VIP Natural Product Synthesis

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Total Synthesis and Configurational Assignment of Pasteurestin A and B**

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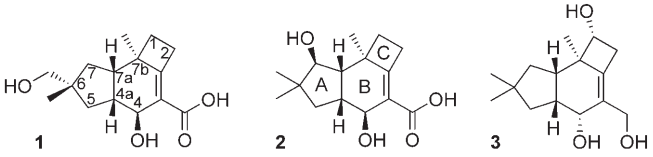
The isolation and biological properties of two novel basidiomycete sesquiterpenoids, pasteurestin A (**1**) and pasteurestin B (**2**), were recently reported in a Japanese patent.[1] Both

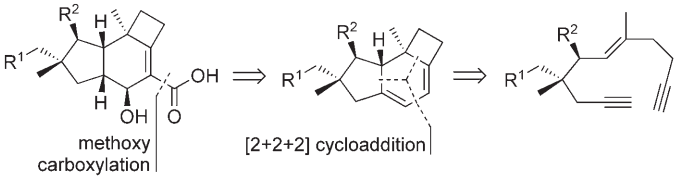


compounds were obtained by fermentation of *Agrocybe aegeritta* and are of considerable interest for veterinary applications, as they exhibit strong and selective antibacterial activities against some strains of *Mannheimia haemolytica*, a pathogen for bovine respiratory disease (BRD).[2]

The carbon skeleton of both compounds is identical to that of other members of the protoilludane family such as illudol (**3**).[3,4] However, the absolute and relative configurations of **1** and **2** are unknown, since only ^{1}H and ^{13}C NMR, IR, and mass spectra as well as optical rotations have been published. The relative configurations at C-4a, C-7a, and C-7b were assumed to be the same as in other protoilludanes,[3] but those at C-4 and C-6 in **1** and C-4 and C-7 in **2**, respectively, and the absolute configurations had to be established by total synthesis, all the more so as we were unable to procure authentic samples of **1** and **2**.

Retrosynthetically, a Vollhardt [2+2+2] cycloaddition[4c,5] of enediynes **4** and **5** should lead to the tricyclic intermediates **6** and **7**, which contain virtually the full carbon skeleton of **1** and **2** (Scheme 1). It was an open question how the stereogenic centers in **4** and **5** would influence the stereochemical course of the cycloaddition.

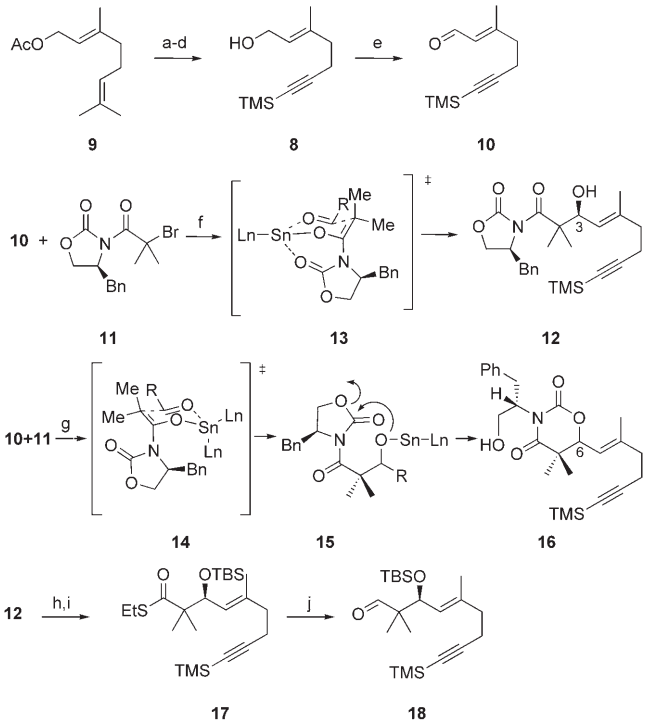
The synthesis of pasteurestin B (**2**) started from allylic alcohol **8**, easily available from geranyl acetate (**9**; Scheme 2)



1 R^1 = OH, R^2 = H; **2** R^1 = H, R^2 = OH; **6** R^1 = OTBDPS, R^2 = H; **7** R^1 = H, R^2 = OTBS; **4** R^1 = OTBDPS, R^2 = H; **5** R^1 = H, R^2 = OTBS

Scheme 1. Retrosynthetic analysis for pasteurestin A (**1**) and B (**2**). TBDPS = *tert*-butyldiphenylsilyl; TBS = *tert*-butyldimethylsilyl.

