# A New Stereoselective Route to (–)-Octalactin A Based on Intramolecular $SmI_2$ Promoted Reformatsky Reaction

Susumu Inoue, Yoshiharu Iwabuchi, Hiroshi Irie, Susumi Hatakeyama*

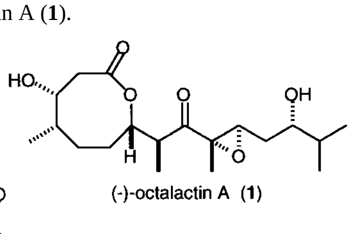
Faculty of Pharmaceutical Sciences, Nagasaki University, Nagasaki 852-8131, JAPAN

Fax 81-95-848-4286

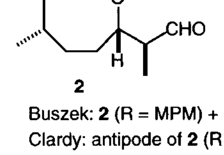
*Received 31 March 1998*

**Abstract:**A novel stereoselective synthesis of the key left-hand fragment of (-)-octalactin A has been achieved from methyl (*R*)-3-hydroxy-2-methylpropionate employing $SmI_2$ promoted intramolecular Reformatsky reaction of a δ-(bromoacetoxy)aldehyde as a key step.

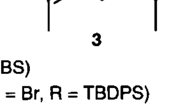
Octalactin A (**1**) and octalactin B, a closely related congener, were isolated from a marine actinomycete of the genus *Streptomyces* found on the surface of a gorgonian octacoral.[1] Octalactin A (**1**) displays potent *in vitro* cytotoxicity against B-16-F10 murine melanoma and HCT-116 human colon tumor cell lines.[1] The unique structure containing a characteristic eight-membered lactone moiety as well as the above-mentioned intriguing biological activity has spurred much research on the synthesis of octalactin A (**1**).[2] Buszek[2a] and Clardy[2b] have independently established an efficient convergent approach involving coupling of a left-hand fragment **2** and a right-hand fragment **3**. We describe herein a novel stereoselective synthesis of the key left-hand fragment **2** (R = TBS), which constitutes a formal synthesis of natural (–)-octalactin A (**1**).



(-)-octalactin A (**1**)



**2**

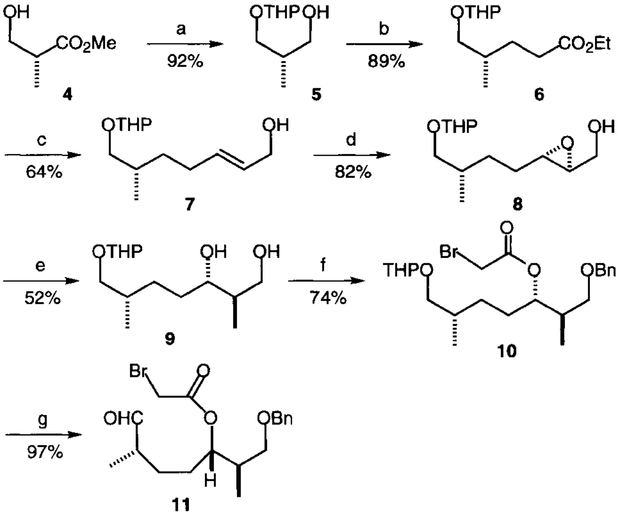


**3**

Buszek: **2** (R = MPM) + **3** (X = I, R = TBS)
Clardy: antipode of **2** (R = TBS) + **3** (X = Br, R = TBDPS)

The strategy we have employed to construct the eight-membered lactone structure of **2** relies upon $SmI_2$ promoted intramolecular Reformatsky reaction[3] of an δ-(bromoacetoxy)aldehyde which follows the Inanaga's protocol.[4]

The required δ-(bromoacetoxy)aldehyde **11** was prepared as shown in Scheme 1. Commercially available methyl (*R*)-3-hydroxy-2-methylpropionate (**4**) was first subjected to a conventional nine-step straightforward chain-elongation to give (*E*)-allylic alcohol **7**[5] in 52% overall yield. Katsuki-Sharpless catalytic asymmetric epoxidation[6] of **7** gave epoxide **8** which, upon nucleophilic opening with methyllithium in the presence of a catalytic amount of CuCN followed by $NaIO_4$ oxidation,[7] gave diol **9** in 52% yield. Selective monobenzylation of **9** followed by bromoacetylation of the resulting secondary alcohol afforded bromoacetate **10** in 74% yield. Upon sequential acidic methanolysis and Swern oxidation, **10** gave δ-(bromoacetoxy)aldehyde **11** in 97% yield.



