A β-Lactone-Based Strategy Applied to the Total Synthesis of (8*S*,21*S*,22*S*,23*R*)- and (8*R*,21*S*,22*S*,23*R*)-Okinonellin B

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Although β-lactones undergo a number of unique and stereospecific reactions,[1] they have had limited use as intermediates in the context of natural product total synthesis.[2] This may in part be due to the lack of direct and general methods for their synthesis in optically pure form.[3] As part of a program aimed at the utilization of β-lactones as intermediates in natural product synthesis, we now report the application of a β-lactone-based strategy to the first total syntheses of (8*S*,21*S*,22*S*,23*R*)-okinonellin B (**1**) and (8*R*,21*S*,22*S*,23*R*)-okinonellin B (**2**). Isolated by Fusetani and co-workers,[4] the cytotoxin okinonellin B is a member of a family of marine furanosesterterpenes that display a variety of biological activities, including antibacterial, cytotoxic, and antispasmodic activity.[5] The reduced butenolide of okinonellin B makes it unique from other sesterterpenoids in this class of marine natural products. Fusetani described the relative stereochemistry of the butyrolactone, but the relative stereochemistry between the butyrolactone and the C8 stereocenter in addition to the absolute stereochemistry were not determined. The present synthesis demonstrates the utility of β-lactones as intermediates in the synthesis of natural products and, specifically, in the concise synthesis of all-syn-trisubstituted butyrolactones.

It was envisioned that a tandem Mukaiyama aldol−lactonization (TMAL) reaction (**6** → **5**)[6] and a tandem transacylation−debenzylation of a benzyloxy-substituted β-lactone (**5** → **4**)[7] would deliver the butyrolactone **4** in a highly stereocontrolled manner (Figure 1). A Negishi coupling of the (*R*)- and (*S*)-vinyl iodide **3** and the butyrolactone fragment **4** would then complete the synthesis in a concise fashion.[8] Both enantiomers of vinyl iodide **3** would be synthesized and coupled in order to assign the relative configuration at C8 as well as the absolute configuration of the natural product.

The synthesis of the enantiomeric vinyl iodides **3** began with two sequential alkylations of 1,3-dithiane using the readily available iodides (*S*)- and (*R*)-**8**[9] and 3-(bromomethyl)furan (**10**)[10] to give the dialkylated dithianes **11** (Scheme 1). A two-stage reduction involving Raney nickel and dissolving metal reduction with calcium cleaved the dithiane and benzyl ether and provided the alcohols **12**. Swern oxidation[11] followed by Takai reaction[12] provided the required vinyl iodides **3** for Negishi coupling to the butyrolactone **4**.

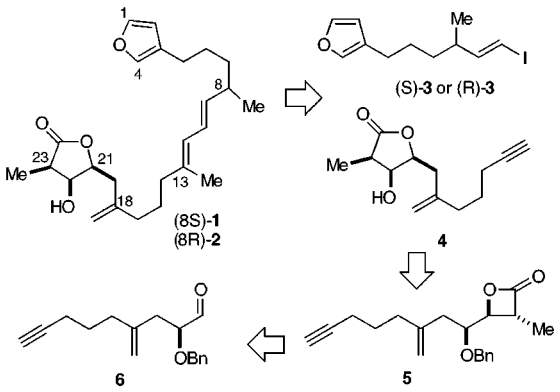

Figure 1. Retrosynthesis of okinonellin B showing the two-step β-lactone-based strategy for the synthesis of butyrolactone **4** from aldehyde **6**.

The synthesis of the butyrolactone **4** began by conversion of the known lactone **13**[13] to the Weinreb amide followed by silylation to give amide **14** (Scheme 2). A carefully controlled addition[14] of the Grignard reagent derived from bromide **15**[15] to amide **14** gave the desired ketone **16** in 87% yield. Tebbe methylenation,[16] simultaneous desilylation of the silyl ether and silylacetylene, and Swern oxidation delivered the aldehyde **6** required for the TMAL reaction. In the event, treatment of aldehyde **6** with $ZnCl_2$ and the ketene acetal **19** at ambient temperature for 14 h gave the β-lactone **5** as a single diastereomer[17] in 73% yield[18] and with <4%

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(1) For a recent review, see: Pommier, A.; Pons, J.-M. *Synthesis* **1993**, 441−449.

