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RESEARCH ARTICLE

Evolution of a Strategy for Concise Enantioselective Total Synthesis of the Salinosporamide Family of Natural Products

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Abstract: Our first strategy for rapidly accessing pyrrolidinone cores of salinosporamides involved combined use of memory of chirality and dynamic kinetic resolution principles in aldol reactions of the serine-derived 5-oxazolidinone substrate, which was ultimately unsuccessful with respect to enantioselectivity. This failure led us to the revised strategy. The influence of the stereocenter in 5-oxazolidinone enabled selective installation of the C-2 stereocenter. The intramolecular aldol reaction of the C-2 stereodefined aldol substrate was successful. An unexpected hydrolytic dynamic kinetic resolution was observed in hydrolyses of the bicyclic aldol products. This unprecedented substrate-driven hydrolytic dynamic kinetic resolution was utilized in preparing the pyrrolidinone core with excellent efficiency. Through this strategy, the concise total syntheses of salinosporamides A and B as well as cinnabaramides A, E, and F were achieved with high selectivity.

Introduction

Salinosporamides constitute a family of natural products produced by marine bacteria of the genus *Salinispora* (Figure 1). The characteristic structural feature of these compounds is a densely functionalized *γ*-lactam-*β*-lactone bicyclic core. The first and representative member of the salinosporamide family is salinosporamide A (**1**), which was isolated from *Salinispora tropica* by Fenical and coworkers in 2003.[1] Compound **1** is a highly potent irreversible inhibitor of the 20S proteasome and exhibits potent in vitro cytotoxicity. Due to its significant biomedical properties,[2] this compound was entered into human clinical trials under the name marizomib.[3] After the identification of **1**, several other salinosporamides were identified from *S. tropica*, including its deschloro analog salinosporamide B (**2**) and methyl congener salinosporamide D (**3**). C-2 epimers of **1** and **3** (salinosporamides F (**4**) and G (**5**), respectively) as well as the C-3 ethyl analog salinosporamide I (**6**) were also identified.[4] The salinosporamide family also encompasses chemically related terrestrial metabolites, cinnabaramides, isolated from a terrestrial strain of *Streptomyces*.[5] The structures of cinnabaramides basically differ from those of salinosporamides in possessing a hexyl substituent at C-2. Cinnabaramides A (**7**) and B (**8**) have bicyclic *γ*-lactam-*β*-lactone ring systems similar to those of salinosporamides, while cinnabaramides D (**9**) and E (**10**) are *seco*-forms of the corresponding *β*-lactone moieties. Cinnabaramides F (**11**) and G (**12**) are thioester derivatives and are considered analogs of the natural product lactacystin. Interestingly, cinnabaramide A (**7**) strongly inhibited the 20S proteasome with a potency similar to that of **1**,[5] even though the former lacked the chlorine substituent essential for the strong activity of the latter.

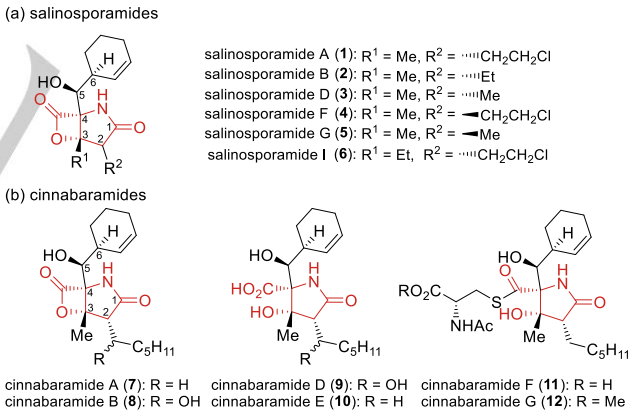

Figure 1. Structures of the salinosporamide family.

