CHEMISTRY
A EUROPEAN JOURNAL

ChemPubSoc
Europe

DOI: 10.1002/chem.201200542

Total Syntheses of (+)-Polygalolide A and (+)-Polygalolide B: Elucidation of the Absolute Stereochemistry and Biogenetic Implications

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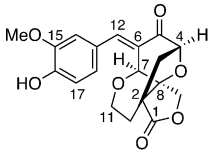
Abstract: The total syntheses of (+)-polygalolide A and (+)-polygalolide B have been completed by using a carbonyl ylide cycloaddition strategy. Three of the four stereocenters, including two consecutive tetrasubstituted carbon atoms at C2 and C8, were incorporated through internal asymmetric induction from the stereocenter at C7 by a $[Rh_2(OAc)_4]$-catalyzed carbonyl ylide formation/intramolecular 1,3-dipolar cycloaddition sequence. The arylmethylidene moiety of these natural products was successfully installed by a Mukaiyama aldol-type reaction of a silyl enol ether with a dimethyl acetal, followed by elimination under basic conditions. We have also developed an alternative approach to the carbonyl ylide precursor based on a hetero-Michael reaction. This approach requires 18 steps, and the natural products were obtained in 9.8 and 9.3% overall yields. Comparison of specific rotations of the synthetic materials and natural products suggests that polygalolides are biosynthesized in nearly racemic forms through a [5+2] cycloaddition between a fructose-derived oxypyrylium zwitterion with an isoprene derivative.

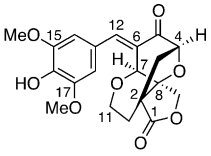
Keywords: aldol reaction · biosynthesis · cycloaddition · total synthesis · ylides

Introduction

In exploring the EtOH percolate of the powdered dried roots and stems of *Polygala fallax* Hemsl. (Polygalaceae), a folk medicinal plant distributed in southern China that is used as a tonic and antihepatitis agent, Wei and co-workers isolated two phenolic constituents, along with three known xanthones.[1,2] Whereas the structure and relative stereochemistry of these compounds, named polygalolides A (**1**) and B (**2**), were determined on the basis of NMR studies, the absolute stereochemistry was not established. It is well-known that α,β-unsaturated styryl ketones possess cytotoxic activity due to their propensity to participate in Michael addition reactions with cellular thiols,[3] but the detailed pharmacological properties of **1** and **2** have not been reported. The unusual molecular architecture of these molecules, which includes a trioxatetracyclic ring system and contiguous quaternary stereogenic centers at C2 and C8, compelled us to embark on a program aimed at their total synthesis. Very recently, the total synthesis of polygalolide A through an intramolecular *C*-glycosylation was reported by Adachi and Nishikawa and co-workers.[4] In this article, we describe the details of our total synthesis of polygalolides A (**1**) and B (**2**) by a carbonyl ylide cycloaddition strategy, a preliminary account of which was published in 2006.[5] The results of this study suggest that these natural products are synthesized in the medicinal plant through a [5+2] cycloaddition in near-racemic form.



Polygalolide A (**1**)



Polygalolide B (**2**)

Results and Discussion

Retrosynthetic analysis: The structures of polygalolides A (**1**) and B (**2**) are characterized by a 5,10,13-trioxatetracyclo[6.5.1.$0^{4,12}$.$0^{8,12}$]tetradecane-2,9-dione core with an array of four stereogenic centers, including contiguous tetrasubstituted carbon atoms at C2 and C8, and the only difference between these natural products resides at C17. We then planned to install the arylmethylidene moiety late in the synthesis by an aldol reaction or a related variant, because the implementation of this strategy would allow the incorporation of a variety of substituents into a common, fully elaborated intermediate **3** (Scheme 1). The scission of the lac-

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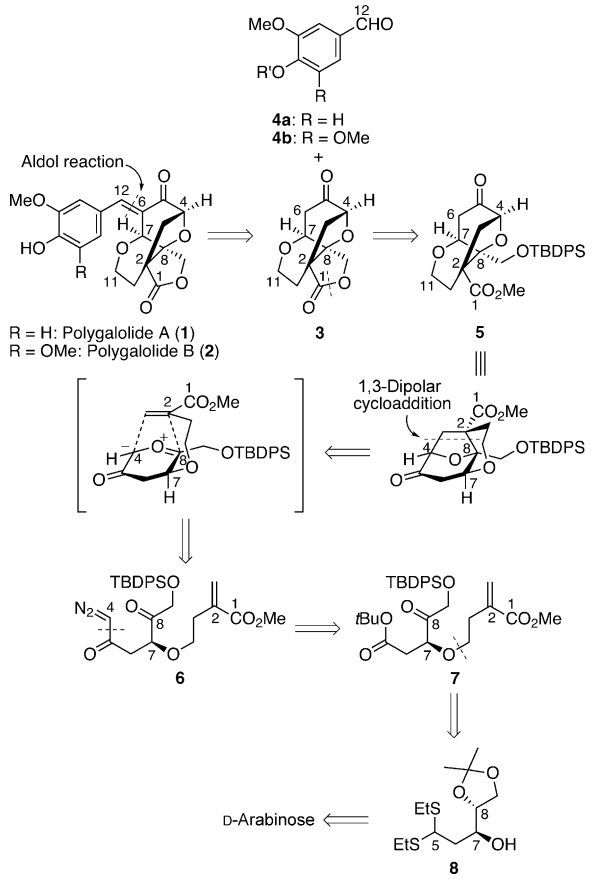
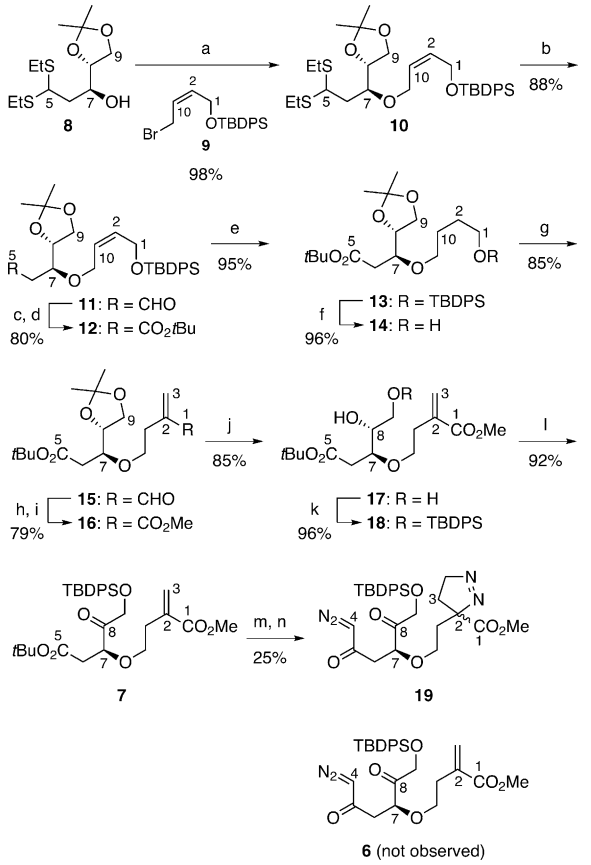
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201200542.



