ORGANIC LETTERS

2005
Vol. 7, No. 13
2783−2786

Total Synthesis of the Proposed Structure for Pyragonicin

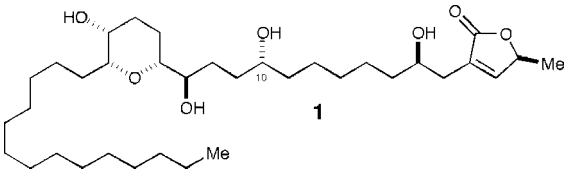
Shunya Takahashi,*,† Narihito Ogawa,† Hiroyuki Koshino,† and Tadashi Nakata*,‡

RIKEN (The Institute of Physical and Chemical Research), Wako, Saitama 351-0198, Japan, and Department of Chemistry, Faculty of Science, Tokyo University of Science, 1-3, Kagurazaka, Shinjuku-Ku, Tokyo 162-8601, Japan

shunyat@postman.riken.go.jp; nakata@rs.kagu.uts.ac.jp

Received April 14, 2005

ABSTRACT



1

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 SmI_2-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 assay[4] 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.

† RIKEN.
‡ Tokyo University of Science.

(1) For recent reviews, see: (a) Zafra-Polo, M. C.; Gonzalez, M. C.; Estornell, E.; Sahpaz, S.; Cortes, D. *Phytochemistry* **1996**, *42*, 253−271. (b) Zeng, L.; Ye, Q.; Oberlies, N. H.; Shi, G.; Gu, Z.-M.; He, K.; McLaughlin, J. L. *Nat. Prod. Rep.* **1996**, *13*, 275−306. (c) Zafra-Polo, M. C.; Figadere, B.; Gallardo, T.; Tormo, J. R.; Cortes, D. *Phytochemistry* **1998**, *48*, 1087−1117. (d) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504−540 and references therein.

(2) (a) Shi, G.; Alfonso, D.; Fatope, M. O.; Zeng, L.; Gu, Z.-M.; Zhao, G.-X.; He, K.; MacDougal, J. M.; McLaughlin, J. L. *J. Am. Chem. Soc.* **1995**, *117*, 10409−10410. (b) Shi, G.; Kozlowski, J. F.; Schwedler, J. T.; Wood, K. V.; MacDougal, J. M.; McLaughlin, J. L. *J. Org. Chem.* **1996**, *61*, 7988−7989. (c) Chavez, D.; Acevedo, L. A.; Mata, R. *J. Nat. Prod.* **1998**, *61*, 419−421. (d) Fall, D.; Duval, R. A.; Gleye, C.; Laurens, A.; Hocquemiller, R. *J. Nat. Prod.* **2004**, *67*, 1041−1043.

(3) Alali, F. Q.; Rogers, L.; Zhang, Y.; McLaughlin, J. L. *Tetrahedron* **1998**, *54*, 5833−5844.

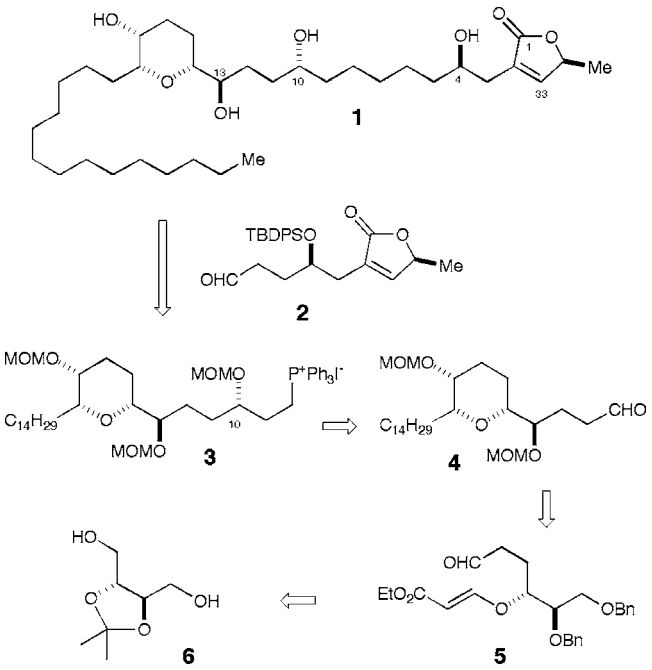
(4) Alali, F.; Zeng, L.; Zhang, Y.; Ye, Q.; Hopp, D. C.; Schwedler, J. T.; McLaughlin J. L. *Bioorg. Med. Chem.* **1997**, *5*, 549−555.