(2) We are aware of only a few examples of the use of β-lactones as intermediates in asymmetric, natural product total synthesis: (a) Bourgeanic Acid: White, J. D.; Johnson, A. T. *J. Org. Chem.* **1994**, *59*, 3347−3358. (b) Lactacystin: Corey, E. J.; Reichard, G. A.; Kania, R. *Tetrahedron Lett.* **1993**, *34*, 6977−6980.

(3) For some recent asymmetric methods for β-lactone synthesis, see: Yang, H. W.; Romo, D. *J. Org. Chem.* **1998**, *63*, 1344−1347 and references therein.

(4) Kato, Y.; Fusetani, N.; Matsugaga, S.; Hashimoto, K. *Experientia* **1986**, *42*, 1299.

(5) (a) Crews, P.; Naylor, S. *Fortschr. Chem. Org. Naturst.* **1985**, *48*, 203−268. (b) Rochfort, S. J.; Atkin, D.; Hobbs, L.; Capon, R. J. *J. Nat. Prod.* **1996**, *59*, 1024−1028.

(6) (a) Hirai, K.; Homma, H.; Mikoshiba, I. *Heterocycles* **1994**, *38*, 281−282. (b) Yang, H. W.; Romo, D. *J. Org. Chem.* **1997**, *38*, 4−5. (c) Yang, H. W.; Zhao, C.; Romo, D. *Tetrahedron* **1997**, *53*, 16471−16488. (d) Reference 3.

(7) (a) Zemribo, R.; Champ, M. S.; Romo, D. *Synlett* **1996**, 278−280. (b) Arrastia, I.; Lecea, B.; Cossio, F. P. *Tetrahedron Lett.* **1996**, *37*, 245−248.

(8) Negishi, E.; Okukado, N.; King, A. O.; Van Horn, D. E.; Speigel, B. I. *J. Am. Chem. Soc.* **1978**, *100*, 2254−2256.

(9) The enantiomeric iodides **8** are available in three steps from (*S*)- and (*R*)-methyl 3-hydroxy-2-methylpropanoate, see: White, J. D.; Kawasaki, M. *J. Org. Chem.* **1992**, *57*, 5292−5300.

(10) The unstable furanyl bromide **10** was prepared immediately prior to use from 3-furanmethanol using PPh_3/Br_2: Bernasconi, S.; Colombo, M.; Jommi, G.; Sisti, M. *Gass. Chem. Ital.* **1986**, *116*, 69−71.

(11) Mancuso, A. J.; Swern, D. *Tetrahedron Lett.* **1981**, *35*, 2473−2476.

(12) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408−7410.

(13) Lactone **13** is available in four steps from (−)-malic acid; see: Bernardi, A.; Cardani, S.; Scolastico, C.; Villa, R. *Tetrahedron* **1990**, *46*, 1987−1998.

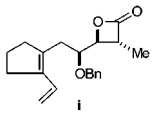
(14) Best results were obtained after titration of the generated Grignard reagent; see: Bergbreiter, D. E.; Pendergrass, E. *J. Org. Chem.* **1981**, *46*, 219−220.

(15) Bromide **15** was obtained by a four-step sequence from commercially available 4-pentyn-1-ol: (a) DHP, TsOH; (b) *n*-BuMgBr, thexyldimethylsilyl chloride; (c) $BF_3{\cdot}OEt_2$, EtSH; (d) PPh_3, Br_2.

(16) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611−3613.

(17) No minor diastereomers could be detected in either $CDCl_3$ or C_6D_6 (300 MHz ^{1}H NMR).