Scheme 1. Retrosynthetic analysis of polygalolides. TBDPS = *tert*-butyldiphenylsilyl.



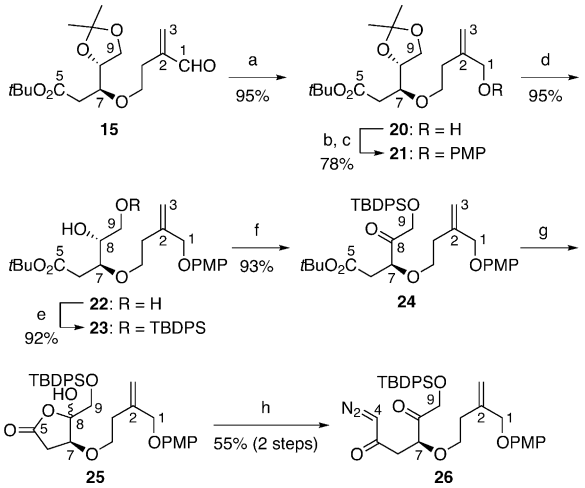
Scheme 2. Attempted synthesis of α-diazoketone **6**. Reagents and conditions: a) allyl bromide **9**, NaH, THF/DMF (10:1), 1.5 h; b) I_2, $NaHCO_3$, aq. acetone, −25 °C, 5 min; c) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, aq. *t*BuOH, 6 h; d) $(Boc)_2O$, DMAP, *t*BuOH, 1 h; e) H_2, 10% Pd/C, EtOAc, 13 h; f) Bu_4NF, AcOH, THF, 15 h; g) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to 0 °C, then $Me_2N{=}CH_2I$, DBU, 20 h; h) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, aq. *t*BuOH, 7 h; i) MeI, K_2CO_3, acetone, 14 h; j) AcOH/THF/H_2O (3:1:1), 40 °C, 6 h; k) TBDPSCl, imidazole, CH_2Cl_2, 20 min; l) Dess–Martin periodinane, CH_2Cl_2, 1 h; m) TFA/CH_2Cl_2 (1:10), 0 °C, 1 h; n) $ClCO_2iBu$, Et_3N, Et_2O, 0 °C, 15 min, then CH_2N_2, 90 min. THF = tetrahydrofuran; DMF = *N*,*N*-dimethylformamide; Boc = *tert*-butoxycarbonyl; DMSO = dimethyl sulfoxide.

tone ring provided tricyclic compound **5**, which was envisioned to arise from α-diazoketone **6** through a carbonyl ylide formation/intramolecular 1,3-dipolar cycloaddition sequence triggered by a rhodium(II) catalyst.[6–8] Diazoketone **6** could be prepared from *tert*-butyl ester **7**, which could be traced back to alcohol **8**,[9] readily obtained from D-arabinose.

Synthesis of carbonyl ylide precursor: An attempt to prepare carbonyl ylide precursor **6** from D-arabinose-derived alcohol **8** is depicted in Scheme 2. Although *O*-alkylation of alcohol **8** with 4-(*tert*-butyldiphenylsilyloxy)-1-iodobutane[10] resulted in low yield (32%) and production of a large amount of an elimination product, the use of allyl bromide **9**[11] as the alkylating agent provided allyl ether **10** in 98% yield. Oxidative hydrolysis of dithioacetal **10** with iodine in the presence of $NaHCO_3$ in acetone[12] furnished aldehyde **11** in 88% yield, which was transformed into *tert*-butyl ester **12** in 80% yield in two steps by oxidation with $NaClO_2$[13] and esterification with $(Boc)_2O$ in the presence of a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine (DMAP).[14] Catalytic hydrogenation of the C2=C10 double bond in **12** using 10% Pd/C was followed by desilylation with AcOH-buffered Bu_4NF to give alcohol **14** in 91% yield in two steps. At this juncture, the C2=C3 double bond, which would serve as a dipolarophile in the key cycloaddition reaction, was installed by employing a slight modification of the protocol reported by Ogasawara and co-workers;[15] Eschenmoser's salt and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[16] were added to the reaction mixture, wherein alcohol **14** underwent a Swern oxidation.[17] The resultant enal **15** was further oxidized with $NaClO_2$ and treated with MeI under basic conditions to provide methyl ester **16** in 79% yield in two steps. The acetonide group needed to be removed at this stage. A complicating aspect of this deprotection was competitive cleavage of the *tert*-butyl ester followed by the formation of a five-membered lactone. After considerable experimentation, we found that exposure of acetonide **16** to aqueous AcOH in tetrahydrofuran (THF) at 40 °C effected the desired transformation to give diol **17** in 85% yield. However, careful control of the temperature was required to access **17**, because lactone formation was ob-

served at temperatures above 45 °C under these conditions. Selective silylation of the primary hydroxyl group at C9 with TBDPSCl was followed by Dess–Martin oxidation[18] to provide γ-ketoester **7** in 88 % yield in two steps. The *tert*-butyl ester in **7** was uneventfully deprotected upon exposure to trifluoroacetic acid (TFA) in CH_2Cl_2 at 0 °C in preparation for the one-carbon homologation. Because acid chlorides derived from γ-ketocarboxylic acids have been reported to exist as cyclic pseudochlorides,[19] an attempt to convert the product into α-diazoketone **6** was performed as a two-step, one-flask procedure, whereby an intermediate mixed anhydride was formed from isobutyl chloroformate in Et_2O at 0 °C before treatment with excess diazomethane. Although the mixed anhydride moiety could be transformed into the corresponding α-diazoketone, the reaction was accompanied by a [3+2] cycloaddition of diazomethane to the enoate moiety, producing dihydropyrazole **19** in 25 % yield in two steps. We attribute this result to the high reactivity of the enoate moiety toward cycloaddition. To prevent this undesired cycloaddition, we elected to carry this portion of the molecule in a reduced oxidation state.