(5) (a) Takahashi, S.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 723−726. (b) Takahashi, S.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 727−730. (c) Takahashi, S.; Maeda, K.; Hirota, S.; Nakata, T. *Org. Lett.* **1999**, *1*, 2025−2028. (d) Takahashi, S.; Fujisawa, K.; Sakairi, N.; Nakata, T. *Heterocycles* **2000**, *53*, 1361−1370. (e) Takahashi, S.; Nakata, T. *J. Org. Chem.* **2002**, *67*, 5739−5752. (f) Takahashi, S.; Kubota, A.; Nakata, *Angew. Chem., Int. Ed.* **2002**, *41*, 4751−4754. (g) Takahashi, S.; Kubota, A.; Nakata, T. *Tetrahedron Lett.* **2002**, *43*, 8661−8664. (h) Takahashi, S.; Kubota, A.; Nakata, T. *Tetrahedron* **2003**, *59*, 1627−1638. (i) Takahashi, S.; Kubota, A.; Nakata, T. *Org. Lett.* **2003**, *5*, 1353−1356.

10.1021/ol0508126 CCC: $30.25
Published on Web 06/02/2005

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]

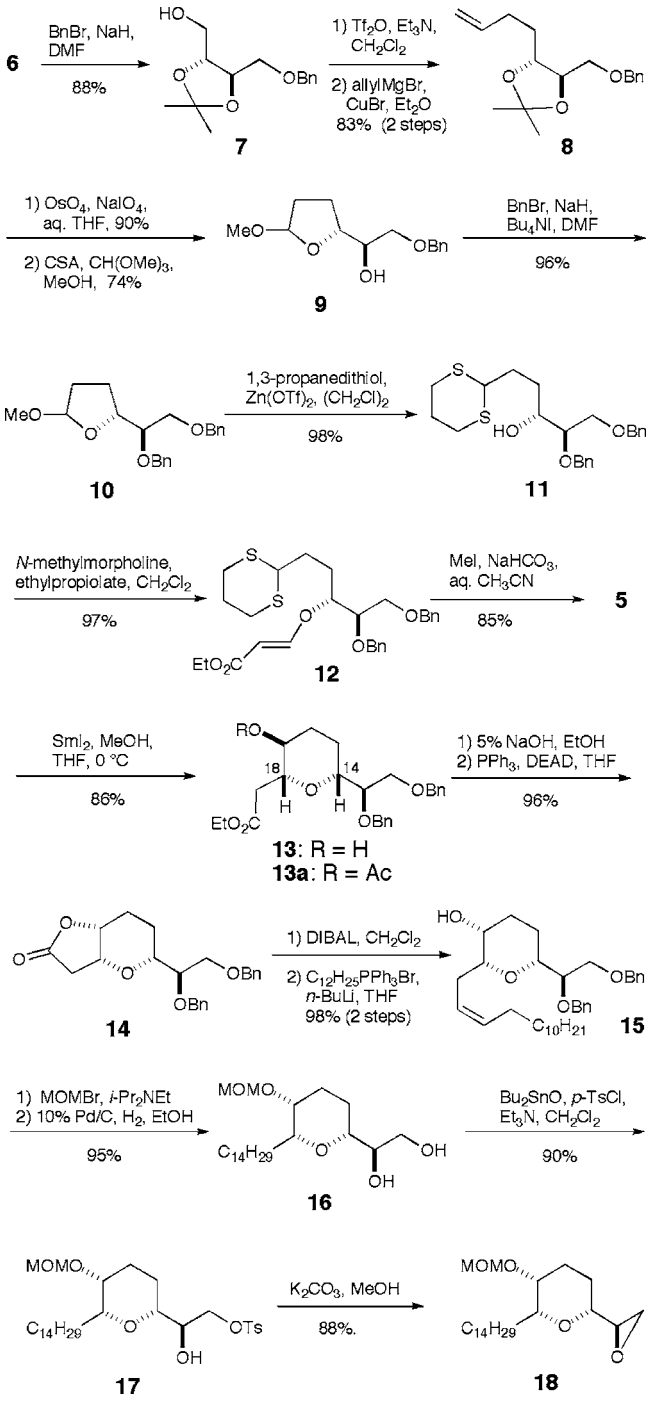
Scheme 1



The chiral center at the C-10 position of **3** was to be introduced by asymmetric allylation[8] to the THP aldehyde **4**. Construction of the 14,18-*syn*-17,18-*cis*-THP ring system would be achieved by SmI_2-induced reductive cyclization[9] 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**

