units with four methylene linkage (**Scheme 1**). To visualize this strategy in an efficient manner, the epoxide



Scheme 1

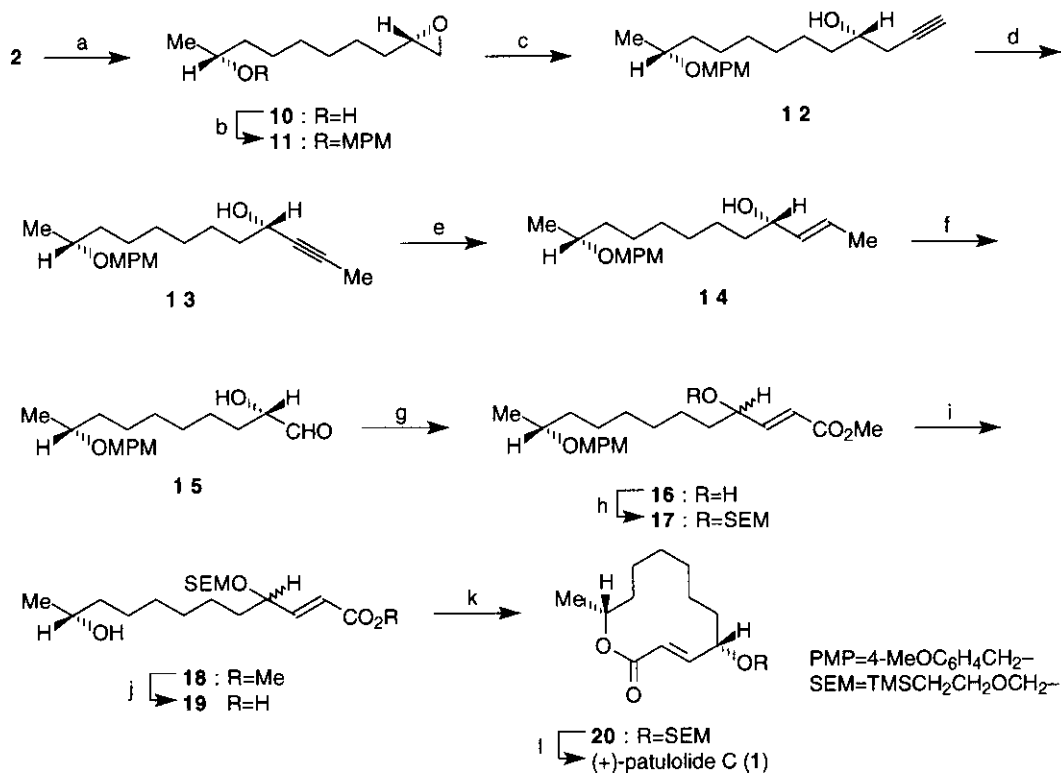
† Dedicated to Professor Dr. Arnold Brossi on the occasion of his 70th birthday.

[(*R*)-**3**] was first transformed into the terminal acetylene^{4,5} (**4**) on reaction with lithium acetylide ethylenediamine complex in DMSO. The acetylene (**4**) was then stirred with a catalytic amount of $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ (2 mol%) and copper(I) iodide (2 mol%) in DMF containing triethylamine (3 equiv.) under atmosphere of oxygen at room temperature to give rise to the homocoupling product⁶ (**5**), $[\alpha]_{\text{D}}^{30} +28.72^\circ$ (*c* 1.19, CHCl_3), in 83% yield as a colorless oil. We have recently found that these conditions bring about a facile homocoupling of a terminal acetylene in good yield.⁷ Hydrogenation of the acetylene linkage of **5** using Adams' catalyst followed by hydrogenolysis of the benzyl groups of the resulting diol (**6**), $[\alpha]_{\text{D}}^{30} +5.49^\circ$ (*c* 1.11, CHCl_3), using Pearlman's catalyst furnished the tetraol (**7**), mp 114-115 $^\circ\text{C}$, $[\alpha]_{\text{D}}^{31} -23.0^\circ$ (*c* 0.97, CHCl_3), in an excellent yield as colorless crystals. In order to obtain the key diepoxide, we employed an efficient procedure for the conversion of a terminal 1,2-glycol functionality into a terminal epoxide functionality developed by us.^{8,9} Thus, **7** was first transformed into the *bis*-benzylidene acetal (**8**) on treatment with benzaldehyde in the presence of *p*-toluenesulfonic acid monohydrate by azeotropic removal of water in boiling benzene. Overall yield of **8** from **5** was 75% in three steps. Upon exposure to 3 equiv. of *N*-bromosuccinimide in carbon tetrachloride,¹⁰ **8** yielded the bromobenzoate (**9**) which without purification was stirred with potassium carbonate in methanol to afford the C_2 -symmetric (*S,S*)-*bis*-epoxide (**2**), bp 170-180 $^\circ\text{C}/20$ torr (Kugelrohr), $[\alpha]_{\text{D}}^{27} -17.0^\circ$ (*c* 0.79, CHCl_3), in 64% overall yield as a colorless oil (Scheme 2).



Scheme 2

Reagents: a) $\equiv\text{-Li}(\text{CH}_2\text{NH}_2)_2$, DMSO, ref. 4; b) $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ (cat.), CuI (cat.), Et_3N , O_2 , DMF, room temperature; c) H_2 , PtO_2 , benzene; d) H_2 , $\text{Pd}(\text{OH})_2\text{-C}$, CHCl_3 (cat.), concd HCl (cat.), MeOH ; e) PhCHO , *p*- $\text{TsOH}\cdot\text{H}_2\text{O}$, benzene, reflux; f) NBS , CCl_4 , room temperature; g) K_2CO_3 , MeOH , room temperature.



