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

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Abstract

Reaction of bisacetoxypyranone **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 4 steps to polygalolides A (**5**) and B (**6**). 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 cartormine (**14**).³ 5-Acetoxyethylfurfural (**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 bisacetoxypyranone **9**. Treatment of **9** 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 cyclo-adducts **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 cartormine (**14**) after deprotection.³

The natural products **13a**, descurainin (**13b**), and cartormine (**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.

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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 Et₃N and 6 equiv⁴ of α -methylenebutylolactone (**15**) in CH₂Cl₂ 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 regio-chemistry 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 Cs₂CO₃ in 1:1 THF/H₂O 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 ¹³C NMR spectra identical to those previously described.¹ The analogous reaction in 1:1 acetone/H₂O⁷ at 25 °C for 20 h provided **4** in 50% yield. Reaction of **16** with KOH or K₂CO₃ in MeOH/H₂O 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. The efficiency and stereo-selectivity 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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References

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2. Ma W, Wei X, Ling T, Xie H, Zhou W. *J Nat Prod* 2003;66:441–443. [PubMed: 12662111]
3. (a) Snider BB, Grabowski JF. *Tetrahedron Lett* 2005;46:823–825. (b) Snider BB, Grabowski JF. *Tetrahedron* 2006;62:5171–5177.
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.

Scheme 1.
Synthesis of Polygalolides A and B

Scheme 2.
Syntheses of Descurainin and Cartorimine

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