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AN ENANTIO- AND DIASTEREOCONTROLLED SYNTHESIS OF (–)-SALINOSPORAMIDE A

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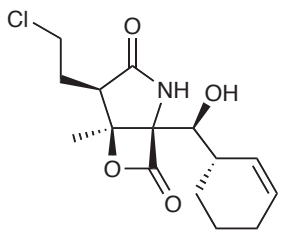
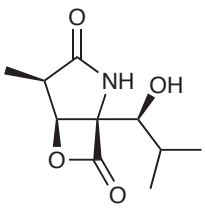
Abstract – The enantio- and diastereocontrolled total synthesis of (–)-salinosporamide A, a potent 20S proteasome inhibitor, was accomplished through organocatalytic aldolization, diastereoselective Claisen condensation, a Rh-catalyzed Reformatsky reaction, and an AZADO-catalyzed oxidative β-lactonization reaction as the key reactions.

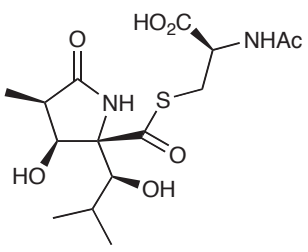
Salinosporamide A (**1**, aka NPI-0052, marizobnib) was discovered by Fenical and coworkers as a cytotoxic principle produced by a marine actinomycete *Salinosopra tropicana*.[1] Structurally, salinosporamide A has the same unique fused β-lactone-γ-lactam core as omuralide (**2**), a well-known 20S proteasome inhibitor derived from lactacystin (**3**),[2] but is distinguished by its five contiguous asymmetric centers consisting of a β-chloroethyl group, two quaternary carbons, and a 2-cyclohexene ring. Salinosporamide A has been reported to be approximately 35 times more effective at proteasome inhibition than omuralide,[1] making it as a candidate for the development of anticancer drugs.[3] The beneficial pharmacological profile of salinosporamide A coupled with its structural complexity has spurred intense efforts to synthesize it.



salinosporamide A (**1**)



omuralide (**2**)

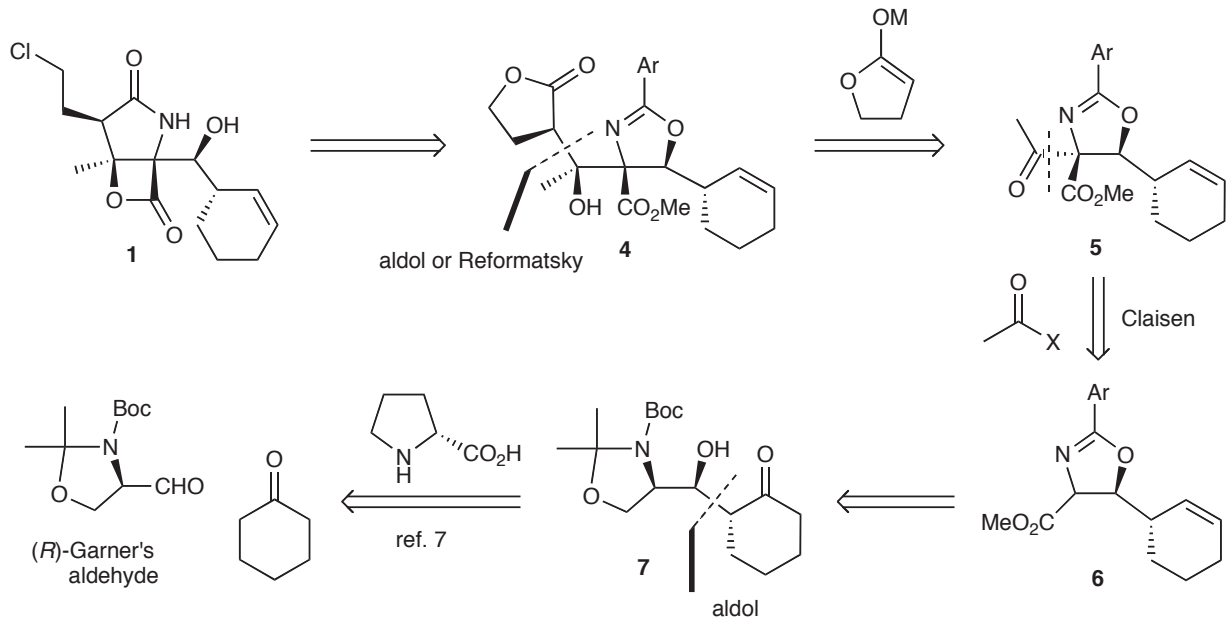


lactacystin (**3**)

