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

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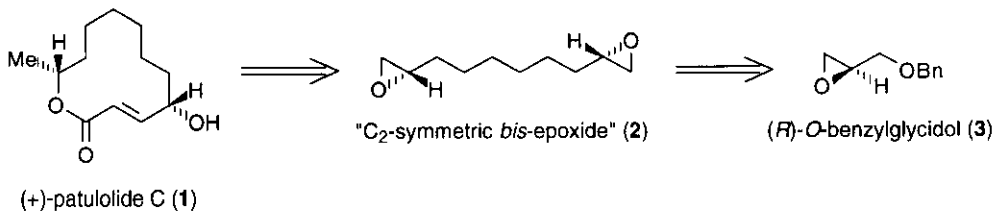
Abstract —— A naturally occurring antifungal macrolide (+)-patulolide C has been synthesized enantioselectively *via* the C_2-symmetric *bis*-epoxide by incorporation of two molecular units of (*R*)-*O*-benzylglycidol.

(+)-Patulolide C[1] (**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 C_2-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*-benzylglycidol[3] (**3**) units with four methylene linkage (**Scheme 1**). To visualize this strategy in an efficient manner, the epoxide

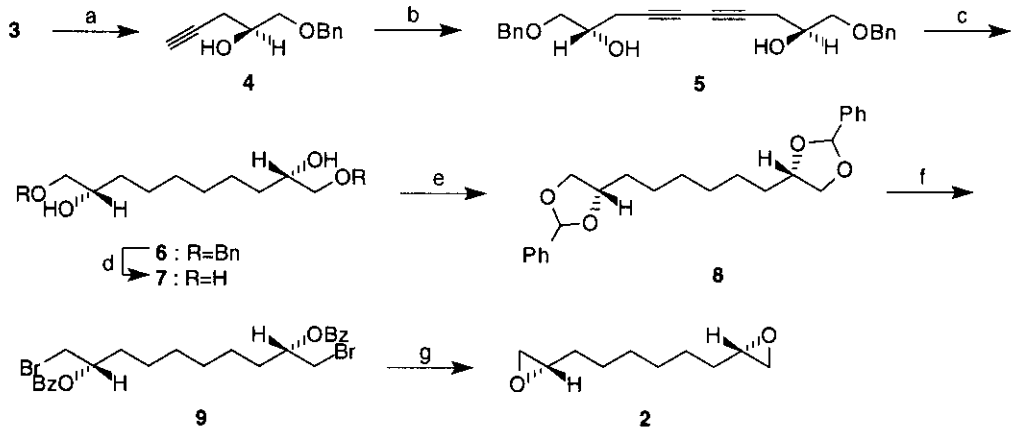


(+)-patulolide C (**1**) "C_2-symmetric *bis*-epoxide" (**2**) (*R*)-*O*-benzylglycidol (**3**)

Scheme 1

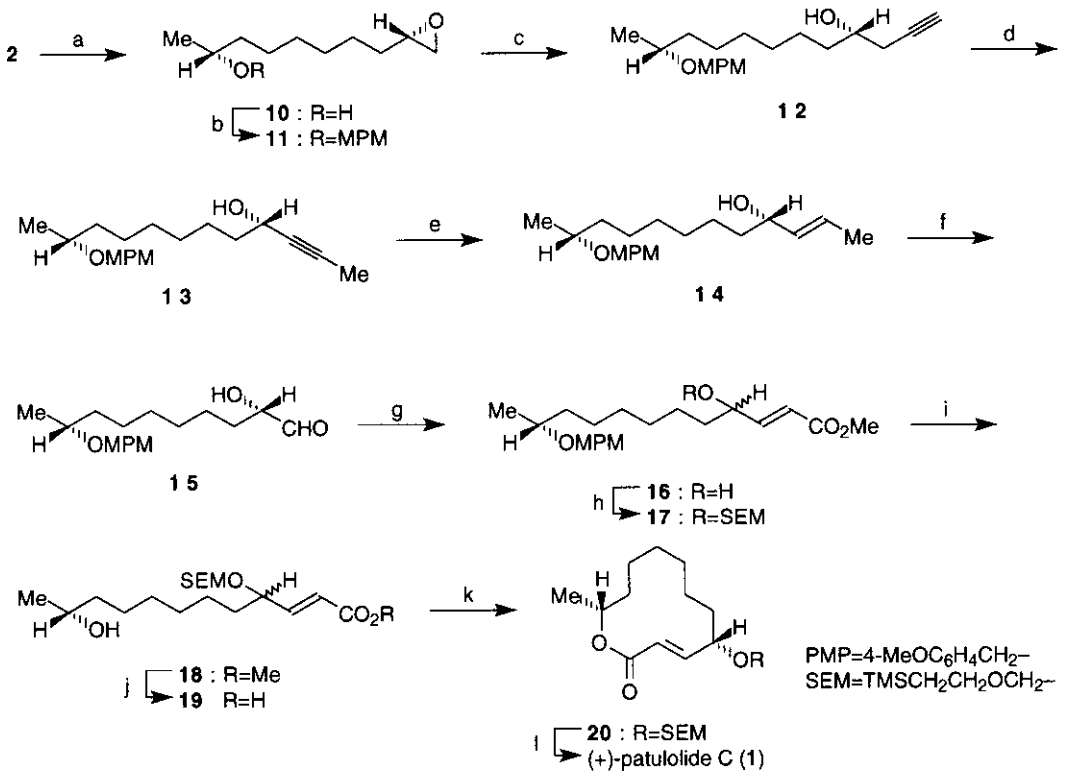
† Dedicated to Professor Dr. Arnold Brossi on the occasion of his 70th birthday.

