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An Expeditious Enantioselective Total Synthesis of Valilactone

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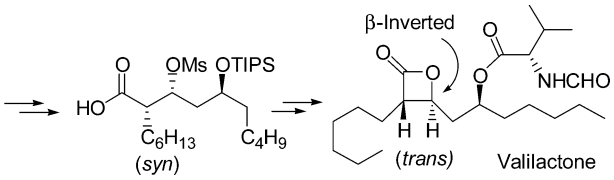

The title compound was synthesized through an expeditious route using Crimmins aldolization to establish the two key stereogenic centers and a hydroxyl group activation (HGA) protocol to construct the anti α,*β*-disubstituted *β*-lactone from the corresponding syn aldol.

Introduction

Obesity, which is always associated with increased risk of hypertension and heart disease,[1] is now broadly recognized as a new global health problem.[2] One of the so far established means to fight obesity is to inhibit pancreas lipase, an enzyme responsible for absorption of fat. Many naturally occurring *β*-lactones possess potent lipase inhibition activity, among them lipstatin after saturation of the carbon−carbon double bonds by hydrogenation has already been successfully developed into a drug (tetrahydrolipstatin **1**, marketed under the name of Orlistat or Xenical. For the structures, see Figure 1).

Valilactone (**2**) was isolated from the MG 147-CF2 strain of *Streptomyces* by Kitahara and co-workers in 1987,[3] with a structure closely related to that of **1**. Although to most researchers it is usually only known as a potent esterase inhibitor, valilactone in fact was also tested on pancreas lipase. The IC_{50} value for lipase inhibition was reported to be 0.00014 μg/mL (0.35 nM)—about 3 orders of magnitude lower than that[4] of **1** (IC_{50} = 0.36 μM)! However, the striking lipase inhibition activity of **2** was somehow completely ignored by the scientific community. While numerous studies[5] of **1** were performed since the 1980s, only one investgation on valilactone was documented in the literature.[6]

It is not clear why this happened. However, judging from the importance of developing new potent antiobesity agents and the outstanding biological activity of valilactone, we believe that valilactone deserves further studies. Here in this article we wish to report an expedient enantioselective total synthesis of natural valilactone, which exploited a lactonization through

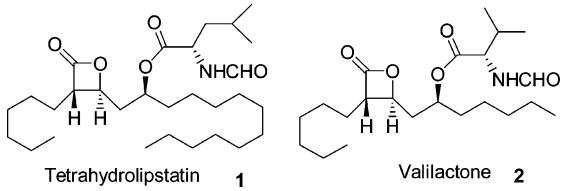

FIGURE 1. The structures of tetrahydrolipstatin and valilactone.

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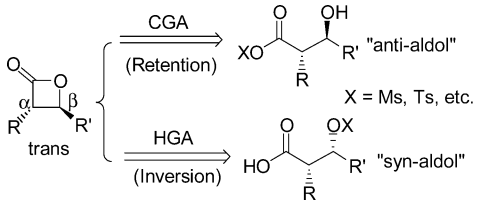


FIGURE 2. Retrosynthetic analyses of formation of the β-lactone ring, which may be constructed from either the "anti aldols" through carboxylic group activation (CGA) or the "syn aldols" through hydroxyl group activation (HGA).

hydroxyl group activation (HGA[7]) with readily accessible enantiopure syn aldol as the precursor.