(18) An interesting byproduct **i** was obtained (5−10%) in the TMAL reaction. We are currently studying this presumed Zn(II) (or trace metal)-mediated reaction. For possible related palladium- and ruthenium-mediated processes, see: Trost, B. M., Tanoury, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 1636−1638. Chatani, N.; Morimoto, T.; Muto, T.; Murai, S. *J. Am. Chem. Soc.* **1994**, *116*, 6049−6050.



i

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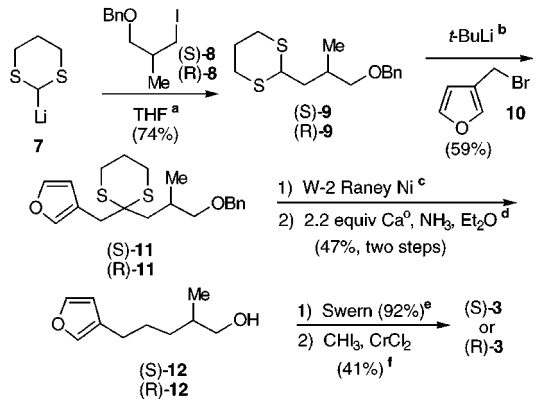
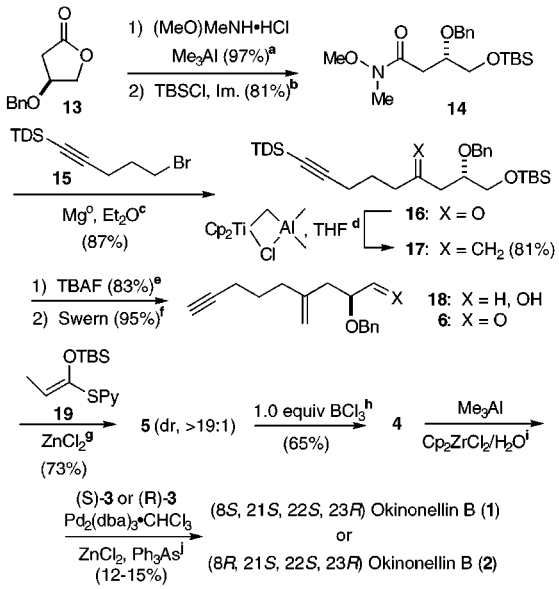
Scheme 1[a]



[a] Key: (a) −45 → −20 °C, 57 h; (b) THF, −78 → −45 °C, 10 h, then **10**, THF, 15 h; (c) EtOH, 40 °C, 3 h; (d) −33 °C, 1.5 h; (e) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, Et_3N, −78 → 0 °C, 25 min; (f) THF, 0 °C, 4 h.

Scheme 2[a]



[a] Key: (a) C_6H_6, 0 °C, 1.5 h; (b) DMF, 24 °C, 2.5 h; (c) reflux then added to **14**, Et_2O, −78 → 0 °C, 39 h; (d) −40 °C, 3 h; (e) THF, 0 → 24 °C, 3 h; (f) DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, Et_3N, −78 °C, 1 h; (g) CH_2Cl_2, 25 °C, 14 h; (h) CH_2Cl_2, −78 °C, 15 min; (i) CH_2Cl_2, −23 °C, 2 h; (j) (1:4, Pd (8 mol %):ligand), NMP, 25 °C, 7.5 h.

epimerization.[19] The stereochemical outcome is consistent with a chelation-controlled initial aldol reaction as determined by conversion to the *all-syn*-butyrolactone **4**.[20] The tandem transacylation−debenzylation of *β*-lactone **5** to the *all-syn*-butyrolactone was effected using BCl_3, which gave improved results over the originally reported $FeCl_3$ (29%).[7a] Thus, in two steps aldehyde **6** is transformed into the highly functionalized, *all-syn*-butyrolactone **4** in a highly stereocontrolled fashion.