Enal **15** was then reduced with $NaBH_4$ in EtOH at 0 °C to give allyl alcohol **20** in 95 % yield, which was transformed into its 4-methoxyphenyl (PMP) ether **21** in 78 % yield through mesylation followed by a nucleophilic substitution with 4-methoxyphenol in MeCN heated to reflux (Scheme 3). Conversion of acetonide **21** into γ-ketoester

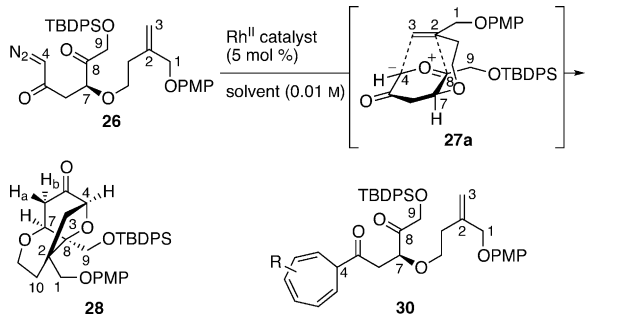


Scheme 3. Synthesis of α-diazoketone **26**. Reagents and conditions: a) $NaBH_4$, EtOH, 0 °C, 30 min; b) MsCl, Et_3N, CH_2Cl_2, 0 °C, 10 min; c) 4-$MeOC_6H_4OH$, K_2CO_3, MeCN, reflux, 6 h; d) AcOH/THF/H_2O (3:1:1), 40 °C, 4 h; e) TBDPSCl, imidazole, CH_2Cl_2, 1 h; f) Dess–Martin periodinane, CH_2Cl_2, 1 h; g) TFA/CH_2Cl_2 (1:10), 0 °C, 1 h; h) $ClCO_2iBu$, Et_3N, Et_2O, 0 °C, 10 min, then CH_2N_2, 90 min. Ms = methanesulfonyl.

24[20] proceeded uneventfully over three steps (hydrolytic removal of the acetonide, selective silylation of the primary alcohol, and Dess–Martin oxidation) in 81 % overall yield. After exposure of the *tert*-butyl ester **24** to TFA, the corresponding mixed anhydride was generated in situ and treated with diazomethane to give the target α-diazoketone **26** in 55 % yield in two steps. It is noteworthy that the ^1H and ^{13}C NMR spectra of the γ-ketocarboxylic acid intermediate indicated that one discernible tautomer existed as a 3.7:1 mixture of diastereomers in $CDCl_3$. This observation revealed a large equilibrium preference for the "closed" hemiacylal structure **25**, despite the potential for ring–chain tautomerism. The modest yield of the overall process might be a result of this tautomerization of **25**, which could prevent the quantitative formation of the mixed anhydride.

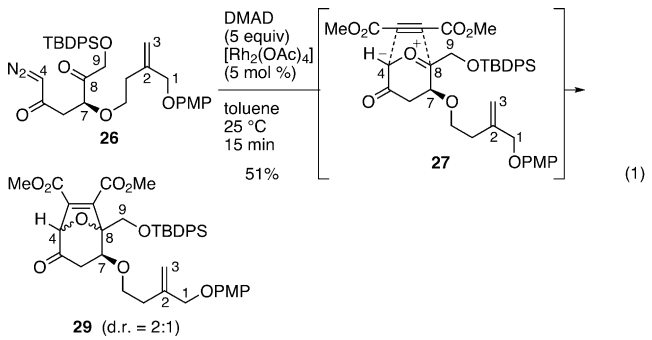
Construction of the trioxatetracyclic ring system: Having completed the synthesis of α-diazoketone **26**, we then addressed the critical carbonyl ylide formation/intramolecular 1,3-dipolar cycloaddition sequence. The reaction involved the dropwise addition of a solution of α-diazoketone **26** over a 3 min period to a solution of 5 mol % Rh^{II} catalyst. We first investigated a $[Rh_2(OAc)_4]$-catalyzed reaction in toluene. Although the α-diazoketone was consumed within 1 h at room temperature, a complex mixture of products was obtained (Table 1, entry 1). In contrast, intermolecular reac-

Table 1. Intramolecular 1,3-dipolar cycloaddition triggered by a Rh^{II} catalyst.



Entry	Rh^{II} catalyst	Solvent	T [°C]	t [min]	Yield [%]
1	$[Rh_2(OAc)_4]$	toluene	25	60	complex mixture
2	$[Rh_2(OAc)_4]$	toluene	60	5	36
3	$[Rh_2(OAc)_4]$	toluene	110	5	68
4	$[Rh_2(OAc)_4]$	benzene	80	5	57
5	$[Rh_2(OAc)_4]$	$(CH_2Cl)_2$	80	5	31
6	$[Rh_2(OAc)_4]$	$PhCF_3$	100	5	73
7	$[Rh_2(OCOC_7H_{15})_4]$	$PhCF_3$	100	5	trace
8	$[Rh_2(OCOC_3F_7)_4]$	$PhCF_3$	100	5	complex mixture
9	$[Rh_2(OCOCPh_3)_4]$	$PhCF_3$	100	5	24
10	$[Rh_2(NHAc)_4]$	$PhCF_3$	100	5	41