Results and Discussion

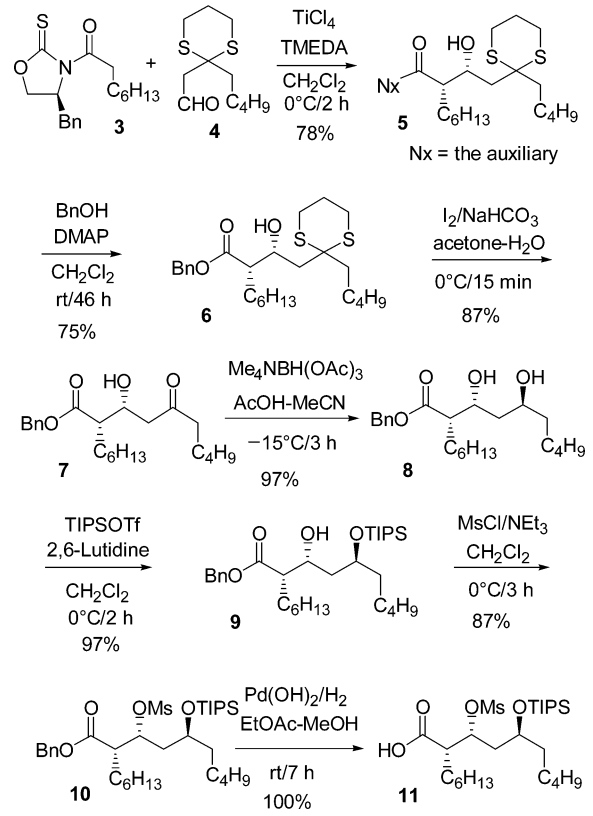
Essentially all the bio-active β-lactones so far known are α,β-disubstitued, with the two substituents on the 2-oxetanone ring trans to each other. The bioactivity of these compounds is dependent critically not only on the presence of an intact β-lactone ring but also on the absolute configurations of the stereogenic centers on the lactone ring. Therefore, construction of the trans disubstitued β-lactone moiety is one of the key issues in the synthesis of these compounds.

In principle, trans β-lactones can be derived from either anti aldols through carboxylic group activation[7] (CGA) or from syn aldols through HGA (cf. Figure 2). In practice, however, HGA is much less common than CGA, although syn aldols are readily attainable in enantiopure forms via, for instance, Evans[8] or Crimmins[9] aldolization.

From the outset of this work we planned to make use of enantiopure syn aldols as the chirality source of the stereogenic centers of the β-lactone moiety. As shown in Scheme 1, the synthesis started with a $TiCl_4$-mediated asymmetric aldol condensation[9] between **3** and **4**,[10] which afforded the syn aldol **5** as the only detectable product in 78% yield (along with 16% of recovered starting **3**). The chiral auxiliary[11a] in **5** was then nondestructively removed[11b−c] with concurrent protection of the carboxylic group as a benzyl ester. The resulting **6** was treated with I_2 in the presence[12] of $NaHCO_3$ to give ketone **7** in 87% yield.

Generation of the 1,3-anti diol motif and the subsequent selective protection of the remote hydroxyl group were done in a manner similar to that in Ghosh's[5b] synthesis of **1**. The substrate chirality induced asymmetric reduction with $Me_4NBH(OAc)_3$[13] was performed at −15 °C, which was more convenient

SCHEME 1



than −40 °C, but the diasteoemeric selectivity (22:1) was the same as that obtained at −40 °C in Ghosh's[5b] synthesis of **1**.

The diastereomers were separated on silica gel, and the remote hydroxyl group (δ to the carbonyl group) in **8** was then selectively protected[5b] with TIPSOTf ($(i\text{-Pr})_3SiOSO_2CF_3$) at 0 °C, leaving the β OH as the only open site for further transformation.

The key β-lactone functionality was constructed through a three step sequence, which was first introduced by Lenz[14a] in the synthesis of 4-methyl-oxetan-2-one (a much less hindered β-lactone with no substituent on the α-carbon and only one small methyl group on the β-carbon): (1) converting the hydroxyl group into a good leaving group by treatment with $MsCl/NEt_3$, (2) cleaving the benzyl group by hydrogenolysis under neutral conditions to release a free carboxylic group without affecting the liable β-OMs functionality, and (3) treating the newly generated carboxylic acid with a base to initiate an intramolecular S_N2 reaction, yielding a β-lactone ring with concurrent configuration inversion at the β carbon. It should be noted that in sharp contrast to the facile conversions observed in the successful literature cases,[14,15] the ring-closure of the α,β-dialkyl substituted substrates was often very tricky when the substituents