Figure 1. Structures of salinosporamide A (**1**), omuralide (**2**), and lactacystin (**3**)

To date, a number of total[4,5] and formal[6] syntheses have been accomplished, most of which employ Corey's approach[4a] to realize the diastereoselective installation of the cyclohexene ring of **1** in the later stage of the synthesis, with the exception of the Nagamitsu-Omura synthesis,[4e] in which the cyclohexene moiety is mounted in the early stage. We now report the enantio- and diastereocontrolled synthesis of (–)-salinosporamide A (**1**) featuring the extensive adoption of aldol and related reactions, where the cyclohexene ring is installed in the early stage of the synthesis.

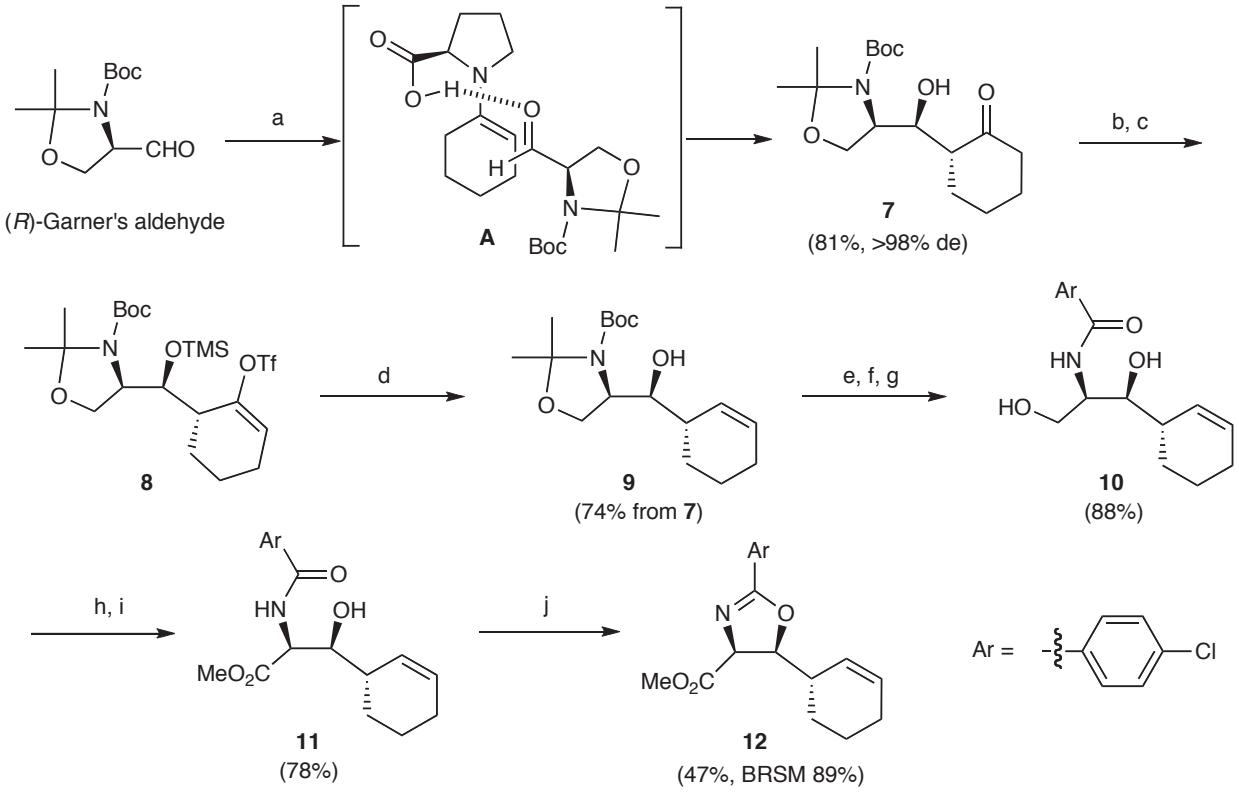
Our retrosynthetic analysis of **1** is illustrated in Scheme 1. We set **4** as a logical subgoal, of which the deprotected oxazoline and the methyl ester moieties could serve as suitable intermediates to obtain **1**. Among several possible disconnections, we chose the intermolecular aldol reaction of the ketone **5** and an enolate derived from γ-butyrolactone, which would ultimately allow us to secure the vicinal asymmetric quaternary centers in a diastereocontrolled manner. The quaternary center of the ketone **5** should be secured from the oxazoline **6** via a diastereocontrolled mixed Claisen condensation with an acetyl counterpart. The precursor of the oxazoline **6** was expediently assigned to the known aldol **7**:[7] the highly diastereocontrolled synthesis of the enantiomeric ***ent*-7** was previously attained via an L-proline-catalyzed aldol reaction of (*S*)-Garner's aldehyde[8a] and cyclohexanone.