tion with dimethyl acetylenedicarboxylate (DMAD) occurred under identical conditions to give a 2:1 mixture of cycloadducts **29** in 51 % yield [Eq. (1)]. This result clearly indicates the formation of carbonyl ylide **27** from **26** under these conditions. We speculate that a) the carbonyl ylide **27** cannot adopt the folded conformation **27a** at room temperature and/or b) compared to DMAD, the unactivated 1,1-disubstituted olefin in **26** is not sufficiently reactive as a dipolarophile. This hypothesis was validated by the observation that when the reaction was performed at 60 °C, the desired cycloadduct **28**[20] was formed as a single isomer in 36 %



yield (Table 1, entry 2), and by the finding that the product yield was improved to 68% by an increase in reaction temperature to 110°C (Table 1, entry 3). Solvent screening revealed that aromatic solvents were superior to dichloroethane and that α,α,α-trifluorotoluene was the optimal solvent[21] for this transformation due to the low electron density of the aromatic ring, which could prevent formation of cycloheptatriene byproduct **30** resulting from a Büchner reaction (Table 1, entries 3–6). A series of rhodium(II) complexes were next evaluated for their ability to catalyze the reaction in α,α,α-trifluorotoluene at 100°C. Although the reaction of α-diazoketone **26** proceeded to completion within 5 min in all cases, employment of catalysts other than $[Rh_2(OAc)_4]$ resulted in low yield (Table 1, entries 6–10). Under the optimized conditions, the cycloaddition could be performed on a 500 mg scale in 70% yield. It is noteworthy that three of the four stereocenters (C2, C4, and C8) in the natural products were established in a single operation through internal asymmetric induction from the C7 stereocenter. Interestingly, ^{1}H NMR NOE correlation between C6-H_a and C7-H suggested that the dihydropyranone ring in cycloadduct **28** would adopt a boat-like conformation in which the H_a-C6-C7-H dihedral angle is approximately 90° (Figure 1). This conformational analysis was supported by

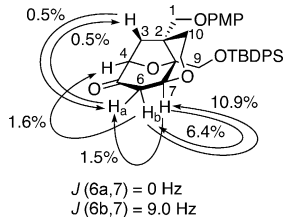
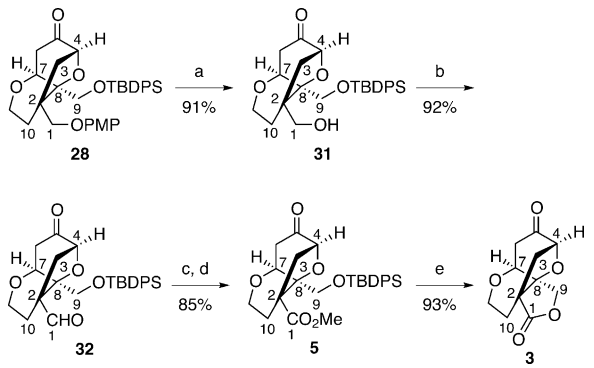


Figure 1. NOE interactions observed with cycloadduct **28**.

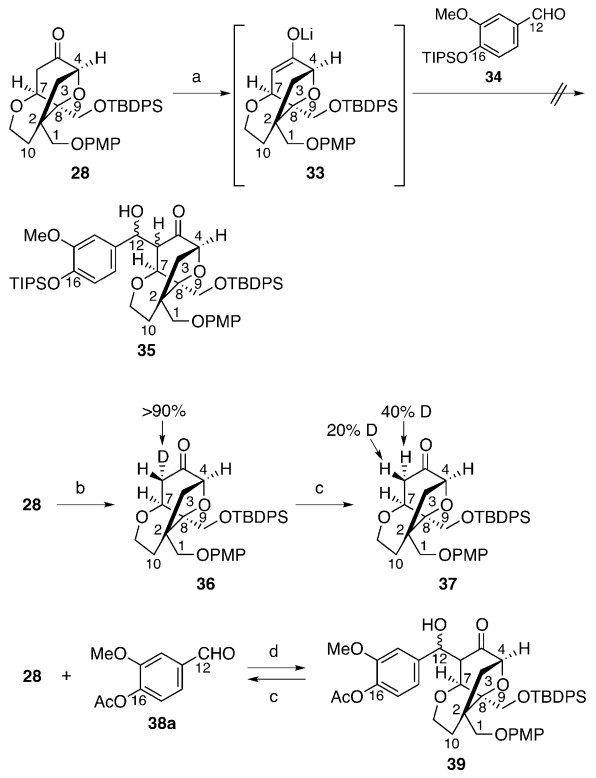
observed vicinal coupling constants between the C6 and C7 protons (J(6a,7) = 0 Hz and J(6b,7) = 9.0 Hz).

With the cycloadduct **28** in hand, the remaining operations necessary for construction of the tetracyclic ring system involved the formation of the five-membered lactone. Oxidative removal of the PMP group with cerium(IV) ammonium nitrate (CAN)[22] buffered with pyridine[23] in aqueous MeCN, furnished alcohol **31** in 91% yield (Scheme 4). The resultant alcohol **31** was oxidized with Dess–Martin periodinane to afford aldehyde **32** in 92% yield, which, upon further oxidation with $NaClO_2$ and subsequent esterification with CH_2N_2, gave methyl ester **5** in 85% yield in two steps. Finally, treatment of TBDPS ether **5** with AcOH-buffered Bu_4NF in THF effected desilylation and lactonization to provide tetracyclic compound **3** in 93% yield.



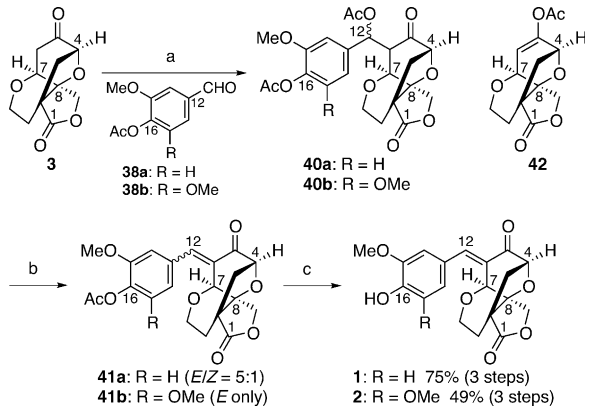
Scheme 4. Synthesis of tetracyclic lactone **3**. Reagents and conditions: a) $(NH_4)_2Ce(NO_3)_6$, pyridine, aq. MeCN, 0°C, 2 h; b) Dess–Martin periodinane, CH_2Cl_2, 2 h; c) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, aq. *t*BuOH, 6 h; d) CH_2N_2, Et_2O, 0°C, 30 min; e) Bu_4NF, AcOH, THF, 20 h.