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SCHEME 2

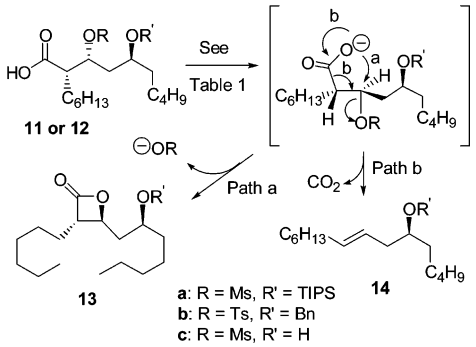


TABLE 1. Representative Results of the Lactonization Exploiting the β-Leaving/Inversion Protocol (cf. Scheme 2)[a]

entry	substituent	R/R′	conditions	results[b]
1	**11**	Ms/TIPS	DBU/THF/15 °C/1 h	A
2	**12a**	Ts/Bn	NaOH/DMSO/14 °C/1.5 h[c]	B
3	**12a**	Ts/Bn	Cs_2CO_3/Et_2O−H_2O/0 °C/18 h	B
4	**12a**	Ts/Bn	Cs_2CO_3/THF/0 °C/4 h	B
5	**12a**	Ts/Bn	NaOH[d]/THF/10 °C/5 h	B
6	**12a**	Ts/Bn	$NaHCO_3$/MeOH/0 °C/2 h	B
7	**12a**	Ts/Bn	DBU/THF/15 °C /8 h	C
8	**12b**	Ts/H	DBU/THF/0 °C/1 h	A
9	**12c**	Ms/H	DBU/THF/0 °C/0.16 h	D
10	**11**	Ms/TIPS	K_2CO_3/THF/19 °C/12 h	E

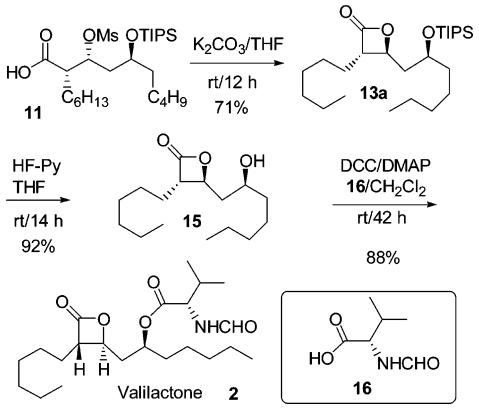
[a] The reactions were run by mixing the reactants at a lower temperature than those listed in the table and then by stirring at the stated temperature (the ambient temperature) for the stated time. [b] (A) The product mixture contained mainly **14a** and traces of the starting acid. (B) The product mixture contained mainly the unreacted starting acid and a small amount of **14b**. (C) All starting acid was consumed, yielding a ca. 33:67 mixture of **13b**/**14c**. (D) All the starting **12c** was converted into **14c**. (E) **13a** and **14a** were isolated in 71% and 25% yield, respectively. [c] Containging about 30% (v/v) of H_2O. [d] In the presence of 1 M equiv (with respect to NaOH) of 18-crown-6.

were not small simple alkyl groups. In the synthesis of nocardiolactone,[16] a compound with two very long alkyl chain on the lactone ring, we already noticed that the existing protocols (Na_2CO_3 or $NaHCO_3$ in a H_2O−Et_2O or H_2O−$CHCl_3$ biphasic medium) was applicable to only very simple/nonhindered substrates and developed a DBU-based procedure. In this work, we encountered similar difficulty again in the lactonization. It appeared that lactonization via HGA in general was far not "a solved problem" as those elegant literature examples seemingly implied.[14] The undesired product in most runs was the decarboxylation-elimination[16] compound alkene **14** (Scheme 2), which shared a common carboxylate intermediate with the lactone **13**.

Using the β-mesyloxy acid **11** or the closely related analogues **12a**−**c**, we tested a range of conditions. Some representative results are listed in Table 1. From these data it can be seen that the undesired decarboxylation-elimination product **14** was often easier to form than **13** (entries 1−6). Such products were not reported in those literature[14] cases, suggesting that changes in, for instance, the size of the substituents and the substitution pattern (β-monosubstituted or α,β-disubstituted) may significantly vary the predominating reaction path.

It is interesting to note that even the best set of conditions (DBU/THF) developed in our synthesis of nocardiolactone failed to give satisfactory results here, although the expected lactone did form in low yield (entry 7).

SCHEME 3



Removal of the protecting group R′ (which was expected to reduce the bulkiness of the chain) did not lead to any descernible improvement (entries 8 and 9). On the contrary, it facilitated generation of the undesired product **14**. It seemed that the functionality on the substituent might also have an influence on the reaction path (path a or b, Scheme 2), at least to some extent.

