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A Short, Formal, Biomimetic Synthesis of (±)-Polygalolides A and B

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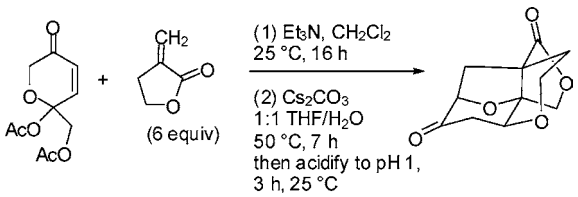
ABSTRACT

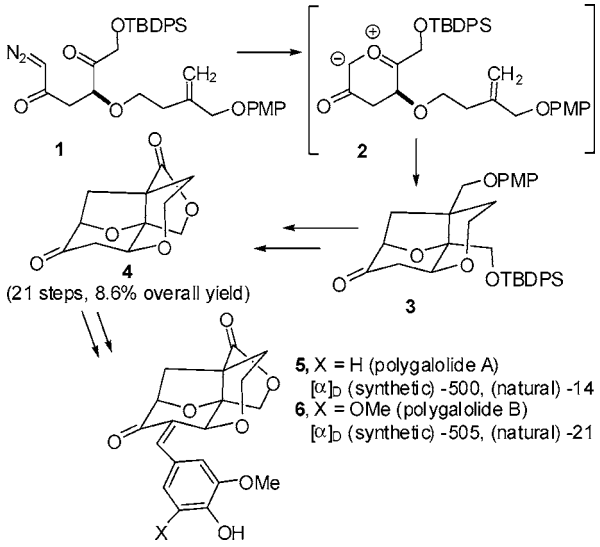


Reaction of bisacetoxy pyranone 9 with Et_3N gave 3-oxidopyrylium ylide 10, which underwent a stereo- and regiospecific [5 + 2] cycloaddition with α-methylenebutyrolactone to afford 16 (34%). Treatment of 16 with Cs_2CO_3 resulted in hydrolysis of the lactone and acetate and conjugate addition of the hydroxyethyl group to the enone. Lactonization on acidification afforded 4 (57%), completing a two-step, formal synthesis of polygalolides A and B.

Some of us (S. N. and S. H.) recently reported the synthesis of polygalolides A (**5**) and B (**6**).[1] The key step was the rhodium-catalyzed conversion of diazo ketone **1** to carbonyl ylide **2**, which underwent an intramolecular 1,3-dipolar cycloaddition to give **3** in 73% yield. Further elaboration gave key intermediate **4**, which was converted in four steps to polygalolides A (**5**) and B (**6**) (Scheme 1). This route afforded optically pure **4** in 8.6% overall yield in 21 steps. Remarkably, synthetic polygalolides A (**5**) and B (**6**) had much higher rotations, $[\alpha]_D$ −500 and −505, respectively, than the natural products, $[\alpha]_D$ −14 and −21, respectively.[2] These values indicate that the enantiomeric excess of natural polygalolides A and B is only 3−4%.

One of us (B. B. S.) recently disclosed biomimetic syntheses of descurainin (**13b**) and cartorimine (**14**) (Scheme 2).[3] 5-Acetoxymethylfurfural (**7**), which is derived from fructose, was reduced to the alcohol, which was treated with bromine in methanol to give pyranone **8** in 80% yield. Acetylation afforded bisacetoxy pyranone **9**. Treatment of **9**

Scheme 1. Synthesis of Polygalolides A and B



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(1) Nakamura, S.; Sugano, Y.; Kikuchi, F.; Hashimoto, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 6532−6535.
(2) Ma, W.; Wei, X.; Ling, T.; Xie, H.; Zhou, W. *J. Nat. Prod.* **2003**, *66*, 441−443.
(3) (a) Snider, B. B.; Grabowski, J. F. *Tetrahedron Lett.* **2005**, *46*, 823−825. (b) Snider, B. B.; Grabowksi, J. F. *Tetrahedron* **2006**, *62*, 5171−5177.

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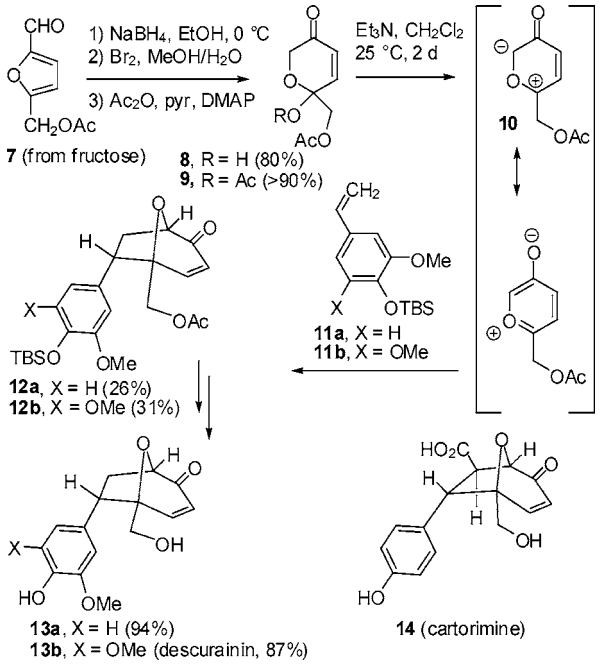
Scheme 2. Syntheses of Descurainin and Cartorimine



