P Natural Product Synthesis

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 ¹H and ¹³C 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 stereo-chemical course of the cycloaddition.

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

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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] SnCl₂, and LiAlH₄.^[8] At -78 °C,



Scheme 2. Reagents and conditions: a) mCPBA, NaOAc, CH₂Cl₂, -21 °C, 98%; b) HIO₄·2 H₂O, THF/Et₂O, 0 °C, 82%; c) K₂CO₃, dimethyl 1-diazo-2-oxopropylphosphonate, MeOH, 23 °C, 90%; d) 1) nBuLi, TMSCl, THF, -78 °C, 2) HCl 2 N, 23 °C, 95%; e) (COCl)₂, DMSO, DIPEA, CH₂Cl₂, -78 °C, 89%; f) SnCl₂, LiAlH₄, THF, 23 °C then **11**, then -78 °C, then **10**, 78%; g) SnCl₂, LiAlH₄, THF, 23 °C then **11**, then **10**, 82%; h) TBSOTf, 2,6-lutidine, CH₂Cl₂, 0 °C, 95%; i) nBuLi, EtSH, THF, 0 °C, 89%; j) DIBAL-H, CH₂Cl₂, -78 °C, 75% (+15% alcohol). Bn = benzyl; Ln = ligand; mCPBA = meta-chloroperbenzoic acid; TMS = trimethylsilyl; DIPEA = diisopropylethylamine; Tf = trifluoromethanesulfonate; DIBAL-H = diisobutylaluminum hydride.



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the desired 3S 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 3R-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 Pridgentype 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 3S adduct 12, removal of the chiral auxiliary, and reduction of the thioester **17**^[12] led to aldehyde **18**.

The 3S 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) Ac₂O, NEt₃, DMAP, CH₂Cl₂, 23 °C, 87%; c) LDA, TMSCl, -78 °C \rightarrow 23 °C, 69%; d) DIC, NEt₃, MeHNOMe·HCl, CH₂Cl₂, 23 °C, 98%; e) DIBAL-H, THF, -78 °C, 95%; f) K₂CO₃, dimethyl 1-diazo-2oxopropylphosphonate; g) *n*BuLi, TMSCl, THF, -78 °C, 95%; h) 80% AcOH, THF, 99%; i) TBSOTf, 2,6-lutidine, CH₂Cl₂, 0 °C, 92%; j) HF-Py, THF, 23 °C, 65%; k) DMP, CH₂Cl₂, 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) MeOCHPPh₃Cl, *n*BuLi, 0°C, then 2 M HCl, 23 °C, 60%; b) K₂CO₃, dimethyl 1-diazo-2-oxopropyl-phosphonate, MeOH, 23 °C, 93%; c) [CoCp(CO)₂], toluene, *hv*, reflux, then CuCl₂·2H₂O, DME, 23 °C, 40%; d) Li (excess), NH₃, tBuOH, THF, -78 °C, 85%; e) BH₃, THF, 23 °C, then K₂CO₃, H₂O₂, THF/H₂O, reflux, 78%; f) DMP, CH₂Cl₂, 23 °C, 95%; g) LDA, HMPA, THF, -78 °C, 45%, 75% (brsm); h) LDA, PhSeCl, THF, -78 °C, 63%; i) NH₄Cl, H₂O₂, H₂O/CH₂Cl₂, 0°C, 72%; j) NaBH₄, CeCl₃·7H₂O, MeOH, 23 °C, 90%; k) HF·Py, THF, 23 °C; l) LiOH, H₂O/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 **25 a,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

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Scheme 5. Reagents and conditions: a) CBr₄, PPh₃, CH₂Cl₂, 0°C, 85%; b) **28**, LDA, HMPA, THF, -78°C, then **29**, 90%; c) DIBAL-H, THF, -78°C, 95%; d) TBDPSCl, DMAP, NEt₃, CH₂Cl₂, 23°C, 90%; e) Et₂AlCl, CH₂Cl₂, -78°C, 87%; f) Pb(OAc)₄, CH₂Cl₂, 23°C, 95%; g) K₂CO₃, MeOH, dimethyl 1-diazo-2-oxopropylphosphonate, 23°C, 71%; h) [CoCp(CO)₂], toluene, *hv*, reflux, then CuCl₂·2 H₂O, DME, 23°C, 46%; Tr=triphenylmethyl.



Scheme 6. Reagents and conditions a) Li (excess), NH₃, tBuOH, THF, -78° C, 85%; b) TBAF, THF, 23°C, 95%; HPLC separation; c) TBSCl, imidazole, DMF, 23°C, 90%; d) BH₃, THF, 23°C, then K₂CO₃, H₂O₂, reflux, 78%; e) DMP, CH₂Cl₂, 23°C, 95%; f) LDA, HMPA, THF, -78° C, then CO₂ (excess), -58° C, then 1 N HCl, 23°C, then TMSCHN₂, 0°C, 55%, 75% (brsm); g) LDA, PhSeCl, THF, -78° C, 55%; h) NH₄Cl, H₂O₂, H₂O/CH₂Cl₂, 0°C, 72%; i) NaBH₄, CeCl₃-7 H₂O, MeOH, 87%; j) HF-Py, THF, 23°C; k) LiOH, H₂O/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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