After numerous failures we were pleased to find that powdered K_2CO_3 in dry THF could revert the product ratio, yielding the anticipated lactone **13** as the main product (entry 10). This gratifying result allowed us to resume the synthesis along the initially designed route after the long halt.

Cleavage of the TIPS protecting group was first attempted with the classic Bu_4NF in THF. The product was a rather complicated mixture. Addition of some AcOH to the reaction system as Ghosh et al.[5b] did in their synthesis of **1** led to **15** as the only product. However, the reaction could not go to completion. Some starting **13a** always remained. Then we tried HF·Py. The initial runs were performed in commercially available THF. The best yield we obtained was around 80%. Later, by chance we attempted dry THF as the reaction solvent and found that the yield of the desilylation could be raised to 92% (Scheme 3).

At this point the only remaining task was to connect an (*S*)-*N*-formylvaline moiety to the hydroxyl group in compound **15**. In the previous synthesis[6] by Ley and co-workers, such a transformation was achieved in three steps. To improve the overall efficiency of the synthesis, in this work we tried to avoid use of any protecting group on the amino group so that the task could be fulfilled in one step. After many tries, we finally succeeded in directly combining the known (*S*)-*N*-formylvaline[17] (**16**) with **15** in the presence of DCC/DMAP,[18] affording the end product valilactone **2** in 88% yield. The physical and spectroscopic data of **2** synthesized in this work were in good consistence[19] with those reported by Ley,[6b] and the ^1H NMR spectrum looked essentially the same as that[3] published by Kitahara.

In summary we have completed an expeditious enantioselective total synthesis of natural valilactone, a potent lipase inhibitor. Two of the three stereogenic centers in the target molecule were initially constructed through chiral auxiliary induced asymmetric aldolization under the conditions of Crimmins. The third stereogenic center was established via a substrate

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chirality induced asymmetric reduction. The syn aldol derived from aldolization was eventually transformed into a trans α,β-disubstituted β-lactone via a hydroxyl group activation. Because of the predeterminable absolute configuration of the newly formed chiral centers, broad functional compatibility and low cost of the auxiliary/reagents ($TiCl_4$/TMEDA), syn aldols are chiral building blocks of great potential in both laboratory and industry. However, up to now direct use of syn aldols in the synthesis of the anti β-lactones represented by valilactone and tetrahydrolipstatin has been impossible because of the lack of a feasible HGA protocol. The present work illustrates the first successful HGA-based approach to synthesis of this class of lipase inhibiting β-lactones and may provide a solid basis for further exploration on lactonization through HGA.

Experimental Section

Synthesis of Compound 5. $TiCl_4$ (0.44 mL, 3.99 mmol) was added dropwise to a solution of **3** (1.061 g, 3.32 mmol) in dry CH_2Cl_2 (16 mL) stirred at 0 °C under N_2. After 10 min, dry TMEDA (1.65 mL, 8.3 mmol) was added dropwise. The dark solution was then stirred at 0 °C for 0.5 h before the aldehyde **4** (1.540 g, 6.64 mmol) was introduced dropwise. Stirring was continued at the same temperature for 2 h. Aqueous NH_4Cl (30 mL) was introduced, followed by diethyl ether (300 mL). The phases were separated, and the organic phase was washed in turn with aqueous NH_4Cl (50 mL × 2) and water and dried over Na_2SO_4. Removal of the solvents and the drying agent left an oily residue, which was chromatographed (9:1 to 3:1 *n*-hexane/EtOAc) on silica gel to give **5** as a pale yellow sticky oil (1.422 g, 78%): $[\alpha]^{24}_D$ +31.3° (*c* 1.05, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38−7.23 (m, 5H), 5.14 (dt, *J* = 4.4, 7.0 Hz, 1H), 4.99 (ddd, *J* = 3.6, 6.5, 9.9 Hz, 1H), 4.33−4.29 (m, 3H), 3.58 (s, 1H), 3.31 (dd, *J* = 3.0, 13.2 Hz, 1H), 3.07−2.92 (m, 2H), 2.78−2.70 (m, 3H), 2.45 (dd, *J* = 9.3, 15.1 Hz, 1H), 2.07−1.86 (m, 5H), 1.73−1.31 (m, 16H), 0.91 (t, *J* = 7.4 Hz, 3H), 0.88 (t, *J* = 7.2 Hz, 3H). FT-IR (film): 3439, 2928, 2857, 1694, 1455, 1365, 1320, 1193, 702 cm^{-1}. ESI-MS *m/z:* 574.0 ($[M + Na]^+$). ESI−HRMS: calcd for $C_{29}H_{45}NO_3S_3Na$ ($[M + Na]^+$), 574.2454; found, 574.2457.

