Total Synthesis

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

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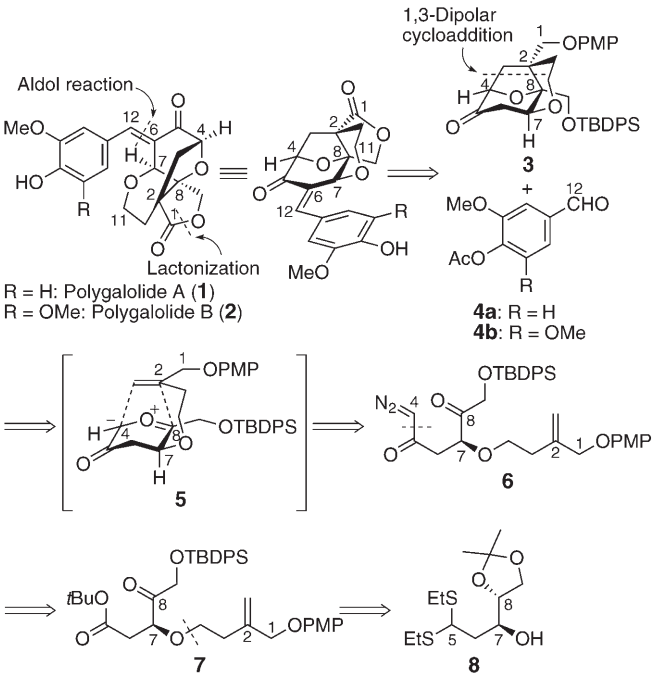
In 2003, Wei and co-workers reported the isolation and structural elucidation of the polygalolides A (**1**) and B (**2**) obtained from *Polygala fallax* Hemsl., a medicinal plant from which extracts are used as tonics and antihepatitis drugs in China.[1] The structure and relative configuration of 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 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 $NaClO_2$ 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 Bu_4NF 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 $NaBH_4$ gave alcohol **13** in 81% yield over both steps. A two-step sequence involving mesylation and nucleophilic substitution with *p*-methoxyphenol was used to convert the allyl alcohol **13** into the PMP ether **14** in 78% overall yield. The acetonide was

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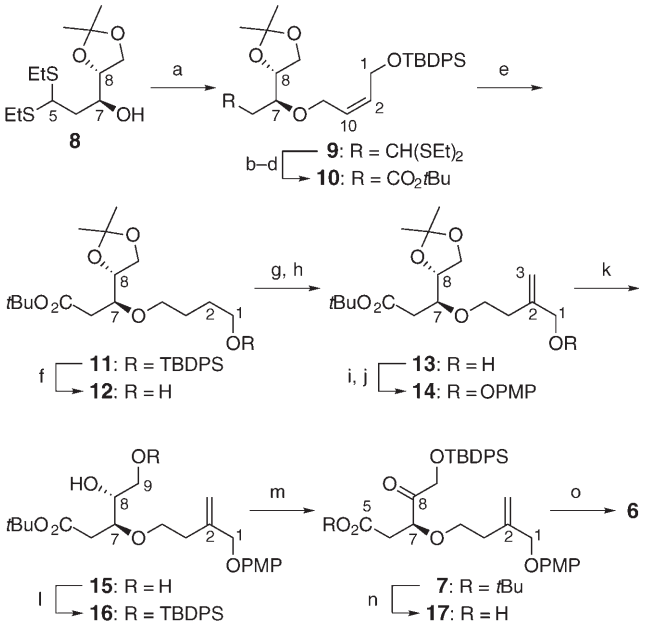
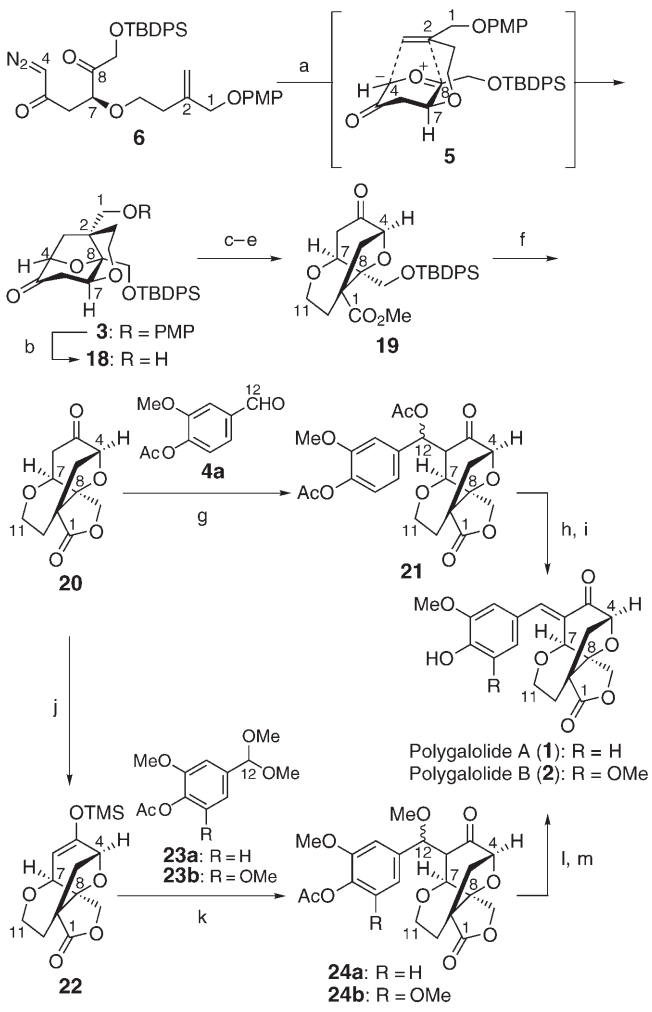
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



