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Total Synthesis of a Cytotoxic Acetogenin, Pyranicin

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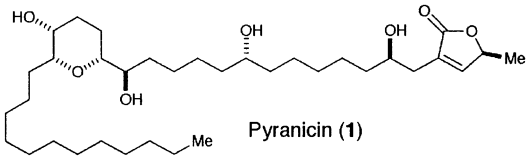
ABSTRACT



Pyranicin (**1**)

The first total synthesis of a new cytotoxic acetogenin, pyranicin (1), is described. SmI_2-induced reductive cyclization of *β*-alkoxy acrylate 4 proceeded stereoselectively to give 16,20-*syn*-19,20-*trans*-THP derivative 14, which was efficiently transformed into the 19,20-*cis*-THP derivative 18 through Mitsunobu lactonization. Wittig reaction of the phosphonium salt 2 obtained therefrom with butenolide 3 at −78 °C followed by reduction and deprotection afforded 1 in good overall yield.

Annonaceous acetogenins are a relatively new class of natural polyketides which have promising anticancer, antiinfective, immunosuppressive, pesticidal, and antifeedant properties.[1] On the basis of the number of tetrahydrofuran (THF) rings within the molecule and their connection patterns, these natural products have been classified into three major groups: mono-THF, adjacent bis-THF, and nonadjacent bis-THF subclasses. Their structural diversity and remarkable biological activities have attracted much attention of synthetic organic chemists.[2]

Recently, several new types of acetogenins bearing a tetrahydropyran (THP) ring have been discovered.[3] Pyranicin (**1**), which was isolated from the stem bark of *Goniothalamus giganteus* Hook. f. & Thomas (Annonaceae), is the first mono-THP acetogenin.[4] Structurally, **1** is related to substituted THP acetogenin such as mucocin and jimenejin, differing remarkably in the absolute configuration of the THP moiety and the presence of an axial hydroxyl group on the THP ring. The acetogenin **1** was quite active in the BST assay[5] and showed selective inhibitory effects against PACA-2 (pancreatic cancer) cell lines with potency 10 times that of adriamycin. Recently, we have been engaged in synthetic studies on the THP-acetogenins, resulting in the total synthesis of mucocin, jimenezin, and muconin.[6] As part of our continuing studies in this field, we describe herein the first total synthesis of **1** in a stereocontrolled manner.

Our retrosynthetic analysis of **1** is illustrated in Scheme 1. Thus, **1** would be synthesized by Wittig reaction of a phosphonium salt **2** with an aldehyde **3**.[7,6f] Construction of

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(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) For recent total synthesis, see: (a) Harcken, C.; Bruckner, R. *New J. Chem.* **2001**, 40−54. (b) Hu, T.-S.; Yu, Q.; Wu, Y.-L.; Wu, Y. *J. Org. Chem.* **2001**, *66*, 853−861. (c) Maezaki, N.; Kojima, N.; Sakamoto, A.; Iwata, C.; Tanaka, T. *Org. Lett.* **2001**, *3*, 429−432. (d) Burke, S. D.; Jiang, L. *Org. Lett.* **2001**, *3*, 1953−1955. (e) Dixon, D. J.; Ley, S. V.; Reynolds, D. J. *Chem. Eur. J.* **2002**, *8*, 1621−1636. (f) Makabe, H.; Hattori, Y.; Tanaka, A.; Oritani, T. *Org. Lett.* **2002**, *4*, 1083−1085 and references therein.

(3) (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. (a) Chavez, D.; Acevedo, L. A.; Mata, R. *J. Nat. Prod.* **1998**, *61*, 419−421

