Total Synthesis of the Proposed Structure for Pyragonicin

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ABSTRACT



The total synthesis of acetogenin 1 reported for pyragonicin and its 10-epimer 32 is described. The common THP ring system was stereoselectively constructed through a Sml₂-induced reductive cyclization of β -alkoxy acrylate 5 followed by Mitsunobu inversion, and each chiral center at C-10 was created by Brown's asymmetric allylation. Compound 1 had spectroscopic data consistent with that of natural pyragonicin, but a different optical rotation.

The annonaceous acetogenins from the Annonaceae plants comprise a class of almost 400 natural products that exhibit a remarkably broad spectrum of biological properties such as anticancer, antiinfective, immunosuppressive, pesticidal, and antifeedant activities.¹ Structurally, most of these compounds belong to several classic types with an unsubstituted tetrahydrofuran (THF) ring: the mono-THF, the adjacent bis-THF, and the nonadjacent bis-THF acetogenins. Recently, several nonclassical acetogenins have been discovered bearing a tetrahydropyran (THP) ring.² Pyragonicin, which was isolated from the stem bark of *Goniothalamus*

giganteus Hook. f. & Thomas (Annonaceae), is a new member of the family.³ The structure was elucidated by chemical and spectral means to be **1** possessing an axial hydroxyl group on the THP ring. The acetogenin was active in the BST assay⁴ and showed a selective inhibitory effect against PACA-2 (pancreatic cancer) cell lines.

Recently, we have been engaged in synthetic studies on the THP-acetogenins, resulting in the total synthesis of mucocin, jimenezin, muconin, and pyranicin.⁵ As part of our continuing studies in this field, we describe herein the first total synthesis of **1** and its 10-epimer **32** and the comparison of their analytical data with those reported for pyragonicin.

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Our synthetic strategy directed toward 1 was based on a convergent process involving the Wittig reaction of aldehyde $2^{6.5f}$ with phosphonium salt 3 as illustrated in Scheme 1.⁷



The chiral center at the C-10 position of **3** was to be introduced by asymmetric allylation⁸ to the THP aldehyde **4**. Construction of the 14,18-*syn*-17,18-*cis*-THP ring system would be achieved by SmI₂-induced reductive cyclization⁹ of the β -alkoxy acrylate **5** having a formyl group followed by stereoinversion at the C-17 position. The acrylate **5** would be prepared through a chain extension of 2,3-*O*-isopropylidene-D-threitol (**6**) reported by Kotsuki et al.¹⁰ In addition, this strategy would enable us to make the C-10 epimer **32** through a change in the chiral ligand.

The synthesis of **3** began with the triflation of threitol derivative **7** (Scheme 2).¹¹ The resulting triflate reacted with allylmagnesium bromide in the presence of copper bromide to give olefin **8** in 83% yield. Lemieux–Johnson oxidation of **8** afforded an aldehyde, which was transformed into methyl acetal **9**. After benzylation of **9**, the benzyl ether **10**

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was subjected to transacetalization¹² to give the thioacetal **11** in 98% yield. Oxy-Michael addition of **11** to ethyl propiolate followed by dethioacetalization of **12** afforded the key intermediate **5** in 82% yield. SmI₂-induced reductive cyclization of **5** was effected by treatment with 2.5 equiv of SmI₂ in the presence of methanol (3.0 equiv) in THF at 0 °C to give THP ester **13** in 86% yield. The stereochemistry around the THP ring system was established by NMR analysis of the corresponding acetate **13a**, including NOE

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experiments. Thus, irradiation of H14 resulted in enhancement of the H18 peak. In the ¹H NMR (CDCl₃) spectra of 13a, the signal corresponding to the proton of C-18 was observed at 3.82 ppm as a triplet of doublets ($J_{17,18} = 9.6$ Hz). These data were consistent with the proposed structure for 13. The high stereoselectivity is attributable to chelation control.^{5f} To accomplish stereoinversion at the C-17 position, the ester 13 was hydrolyzed under basic conditions, giving the corresponding carboxylic acid. Treatment of this with diethyl azodicarboxylate¹³ in the presence of Ph₃P led to formation of a y-lactone ring, affording bicyclic compound 14 in 96% yield from 13. After DIBAL reduction of 14, the resulting hemiacetal underwent Wittig reaction to give olefin 15 in 98% vield. Methoxymethylation of 15 followed by hydrogenation gave diol 16 in 95% yield. Selective tosylation of 16 was achieved by the action of p-TsCl and triethylamine in the presence of Bu₂SnO¹⁴ to afford monotosylate 17. Upon treatment with potassium carbonate, 17 gave epoxide 18 in 79% yield from 16.