For the fragment coupling to provide okinonellin B, we relied on the single-pot procedure of Negishi involving alkyne carboalumination followed by transmetalation to Zn(II) and a Pd(0)-mediated coupling to a vinyl halide.[8] In the event, carboalumination of alkyne **4** using the water-accelerated conditions developed by Wipf[21] followed by addition of $ZnCl_2$, the Pd(0)/Ph_3As catalyst system reported by Farina,[22] and vinyl iodides (*S*)-**3** or (*R*)-**3** gave (8*S*)-okinonellin B (**1**) and (8*R*)-okinonellin B (**2**), respectively (Scheme 2). Significant amounts (∼40%) of quenched vinylmetallic species derived from **4** and methylated products derived from vinyl iodides **3** account in part for the low yields obtained in this carboalumination/coupling sequence.[23]

Not unexpectedly, the diastereomers of okinonellin B (**1** and **2**) did not exhibit any differences by either ^1H or ^{13}C NMR. A significant difference in the CD spectrum of the two diastereomers was observed. However, neither a CD spectrum of the natural product nor the natural product itself was available for comparison.[24] At this time, we can only speculate based on the optical rotation data[25] that natural okinonellin B possesses the 8*R*,21*R*,22*R*,23*S* stereochemistry that is enantiomeric to our synthetic (8*S*,21*S*,22*S*,23*R*)-okinonellin B (**1**).

In conclusion, the described total syntheses of (8*S*,21*S*,22*S*,23*R*)- and (8*R*,21*S*,22*S*,23*R*)-okinonellin B demonstrate the utility of *β*-lactones in natural product synthesis and specifically their use for the synthesis of highly substituted and functionalized butyrolactones. A two-step procedure efficiently and stereoselectively converted the chiral aldehyde **6** to the *all-syn*-butyrolactone **4**. The sequence employed a tandem Mukaiyama aldol−lactonization and a tandem debenzylation−transacylation reaction as key steps. We are currently exploring further novel transformations of *β*-lactones and their application to natural product synthesis.

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Supporting Information Available: Physical and spectral listings, procedures, and ^1H and ^{13}C NMR spectra of selected intermediates; chiral HPLC traces of *β*-lactone **5**; CD spectra of **1** and **2** (29 pages).

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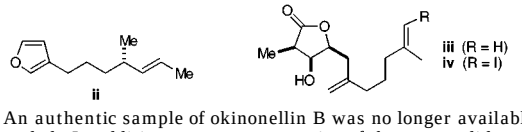
(19) The enantiomeric purity was determined by chiral HPLC (Chiralcel OD) on comparison to the racemic *β*-lactone. See the Supporting Information for details.

(20) Our current mechanistic understanding of the Zn(II)-mediated TMAL reaction will be described in a separate report: Zhao, C.; Yang, H. W.; Romo, D. Manuscript in preparation.

(21) Wipf, P.; Lim, S. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1068−1071.
(22) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585−9595.

(23) It was noted that complete consumption of the vinyl iodide **3** occurred rapidly during the reaction, and a byproduct derived from this material was the methylated olefin **ii**. As a result, substantial amounts of the olefin **iii** were obtained on quenching the reaction. In a separate experiment, the vinyl iodide **iv** could be obtained in 57% yield by iodinolysis. For a lead reference to related reactions of vinyl triflates, see: Saulnier, M.; Kadow, J.; Tun, M. M.; Langley, D.; Vyas, D. *J. Am. Chem. Soc.* **1989**, *111*, 8320−8321.



(24) An authentic sample of okinonellin B was no longer available as it had degraded. In addition, recent re-extraction of the sponge did not afford any detectable okinonellin B (private communication from N. Fusetani and S. Matsunaga, University of Tokyo). We have also noted the instability of okinonellin B even when frozen in benzene.

(25) Natural okinonellin B: $[\alpha]^{20}_D = 17.9$ (*c* 0.15, EtOH). (8*S*,21*S*,22*S*,23*R*)-Okinonellin B (**1**): $[\alpha]^{24}_D = -7.6$ (*c* 0.19, EtOH). (8*R*,21*S*,22*S*,23*R*)-Okinonellin B (**2**): $[\alpha]^{24}_D = -98.0$ (*c* 0.15, EtOH).