Scheme 1. Retrosynthetic analysis of salinosporamide A (**1**)

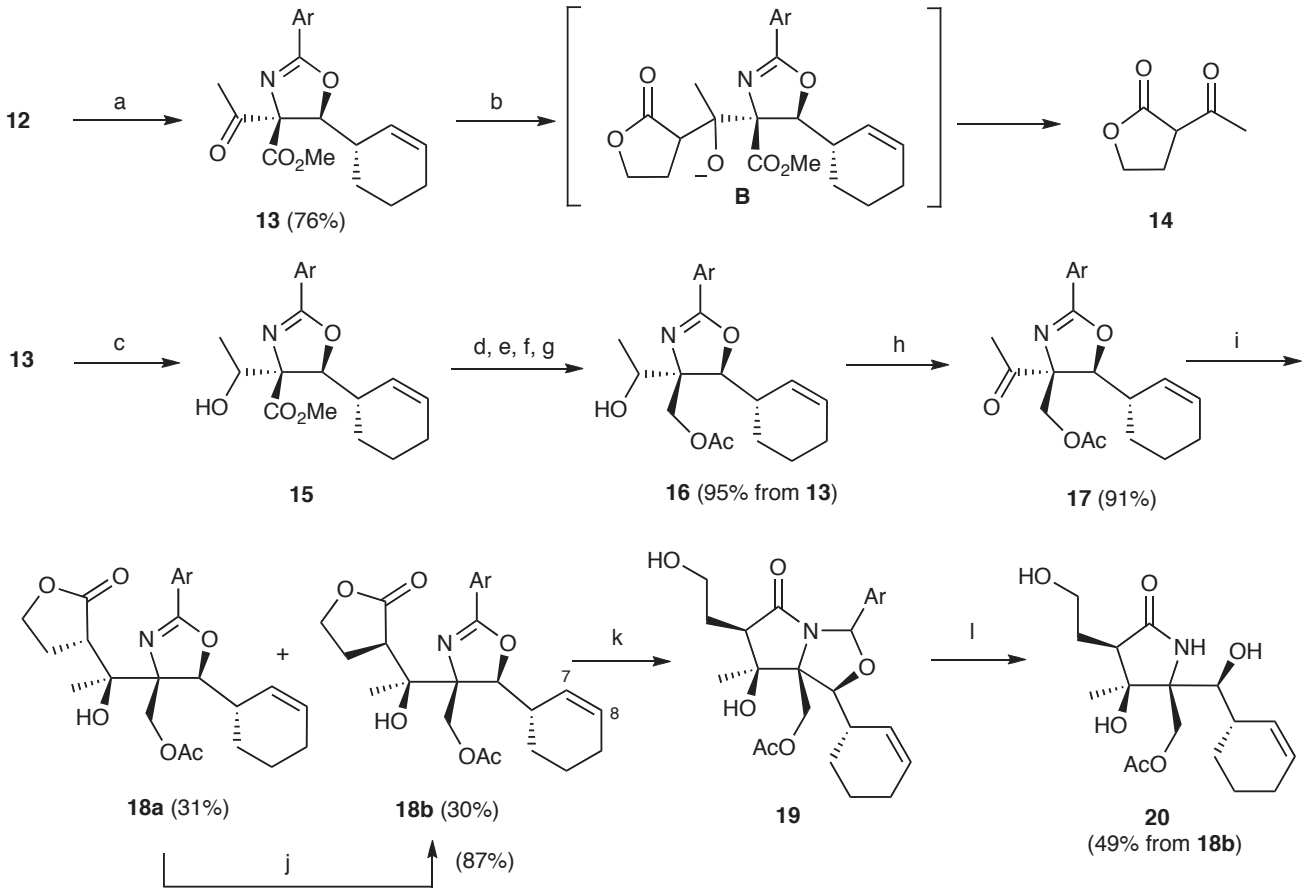
The oxazoline **12**, serving as the stereochemical basis throughout the synthesis, was prepared as shown in Scheme 2. In accordance with the procedure developed by Rode,[7] (*R*)-Garner's aldehyde[8b] was treated with cyclohexanone in the presence of 20 mol% D-proline in $CHCl_3$-DMSO (3:1) in 5 °C to give **7** with 81% yield and a high diaseteroselectivity of over 98% de, of which the diastereochemical preference is