The challenging structural features of salinosporamides, which have a highly functionalized skeleton and five contiguous stereogenic centers, including adjacent quaternary centers, have attracted tremendous interest from the synthesis community. The first total synthesis of salinosporamide was achieved by Corey. [6a] To date, fifteen successful total syntheses of salinosporamide A (**1**) and seven formal syntheses have been reported.[6,7] Total syntheses of other salinosporamides have not been reported. The synthesis of racemic cinnabaramide A (**7**) has been reported once, by Romo.[6n] Most synthetic strategies differ in how they access the highly decorated pyrrolidinone core. An attractive approach to the pyrrolidinone ring involved an intramolecular aldol reaction

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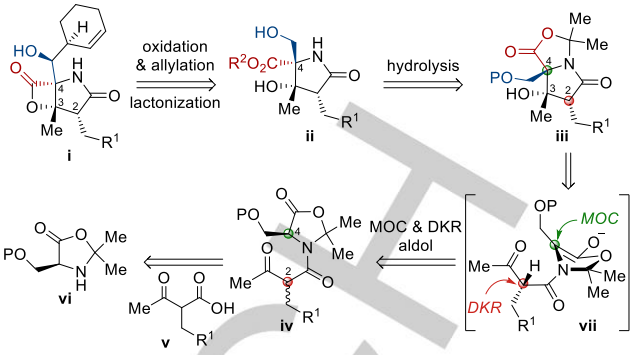
which has been proposed as a plausible biosynthetic step. Several groups used an aldol reaction to connect C-3 and C-4.[6c,f,h,m] However, the selectivity of the reactions was only moderate.

It is surprising, considering the considerable recent advances in synthetic strategies and methods, that most syntheses of these comparably small but complex natural products have required more than 15 steps.[6a–e,g,i,k,l] Given our recent interest in asymmetric and concise total synthesis using a minimum number of chiral sources,[8,9] we sought a retrosynthetic scheme that would lead to the amino acid as the only chiral source in the synthesis of salinosporamides. Herein, we report efficient and concise total syntheses of salinosporamides A (**1**) and B (**2**) as well as cinnabaramides A (**7**), E (**10**), and F (**11**) from serine through a strategy that features a number of chirality induction processes.

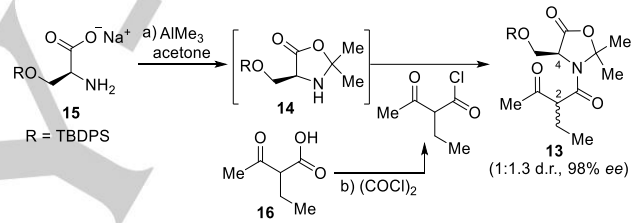
Results and Discussion

Our retrosynthetic analysis is shown in Scheme 1. We envisioned that salinosporamides **i** could be readily accessed from pyrrolidinone **ii** with the proper configuration required to proceed swiftly to the target natural products. The planned transformation included the oxidation of C-4 hydroxy methylene group (natural product numbering), the addition of a cyclohexenyl moiety to the resulting C-4 aldehyde group, and subsequent β-lactone ring formation. The densely functionalized pyrrolidinone **ii** would be accessible from bicycle **iii** via the hydrolysis of oxazolidinone moiety. We planned to conduct an intramolecular aldol reaction of 5-oxazolidinone **iv** to construct the pyrrolidinone ring of **iii** and to introduce the three contiguous stereocenters. In turn, it was envisaged that **iv** could be obtained from β-keto acid **v** and serine derivative **vi**. The stereochemical outcome of the aldol reaction of **iv** was postulated on the basis of our previous "memory of chirality" (MOC)[10] and "dynamic kinetic resolution" (DKR)[11] involved aldol reactions.[8] However, there were several stereochemical concerns to be addressed. One of the major questions was whether the chiral endocyclic enolate **vii** would have a sufficiently sizeable energy barrier for racemization to allow the MOC aldol reaction. Previously, the bulky naphthamide moiety has been employed to enhance the stability of the dynamic axial chirality in the endocyclic enolate.[12] However, our designed aldol substrate **iv** possesses a sterically less demanding alkyl amide group. Another major stereochemical concern was whether the DKR process would occur at the C-2 position of **iv** during the aldol reaction. While a stereocenter adjacent to two carbonyl groups is generally readily epimerizable, the epimerization would not easily occur in some special systems, such as with Evans' 2-oxazolidinone-substituted β-ketoimides.[13] To the best of our knowledge, no study has reported epimerization of a 5-oxazolidinone-substituted β-ketoamide system. Despite these uncertainties, we decided to pursue the total synthesis using 5-oxazolidinone **13** (Scheme 2) as a model study and a possible intermediate to salinosporamide B (**2**).



Scheme 1. Retrosynthetic analysis of salinosporamides.