Completion of the total synthesis of polygalolides A and B: Having constructed the common tetracyclic core of the natural products, all that remained to complete the total synthesis was installation of the arylmethylidene moiety. We first performed exploratory experiments using cycloadduct **28** lacking the lactone ring (Scheme 5). An attempt to couple ketone **28** and triisopropylsilyl (TIPS)-protected vanillin **34**[24] under basic conditions resulted in no reaction and clean recovery of starting materials. Deuterium quenching experiments and ^{1}H NMR spectroscopic analysis of the crude product revealed that lithium enolate **33** was generated from ketone **28** upon treatment with lithium diisopropylamide (LDA) and that deuterium incorporation occurred in a stereoselective manner to produce **36**. However, appreciable deuterium loss and epimerization during purification of **36** by preparative thin-layer chromatography (TLC) were observed, suggesting that tricyclic ketone **28** is prone to enolization. Although the exact origin of this propensity is unclear at the present time, it was speculated that the aldol product **35** underwent retro aldolization upon warming to room temperature after quenching with saturated aqueous NH_4Cl. Switching protection of the phenolic C16 hydroxyl group from a TIPS ether to an acetate gave aldol adduct **39**, although analysis of the unpurified reaction mixture by ^{1}H NMR spectroscopy revealed approximately 10% conversion. Furthermore, changing the metal counterion to zinc resulted in an increase in conversion to approximately 20% (as judged by ^{1}H NMR spectroscopic analysis). However, we were disappointed to find that aldol product **39** reverted to the starting materials **28** and **38a**[25] during purification by silica gel. From these results, a decision was made to trap the alkoxide formed by the aldol reaction in situ with an electrophile such as Ac_2O to prevent the retro aldol reaction.



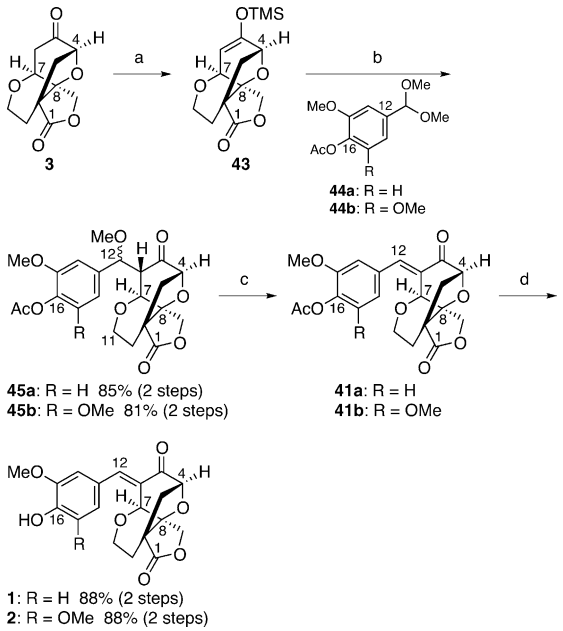
Scheme 5. Exploratory experiments using ketone **28**. Reagents and conditions: a) LDA, THF, −78 °C, then aldehyde **34**; b) LDA, THF, −78 °C, then D_2O, −78 °C to RT; c) SiO_2, EtOAc/hexane; d) LDA, $ZnCl_2$, THF, −78 °C, then aldehyde **38a**.

Gratifyingly, desired product **40a** could be obtained when the zinc enolate derived from tetracyclic ketone **3** was reacted with aldehyde **38a** at −78 °C for 30 min, followed by addition of Ac_2O and gradual warming to room temperature (Scheme 6). Because purification of β-acetoxyketone **40a** by silica gel chromatography caused partial elimination of the C12 acetoxy group (probably due to the enolization-prone carbonyl group), the crude mixture was exposed to silica gel in CH_2Cl_2 for 24 h, affording enone **41a** as a 5:1 mixture of *E*/*Z* isomers.[26] It should be noted that these isomers were in equilibrium, as judged by two-dimensional TLC. For this reason, only low-molecular-weight impurities such as excess aldehyde **38a** were removed by gel permeation chromatography at this stage for the final deprotection event. Deacetylation of **41a** was successfully performed with K_2CO_3 in MeOH to afford polygalolide A (**1**) in 75% yield for the three-step sequence. No evidence for the presence of the (*Z*)-stereoisomer of **1** was found, suggesting that olefin isomerization occurred during deacetylation. This speculation was supported by an experiment using acetate **41a** (*E*/*Z* = 1:4), wherein polygalolide A (**1**) was obtained as the sole product.



Scheme 6. Completion of the total synthesis of polygalolides A (**1**) and B (**2**). Reagents and conditions: a) LDA, $ZnCl_2$, THF, −78 °C, 1 h, aldehyde **38a** or **38b** (2 equiv), 30 min, then Ac_2O, −78 °C to RT, 16 h; b) SiO_2, CH_2Cl_2, 24 h; c) K_2CO_3, MeOH.