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

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

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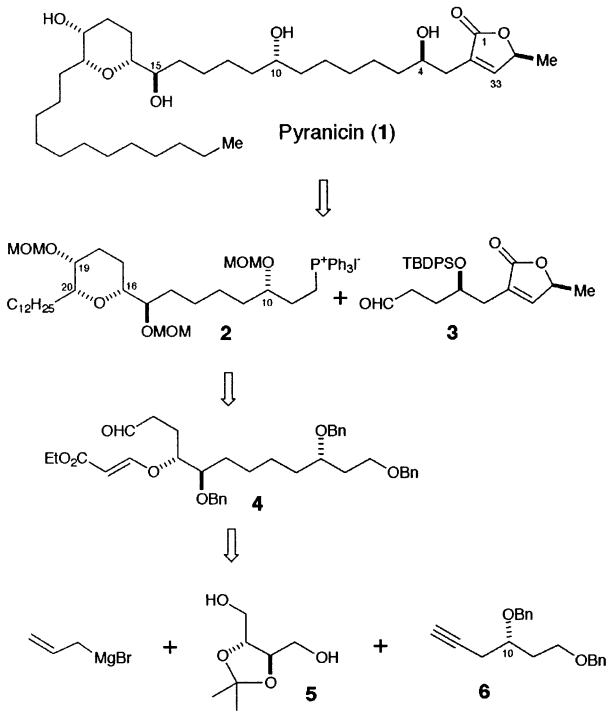
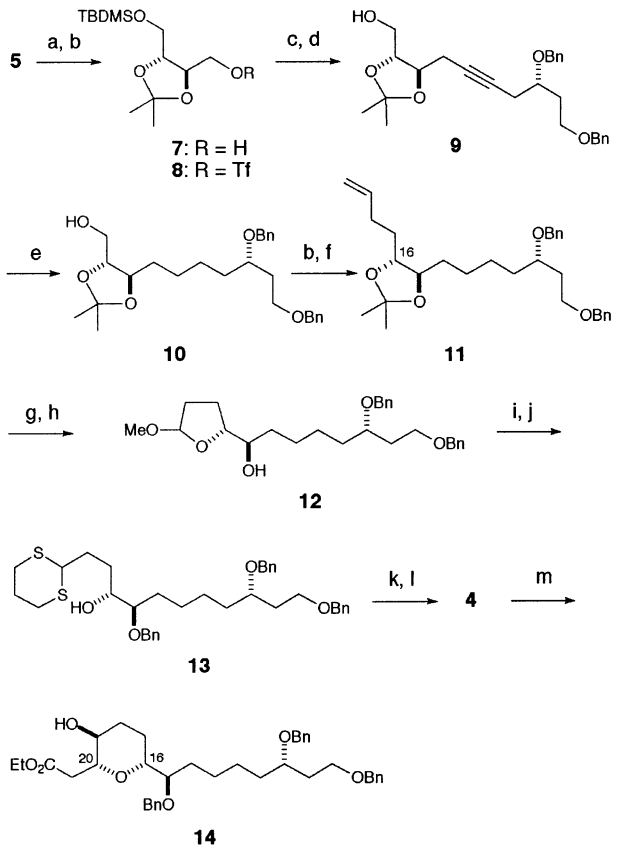
Scheme 1



the 16,20-*syn*-19,20-*cis*-THP ring system in **2** would be achieved by SmI_2-induced reductive cyclization[8] of β-alkoxy acrylate **4** having a formyl group followed by stereoinversion at the C-19 position. The acrylate **4** should be prepared through a two-directional chain extension of 2,3-*O*-isopropylidene-D-threitol (**5**) reported by Kotsuki et al.[9] For this purpose, allylmagnesium bromide and chiral acetylene **6**[10,11] were designed as synthons for the chains.

Synthesis of **2** began with triflation[12] of threitol derivative **7** (Scheme 2).[13] The resulting triflate **8** was coupled with a lithium acetylide derived from terminal acetylene **6** in the presence of *N*,*N*′-dimethylpropyleneurea (DMPU),[9b] and subsequent de-silylation with TBAF afforded alcohol **9** in 70% overall yield from **7**. Reduction of the triple bond in **9** was performed by using the Wilkinson catalyst (5.0 mol %) in benzene to give saturated compound **10** in 95% yield. The alcohol **10** was, again, converted into the corresponding triflate, which reacted with allylmagnesium bromide in the presence of cuprous bromide in ether to give a terminal olefin **11**[14] in 74% yield from **10**. For introduction of the β-alkoxy acrylate residue into the C-16 position of **11**, discrimination of two oxygen functions at the C-15 and 16 positions was needed. Therefore, olefin **11** was oxidized under Lemieux−Johnson conditions and then treated with CSA and HC-

Scheme 2[a]