rationalized by the transition state model **A**.[7] Upon TMS etherification, triflation of the kinetically generated enolate of **7** afforded **8**. Pd-catalyzed reduction of the triflate **8** employing formic acid gave **9** with concomitant desilylation. The exposure of **9** to a mixture of *c*HCl and AcOEt effected the deprotection of the acetonide and the Boc group to give the corresponding amino-diol, which was then condensed with *p*-chlorobenzoyl chloride to give **10**. Note that the installation of the *p*-chlorobenzoyl group was not the result of a capricious choice (*vide infra*).[9] Treatment of **10** with a catalytic amount of TEMPO in the presence of $PhI(OAc)_2$[10] in CH_3CN-H_2O (1:1) led to the selective oxidation of the primary alcohol moiety, which upon treatment with diazomethane gave the methyl ester **11**. The cyclization of **11** to the oxazoline **12** was accomplished in boiling toluene using a catalytic amount of *p*-TsOH and Dean-Stark apparatus.



Scheme 2. Synthesis of oxazoline **12**, equivalent to **6**. *Reagents and conditions*: (a) D-proline (0.2 equiv), cyclohexanone (2 equiv), $CHCl_3$-DMSO (3:1), 5 °C, 3 d; (b) TMSCl (2 equiv), Et_3N (4 equiv), DMAP (0.1 equiv), CH_2Cl_2, 0 °C, 1.5 h; (c) KHMDS (1.3 equiv), $PhNTf_2$ (1.1 equiv), THF, –78 to –40 °C, 1 h; (d) $Pd(OAc)_2$ (0.05 equiv), PPh_3 (0.1 equiv), HCO_2H (2.5 equiv), *n*-Bu_3N (3 equiv), DMF, 60 °C, 12 h; (e) *c*HCl, AcOEt, rt, 0.5 h; (f) *p*-chlorobenzoyl chloride (1.5 equiv), Et_3N (4 equiv), DMAP (0.03 equiv), CH_2Cl_2, rt, 0.5 h; (g) K_2CO_3 (10 equiv), MeOH, rt, 2 h; (h) TEMPO (0.25 equiv), $PhI(OAc)_2$ (2.6 equiv), MeCN-H_2O (1:1), 0 °C, 15 h; (i) CH_2N_2 in Et_2O, MeOH, 0 °C; (j) *p*-TsOH (0.05 equiv), toluene, Dean-Stark, reflux, 12 h.

Having formed the projected chiral platform **12**, we considered the formation of the vicinal quaternary centers in **1** (Scheme 3). The deprotonation of **12** with lithium diisopropylamide in THF and acylation of the resulting enolate with acetyl chloride afforded the required **13** exclusively with 76% yield. The next step, the attachment of γ-butyrolactone, turned out to be troublesome: all the attempted aldol reactions failed to give even a trace amount of the anticipated product and instead gave 2-acetyl-γ-butyrolactone (**14**) as a major product, indicating the formation of the primary adduct **B** and the prompt collapse via a retro-Claisen reaction. After many unsuccessful trials, we decided to make a detour so as to accommodate the transient oxy-anion species generated by the nucleophilic attack of the enolate counterpart (Scheme 3).