Following the same reaction sequence, polygalolide B (**2**) could be synthesized from ketone **3** and aldehyde **38b**,[27] however, the overall yield was only 49%. The low efficiency of the sequence was caused by incomplete conversion of the aldol coupling, wherein enol acetate **42** was obtained in approximately 20% yield. Whereas this result could be attributed to the poor electrophilicity of **38b**, the use of aldehyde having a trifluoromethanesulfonate at C16 instead of **38b** gave polygalolide B in 35% overall yield (aldol reaction, β-elimination and deprotection of the trifluoromethanesulfonyl (Tf) group with Bu_4NF[28] in THF).[29] We considered that the application of an irreversible reaction could improve the efficacy of the coupling process. Thus, tetracyclic ketone **3** was converted into the corresponding trimethylsilyl (TMS) enol ether **43** using TMSOTf and Et_3N in preparation for the Mukaiyama aldol-type reaction (Scheme 7).[30]

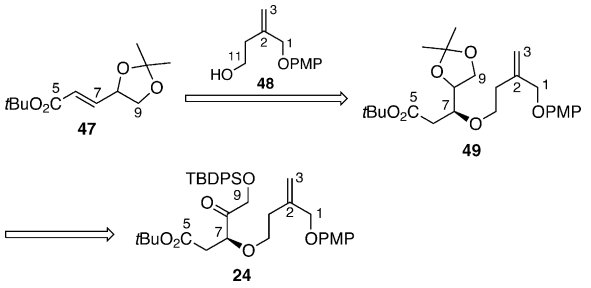


Scheme 7. Conversion of tetracyclic ketone **3** to polygalolides A (**1**) and B (**2**) through a Mukaiyama aldol-type reaction. Reagents and conditions: a) TMSOTf, Et_3N, CH_2Cl_2, 0 °C, 5 h; b) acetal **44a** or **44b** (2 equiv), TMSOTf, pulverized 3 Å MS, CH_2Cl_2, 0 °C, 15 min; c) DBU, CH_2Cl_2, 10 min; d) K_2CO_3, MeOH. MS = molecular sieves.

Initial attempts to couple silyl enol ether **43** with dimethyl acetal **44a** by either $BF_3{\cdot}OEt_2$, (*i*PrO)$TiCl_3$ or $Sc(OTf)_3$ met with failure. After considerable experimentation, we found that the TMSOTf-promoted reaction[31] proceeded at −78 °C to give coupling product **45a**[32] in 70 % yield from ketone **3**. The yield of the two-step process was improved to 85 % at a higher temperature of 0 °C (Scheme 7). Elimination of the methoxy group was effected by short exposure (10 min) of the product **45a** to DBU in CH_2Cl_2,[33] and subsequent deacetylation using K_2CO_3 in MeOH gave polygalolide A (**1**) in 88 % yield in two steps. In the same manner, and in approximately the same yields, silyl enol ether **43** was united with dimethyl acetal **44b**[34] and the product **45b** was advanced to polygalolide B (**2**) (Scheme 7). Although application of the Mukaiyama aldol-type reaction did not offer advantages in the synthesis of **1**, the overall yield from **3** to **2** (71 %) could be dramatically improved by applying the four-step sequence.

The synthetic compounds proved to be identical to natural products as judged by ^1H and ^{13}C NMR, IR, UV and HRMS analyses. Their specific rotations were equal in sign; however, the magnitudes ($[\alpha]_D = -499.9$ ($c = 0.022$ in MeOH) and −505.2 ($c = 0.018$ in MeOH), respectively) were inconsistent with those observed for natural polygalolides A and B ($[\alpha]_D = -14.4$ ($c = 0.018$ in MeOH) and −21.3 ($c = 0.015$ in MeOH), respectively), indicating the possibility that the natural products are biosynthesized in near-racemic form.

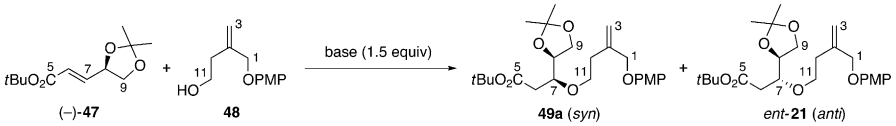
Improved synthesis of intermediate 24: Although the stereocontrolled total synthesis could be realized by taking advantage of the carbonyl ylide cycloaddition strategy, the overall length (29 steps from D-arabinose) left room for improvement. We therefore wanted to develop an improved synthesis of polygalolides. Because the length of the sequence was due, in part, to the transformations required for installation of the C2=C3 olefin that functioned as a dipolarophile in the 1,3-dipolar cycloaddition, we considered that conjugate addition of alcohol **48** to enoate **47** would shorten the synthetic route to γ-ketoester **24** (Scheme 8). In this regard, Mulzer and co-workers reported diastereoselective conjugate addition reactions of sodium alkoxides to enoate **47**, wherein the preferential formation of *syn* adducts was documented.[35] However, the corresponding alcohols were employed as solvents in all cases, and the reaction with a less reactive alkoxide (sodium benzylate) resulted in only modest diastereoselectivity (*syn*/*anti* = 76:24) due to the high temperature (−10 °C) that was required for the reaction to take place. The difficulty of using solid **48** as a solvent together with the lack of sufficient reactivity of the alkoxide derived from **48** for the reaction at low temperatures prompted us to explore the optimal conditions for the reaction of enoate (−)-**47**[36,37] with alcohol **48**.[39]



Scheme 8. Synthetic plan based on conjugate addition of an alcohol nucleophile.

Initial attempts to effect the reaction using NaH as a base in either THF or 1,2-dimethoxyethane (DME) at −23 °C and at a concentration of the enoate (−)-**47** of 0.1 M provided a mixture of coupling products **49a** and *ent*-**21** in moderate combined yield and poor stereoselection (Table 2, entries 1 and 2). Solvent screening revealed that, although low yields were obtained, good to high *syn* selectivities were achieved in Et_2O, toluene, and CH_2Cl_2, with CH_2Cl_2 being the optimal solvent (**49a**/*ent*-**21** = 27.0:1; Table 2, entries 3–5); it should be noted that CH_2Cl_2 is not normally used in this type of reaction.[40] Despite the improvement in chemical yield (21→60 %), the use of elevated temperature led to

Table 2. Conjugate addition of alcohol **48** to enoate (−)-**47**.