Scheme 2



was subjected to transacetalization[12] 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. SmI_2-induced reductive cyclization of **5** was effected by treatment with 2.5 equiv of SmI_2 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

(6) Sinha, S. C.; Sinha, A.; Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1997**, *119*, 12014−12015.

(7) The numbering system in ref 3 was adopted.

(8) (a) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092−2093. (b) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1987**, *52*, 319−320.

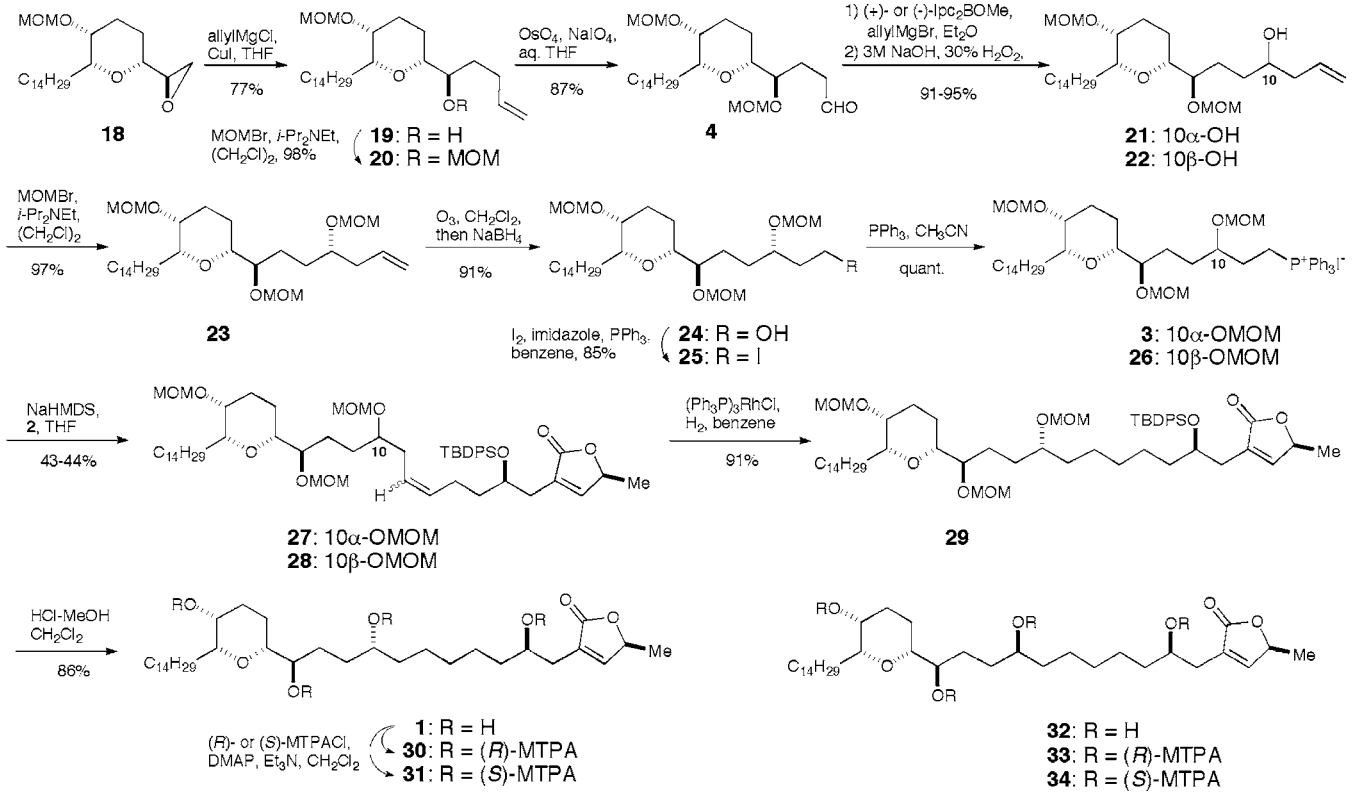
(9) (a) Hori, N.; Matsukura, H.; Matsuo, G.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 2811−2814. (b) Matsuo, G.; Hori, N.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 8859−8863. (c) Hori, N.; Matsukura, H.; Nakata, T. *Org. Lett.* **1999**, *1*, 1099−1101. (d) Hori, N.; Matsukura, H.; Matsuo, G.; Nakata, T. *Tetrahedron* **2002**, *58*, 1853−1864. (e) Matsuo, G.; Kadohama, H.; Nakata, T. *Chem. Lett.* **2002**, 148−149.