Nucleophilic addition of allylmagnesium chloride to **18** in the presence of copper iodide gave alcohol **19** in 77% yield (Scheme 3). This compound was converted into aldehyde **4** via **20** in 85% yield (2 steps). Brown's asymmetric allylation of **4** proceeded nicely to give the desired α -alcohol **21** in 91% yield.¹⁵ The newly created stereochem-

istry and the optical purity (93% de) were determined by the modified Mosher's method of the corresponding MTPA esters. After methoxymethylation of 21, the resulting compound 23 was subjected to ozonolysis and subsequent reductive workup with NaBH4 in one pot to provide alcohol 24 in 91% yield. Iodination of 24 afforded 25, which was treated with Ph₃P in acetonitrile at 60 °C, giving the phosphonium salt 3 in high yield. Construction of the complete carbon skeleton of 1 relied on the Wittig reaction as follows. Generation of the Wittig reagent derived from 1.0 equiv of 3 and 0.95 equiv of sodium bis(trimethylsilyl)amide in THF at 0 °C followed by addition of 2 at -78 °C provided coupling product 27 in 44% yield. Finally, hydrogenation of 27 using the Wilkinson catalyst afforded lactone 29, in which all of the hydroxy protecting groups were removed by HCl to produce 1 in high yield. ¹H and ¹³C NMR spectral data of synthetic 1 were in good agreement with the reported data of the natural product. Their specific optical rotations, however, showed sharp contrast. Whereas synthetic **1** showed $[\alpha]^{24}_{D}$ +13.8 (c 0.11, CHCl₃), the $[\alpha]^{23}_{D}$ value of natural 1 was reported to be -25.6 (c 0.008, CHCl₃). The discrepancy suggested synthetic 1 was possibly an enantiomer of natural product. The assignment of the relative and absolute configuration of the seven stereocenters of natural pyragonicin was based on NMR measurements including Mosher ester methodology.¹⁶ Therefore, we prepared the corresponding MTPA esters (30 and 31) from 1 and carried out extensive NMR analyses. Table 1 lists the comparisons of ¹H NMR data.¹⁷ In (R)-MTPA derivatives, NMR spectral

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⁽¹⁵⁾ Reaction without a chiral ligand gave a 1:1 mixture of epimers.

Table 1.	¹ H NMR	Data ((δ)	for	Compounds	30,	31,	33,	and 34
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		(R)-MTPA ester		(S)-MTPA ester			
position	natural	30	33	natural	31	34	
3	2.57, 2.67	2.58, 2.66	2.59, 2.67	2.54, 2.60	2.54, 2.59	2.54, 2.58	
4	5.34	5.34	5.35	5.30	5.30	5.28	
5	1.56	1.53, 1.62	1.50, 1.63	1.61	1.60, 1.67	1.54, 1.63	
10	5.02	4.90	4.90	4.99	5.01	5.05	
13	4.99	5.00	4.95	5.02	4.99	5.09	
14	3.48	3.48	3.41	3.38	3.41	3.46	
15	1.26, 1.32	1.26	1.14, 1.21	1.32, 1.40	1.19, 1.34	1.21, 1.40	
16	1.70, 2.07	1.70, 2.07	1.69, 2.04	1.58, 2.05	1.68, 2.06	1.71, 2.07	
17	5.02	5.02	5.02	4.99	4.98	4.99	
18	3.40	3.40	3.38	3.32	3.32	3.34	
19	1.35, 1.42	1.36, 1.43	1.36, 1.41	1.14, 1.25	1.15, 1.20	1.15, 1.21	
33	6.95	6.95	6.95	6.73	6.73	6.72	
34	4.91	4.90	4.90	4.86	4.85	4.85	
35	1.30	1.30	1.30	1.27	1.28	1.28	

data of synthetic **30** were quite similar to those of the natural derivative except for the chemical shift of H-10. In contrast, the four signals for H-10, -13, -14, and -15 of 31 deviated by 0.02–0.13 ppm compared with the respective signals of the (S)-MTPA ester derived from natural pyragonicin in the ¹H NMR spectrum. These results suggested a difference in the stereochemistry around the C-10 position and prompted us to prepare the corresponding 10-epimer 32. Asymmetric allylation of the intermediate 4 using (-)-B-methoxydiisopinocamphenylborane afforded the epimer 22 in 95% yield (92% de). According to the procedure for the preparation of 3, the alcohol 22 was transformed into phosphonium salt 26 in 77% overall yield (4 steps). Wittig reaction of 26 with 2 afforded 28 in 43% yield. Hydrogenation of 28 followed by deprotection reaction provided the C-10 epimer **32** { $[\alpha]^{21}_{D}$ +16.8 (*c* 0.30, CHCl₃)} in 79% yield from **28**. ¹H and ¹³C NMR spectral data of **32** were not matched with those of the natural product. Similarly, ¹H NMR data of the corresponding MTPA esters (33 and 34) were different from those of naturally derived esters (Table 1). On the basis of the present data, it should be mentioned that reported spectral data of pyragonicin are quite similar to those of structure 1 rather than 32. However, there is a discrepancy in the magnitude and sign of the optical rotation for the natural

product and compound 1.¹⁸ These results prevent us from unequivocally stating that natural pyragonicin and compound 1 are identical. To clarify this, a direct comparison of our synthetic sample with the authentic natural product is necessary. We provide complete ¹³C NMR assignments¹⁷ including methylene carbons around oxygenic functional groups for synthetic compounds 1 and 32, which would also be useful to discuss the structure of natural pyragonicin.

In summary, we have succeeded in a convergent synthesis of 1 and its 10-epimer 32, employing the SmI_2 -induced radical cyclization reaction of 5 and coupling reaction between 2 and 3 or 26 as the key steps.

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Supporting Information Available: Experimental procedures and NMR spectra of 1, 3–5, 8–34, and 13a. This material is available free of charge via the Internet at http://pubs.acs.org.

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