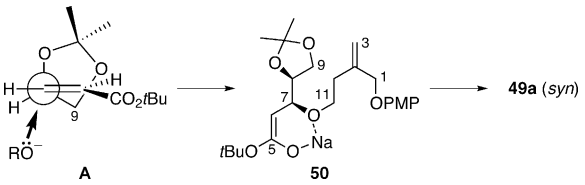


Entry	Base [equiv]		Solvent	*c* [M]	*T* [°C]	*t* [h]	Yield [%]	Recov. [%] (−)-**47**	Ratio[a] **49a**/*ent*-**21**	Entry	Base [equiv]		Solvent	*c* [M]	*T* [°C]	*t* [h]	Yield [%]	Recov. [%] (−)-**47**	Ratio[a] **49a**/*ent*-**21**
1	NaH	1.5	THF	0.1	−23	4	55	23	1:1.5	7	BuLi	1.5	CH_2Cl_2	0.1	−23	48	–	100	–
2	NaH	1.5	DME	0.1	−23	4	61	21	1:2.1	8	KH	0.3	CH_2Cl_2	0.1	−23	48	76	16	8.3:1
3	NaH	1.5	Et_2O	0.1	−23	24	39	27	6.3:1	9[b]	NaH	3.0	CH_2Cl_2	0.1	−23	48	79	17	26.7:1
4	NaH	1.5	toluene	0.1	−23	24	45	33	13.5:1	10	NaH	1.5	CH_2Cl_2	0.2	−23	48	70	25	22.9:1
5	NaH	1.5	CH_2Cl_2	0.1	−23	48	21	75	27.0:1	11	NaH	1.5	CH_2Cl_2	0.2	−23	72	77	17	20.7:1
6	NaH	1.5	CH_2Cl_2	0.1	0	48	60	24	6.0:1	12	NaH	1.5	CH_2Cl_2	0.2	−23	144	82	12	16.6:1

[a] Determined by HPLC analysis (column, Zorbax® Sil, 4.6×250 mm; eluent, 6 % THF in hexane; flow rate, 1.0 mL min^{-1}); $t_R = 18.6$ (*ent*-**21**, *anti*), 21.4 min (**49a**, *syn*). [b] Using 3 equiv of alcohol **48**. (Recov. = recovered).

a decline in the stereoselectivity (Table 2, entries 5 vs. 6). Of the bases screened, NaH proved the best in terms of stereoselectivity (Table 2, entries 6–8). When the amounts of both alcohol **48** and NaH were increased from 1.5 to 3.0 equiv, a higher yield (79%) was obtained (Table 2, entries 5 vs. 9). Chemical yield (70%, 93% based on recovered starting material) was also improved by increasing the concentration of enoate (−)-**47** from 0.1 to 0.2 M (Table 2, entry 10). From these results, we decided to perform the reaction at a concentration of 0.2 M using 1.5 equiv of alcohol **48** for reasons of synthetic economy. It is noteworthy that erosion of the *syn* selectivity was observed with extended reaction times (Table 2, entries 10–12), indicating that the excellent selectivity comes about as a result of kinetic control.[41]

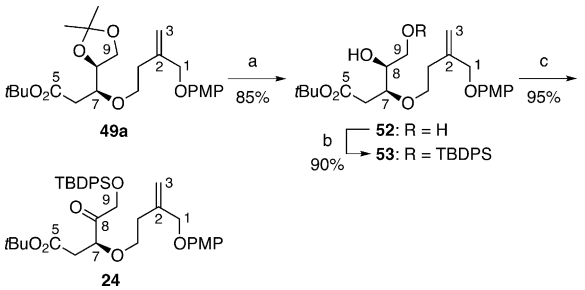
As is reported in the literature,[35] the stereochemical course of the hetero-Michael reaction can be rationalized by Felkin–Anh model **A**, wherein the electron-withdrawing alkoxy group is aligned *anti* to the forming bond and the sterically unencumbered hydrogen atom occupies the outside position (Scheme 9). Because enolate **50**, thus formed,



Scheme 9. Stereochemical model for the predominant formation of *syn*-isomer **49a**.

is capable of internal chelation with the β-heteroatom, isomerization through a retro-Michael reaction is presumably retarded by the use of a nonpolar solvent such as CH_2Cl_2, leading to the predominant formation of *syn*-isomer **49a**.[42]

After chromatographic separation of adducts **49a** and *ent*-**21**, major isomer **49a** was subjected to the same series of transformations that was performed on acetonide **21**, to afford **24** in 73% overall yield (Scheme 10). Ketone **24**, thus obtained, was identical in all respects to the material prepared by using the previous sequence. The improved route to ketone **24** proceeds with 11 fewer steps and considerably



Scheme 10. Conversion of **49a** into ketone **24**. Reagents and conditions: a) AcOH/THF/H_2O (3:1:1), 40 °C, 6 h; b) TBDPSCl, imidazole, CH_2Cl_2, 30 min; c) Dess–Martin periodinane, CH_2Cl_2, 1 h.

higher efficiency (49 vs. 21% overall yield) compared with the previous route.

Plausible biosynthetic pathway: Given the lack of information in the literature regarding the biosynthesis of polygalolides, a search for natural products with similar molecular architecture was performed. Although the CAS database contains no records of tetracyclic compounds similar to polygalolides, the 8-oxabicyclo[3.2.1]octan-2-one skeleton, which is a partial structure of polygalolides, could be found in three natural products **54**–**56** (Figure 2).[44] We also found that ex-

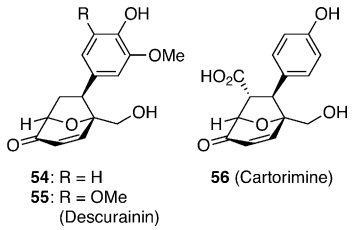
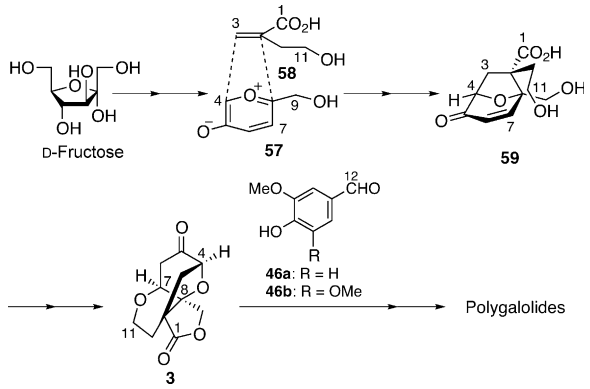


Figure 2. Natural products having an 8-oxabicyclo[3.2.1]octan-2-one skeleton.