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) I_2, $NaHCO_3$, aq acetone, −25 °C, 5 min, 88%; c) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, aq *t*BuOH, 6 h; d) $(Boc)_2O$, DMAP, *t*BuOH, 1 h, 80% (2 steps); e) H_2, 10% Pd/C, EtOAc, 13 h, 95%; f) Bu_4NF, AcOH, THF, 15 h, 96%; g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78→0 °C, then $Me_2N{=}CH_2I$, DBU, 20 h, 85%; h) $NaBH_4$, EtOH, 0 °C, 30 min, 95%; i) MsCl, Et_3N, CH_2Cl_2, 0 °C, 10 min; j) 4-$MeOC_6H_4OH$, K_2CO_3, MeCN, reflux, 6 h, 78% (2 steps); k) AcOH/THF/H_2O (3:1:1), 40 °C, 4 h, 95%; l) TBDPSCl, imidazole, CH_2Cl_2, 1 h, 92%; m) Dess–Martin periodinane, CH_2Cl_2, 1 h, 93%; n) TFA/CH_2Cl_2 (1:10), 0 °C, 1 h; o) $ClCO_2iBu$, Et_3N, Et_2O, 0 °C, 10 min, then CH_2N_2, 90 min, 55% (2 steps). Boc = *tert*-butoxycarbonyl, DMAP = 4-dimethylaminopyridine, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, Ms = methanesulfonyl, TFA = trifluoroacetic acid.



Scheme 3. Total synthesis of polygalolides A (**1**) and B (**2**). a) $Rh_2(OAc)_4$ (5 mol%), $PhCF_3$, 100 °C, 5 min, 73%; b) $(NH_4)_2Ce(NO_3)_6$, pyridine, aq MeCN, 0 °C, 2 h, 91%; c) Dess–Martin periodinane, CH_2Cl_2, 2 h, 92%; d) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, aq *t*BuOH, 6 h; e) CH_2N_2, Et_2O, 0 °C, 30 min, 85% (2 steps); f) Bu_4NF, AcOH, THF, 20 h, 93%; g) LDA, $ZnCl_2$, THF, −78 °C, 1 h, aldehyde **4a**, −78 °C, 30 min, then Ac_2O, 0 °C, 1 h; h) SiO_2, CH_2Cl_2, 24 h; i) $NaHCO_3$, aq MeOH, 18% (3 steps); j) TMSOTf, Et_3N, CH_2Cl_2, 0 °C, 5 h, 90%; k) **23a** or **23b** (5 equiv), TMSOTf, molecular sieves (3 Å), CH_2Cl_2, −78 °C, 30 min, 58% (for **24a**) or 57% (for **24b**); l) DBU, CH_2Cl_2, 10 min; m) $NaHCO_3$, aq MeOH, 85% (for **1**) or 72% (for **2**). LDA = lithium diisopropylamide; TMS = trimethylsilyl; Tf = trifluoromethanesulfonyl.

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 pseudochloride,[11] activation of the acid through the intermediacy of its mixed anhydride and subsequent treatment with CH_2N_2 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 $Rh_2(OAc)_4$, 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 110 °C. We screened the solvents and Rh^{II} catalysts[13] and found $Rh_2(OAc)_4$ 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 CH_2N_2 gave the methyl ester **19** in 78% yield over three steps. Desilylation and concomitant lactone formation was effected with Bu_4NF 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

conditions. The formation of the aldol adduct was detected by ^{1}H 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 Ac_2O. 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 **23a**.[17] Ketone **20** was easily converted into the silyl enol ether **22**. Gratifyingly, the TMSOTf-promoted coupling of **22** with **23a** 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 (^{1}H and ^{13}C 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: $[\alpha]_D = -499.9$ ($c = 0.022$ in MeOH) and −505.2 ($c = 0.018$ in MeOH) compared with $[\alpha]_D = -14.4$ ($c = 0.018$ 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 (±)-cartorimine and (±)-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 $[\alpha]_D$ 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 $Rh_2(OAc)_4$ in other solvents: benzene (57%), $(CH_2Cl)_2$ (31%). Other Rh^{II} catalysts afforded lower product yields: $Rh_2(OCOC_7H_{15})_4$ (trace), $Rh_2(OCOC_3F_7)_4$ (complex mixture), $Rh_2(OCOCPh_3)_4$ (24%), $Rh_2(NHAc)_4$ (41%).
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[18] A plausible biogenesis of polygalolides is illustrated schematically below.