[a] Reagents and conditions: (a) TBDMSCl, NaH, DME, THF, 0 °C to room temperature, 90%; (b) Tf_2O, Et_3N, CH_2Cl_2, −15 °C; (c) **6**, *n*-BuLi, DMPU, THF, −15 °C; (d) TBAF, THF, room temperature, 70% (three steps from **7**); (e) $(Ph_3P)_3RhCl$, H_2, benzene, room temperature, 95%; (f) allylMgBr, CuBr, Et_2O, −15 °C to room temperature, 74% (two steps); (g) OsO_4, $NaIO_4$, THF/H_2O, room temperature; (h) CSA, $CH(OMe)_3$, MeOH, 0 °C, 76% (two steps); (i) BnBr, NaH, Bu_4NI, DMF, 0 °C to room temperature, 98%; (j) 1,3-propanedithiol, $Zn(OTf)_2$, $(CH_2Cl)_2$, 50 °C, 97%; (k) ethylpropiolate, *N*-methylmorpholine, CH_2Cl_2, room temperature, 94%; (l) MeI, $NaHCO_3$, CH_3CN/H_2O, 0 °C to room temperature, 92%; (m) SmI_2, MeOH, THF, 0 °C, 95%.

(6) (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.

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

(8) (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.

(9) (a) Kotsuki, H.; Kadota, I.; Ochi, M. *J. Org. Chem.* **1990**, *55*, 4417−4422. (b) Kotsuki, H.; Kadota, I.; Ochi, M. *Tetrahedron Lett.* **1990**, *32*, 4609−4612.

(10) This compound was prepared from (*R*)-1,2-anhydro-4-*O*-benzylbutane-1,2,4-triol[11] in three steps as follows: (i) lithium (trimethylsilyl)-acetylide, $BF_3{\cdot}Et_2O$, THF, −78 °C; (ii) K_2CO_3, MeOH, room temperature, 91% (two steps); (iii) BnBr, NaH, *n*-Bu_4NI, DMF, 0 °C, 99%.

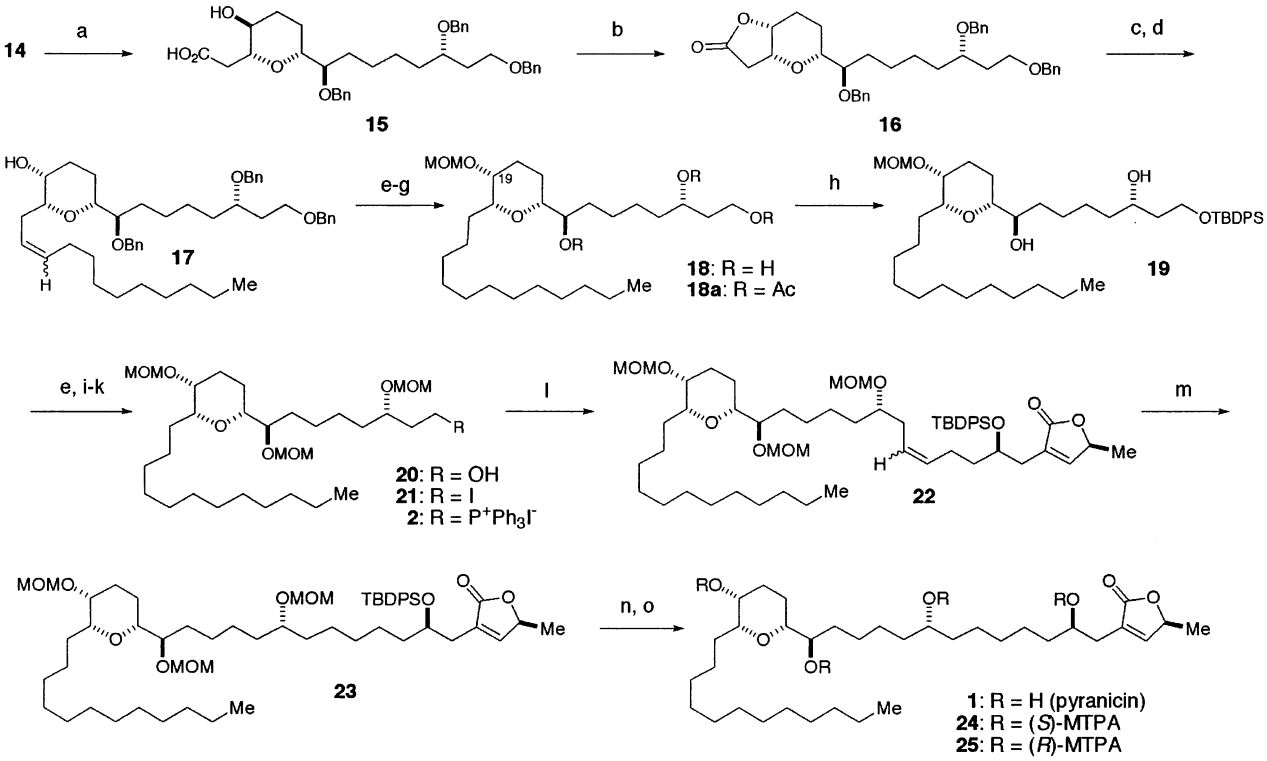
(11) Nakata, T.; Suenaga, T.; Oishi, T. *Tetrahedron Lett.* **1989**, *30*, 6525−6528.