tremely short, racemic syntheses of these molecules had been reported by Snider and Grabowski.[45] They demonstrated that [5+2] cycloaddition of an oxypyrylium zwitterion,[46,47] generated from a pyranulose derivative, with either styrenes or a cinnamate ester proceeded in a regio- and diastereoselective manner to provide 8-oxabicyclo[3.2.1]oct-3-en-2-one derivatives, which were deprotected to give natural products **54**–**56** in 24, 27 and 13% overall yields, respectively. Because the pyranulose derivative is generated by dehydration and oxidation of fructose, they suggested that these natural products would be biosynthesized by similar [5+2] cycloaddition of achiral compounds, and that the small $\Delta\varepsilon$ for **54** and the small $[\alpha]_D$ values for **55** and **56** indicate asymmetric induction during cycloadditions in chiral environments. Recently, Peterson and co-workers reported that compound **54** was obtained from glucose, glycine, and ferulic acid in a simulated baking model system.[48] This result suggests that, under these conditions, the oxypyrylium zwitterion was generated from glucose and glycine by Amadori degradation followed by dehydration and cyclization, and was trapped by 2-methoxy-4-vinylphenol, a decarboxylated product of ferulic acid. On the basis of the reasonable proposal by the Snider group, we speculated that polygalolides could be synthesized in the medicinal plant through cycloaddition of oxypyrylium zwitterion **57** with an isoprene derivative such as **58**, followed by intramolecular hetero-Michael addition, lactone formation, and aldol reaction with vanillin derivative **46** (Scheme 11). Our results clearly reveal that poor enantiofacial differentiation (3–4% *ee*) occurs in the cycloaddition event.[49] After the publication of our preliminary communication in 2006,[5] a biomimetic, two-step synthetic approach to tetracyclic compound (±)-**3** was developed by the Snider group.[50,51]



Scheme 11. Plausible biogenesis of polygalolides.

Conclusion

Stereocontrolled total synthesis of polygalolides A (**1**) and B (**2**) has been achieved. The synthesis proceeded in 25 steps and produced polygalolides A (**1**) and B (**2**) in 6.4 and 6.1% overall yields, respectively, from known alcohol **8** (4.2 and 4.0% overall yields, respectively, 29 steps from D-arabinose). The synthesis illustrates the power of the carbonyl ylide cycloaddition methodology, which enables rapid assembly of the unusual dioxatricyclic ring system, which is otherwise difficult to construct. The synthetic sequence could be greatly shortened by exploiting the hetero-Michael reaction of the alkoxide nucleophile, wherein the use of CH_2Cl_2 as a solvent plays a pivotal role in achieving high *syn* selectivity. To the best of our knowledge, this is the first report of a diastereoselective, intermolecular hetero-Michael reaction of an alkoxide to an enoate without using an excess amount of alcohol. The improved route is much more efficient in terms of overall yield than the previous approach. As a consequence, total syntheses of polygalolide A (**1**) and B (**2**) can be realized in 16 steps with overall yields of 13 and 12%, respectively, from known enoate (−)-**47** (9.8 and 9.3% overall yields, respectively, 18 steps from commercially available (−)-methyl (*S*)-2,2-dimethyl-1,3-dioxolane-4-carboxylate) by this route.

Comparison of the specific rotations indicates that the natural products would be biosynthesized in near-racemic form. Our total synthesis serves to provide a stereochemical insight into the biogenesis of this class of natural products.

Acknowledgements

This research was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan. We also acknowledge the Japan Society for the Promotion of Science for graduate fellowships to Y. S. We are grateful to Professor Xiaoyi Wei for providing spectra of natural products. We thank Ms. Hiroko Matsumoto, Ms. Akiko Maeda, Ms. Seiko Oka, Ms. Miwa Kiuchi, and Mr. Tomohiro Hirose of the Center for Instrumental Analysis, Hokkaido University, for technical assistance in mass and elemental analysis.

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[32] Coupling product **45a** was obtained as a mixture of two diastereomers; the stereochemistry at C6 was verified by the ^{1}H NOE correlation between C6-H and C11-H.
[33] Prolonged exposure of **45a** to DBU led to partial formation of (*Z*)-**41a**, indicating that olefin isomerization occurs under basic conditions.
[34] Dimethyl acetal **44b** was prepared in 91% yield from 4-hydroxy-3,5-dimethoxybenzaldehyde (**46b**) by the following two-step sequence: 1) $HC(OMe)_3$, TsOH, MeOH, reflux, 2.5 h; 2) Ac_2O, Et_3N, CH_2Cl_2, 12 h.
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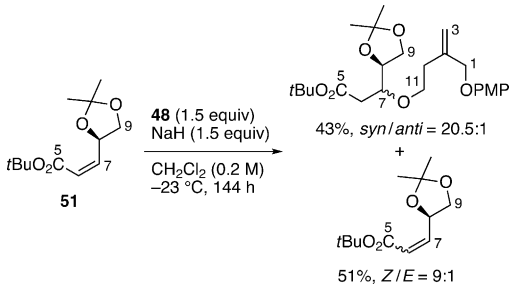
[40] The beneficial effect of CH_2Cl_2 in base-mediated reactions finds precedent in our synthesis of zaragozic acids; see reference.[8l]
[41] In an effort to attain the equilibrium, isomers **49a** and *ent*-**21** were enolized with $NaN(TMS)_2$ (1 equiv) in THF at −78 °C, followed by treatment with sodium alkoxide derived from **48** (1.5 equiv) at −23 °C for 96 and 48 h, respectively. Nearly identical ratios (1:1.8 and 1:2, respectively) of isomers **49a** and *ent*-**21** were obtained under these conditions.
[42] Compared with (*E*)-enoate (−)-**47**, the reaction of the corresponding (*Z*)-isomer **51**[43] with alcohol **48** was extremely sluggish under the optimal conditions. Even after 144 h, a diastereomeric mixture of adducts **49a** and *ent*-**21** was obtained in only 43% yield in a ratio of 20.5:1, favoring the *syn*-isomer **49a**, and a 9:1 *Z*/*E* mixture of enoates **51** and (−)-**47** was recovered.



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Received: February 18, 2012
Revised: May 2, 2012
Published online: July 3, 2012