(10) (a) Kotsuki, H.; Kadota, I.; Ochi, M. *J. Org. Chem.* **1990**, *55*, 4417−4422. (b) Kotsuki, H.; Kadota, I.; Ochi, M. *Tetrahedron Lett.* **1990**, *31*, 4609−4612.

(11) Schnurrenberger, P.; Hungerbühler, E.; Seebach, D. *Tetrahedron Lett.* **1984**, *25*, 2209−2212.

(12) Corey, E. J.; Shimoji, K. *Tetrahedron Lett.* **1983**, *24*, 1289−1292.

Scheme 3



experiments. Thus, irradiation of H14 resulted in enhancement of the H18 peak. In the ^{1}H NMR ($CDCl_3$) 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 azodicarboxylate[13] in the presence of Ph_3P led to formation of a γ-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% yield. 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 Bu_2SnO[14] 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 stereochemistry 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 $NaBH_4$ in one pot to provide alcohol **24** in 91% yield. Iodination of **24** afforded **25**, which was treated with Ph_3P 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. ^{1}H and ^{13}C 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, $CHCl_3$), the $[\alpha]^{23}_D$ value of natural **1** was reported to be −25.6 (*c* 0.008, $CHCl_3$). 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 ^{1}H NMR data.[17] In (*R*)-MTPA derivatives, NMR spectral

(13) Mitsunobu, O. *Synthesis* **1981**, 1−28.
(14) Martinelli, M. J.; Nayyar, N. K.; Moher, E. D.; Dhokte, U. P.; Pawlak, J. M.; Vaidyanathan, R. *Org. Lett.* **1999**, *1*, 447−450.
(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**

	(*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 ^{1}H 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, $CHCl_3$)} in 79% yield from **28**. ^{1}H and ^{13}C NMR spectral data of **32** were not matched with those of the natural product. Similarly, ^{1}H 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 ^{13}C NMR assignments[17] 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.

Acknowledgment. This work was supported by the Chemical Biology Project (RIKEN). We are grateful to Ms. K. Harata for mass spectral measurements and Dr. T. Chihara and his staff in RIKEN for the elemental analyses.

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.

OL0508126

(16) In annonaceous acetogenins bearing a hydroxyl group at C-4, it is reported that this method could give the information in relation to the stereochemistry of the methine proton at C-34 as well as the hydroxyl groups. See: Hoye, T. R.; Hanson, P. R.; Hasenwinkel, L. E.; Ramirez, E. A.; Zhuang, Z. *Tetrahedron Lett.* **1994**, *35*, 8529−8532.

(17) 2D-NMR experiments were used. See Supporting Information.

(18) Discrepancies between the optical rotations of synthesized samples and extracted samples of otherwise apparently identical compounds have occurred previously: (a) Sinha, S. C.; Sinha, S. C.; Keinan, E. *J. Org. Chem.* **1999**, *64*, 7067−7073. (b) Maezaki, N.; Kojima, N.; Sakamoto, A.; Iwata, C.; Tanaka, T. *Org. Lett.* **2001**, *3*, 429−432. (c) Reference 5i. (d) Makabe, H.; Miyawaki, A.; Takahashi, R.; Hattori, Y.; Konno, H.; Abe, M.; Miyoshi, H. *Tetrahedron Lett.* **2004**, *45*, 973−977. (e) Strand, D.; Rein, T. *Org. Lett.* **2005**, *7*, 199−202.