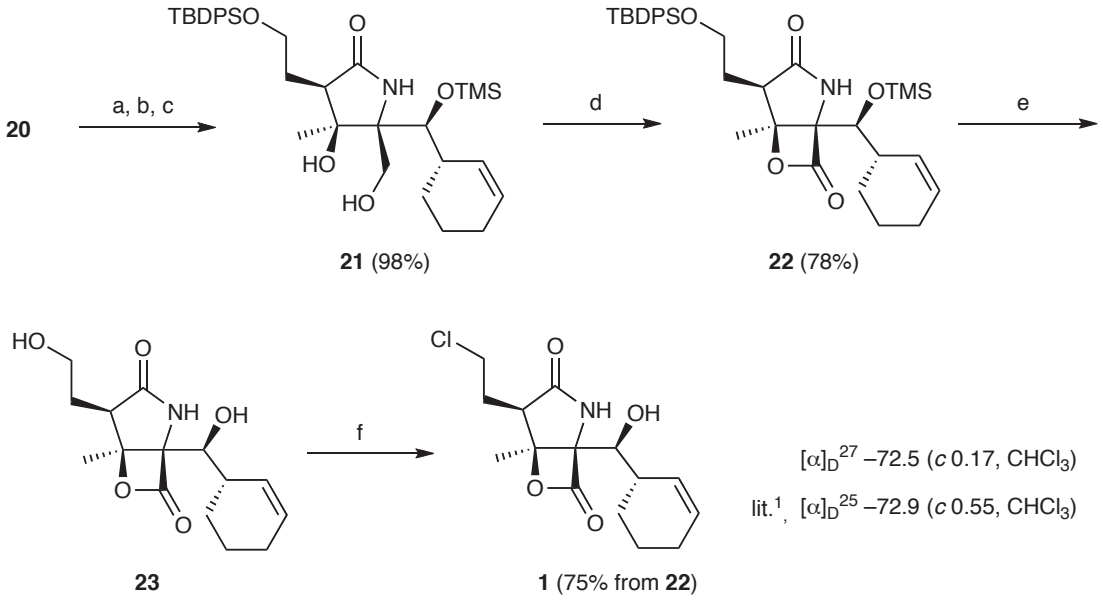
Scheme 3. Synthesis of γ-lactam **20**. *Reagents and conditions* (Ar = *p*-Cl-C_6H_4-): (a) *n*-BuLi (2 equiv), *i*-Pr_2NH (2.2 equiv), THF, –78 °C; AcCl (3 equiv), 15 min; (b) γ-butyrolactone, LDA, THF, –78 °C; (c) $NaBH_4$ (1.5 equiv), MeOH, –40 °C, 2 h; (d) DHP (5 equiv), PPTS (0.22 equiv), CH_2Cl_2, reflux, 3 h; (e) DIBALH (3 equiv), THF, –5 °C, 9 h; (f) Ac_2O (3 equiv), Et_3N (6 equiv), DMAP (0.1 equiv), CH_2Cl_2, reflux, 3 h; (g) Me_2AlCl in hexane (2 equiv), CH_2Cl_2, 0 °C to rt, 0.5 h; (h) 1-Me-AZADO (0.11 equiv), $PhI(OAc)_2$ (1.65 equiv), CH_2Cl_2, rt, 12 h; (i) $(Ph_3P)_3RhCl$ (0.05 equiv), α-bromo-γ-butyrolactone (4 equiv), Et_2Zn (4 equiv), THF, –20 °C, 3 h; (j) DBU (1.1 equiv), CH_2Cl_2, 0 °C, 12 h; (k) $NaBH_3CN$ (5 equiv), AcOH-THF (2:1), 0 °C, 6 d; (l) 1,2-propanedithiol (4.2 equiv), *c*HCl, CF_3CH_2OH, rt, 0.5 h.