Synthesis of Compound 8. $Me_4NBH(OAc)_3$ (386 mg, 1.47 mmol) was added to dry CH_3CN (0.9 mL) and glacial acetic acid (0.9 mL). The mixture was stirred at the ambient temperature for 0.5 h to give a solution. The solution was cooled to −15 °C and a solution of **7** (69 mg, 0.184 mmol) in dry CH_3CN (0.9 mL) was added dropwise. The mixture was stirred at −15 °C until TLC showed disappearance of the starting material (ca. 3 h). To the reaction mixture were added 0.5 N potassium sodium tartrate (3 mL) and diethyl ether (200 mL), followed by solid Na_2CO_3 (1.67 g, 15.75 mmol). The phases were separated, and the aqueous phase was back extracted with diethyl ether (30 mL × 4) after being adjusted to pH 8 with $NaHCO_3$. The combined organic phases were washed with water and brine and dried over Na_2SO_4. The solvent was removed by rotary evaporation, and the residue was chromatographed on silica gel (2:1 *n*-hexane/EtOAc) to give **8** as a colorless oil (67 mg, 97% yield): $[\alpha]^{26}_D$ −1.7° (*c* 1.20, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37−7.26 (m, 5H), 5.15 (s, 2H), 4.20−3.98 (m, 1H), 3.95−3.83 (m, 1H), 3.16 (d, *J* = 4.7 Hz, 1H), 2.53 (q, *J* = 6.8 Hz, 1H), 2.11 (s, 1H), 1.72−1.57 (m, 4H), 1.51−1.24 (m, 16H), 0.86 (t, *J* = 7.1 Hz, 6H). FT-IR (film): 3402, 2926, 2857, 1732, 1456, 1379, 1160, 697 cm^{-1}. ESI-MS *m/z:* 379.1 ($[M + H]^+$). ESI−HRMS: calcd for $C_{23}H_{38}O_4Na$ ($[M + Na]^+$), 401.2662; found, 401.2666.

Lactonization of 11 (Leading to 13a and 14a). A mixture of **11** (60 mg, 0.115 mmol) and powdered K_2CO_3 (21 mg, 0.15 mmol) in dry THF (12 mL) was stirred at the ambient temperature (ca. 19 °C) for 12 h. The reaction mixture was then diluted with diethyl ether (50 mL), washed with water and brine (10 mL each), and dried over Na_2SO_4. After removal of the solvent, the residue was chromatographed on silica gel (12:1 *n*-hexane/Et_2O) to give **13a** as a colorless oil (35 mg, 0.083 mmol, 71% yield) along with alkene **14a** (12 mg, 0.031 mmol, 25% yield). Data for **13a**: $[\alpha]^{21}_D$ −20.9° (*c* 1.05, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.48 (dt, *J* = 4.1, 6.3 Hz, 1H), 4.16−3.92 (m, 1H), 3.26 (dt, *J* = 4.1, 7.5 Hz, 1H), 2.09−1.94 (m, 2H), 1.82−1.71 (m, 2H), 1.58−1.11 (m, 16H), 1.10−0.99 (m, 21H), 0.88 (br t, *J* = 5.8 Hz, 6H). FT-IR (film): 2931, 2866, 1826, 1464, 1381, 1122, 882 cm^{-1}. EI-MS *m/z* (%): 383 (4.0), 339 (19.7), 335 (31.3), 283 (29.3), 257 (62.6), 215 (100.0), 131 (33.5), 103 (25.9), 75 (36.5), 57 (77.0), 43 (27.3). ESI-HRMS: calcd for $C_{25}H_{51}O_3Si$ ($[M + H]^+$), 427.3602; found, 427.3617. Data for **14a**: $[\alpha]^{25}_D$ −6.5° (*c* 0.45, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.44−5.40 (m, 2H), 3.85−3.75 (m, 1H), 2.27−2.17 (m, 2H), 2.10−1.93 (m, 2H), 1.57−1.19 (m, 19H), 1.06 (s, 18H), 0.88 (t, *J* = 6.6 Hz, 6H). FT-IR (film): 2927, 2866, 1464, 1106, 883, 677 cm^{-1}. EI-MS *m/z:* 381 (0.58), 339 (84.8), 297 (25.4), 257 (66.1), 215 (42.0), 131 (100), 103 (65.7), 75 (66.4), 43 (48.4). Anal. Calcd for $C_{24}H_{50}OSi$: C, 75.31; H, 13.17. Found: C, 75.41; H, 13.22.