Our initial study began with the preparation of aldol substrate **13** (Scheme 2). First, oxazolidinone **14** was prepared from the sodium salt of silyl-protected serine **15**[14] by applying the procedure described by Alezra.[12] As this compound was unstable, it was coupled *in situ* with the known β-ketoacid **16** to afford **13** as a 1:1.3 mixture of C-2 diastereomers.



Scheme 2. Synthesis of aldol substrate **13**. Reagents and conditions: (a) $AlMe_3$ (1.0 equiv), 4 Å molecular sieves (excess), acetone, rt, 16 h, then the acid chloride of **16** (1.5 equiv), rt, 2 h, 68%; (b) $(COCl)_2$ (1.2 equiv), cat. DMF, CH_2Cl_2, 0 °C to rt, 2 h. DMF = dimethylformamide.

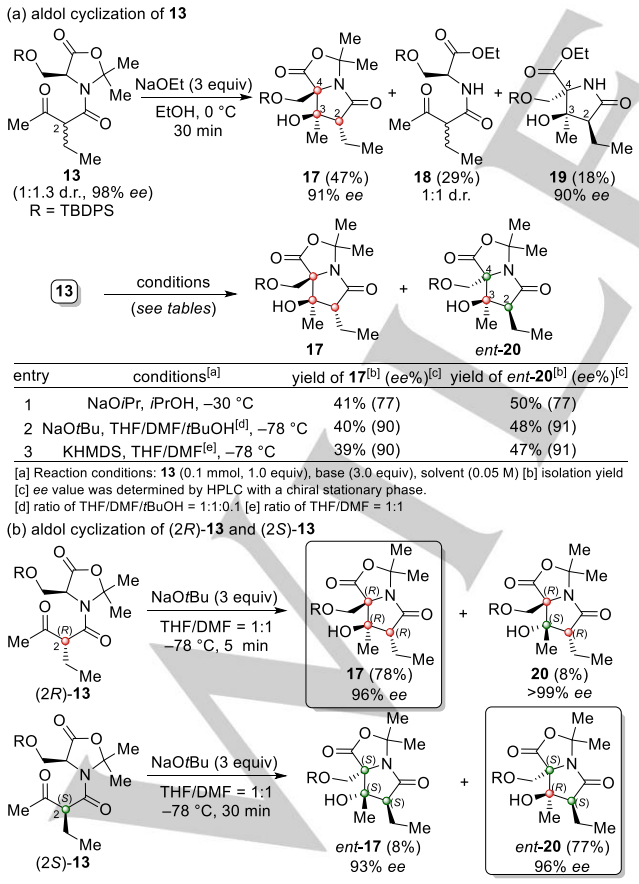
With a diastereomeric mixture of **13** in hand, we investigated the intramolecular aldol reaction. Initially, **13** was subjected to the previously established reaction conditions[8] (NaOEt in EtOH at 0 °C) for the MOC- and DKR-involved aldol reaction (Scheme 3). Unlike in our previous work, the reaction of **13** was not selective and afforded three different products. The major product (47%) was bicyclic aldol product **17**, for which the enantiopurity was 91% *ee*. A structural determination by NMR showed that the C-3 stereocenter was epimeric to those of the target natural products, while two stereocenters at C-2 and C-4 had the desired configurations. Another product (29%) was acyclic compound **18**, which arose from the oxazolidinone ring-opening reaction of the starting substrate **13** with ethoxide. The other minor product was pyrrolidinone **19**, which was formed with a yield of 18% and enantiopurity of 90% *ee*. The relative stereochemistry of **19**, as determined by 2D NMR analysis, suggested first that **19** was derived from the oxazolidinone ring-opening reaction of our initially envisioned bicyclic aldol product **20**. Later, it was found that **19** was derived from the ring-opening reaction of *ent*-**20**, not from the reaction of **20** (vide infra).[15]

Other sodium alkoxides with bulky organic substituents were employed to suppress ring-opening of the oxazolidinone moiety. NaO*i*Pr and NaO*t*Bu also afforded bicyclic **17** at low temperatures (Scheme 3a, table, entries 1–2). Instead of the oxazolidinone ring

10.1002/anie.202210317

cleavage products **18** and **19**, these bases afforded another bicyclic aldol product. The obtained bicyclic species was not our initially envisioned aldol product **20**, but was, to our surprise, the enantiomer of **20** (*ent*-**20**).[16] The combined yield of the two aldol products **17** and *ent*-**20** was very high (ca. 90%), and the product ratio was 1:1.2. The enantiopurities of **17** and *ent*-**20** obtained from the reaction with NaO*t*Bu in THF/DMF/*t*BuOH were 90% and 91% *ee*, respectively. A sterically hindered strong organic base, KHMDS, also afforded the same two products with 90% *ee* and a yield and ratio similar to those of NaO*t*Bu (entry 3).