(12) Mukai, C.; Kim, J. S.; Uchiyama, M.; Sakamoto, S.; Hanaoka, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2903−2915.

(13) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1987**, *52*, 3337−3342.

(14) Attempts for a one-pot double alkylation into the tosyltriflate of **5** gave unsatisfactory results.

Scheme 3[a]



[a] Reagents and conditions: (a) 5%NaOH, EtOH, room temperature, 97%; (b) PPh_3, DEAD, THF, 0 °C, 92%; (c) DIBAL, CH_2Cl_2, −78 °C; (d) $C_{10}H_{21}PPh_3Br$, *n*-BuLi, THF, −15 °C, 87% (two steps from **16**); (e) MOMBr, *i*-Pr_2NEt, $(CH_2Cl)_2$, 0−50 °C; (f) 10% Pd/C, H_2, EtOH, room temperature, 89% (two steps from **17**); (g) Ac_2O, DMAP, pyridine, room temperature (quant); (h) TBDPSCl, *i*-Pr_2NEt, CH_2Cl_2, room temperature, 97%; (i) TBAF, THF, room temperature, 97% (two steps from **19**); (j) I_2, PPh_3, imidazole, benzene, 0 °C, 98%; (k) PPh_3, CH_3CN, 60 °C, 93%; (l) **3**, NaHMDS, THF, −78 °C, 69%; (m) $(Ph_3P)_3RhCl$, H_2, benzene, room temperature, 88%; (n) HCl−MeOH, CH_2Cl_2, room temperature, 95%; (o) (*R*)- or (*S*)-MTPACl, DMAP, Et_3N, CH_2Cl_2, room temperature.

$(OMe)_3$ in methanol to provide acetal **12** in 76% yield. After benzylation of **12**, the benzyl ether was subjected to transacetalization[15] to give thioacetal **13** in 97% yield. Oxy-Michael addition of **13** to ethyl propiolate followed by dethioacetalization afforded the key intermediate **4** in 86% yield. SmI_2-induced reductive cyclization of **4** was effected by treatment with 3.5 equiv of SmI_2 in the presence of methanol (4.4 equiv) in THF at 0 °C to give a 16,20-*cis*-19,20-*anti*-THP derivative **14** in 95% yield. The stereochemistry around the THP ring system was established by the NMR analyses including NOE experiments. Thus, irradiation of H_{20} results in enhancement of the H_{16} peak. In the ^1H NMR (C_6D_6) spectra of **14**, the signal corresponding to the proton of C-19 was observed at 3.09 ppm as triplets of doublet ($J_{19,20}$= 9.2 Hz). These data are consistent with the proposed structure for **14**. The high stereoselectivity would be explained by the transition state via a cyclic chelate.[6f]

As we could secure the key intermediate in high yield, our attention was then turned to stereoinversion at the C-19 position (Scheme 3). To accomplish the transformation efficiently, we planned utilization of Mitsunobu lactonization.[16] Prior to the transformation, the ester **14** was hydrolyzed under basic conditions, giving carboxylic acid **15** in 97% yield. Treatment of this with diethyl azodicarboxylate in the presence of Ph_3P led to formation of a γ-lactone ring, affording bicyclic compound **16** in 92% yield. After DIBAL reduction of **16**, the resulting hemiacetal underwent Wittig reaction to give olefin **17** in 87% yield. Methoxymethylation of **17** and subsequent hydrogenation provided triol **18** in 89% yield from **17**. The stereochemistry of the C-19 position in **18** was confirmed mainly by ^1H NMR analyses of the triacetate **18a** including decoupling experiments; the spectrum of **18a** revealed the C-19 proton at δ 3.40 as a broad singlet (W_H = 6.0 Hz) and the C-20 proton at δ 3.27 as a broad doublet of doublets with $J_{20,21}$ = 8.7 Hz and $J_{20,21'}$ = 4.4 Hz. The small coupling constant of the protons at C-19 and 20 indicates the presence of an axially oriented methoxymethoxy group in the THP ring of **18a**.