[(*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 $(Ph_3P)_2PdCl_2$ (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 product[6] (**5**), $[\alpha]_D^{30}$ +28.72° (*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**), $[\alpha]_D^{30}$ +5.49° (*c* 1.11, $CHCl_3$), using Pearlman's catalyst furnished the tetraol (**7**), mp 114-115 °C, $[\alpha]_D^{31}$ –23.0° (*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 azeotropical 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 °C/20 torr (Kugelrohr), $[\alpha]_D^{27}$ –17.0° (*c* 0.79, $CHCl_3$), in 64% overall yield as a colorless oil (**Scheme 2**).



Scheme 2

Reagents: a) ≡-Li(CH_2NH_2)$_2$, DMSO, ref. 4; b) $(Ph_3P)_2PdCl_2$ (cat.), CuI (cat.), Et_3N, O_2, DMF, room temperature; c) H_2, PtO_2, benzene; d) H_2, $Pd(OH)_2$-C, $CHCl_3$ (cat.), concd HCl (cat.), MeOH; e) PhCHO, *p*-TsOH·H_2O, 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-$MeOC_6H_4CH_2Cl$, NaH, DMF; c) ≡-$Li(CH_2NH_2)_2$, DMSO, 0 °C; d) *tert*-BuOK, DMSO, 0 °C; e) $LiAlH_4$, THF, reflux; f) O_3, MeOH, –78 °C, then Me_2S; g) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, room temperature; h) SEM-Cl, Hünig base, *n*-Bu_4NI, CH_2Cl_2, room temperature; ı) DDQ, CH_2Cl_2-H_2O (18:1 v/v); j) LiOH·H_2O, aq. THF (50%), $BnEt_3NCl$ (cat); k) 2,4,6-trichlorobenzoyl chloride, DMAP, toluene, reflux then separation by SiO_2 plate, l) $BF_3{\cdot}OEt_2$ (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**, $[\alpha]_D^{25}$ –21.3° (*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**), $[\alpha]_D^{29}$ –20.21° (*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**), $[\alpha]_D^{32}$ –15.03° (*c* 0.50, $CHCl_3$), in 72% overall yield from **10**. Upon exposure to potassium *tert*-butoxide (6 equiv.) in DMSO[4] at 0 °C for 15 min, the

terminal acetylene (**12**) rearranged facilely to give the internal acetylene (**13**), $[\alpha]_D^{34}$ –10.73° (*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° (*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, ^{1}H 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) ether[13] (**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° (*c* 0.70, $CHCl_3$), and its C_4-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 group[16] to give (+)-patulolide C (**1**), $[\alpha]_D^{30}$ +5.63° (*c* 0.22, EtOH) [lit : $[\alpha]_D^{20}$ +6.6° (*c* 0.40, EtOH)[2c,2g]; $[\alpha]_D$ +6.8° (*c* 0.15, EtOH)[2d]], in 78% yield[17] (**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 C_2-symmetric (*S*:*S*)-*bis*-epoxide intermediate (**2**) though some unexpected epimerization has taken place.

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