These results led us to suspect that the C-2 stereochemistry might be an important factor in determining the stereochemical outcome of the process. To comprehend the reaction, we performed additional experiments. When the two separated C-2 diastereomers of **13** were independently subjected to the aldol reaction conditions with NaO*t*Bu in THF/DMF, each diastereomer produced a 9:1 mixture of diastereomeric aldol products (Scheme 3b). The (2*R*)-**13** isomer rapidly produced (2*R*,3*R*,4*R*)-**17** as the major diastereomer along with its C-3 epimer **20**, while the reaction of the (2*S*)-**13** isomer[17] less rapidly afforded *ent*-**20** with the (2*S*,3*R*,4*S*) configuration as the major isomer and its C-3 epimer *ent*-**17** as the minor isomer. The enantiopurities of the obtained isomers were excellent to very high. Conducting the reaction in the presence of a protic solvent resulted in a very similar outcome (see the Supporting Information for details). These results explained the stereoselectivities obtained for the reaction with the C-2 diastereomeric mixture **13**. In addition, these results led us to conclude that the stereochemical outcome was controlled by the C-2 stereocenter.

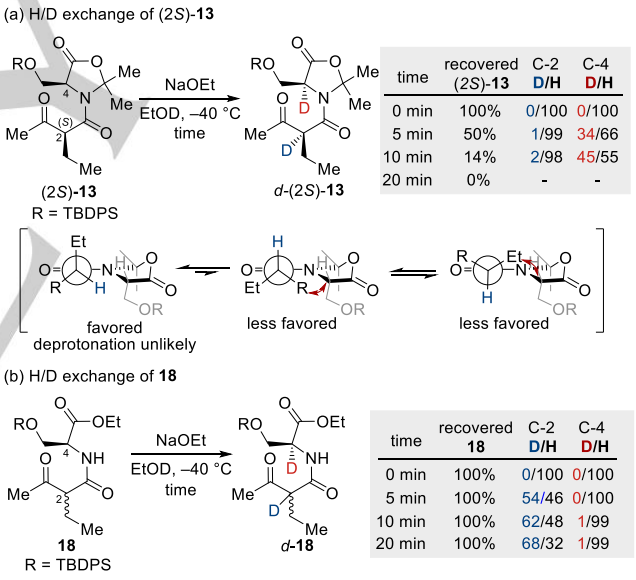


entry	conditions[a]	yield of **17**[b] (*ee*%)[c]	yield of *ent*-**20**[b] (*ee*%)[c]
1	NaO*i*Pr, *i*PrOH, –30 °C	41% (77)	50% (77)
2	NaO*t*Bu, THF/DMF/*t*BuOH[d], –78 °C	40% (90)	48% (91)
3	KHMDS, THF/DMF[e], –78 °C	39% (90)	47% (91)

[a] Reaction conditions: **13** (0.1 mmol, 1.0 equiv), base (3.0 equiv), solvent (0.05 M) [b] isolation yield
[c] *ee* value was determined by HPLC with a chiral stationary phase.
[d] ratio of THF/DMF/*t*BuOH = 1:1:0.1 [e] ratio of THF/DMF = 1:1

Scheme 3. Aldol cyclization of **13**.