Direct iodination of **18** followed by methoxymethylation (methylal-phosphorus pentaoxide) furnished iodide **21** in a low yield (31%). Therefore, a stepwise procedure was adopted for preparation of **21**. The primary hydroxyl group in **18** was temporarily protected to give silyl ether **19** in 97% yield. Hydroxy protection−deprotection sequence to **19** provided alcohol **20** in 97% yield. Iodination of **20** proceeded

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

(16) Mitsunobu, O. *Synthesis* **1981**, 1−28.

nicely to give the desired iodide **21** in 98% yield. Preparation of the phosphonium salt **2** from **21** was accomplished by heating the latter with 2.0 equiv of triphenylphosphine in acetonitrile at 60 °C, giving the phosphonium salt **2** 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 **2** and 0.95 equiv of sodium hexamethyldisilazide in THF at 0 °C followed by addition of **3** at −78 °C cleanly provided a coupling product **22** in 69% yield. The reaction at higher temperature (−20 to 0 °C) caused destruction, giving **22** in a low yield (∼35%). Finally, hydrogenation of **22** using the Wilkinson catalyst afforded a fully protected pyranicin **23** in which all the hydroxy protecting groups were removed by HCl in MeOH−CH_2Cl_2 to produce pyranicin **1** (mp 82−83 °C)[17] in high yield. ^{1}H and ^{13}C NMR spectral data of synthetic **1** were identical with those of the natural product. On the other hand, their specific optical rotations showed sharp contrast. While synthetic **1** showed $[\alpha]^{24}_D$ +19.5 (*c* 0.55, $CHCl_3$), the $[\alpha]^{23}_D$ value of natural **1** was reported to be −9.7 (*c* 0.008, $CHCl_3$). The discrepancy suggested synthetic **1** to be an enantiomer of the natural product. Therefore, we prepared the corresponding MTPA esters (**24** and **25**) from synthetic **1** and carried out extensive NMR analyses. Consequently, NMR data of the corresponding MTPA esters (**24** and **25**) were revealed to be well matched with those reported.[18] These results made us conclude that synthetic **1** should not be an enantiomer of natural product. Taking into account that the optical rotation of natural product was measured at very low concentration, the difference may be due to experimental error or the presence of impurities.[19] To clarify this, a direct comparison of our synthetic sample with the authentic natural product would be necessary.[20]

In summary, we have succeeded in a convergent synthesis of **1** employing SmI_2-induced radical cyclization reaction of **4** and coupling reaction between **2** and **3** as the key steps. This procedure would also be useful for preparation of a variety of analogues of **1**.

Acknowledgment. We are grateful to Dr. J. L. McLaughlin (Purdue University) for providing us copies of the NMR spectra of natural pyranicin. We also express our thanks to Dr. H. Koshino for measurement of 2D-NMR spectra, Ms. K. Harata for mass spectral measurements, and Dr. T. Chihara and his staff in RIKEN for the elemental analyses.

Supporting Information Available: Physical and spectroscopic data for compounds **1**, **2**, **4**, **6**, and **9**−**23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) The melting point of natural **1** is not denoted.

(18) Differences in the chemical shifts (Δ_δ) between **24** and **25** are as follows: H_2-3 (−0.03, −0.07), H_2-5 (+0.04, +0.05), H_2-6 (+0.10), H_2-14 (+0.08, +0.08), H-16 (−0.03), H_2-17 (+0.10, +0.29), H_2-18 (+0.01, +0.01), H-20 (−0.07), H_2-21 (−0.19, −0.20), H-33 (−0.23), H-34 (−0.04), H-35 (−0.02).

(19) The discrepancy with the optical rotation value of synthetic product with that reported for the natural product has been reported so far: (a) Sinha, S. C.; Sinha, S. C.; Keinan, E. *J. Org. Chem.* **1999**, *64*, 7067−7073. (b) ref 2c.

(20) Natural pyranicin was unavailable (personal communication by Dr. McLaughlin).