Synthesis of Valilactone (2). A mixture of *N*-formal-L-valine (28 mg, 0.19 mmol), DCC (39 mg, 0.19 mmol), and DMAP (3 mg, 0.025 mmol) in dry CH_2Cl_2 (0.5 mL) was stirred at the ambient temperature for 10 min before a solution of **15** (34 mg, 0.126 mmol) in dry CH_2Cl_2 (0.5 mL) was introduced dropwise. The mixture was then stirred at the ambient temperature for 21 h before being diluted with diethyl ether, washed with water and brine, and dried over Na_2SO_4. After removal of the solvent, the residue was chromatographed on silica gel (1:1 *n*-hexane/EtOAc) to give **2** as a white solid (44 mg, 0.111 mmol, 88% yield). Mp: 55−56 °C (lit.[6b] 55−56 °C). $[\alpha]^{21}_D$ −33.7° (*c* 0.12, $CHCl_3$) (lit.[6b] $[\alpha]^{23}_D$ −33.6° (*c* 0.7, $CHCl_3$)). ^{1}H NMR (300 MHz, $CDCl_3$):[20] δ 8.27 (s, 1H), 6.05 (d, *J* = 8.7 Hz, 1H), 5.06−4.98 (m, 1H), 4.63 (dd, *J* = 4.8, 8.7 Hz, 1H), 4.29 (dt, *J* = 4.3, 8.6 Hz, 1H), 3.22 (dt, *J* = 4.1, 7.8 Hz, 1H), 2.30−2.10 (m, 2H), 2.04−1.96 (m, 1H), 1.84−1.50 (m, 4H), 1.42−1.20 (m, 14H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.90 (d, *J* = 6.9 Hz, 3H), 0.90−0.85 (m, 6H). FT-IR (film) 3330, 2958, 2926, 2857, 1821, 1736, 1686, 1459, 1193, 1122, 1012 cm^{-1}. ESI-MS *m/z:* 398.3 ($[M + H]^+$). ESI-HRMS: calcd for $C_{22}H_{39}NO_5Na$ ($[M + Na]^+$), 420.2720; found, 420.2719.

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Supporting Information Available: General remarks on Experimental Section, procedures for synthesis of **3**, **6**, **7**, **9**−**11**, **15**, and ^{1}H NMR spectra of **3**, **5**, **7**−**11**, **13a**, **2**, and the ^{1}H NMR spectrum (copied from the literature for comparison) of natural valilactone in pdf format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) There was a typographical error in the ^{1}H NMR data in ref 6b: the signal at δ 3.22 (1H, dt, 8.0, 4.1 Hz, H-2) should be 3.22 (1H, dt, 4.1, 8.0 Hz, H-2), because the smaller *J* value stemmed from the coupling between H-2 and H-3 (the two protons at the β-lactone ring), which is around 4 Hz when the two protons are trans to each other. Otherwise our data for **2** agreed well with those in ref 6b.

(20) It perhaps should be mentioned that in the ^{1}H NMR spectrum of both natural valilactone (ref 3) and the **2** synthesized in this work there existed some weak signals at around δ 8.01 and 3.92 (conformational isomer?), which are not included in data listing because their integrals are too small. These signals did not change after repeated chromatographic purification. They were not listed in the ref 6b but presumably also existed because the authors claimed their valilactone was identical in all aspects to Kitahara's.