**Scheme 1.** (a) 1) DHP, PPTS, $CH_2Cl_2$, 2) $LiAlH_4$, THF; (b) 1) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, –60 to 25 °C, 2) $(EtO)_2P(O)CO_2Et$, NaH, THF, –78 °C, 3) $H_2$, 10% Pd-C, benzene; (c) 1) DIBAH, $CH_2Cl_2$,–78 °C, 2) as in (b)-1), 3) as in (b)-2), 4) as in c)-1); (d) diisopropyl L-tartrate (0.09 equiv), $Ti(O\text{-}i\text{-}Pr)_4$ (0.07 equiv), *t*-BuOOH (2 equiv), 4 Å molecular sieves, $CH_2Cl_2$, –23 °C; (e) 1) MeLi (10 equiv), CuCN (0.5 equiv), $Et_2O$, –23 °C, 2) $NaIO_4$, 50% aqTHF; (f) 1) $PhCH_2Br$, NaH, THF-DMF (5:1), –20 °C, 2) $BrCH_2COCl$, pyridine, $CH_2Cl_2$, 0 °C; (g) 1) PPTS, MeOH, 2) as in (b)-1)

The crucial $SmI_2$ promoted cyclization of **11** was carried out according to the procedure reported by Inanaga and co-workers.[4] Thus, treatment of a diluted THF solution of **11** (2 x $10^{-3}$ mol·$dm^{-3}$) with $SmI_2$ at 0 °C allowed intramolecular Reformatsky type of reaction to provide a 2:1 epimeric mixture of (3*S*)-hydroxylactone **12**, $[\alpha]_D^{18}$ –28.7 (*c* 0.90, $CHCl_3$), and (3*R*)-hydroxylactone **13**, $[\alpha]_D^{18}$ –23.7 (*c* 0.54, $CHCl_3$), in 63% yield. The poor diastereoselectivity of this $SmI_2$ promoted reaction was not problematic, however, because the undesired isomer **12** could be converted to the desired isomer **13** almost quantitatively by sequential Dess-Martin oxidation[8,9] and $NaBH_4$ reduction.[10] Protection of **13** as its *tert*-butyldimethylsilyl ether followed by hydrogenolytic removal of the benzyl ether protecting group afforded alcohol **14**, $[\alpha]_D^{18}$ –61.9 (*c* 0.32, $CHCl_3$) {antipode: [11] $[\alpha]_D^{20}$ +56.3 (*c* 1.05, $CHCl_3$)}, in 73% yield. Finally, Dess-Martin oxidation of **14** furnished the key left-hand fragment **2** (R = TBS), $[\alpha]_D^{22}$ –94.0 (*c* 1.08, $CHCl_3$) {antipode:[11] $[\alpha]_D^{24}$ +87.2 (*c* 1.02, $CHCl_3$)}, in 95% yield. Both **14** and **2** (R = TBS) exhibited identical spectral properties ($^1H$ and $^{13}C$ NMR, IR, HRMS) with those of their antipodes synthesized by Clardy and McWilliams.[2b] Since the antipode of **2** (R = TBS) has already been converted to (+)-octalactin A by Clardy and McWilliams,[2b] the present work provides a new route to natural (–)-octalactin A.

