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Total Synthesis

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Total Synthesis and Absolute Stereochemistry of Polygalolides A and B**

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In 2003, Wei and co-workers reported the isolation and structural elucidation of the polygalolides A (1) and B (2) obtained from *Polygala fallax* Hemsl., a medicinal plant from which extracts are used as tonics and antihepatitis drugs in China.^[1] The structure and relative configuration of the polygalolides were determined on the basis of NMR spectroscopic data. However, the issue of the absolute stereochemistry of the molecules has not been resolved. The structural complexity of these molecules, which include an unprecedented trioxatetracyclic ring system and contiguous quaternary stereogenic centers at C2 and C8, poses a considerable synthetic challenge. Herein, we describe the first total synthesis of (–)-polygalolides A (1) and B (2). The synthesis

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takes advantage of a transformation consisting of a tandem carbonyl ylide formation/1,3-dipolar cycloaddition, which has been extensively studied, especially in the research group of Padwa.^[2–5]

Our retrosynthetic analysis of the polygalolides is illustrated in Scheme 1. We elected to introduce the arylmethylidene moiety at a late stage in the synthesis, and the



Scheme 1. Retrosynthetic analysis of polygalolides A and B. PMP = *p*-methoxyphenyl, TBDPS = *tert*-butyldiphenylsilyl.

scission of the lactone ring provided **3** as a common intermediate. The tricyclic compound **3** was assumed to arise from an intramolecular 1,3-dipolar cycloaddition of carbonyl ylide **5**, generated from α -diazoketone **6** in the presence of a Rh^{II} catalyst. Compound **6** arises from homologation of the *tert*-butyl ester **7**, which would be elaborated from the known alcohol **8**,^[6] which in turn can readily be obtained from D-arabinose.

We initiated the synthesis by alkylating alcohol 8 with (Z)-1-bromo-4-(*tert*-butyldiphenylsilyl)oxy-2-butene^[7] to provide the allyl ether 9 in 98% yield (Scheme 2). The oxidative hydrolysis of the dithioacetal with iodine was followed by oxidation with NaClO₂ and esterification with $(Boc)_2O^{[8]}$ to give tert-butyl ester 10 in 70% yield over three steps. Catalytic hydrogenation of alkene 10 provided the TBDPS ether 11 in 95% yield, and 11 was then treated with Bu₄NF in the presence of AcOH to give alcohol 12 in 96% yield. Installation of the C2=C3 bond was accomplished by employing a modification of the procedure reported by Ogasawara and co-workers,^[9] and subsequent reduction with NaBH₄ gave alcohol 13 in 81 % yield over both steps. A two-step sequence involving mesylation and nucleophilic substitution with pmethoxyphenol was used to convert the allyl alcohol 13 into the PMP ether 14 in 78% overall yield. The acetonide was





Scheme 2. Synthesis of cyclization precursor 6. a) (Z)-1-bromo-4-(*tert*-butyldiphenylsilyl)oxy-2-butene, NaH, THF/DMF (10:1), 1.5 h, 98%; b) I₂, NaHCO₃, aq acetone, -25°C, 5 min, 88%; c) NaClO₂, NaH₂PO₄, 2-methyl-2-butene, aq tBuOH, 6 h; d) (Boc)₂O, DMAP, tBuOH, 1 h, 80% (2 steps); e) H₂, 10% Pd/C, EtOAc, 13 h, 95%; f) Bu₄NF, AcOH, THF, 15 h, 96%; g) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78 \rightarrow 0°C, then Me₂N=CH₂I, DBU, 20 h, 85%; h) NaBH₄, EtOH, 0°C, 30 min, 95%; i) MsCl, Et₃N, CH₂Cl₂, 0°C, 10 min; j) 4-MeOC₆H₄OH, K₂CO₃, MeCN, reflux, 6 h, 78% (2 steps); k) AcOH/THF/H₂O (3:1:1), 40°C, 4 h, 95%; j) TBDPSCl, imidazole, CH₂Cl₂, 1 h, 92%; m) Dess–Martin periodinane, CH₂Cl₂, 1 h, 93%; n) TFA/CH₂Cl₂ (1:10), 0°C, 1 h; o) ClCO₂*i*Bu, Et₃N, Et₂O, 0°C, 10 min, then CH₂N₂, 90 min, 55% (2 steps). Boc = *tert*-butoxycarbonyl, DMAP=4-dimethylaminopyridine, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, Ms = methanesulfonyl, TFA = trifluoro-acetic acid.