Scheme 3

Reagents: a) LiAlH_4 (1 equiv.), THF, -20°C ; b) 4-MeOC₆H₄CH₂Cl, NaH, DMF; c) $\equiv\text{-Li}(\text{CH}_2\text{NH}_2)_2$, DMSO, 0°C ; d) *tert*-BuOK, DMSO, 0°C ; e) LiAlH_4 , THF, reflux; f) O_3 , MeOH, -78°C , then Me_2S ; g) $\text{Ph}_3\text{P=CHCO}_2\text{Me}$, CH_2Cl_2 , room temperature; h) SEM-Cl, Hünig base, *n*-Bu₄NI, CH_2Cl_2 , room temperature; i) DDQ, $\text{CH}_2\text{Cl}_2\text{-H}_2\text{O}$ (18:1 v/v); j) $\text{LiOH}\cdot\text{H}_2\text{O}$, aq. THF (50%), BnEt_3NCl (cat.); k) 2,4,6-trichlorobenzoyl chloride, DMAP, toluene, reflux then separation by SiO_2 plate, l) $\text{BF}_3\cdot\text{OEt}_2$ (4 equiv.), CH_2Cl_2 , room temperature.

Having obtained the desired *bis*-epoxide (**2**), we next attempted to cleave one of two epoxide bonds in a selective manner. Although we could not find optimal conditions to give the hydroxy-epoxide (**10**) in a good yield in complete conversion of the *bis*-epoxide (**2**), we could obtain **10**, $[\alpha]_{\text{D}}^{25} -21.3^{\circ}$ (*c* 0.54, CHCl_3), in 42% yield (76% based on consumed **2**) in 55% conversion with a minimum loss of the starting *bis*-epoxide (**2**). After protection of the secondary hydroxy group of **10** by 4-methoxybenzyl (MPM) group, the resulting MPM ether (**11**), $[\alpha]_{\text{D}}^{29} -20.21^{\circ}$ (*c* 0.38, CHCl_3), was treated with lithium acetylide ethylenediamine complex in DMSO at 0 °C as above to give the terminal acetylene (**12**), $[\alpha]_{\text{D}}^{32} -15.03^{\circ}$ (*c* 0.50, CHCl_3), in 72% overall yield from **10**. Upon exposure to potassium *tert*-butoxide (6 equiv.) in DMSO⁴ at 0 °C for 15 min, the

terminal acetylene (**12**) rearranged facilely to give the internal acetylene (**13**), $[\alpha]_D^{34} -10.73^\circ$ (*c* 0.20, CHCl_3), in 80% yield. The original chiral integrity could be preserved under these basic conditions.⁴ This compound was then refluxed with lithium aluminum hydride in THF^{4,11,12} to give rise to the allyl alcohol (**14**), $[\alpha]_D^{28} -14.87^\circ$ (*c* 0.93, CHCl_3), in 93% yield.

Ozonolysis of **14** followed by the Horner-Emmons reaction of the resulting crude aldehyde (**15**) afforded the (*E*)- α,β -unsaturated ester (**16**) in 81% overall yield. However, ^1H nmr revealed the product to be a 2.6:1 mixture of the epimers at the allylic C-4 stereogenic center. Since the mixture could not be separated at this stage, the following conversion was carried out using the diastereomeric mixture.

Thus, the ester (**16**) containing the C-4 epimer after having transformed into the trimethylsilylethoxymethyl (SEM) ether¹³ (**17**) was treated with DDQ in a wet dichloromethane to give the seco-ester (**18**),¹⁴ which was saponified with lithium hydroxide in aq. THF (50%) to give the seco-acid (**19**) (0.11 mmol) in 84% overall yield.

Employing the modified Yamaguchi protocol,¹⁵ the acid (**19**) was first treated with 2,4,6-trichlorobenzoyl chloride in the presence of triethylamine to give the crude mixed anhydride which in toluene (50 ml) was then added dropwise to a refluxing toluene (10 ml) containing 4-*N,N*-dimethylaminopyridine (DMAP) over a 12 h period to generate the macrolide mixture from which the desired lactone (**20**), $[\alpha]_D^{30} -40.6^\circ$ (*c* 0.70, CHCl_3), and its C₄-epimer were obtained in 48 and 19% yields after separation by silica gel preparative thin layer chromatography (1 mm). Finally, **20** was treated with boron trifluoride etherate at room temperature to remove the SEM-protecting group¹⁶ to give (+)-patulolide C (**1**), $[\alpha]_D^{30} +5.63^\circ$ (*c* 0.22, EtOH) [lit : $[\alpha]_D^{20} +6.6^\circ$ (*c* 0.40, EtOH)^{2c,2g}; $[\alpha]_D +6.8^\circ$ (*c* 0.15, EtOH)^{2d}], in 78% yield¹⁷ (Scheme 3).

In conclusion, the strategy employed in the present investigation successfully leads to (+)-patulolide C (**1**) starting from a single chiral building block (*R*)-*O*-benzylglycidol (**3**) via the C₂-symmetric (*S:S*)-bis-epoxide intermediate (**2**) though some unexpected epimerization has taken place.

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