To this end, ketone **13** was selectively reduced to the alcohol **15** by treatment with $NaBH_4$ in MeOH at –40 °C. Upon THP protection, the reduction of the ester moiety with DIBALH, acetylation, and the removal of the THP group, we obtained **16** from **15**. Oxidation of the highly congested alcohol **16** was easily achieved under 1-Me-AZADO[11]-catalyzed conditions using $PhI(OAc)_2$ to give **17** as a revised substrate for attaching the γ-butyrolactone moiety. Owing to the challenging steric hindrance of **17**, most of attempted aldolizations including the Mukaiyama aldolization[12] using (4,5-dihydrofuran-2-yloxy)trimethylsilane were unsuccessful and only Shibasaki's protocol[13] using $CuF{\cdot}3PPh_3{\cdot}2EtOH/(EtO)_3SiF$ gave the desired adduct with 8% yield. Eventually, we found that the Honda variant[14] of the Reformatsky conditions gave the best results. Thus, **17** was treated with α-bromo-γ-butyrolactone and Et_2Zn in the presence of 5 mol% Wilkinson's catalyst to give **18a** and **18b** in 31% and 30% isolated yields, respectively. The relative stereochemistry of **18a** was confirmed by X-ray analysis of the corresponding $\Delta^{7,8}$-hydrogenated derivative.[15] Fortunately, **18a** was cleanly isomerized to the desired epimer **18b** upon treatment with DBU. Detachment of the chlorophenylmethylene portion of **18b** was best effected in a two-step sequence through the convenient formation of γ-lactam: (1) reduction of oxazoline with $NaBH_3CN$[4a] to form **19** via an intramolecular translactamization, (2) removal of the *p*-chlorobenzylidene group with *c*HCl and 1,3-propanedithiol[16] to give **20**. It should be stressed that the *p*-methoxy counterpart[4a] of **18b** was significantly resistant[9] to reduction, resulting in a significant yield loss (Scheme 3).

To progress from **20** to (–)-**1** (Scheme 4), the primary and secondary hydroxyl groups had selectively to be protected in a discriminable manner, with the acetate group detached, of which purpose was expediently attained via the selective TBDPS etherification, deacetylation, selective TMS etherification of the primary and secondary hydroxyl groups, and selective removal of the primary TMS ether on treatment with silica gel to furnish **21**. Fortunately, upon the attempted oxidation of the primary alcohol under AZADO[11]-catalyzed conditions using $PhI(OAc)_2$, **21** directly afforded β-lactone **22**. Note that the use of TEMPO[17] significantly retarded the formation of β-lactone. Global deprotection of the silyl groups in **22**, followed by treatment of the resulting diol with Ph_3PCl_2[4a] finally gave (–)-salinosporamide A. The specific rotation, melting point, and spectroscopic properties of the synthetic **1** were full accordance with the reported data.

In conclusion, we have developed an enantio- and diastereocontrolled route to synthesize (–)-salinosporamide A from (*R*)-Garner aldehyde. The key features of the synthetic route are the Rh-catalyzed Reformatsky reaction of **17** to **18**, and the simple, one-step, oxidative β-lactonization of **22** catalyzed by AZADO. Additional information on the chemo- and diastereoselective manipulations

around the β-lactone-γ-lactam motif should provide useful insight for the design and synthesis of advanced 20S proteasome inhibitors related to salinosporamide A/lactacystin.



Scheme 4. Total synthesis of salinosporamide A (**1**). *Reagents and conditions*: (a) TBDPSCl (10 equiv), Et_3N (30 equiv), DMAP (2 equiv), CH_2Cl_2, rt, 12 h; (b) Amberlyst-26, MeOH, rt, 2.5 h; (c) TMSCl (5 equiv), Et_3N (10 equiv), DMAP (0.5 equiv), CH_2Cl_2, rt, 12 h; SiO_2, $CHCl_3$-AcOEt, 15 min; (d) AZADO (0.07 equiv), $PhI(OAc)_2$ (4 equiv), CH_2Cl_2, rt, 4 h; (e) aq. HF, MeCN, rt, 1.5 h; (f) Ph_3PCl_2 (17 equiv), pyridine-MeCN (1:1), rt, 2 h.