removed using AcOH in aqueous THF at 40 °C to afford the diol **15** in 95% yield. Selective silylation of the C9 hydroxy group in **15** furnished the TBDPS ether **16** in 92% yield, and **16** was oxidized with Dess–Martin periodinane to give ketone $7^{[10]}$ in 93% yield. A carboxylic acid function at C5, available for a one-carbon homologation, was liberated upon exposure of the *tert*-butyl ester **7** to TFA. Although the carboxyl group in **17** could not be converted into the acid chloride because of the inevitable formation of the corresponding pseudo-chloride,^[11] activation of the acid through the intermediacy of its mixed anhydride and subsequent treatment with CH₂N₂ afforded α -diazoketone **6** in 55% yield over the two steps.

With the cyclization precursor **6** in hand, we set out to investigate the critical carbonyl ylide formation/intramolecular 1,3-dipolar cycloaddition reaction sequence (Scheme 3). The reaction involved the addition of α -diazoketone **6** (ca. 30 mg) over five minutes to a solution of a Rh^{II} catalyst. Although **6** was completely consumed even at room temperature in the presence of Rh₂(OAc)₄, the reaction gave a complex mixture of products.^[12] After some experimentation, we found that cycloadduct **3**^[10] was produced as a single isomer in 36 % yield at 60 °C in toluene; the product yield was improved to 68 % by an increase in reaction temperature to



Scheme 3. Total synthesis of polygalolides A (1) and B (2). a) $Rh_{2^{-}}(OAc)_4$ (5 mol%), PhCF₃, 100°C, 5 min, 73%; b) (NH₄)₂Ce(NO₃)₆, pyridine, aq MeCN, 0°C, 2 h, 91%; c) Dess–Martin periodinane, CH₂Cl₂, 2 h, 92%; d) NaClO₂, NaH₂PO₄, 2-methyl-2-butene, aq tBuOH, 6 h; e) CH₂N₂, Et₂O, 0°C, 30 min, 85% (2 steps); f) Bu₄NF, AcOH, THF, 20 h, 93%; g) LDA, ZnCl₂, THF, -78°C, 1 h, aldehyde **4a**, -78°C, 30 min, then Ac₂O, 0°C, 1 h; h) SiO₂, CH₂Cl₂, 2 4 h; i) NaHCO₃, aq MeOH, 18% (3 steps); j) TMSOTf, Et₃N, CH₂Cl₂, 0°C, 5 h, 90%; k) **23 a** or **23 b** (5 equiv), TMSOTf, molecular sieves (3 Å), CH₂Cl₂, -78°C, 30 min, 58% (for **24 a**) or 57% (for **24 b**); l) DBU, CH₂Cl₂, 10 min; m) NaHCO₃, aq MeOH, 85% (for **1**) or 72% (for **2**). LDA = lithium diisopropylamide; TMS = trimethylsilyl; Tf = trifluoromethanesulfonyl.

110 °C. We screened the solvents and Rh^{II} catalysts^[13] and found Rh₂(OAc)₄ in benzotrifluoride^[14] to be optimal, affording cycloadduct **3** in 73 % yield.^[15] After oxidative removal of the PMP group at C1 with $(NH_4)_2Ce(NO_3)_6$,^[16] two successive oxidations and an esterification with CH₂N₂ gave the methyl ester **19** in 78 % yield over three steps. Desilylation and concomitant lactone formation was effected with Bu₄NF in the presence of AcOH to provide the tetracyclic lactone **20**.