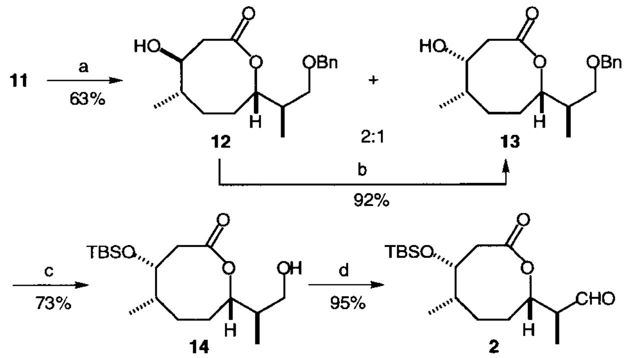
**Acknowledgment.** We gratefully thank Professor Jon Clardy (Cornell University) for providing us with spectral data and specific rotations of the antipode of **14** and **2** (R = TBS).

## References and Notes

(1) Tapiolas, D. M.; Roman, M.; Fenical, W.; Stout, T. J.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 4682.

(2) (a) Buszek, K. R.; Sato, N.; Jeong, Y. *J. Am. Chem. Soc.* **1994**, *116*, 5510. (b) McWilliams, J. C.; Clardy, J. *J. Am. Chem. Soc.*

Downloaded by: University of Arizona Library. Copyrighted material.



**Scheme 2.** (a) $SmI_2$, THF (2 x $10^{-3}$ mol·dm$^{-3}$), 0 °C; (b) 1) Dess-Martin periodinane, $CH_2Cl_2$, 2) $NaBH_4$, MeOH, –23 °C; (c) 1) 4-(*tert*-butyldimethylsilyl)oxy-3-penten-2-one, CSA, DMF, 2) $H_2$, 5% $Pd(OH)_2$-C, MeOH; (d) as in (b)-1)

**1994**, *116*, 8378. (c) Bach, J.; Berenguer, R.; Garcia, J.; Vilarrasa, J. *Tetrahedron Lett.* **1995**, *36*, 3425. (d) Buszek, K. R.; Jeong, Y. *Tetrahedron Lett.* **1995**, *36*, 7189. (e) Andrus, M. B.; Argade, A. B. *Tetrahedron Lett.* **1996**, *37*, 5049. (f) Kodama, M.; Matsushita, M.; Terada, Y.; Takeuchi, A.; Yoshio, S.; Fukuyama, Y. *Chem. Lett.* **1997**, 117. (g) Hulme, A. N.; Howells, G. E. *Tetrahedron Lett.* **1997**, *38*, 8245.

(3) For a recent review on $SmI_2$ promoted reactions, see: Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307.

(4) Tabuchi, T.; Kawamura, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 3889.