with Et_3N in CH_2Cl_2 at 25 °C afforded 3-oxidopyrylium ylide **10**, which underwent stereospecific [5 + 2] cycloadditions with styrenes **11a** and **11b** to give cycloadducts **12a** (26%) and **12b** (31%), respectively. Deprotection afforded the natural products **13a** and descurainin (**13b**), respectively. Cycloaddition of **10**, generated thermally from **9**, with methyl *p*-acetoxycinnamate afforded cartorimine (**14**) after deprotection.[3]

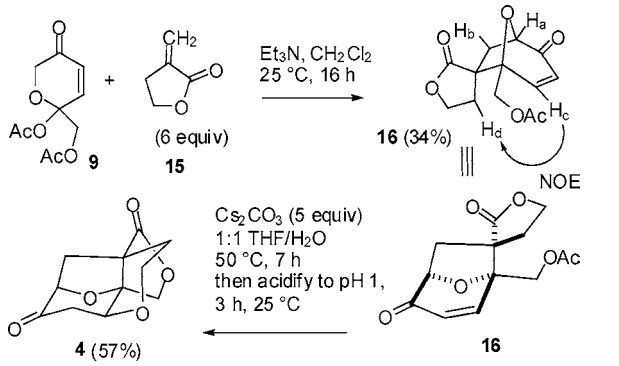
The natural products **13a**, descurainin (**13b**), and cartorimine (**14**) are probably biosynthesized by similar [5 + 2] cycloadditions of achiral compounds but were isolated with small $[\alpha]_D$ (+1.7 for **13b**, −2.6 for **14**) and $\Delta\epsilon$ (+0.01 for **13a**), indicating that they are not completely racemic. However, a [5 + 2] cycloaddition in a chiral environment could lead to an optically enriched product. A similar intermolecular [5 + 2] cycloaddition of an 3-oxidopyrylium ylide lacking the acetate protecting group of **10** with an isoprenoid fragment analogous to **15** might be involved in the biosynthesis of polygalolides A and B, which were isolated in only 3−4% enantiomeric excess.[1]

This biomimetic route can be carried out very efficiently providing a short route to the late polygalolide intermediate **4**. We were surprised and delighted to find that treatment of bisacetoxypyranone **9** with 2.5 equiv of Et_3N and 6 equiv[4] of α-methylenebutyrolactone (**15**) in CH_2Cl_2 for 16 h at 25 °C provided the desired [5 + 2] cycloadduct **16** with ~90% selectivity in 34% yield.[5] We had not expected such a high degree of stereocontrol based on the limited literature precedent.[6] The regiochemistry of the cycloaddition follows from the 8.6 Hz coupling constant between H_a and H_b. The stereochemistry was established by the NOE between H_c and H_d.

Conversion of **16** to the polygalolide intermediate **4** requires hydrolysis of the lactone and acetate, conjugate addition of the hydroxyethyl side chain to the enone, and lactonization of the hydroxy acid. This was accomplished by stirring **16** with Cs_2CO_3 in 1:1 THF/H_2O at 50 °C for 7 h, cooling to 25 °C, acidification to pH 1, and stirring for 3 h to effect lactonization giving **4** (57%) with ^1H and ^{13}C NMR spectra identical to those previously described.[1] The analogous reaction in 1:1 acetone/H_2O[7] at 25 °C for 20 h provided **4** in 50% yield. Reaction of **16** with KOH or K_2CO_3 in MeOH/H_2O afforded **4** in only 20−30% yield.

This sequence converts **9** and **15** to the late intermediate **4** in the polygalolides A and B synthesis in only two steps and 19.4% overall yield, making these natural products readily available (Scheme 3). The efficiency and stereoselectivity of this sequence supports the suggestion, originally based on the low enantiomeric excess of the natural products,[1] that these natural products are biosynthesized by an analogous [5 + 2] cycloaddition.

Scheme 3. Biomimetic Two-Step Synthesis of **4**



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Supporting Information Available: Full experimental details and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) The yield decreased to 24% and 9% with 3 and 1 equiv of **15**, respectively.

(5) The minor impurity could not be separated or characterized.

(6) See the Supporting Information for references to [5 + 2] cycloadditions of 3-oxidopyrylium ylides.

(7) Luppi, G.; Tomasini, C. *Synlett* **2003**, 797−800.