in four steps.[6] Swern oxidation gave the α,β-unsaturated aldehyde **10**, which was subjected to a tin(II) Reformatsky addition with bromide **11**,[7,8c] $SnCl_2$, and $LiAlH_4$.[8] At −78 °C,



Scheme 2. Reagents and conditions: a) *m*CPBA, NaOAc, CH_2Cl_2, −21 °C, 98%; b) $HIO_4 \cdot 2H_2O$, THF/Et_2O, 0 °C, 82%; c) K_2CO_3, dimethyl 1-diazo-2-oxopropylphosphonate, MeOH, 23 °C, 90%; d) 1) *n*BuLi, TMSCl, THF, −78 °C, 2) HCl 2 N, 23 °C, 95%; e) $(COCl)_2$, DMSO, DIPEA, CH_2Cl_2, −78 °C, 89%; f) $SnCl_2$, $LiAlH_4$, THF, 23 °C then **11**, then −78 °C, then **10**, 78%; g) $SnCl_2$, $LiAlH_4$, THF, 23 °C then **11**, then **10**, 82%; h) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 95%; i) *n*BuLi, EtSH, THF, 0 °C, 89%; j) DIBAL-H, CH_2Cl_2, −78 °C, 75% (+15% alcohol). Bn = benzyl; Ln = ligand; *m*CPBA = *meta*-chloroperbenzoic acid; TMS = trimethylsilyl; DIPEA = diisopropylethylamine; Tf = trifluoromethanesulfonate; DIBAL-H = diisobutylaluminum hydride.

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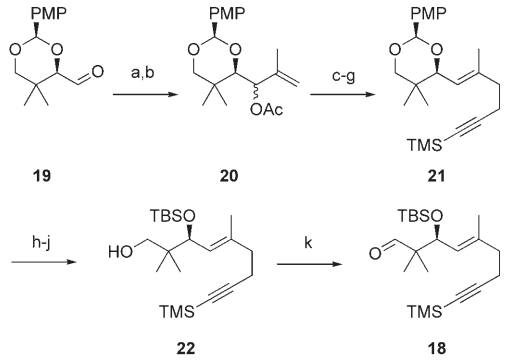
the desired 3*S* adduct **12** was obtained in >99% *de* under complete retention of the *E* configuration of the alkene unit. This result was surprising, as such aldol additions have been reported to be 3*R*-selective.[8b,c] The discrepancy with our result must arise from the reaction temperature, as we performed the aldehyde addition at −78 °C, whereas ambient temperature had been used in the literature.[8] This remarkable temperature effect might be interpreted in terms of a fully complexed transition state **13** (Nerz–Stormes–Thornton model) at low temperature[9] and an uncomplexed Pridgen-type transition state **14** at ambient temperature.[10] Under these conditions, the primary aldol adduct **15** was unstable and isomerized to the 1,3-oxazine-2,6-dione **16**,[11] presumably owing to a *gem*-dimethyl effect. Protection of 3*S* adduct **12**, removal of the chiral auxiliary, and reduction of the thioester **17**[12] led to aldehyde **18**.

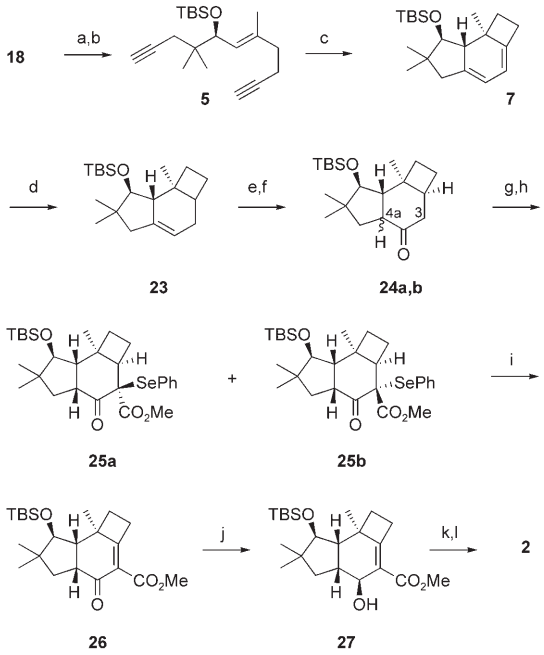
The 3*S* configuration in **18** was confirmed by an unambiguous synthesis (Scheme 3) from aldehyde **19**, which is readily available from (*R*)-pantolactone in three steps.[13] The