(5) All new compounds exhibited satisfactory spectral ($^1$H and $^{13}$C NMR, IR, HRMS) data. Selected $^1$H NMR (500 MHz, $CDCl_3$) and $^{13}$C NMR (125 MHz, $CDCl_3$) data are following. **12**: 7.35-7.25 (m, 5H), 4.54 (q, 1H, $J$ = 7.6 Hz), 4.47 (s, 2H), 3.56 (dd, 1H, $J$ = 9.3, 4.8 Hz), 3.53 (dt, 1H, $J$ = 4.3, 10.1 Hz), 3.39 (dd, 1H, $J$ = 9.3, 4.3 Hz), 2.78 (t, 1H, $J$ = 12.1 Hz), 2.73 (dd, 1H, $J$ = 12.1, 4.3 Hz), 2.36 (br s, 1H), 2.08-1.98 (m, 1H), 1.72-1.64 (m, 2H), 1.52 (dq, 1H, $J$ = 9.5, 6.9 Hz), 1.45 (dt, 1H, $J$ = 15.8, 4.1 Hz), 1.10 (d, 3H, $J$ = 6.9 Hz), 1.30-1.18 (m, 1H), 1.02 (d, 3H, $J$ = 7.0 Hz); 172.6, 138.3, 128.4, 127.6, 78.4, 75.3, 73.2, 71.4, 40.8, 39.6, 38.3, 32.1, 27.7, 21.0, 13.7. **13**: 7.36-7.27 (m, 5H), 4.46 (s, 2H), 4.47 (q, 1H, $J$ = 7.8 Hz), 3.99 (br s, 1H), 3.60 (dd, 1H, $J$ = 9.0, 4.6 Hz), 3.38 (dd, 1H, $J$ = 9.0, 4.0 Hz), 2.84 (dd, 1H, $J$ = 13.0, 1.8 Hz), 2.68 (dd, 1H, $J$ = 13.0, 6.3 Hz), 2.11 (br s, 1H), 2.04-1.97 (m, 1H), 1.78-1.61 (m, 4H), 1.20-1.16 (dt, 1H, $J$ = 14.4, 4.1 Hz), 1.11 (d, 3H, $J$ = 7.1 Hz), 1.02 (d, 3H, $J$ = 7.1 Hz); 172.8, 138.3, 128.4, 127.8, 78.5, 73.2, 71.4, 53.5, 39.1, 38.3, 38.1, 32.0, 23.8, 21.7, 13.9. **14**: 4.37 (ddd, 1H, $J$ = 10.8, 8.0, 4.0 Hz), 3.94 (dt, 1H, $J$ = 6.5, 2.0 Hz), 3.76 (br d, 1H, $J$ = 10.5 Hz), 3.59 (br d, 1H, $J$ = 10.5 Hz), 2.72 (dd, 1H, $J$ = 12.6, 2.3 Hz), 2.65 (dd, 1H, $J$ = 12.6, 6.6 Hz), 2.04-1.85 (m, 2H), 1.75-1.62 (m, 3H), 1.12 (dt, 1H, $J$ = 15.3, 4.3 Hz), 1.03 (d, 3H, $J$ = 7.1 Hz), 1.00 (d, 3H, $J$ = 7.1 Hz), 0.91 (s, 9H), 0.17 (s, 3H), 0.05 (s, 3H); 171.7, 79.2, 73.0, 64.5, 40.3, 39.8, 38.7, 31.6, 25.8, 23.6, 21.0, 18.1, 13.6, –4.2, –5.2. **2** (R = TBS): 9.73 (d, 1H, $J$ = 1.4 Hz), 4.65 (ddd, 1H, $J$ = 11.9, 7.3, 3.2 Hz), 3.96 (d, 1H, $J$ = 6.6 Hz), 2.78 (dd, 1H, $J$ = 12.8, 1.8 Hz), 2.74 (dt, 1H, $J$ = 1.6, 7.3 Hz), 2.69 (dd, 1H, $J$ = 12.8, 6.6 Hz), 2.02-1.93 (m, 1H), 1.78-1.54 (m, 5H), 1.13 (d, 3H, $J$ = 7.6 Hz), 1.04 (d, 3H, $J$ = 7.1 Hz), 0.91 (s, 9H), 0.18 (s, 3H), 0.05 (s, 3H); 202.4, 170.8, 72.8, 50.6, 39.7, 38.6, 31.4, 25.8, 23.1, 21.5, 18.1, 10.5, –4.2, –5.1.

(6) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Org. Chem.* **1987**, *109*, 5765.

(7) This operation was neccessary to remove the corresponding 1,2-diol.

(8) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156.

(9) Swern oxidation of **12** always produced 9-benzyloxy-2,2-dichloro-4,8-dimethyl-3-oxo-7-nonanolide as a major product due to chlorination of initially formed 9-benzyloxy-4,8-dimethyl-3-oxo-7-nonanolide.

(10) Reduction of the corresponding $\beta$-keto lactone proceeded with complete diastereoselectivity. This stereochemical outcome could arise from the conformational rigidity of the eight-membered $\beta$-keto lactone ring system. Cf.: Petasis, N. A.; Patane, M. A. *J. Chem. Soc., Chem. Commun.* **1990**, 836.

(11) The specific rotation was measured by Clardy and McWilliams.

Downloaded by: University of Arizona Library. Copyrighted material.