With the construction of the common tetracyclic core accomplished, we addressed the late-stage installation of the arylmethylidene moiety. Our initial attempts focused on the aldol reaction of ketone 20 with aldehyde 4a under basic

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conditions. The formation of the aldol adduct was detected by ¹H NMR spectroscopy of the crude mixture when the zinc enolate derived from 20 was reacted with 4a, but the desired product readily underwent retroaldol reaction upon exposure to silica gel. The coupling product 21 could be obtained along with considerable amounts of starting material 20 when the reaction mixture was treated with Ac₂O. Although the total synthesis of polygalolide A (1) could be completed through exposure of the mixture to silica gel followed by deacetylation, the low efficiency of this sequence (18% yield over three steps without intervening purification) left room for improvement. Accordingly, the decision was made to employ the Mukaiyama aldol-type reaction using dimethyl acetal 23 a.^[17] Ketone 20 was easily converted into the silvl enol ether 22. Gratifyingly, the TMSOTf-promoted coupling of 22 with 23 a in CH_2Cl_2 in the presence of molecular sieves (3 Å) at -78 °C proceeded to provide coupling product 24a in 58% yield. The β -methoxyketone 24a was smoothly converted into polygalolide A (1) by treatment with DBU, followed by deacetylation. Polygalolide B (2) was also synthesized in 41% yield from intermediate 22 following an identical reaction sequence. The spectroscopic data (¹H and ¹³C NMR, IR, UV, and HRMS) of the products resulting from these syntheses correspond to those reported for the natural products, except for their specific rotations, which were equal in sign, but with magnitudes inconsistent with those previously reported: $[\alpha]_{\rm D} = -499.9$ (c = 0.022 in MeOH) and -505.2 (c = 0.018 in MeOH) compared with $[\alpha]_{\rm D} = -14.4$ (c = 0.018 in MeOH) and -21.3 (c = 0.015 in MeOH).^[1] This difference suggests that polygalolides might be biosynthesized in near-racemic form. In this context, it is interesting that Snider and Grabowski recently proposed in their total syntheses of (\pm) -cartorimine and (\pm) -descurainin that the 8-oxabicyclo[3.2.1]octenone skeleton of these molecules would be biosynthesized by a [5+2] cycloaddition between a oxypyrylium zwitterion and an alkene.^[5e,f] They speculated that [5+2] cycloadditions in a chiral environment could lead to optically enriched products as the very small $[\alpha]_{\rm D}$ values of these natural products indicate that they are not completely racemic. We surmise that polygalolides would also be synthesized in the medicinal plant through [5+2] cycloaddition of the fructose-derived oxypyrylium zwitterion 25 with an isoprene derivative, followed by an intramolecular hetero-Michael addition, a lactone formation, and an aldol reaction with vanillin derivatives.^[18] Our result would provide an experimental proof for the intriguing speculation by the Snider group.

In conclusion, we have accomplished the first total synthesis of polygalolides A (1) and B (2) from alcohol 8, with a longest linear sequence of 25 steps and with overall yields of 3.8% and 3.2%, respectively. This total synthesis serves to confirm the absolute stereochemistry of these natural products. The synthesis illustrates the power of the carbonyl ylide cycloaddition methodology for the rapid assembly of the unusual dioxatricyclic ring system, which is difficult to construct by other means.

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- [13] Product yields obtained with Rh₂(OAc)₄ in other solvents: benzene (57%), (CH₂Cl)₂ (31%). Other Rh^{II} catalysts afforded lower product yields: Rh₂(OCOC₇H₁₅)₄ (trace), Rh₂(OCOC₃F₇)₄ (complex mixture), Rh₂(OCOCPh₃)₄ (24%), Rh₂(NHAc)₄ (41%).
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- [18] A plausible biogenesis of polygalolides is illustrated schematically below.