Scheme 3. Reagents and conditions: a) 2-propenylMgBr, THF, 0 °C, 92%; b) Ac_2O, NEt_3, DMAP, CH_2Cl_2, 23 °C, 87%; c) LDA, TMSCl, −78 °C→23 °C, 69%; d) DIC, NEt_3, MeHNOMe·HCl, CH_2Cl_2, 23 °C, 98%; e) DIBAL-H, THF, −78 °C, 95%; f) K_2CO_3, dimethyl 1-diazo-2-oxopropylphosphonate; g) *n*BuLi, TMSCl, THF, −78 °C, 95%; h) 80% AcOH, THF, 99%; i) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 92%; j) HF·Py, THF, 23 °C, 65%; k) DMP, CH_2Cl_2, 23 °C, 92%. PMP = *para*-methoxy phenyl; DMAP = 4-dimethylaminopyridine; LDA = lithium diisopropylamide; DIC = *N*,*N*′-diisopropylcarbodiimide; Py = pyridine; DMP = Dess–Martin periodinane.

key step in this sequence was the Claisen–Ireland rearrangement[14] of the epimeric alcohols **20**. The rearranged compound was converted to aldehyde **18**,[15] which is identical in all respects to the material obtained above.

C1-homologation of **18** was accomplished by Wittig reaction and subsequent hydrolysis (Scheme 4). The resulting aldehyde was treated with the Bestmann–Ohira reagent[16] to give enediyne **5**. Subsequent [$CoCp(CO)_2$]-mediated cyclization (Cp = cyclopentadienyl) delivered diene **7** in a highly diastereoselective manner. Regioselective Birch reduction of the C2a–C3 π bond to give *cis* bicyclo[4.2.0]octane **23** and subsequent hydroboration–oxidation of the remaining double bond followed by Dess–Martin oxidation of the newly formed alcohol furnished a 2:1 mixture of the *syn*/*anti* isomers **24a**,**b**. Functionalization of C-3 in **24** was accomplished by carboxylation of the kinetically favored enolate with carbon dioxide

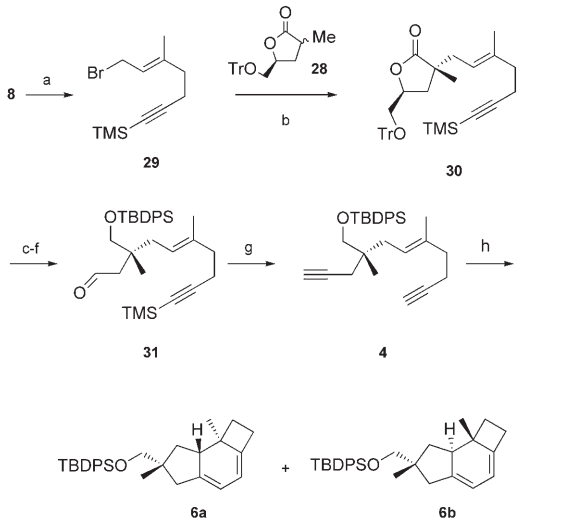


Scheme 4. Reagents and conditions: a) $MeOCHPPh_3Cl$, *n*BuLi, 0 °C, then 2 M HCl, 23 °C, 60%; b) K_2CO_3, dimethyl 1-diazo-2-oxopropylphosphonate, MeOH, 23 °C, 93%; c) [$CoCp(CO)_2$], toluene, *hν*, reflux, then $CuCl_2 \cdot 2H_2O$, DME, 23 °C, 40%; d) Li (excess), NH_3, *t*BuOH, THF, −78 °C, 85%; e) BH_3, THF, 23 °C, then K_2CO_3, H_2O_2, THF/H_2O, reflux, 78%; f) DMP, CH_2Cl_2, 23 °C, 95%; g) LDA, HMPA, THF, −78 °C, then CO_2 (excess), −58 °C, then 1 N HCl, 23 °C, then $TMSCHN_2$, 0 °C, 45%, 75% (brsm); h) LDA, PhSeCl, THF, −78 °C, 63%; i) NH_4Cl, H_2O_2, H_2O/CH_2Cl_2, 0 °C, 72%; j) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 23 °C, 90%; k) HF·Py, THF, 23 °C; l) LiOH, H_2O/THF, 23 °C, 59%; Cp = cyclopentadienyl; DME = 1,2-dimethoxyethane; HMPA = hexamethylphosphoramide; brsm = based on recovered starting material.