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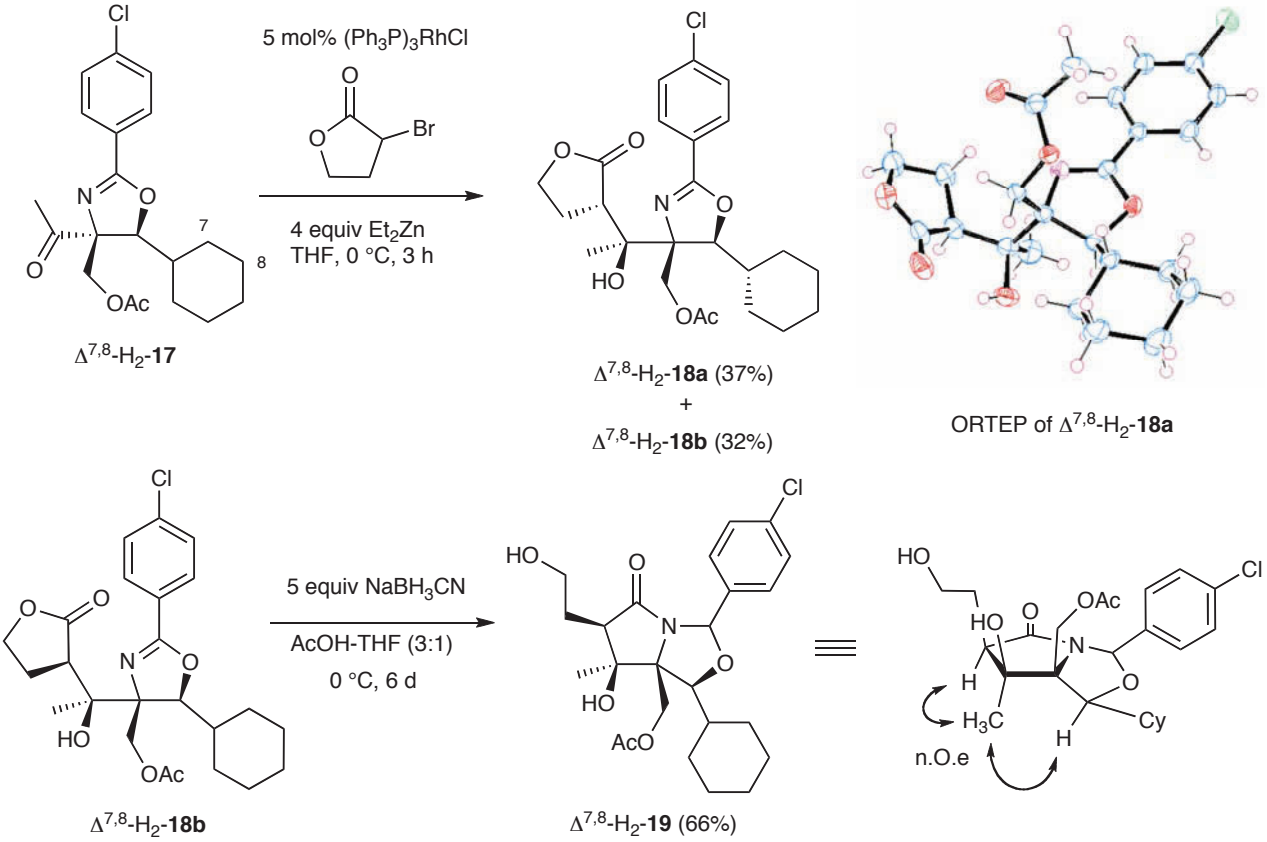
15. $\Delta^{7,8}$-H_2-**18a** was prepared from $\Delta^{7,8}$-H_2-**17**, together with $\Delta^{7,8}$-H_2-**18b**, under the same Honda-Reformatsky reaction conditions. The relative stereochemistry of $\Delta^{7,8}$-H_2-**18b** was

confirmed by observing the n.O.e of $\Delta^{7,8}$-H_2-**19**.



Full account of our synthetic venture toward salinosporamide A will be reported elsewhere.

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