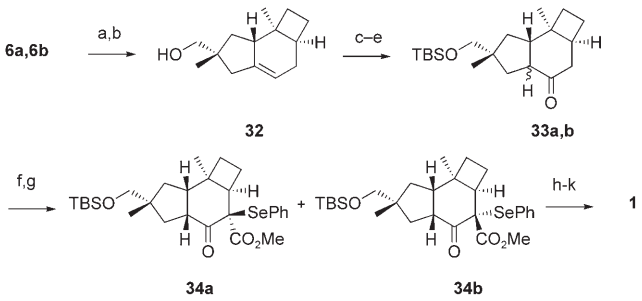
and subsequent methylation with trimethylsilyldiazomethane. The β-ketoester was treated with 2.5 equiv of LDA and phenylselenyl chloride. Under these conditions diastereomers **25a**,**b** equilibrated to give exclusively the epimer with a *cis* ring juncture between the five- and six-membered rings. Subsequent oxidation gave **26**, and diastereoselective reduction under Luche conditions[17] delivered alcohol **27**, which was deprotected with HF·pyridine and hydrolyzed to pasteurestin B (**2**), whose analytical data matched those of the natural product.[1]

For the synthesis of pasteurestin A (**1**), butyrolactone **28** was prepared in two steps from (*R*)-glycidol.[18] α-Allylation with bromide **29** furnished lactone **30** with d.r. 98:2,[19] which was elaborated into aldehyde **31** (Scheme 5). C1-Homologation and deprotection gave enediyne **4** in 45% yield over six steps, which was cyclized to give a 4:3 mixture of **6a** and **6b**. Birch reduction and desilylation followed by HPLC separation furnished diastereomerically pure **32** (Scheme 6). The endgame was performed in analogy to the synthesis of pasteurestin B (**2**). Thus, conversion of the epimeric mixture of **33a** and **33b** furnished **34a** and **34b** in a 1:3 ratio. This mixture was processed through to pasteurestin A (**1**), whose analytical data were in accord with those reported.[1]

In conclusion, pasteurestin A (**1**) was prepared in 22 linear steps with an overall yield of 0.5%, and the synthesis of



Scheme 5. Reagents and conditions: a) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 85 %; b) **28**, LDA, HMPA, THF, −78 °C, then **29**, 90 %; c) DIBAL-H, THF, −78 °C, 95 %; d) TBDPSCl, DMAP, NEt_3, CH_2Cl_2, 23 °C, 90 %; e) Et_2AlCl, CH_2Cl_2, −78 °C, 87 %; f) $Pb(OAc)_4$, CH_2Cl_2, 23 °C, 95 %; g) K_2CO_3, MeOH, dimethyl 1-diazo-2-oxopropylphosphonate, 23 °C, 71 %; h) $[CoCp(CO)_2]$, toluene, *hν*, reflux, then $CuCl_2 \cdot 2H_2O$, DME, 23 °C, 46 %; Tr = triphenylmethyl.



Scheme 6. Reagents and conditions a) Li (excess), NH_3, *t*BuOH, THF, −78 °C, 85 %; b) TBAF, THF, 23 °C, 95 %; HPLC separation; c) TBSCl, imidazole, DMF, 23 °C, 90 %; d) BH_3, THF, 23 °C, then K_2CO_3, H_2O_2, reflux, 78 %; e) DMP, CH_2Cl_2, 23 °C, 95 %; f) LDA, HMPA, THF, −78 °C, then CO_2 (excess), −58 °C, then 1 N HCl, 23 °C, then $TMSCHN_2$, 0 °C, 55 %, 75 % (brsm); g) LDA, PhSeCl, THF, −78 °C, 55 %; h) NH_4Cl, H_2O_2, H_2O/CH_2Cl_2, 0 °C, 72 %; i) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 87 %; j) HF·Py, THF, 23 °C; k) LiOH, H_2O/THF, 23 °C, 55 % over two steps. TBAF = tetrabutylammonium fluoride.

pasteurestin B required 20 steps with an overall yield of 0.8 %. The [2+2+2] cycloaddition was completely diastereoselective in the synthesis of pasteurestin B (**2**), owing to the neighboring stereocenter in **5**, whereas the stereocenter in **4** is too remote to have any influence on the stereochemical outcome.

Screening against a wide variety of bacteria showed that **1** exhibits micromolar activity and high selectivity for some very versatile pathogenic strains of *Pasteurella multocida*.[20] Other bacteria tested such as *Escherichia coli* and *Mannheimia haemolytica* remained unaffected.[21] These results prompt us to continue with biological testing and the synthesis of suitable analogues.

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