At the outset of this study, we assumed that the configuration at the C-2 stereocenter would not be important because the DKR might occur at the epimerizable C-2 position. However, unlike our previous studies with oxazolidine-4-carboxylate,[8b] DKR was not operating with the 5-oxazolidinone substrate **13**. A deuteration study of (2*S*)-**13** with NaOEt/EtOD at –40 °C showed a negligible level of deuterium incorporation at C-2 (Figure 2a). On the other hand, appreciable deuterium exchange was observed at C-4. Interestingly, the stereocenters of recovered (2*S*)-**13** were not racemized.[8a] The obtained aldol product showed no detectable deuterium incorporation at C-2 (see the Supporting Information for details). The deuteration study of (2*R*)-**13** was aborted because of its very fast aldol reaction rate. However, it provided information indicating that the aldol product also did not contain deuterium at the C-2 position (see the Supporting Information for details). These results implied a low kinetic acidity for the C-2 hydrogen atom of substrate **13** under the reaction conditions. One reasonable explanation for the low kinetic acidity exhibited by the hydrogen atom on C-2 adjacent to two carbonyl groups could be 1,3-allylic strain in the deprotonation transition state, which could arise from the presence of the 5-oxazolidinone amide group, as shown in the brackets.[13] This explanation was supported by the observation that oxazolidinone ring *seco* substrate **18** showed facile basic deuteration at C-2 (Figure 2b).



time	recovered (2*S*)-**13**	C-2 D/H	C-4 D/H
0 min	100%	0/100	0/100
5 min	50%	1/99	34/66
10 min	14%	2/98	45/55
20 min	0%	-	-

time	recovered **18**	C-2 D/H	C-4 D/H
0 min	100%	0/100	0/100
5 min	100%	54/46	0/100
10 min	100%	62/48	1/99
20 min	100%	68/32	1/99

Figure 2. H/D exchange of **13** and **18** in EtOD.

Based on these results and our earlier reports, an aldol reaction mechanism of **13** was proposed, as shown in Scheme 4. An axially chiral enolate **A**, generated from the favored conformer (2*R*)-**13**, undergoes a rapid aldol reaction via conformer **A-II** to yield aldol product **17**. The reaction via conformer **A-I** would be less preferred because of the unfavorable dipole interaction between two carbon-oxygen bonds in a synclinal disposition. In the aldol reaction of (2*S*)-**13**, axial chiral enolate **A-III** was generated, similar to the reaction of (2*R*)-**13**. However, the C-2 alkyl group in **A-III** hinders enolate addition to the carbonyl group and prevents formation of the corresponding aldol product. Because the C-2 stereocenter of **13** is not readily epimerizable, (2*S*)-**13** takes an alternative reaction pathway that involves

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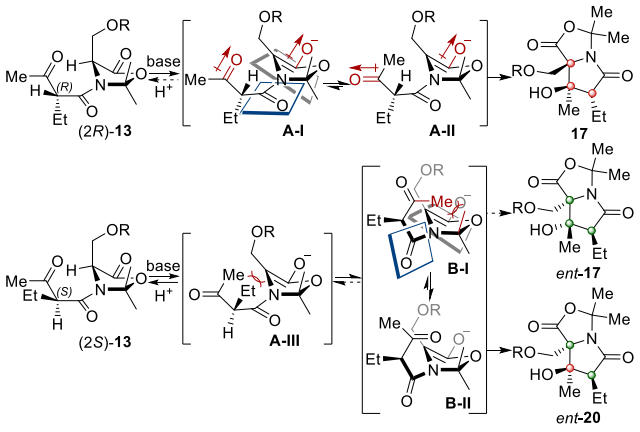
epimerization of the chiral enolate. In this event, the C-2 alkyl group no longer blocks the enolate addition to the carbonyl group as shown in conformer **B**. The conformer **B-I** would suffer from a severe steric interaction between the methyl group and the gem-dimethyl moiety of the oxazolidinone ring. Thus, the aldol reaction of (2*S*)-**13** would proceed via conformer **B-II** to give *ent*-**20** despite the dipole interaction.



Scheme 4. Plausible aldol reaction mechanism of **13**.

We observed an interesting phenomenon in attempted basic hydrolyses of bicyclic aldol products. While hydrolysis of the oxazolidinone ring of *ent*-**20** with KOH in THF/water was very fast and gave the corresponding hydrolysis product *ent*-**21**, the hydrolysis of **17** was sluggish and produced the C-3 epimerized hydrolysis product **21** without loss of enantiopurity (Figure 3a). To understand this unexpected C-3 epimerization, we performed the basic hydrolysis of **17** in deuterated THF with D_2O (Figure 3b). Monitoring of the reaction by NMR indicated the presence of peaks for **20** or *ent*-**20**. Hydrolysis product **21** was progressively formed without detectable deuterium incorporation at C-2 as the reaction progressed. The ratio of **17** to **20** was unchanged (15:1) throughout the experimental period. These observations suggested that **20** was an intermediate for formation of **21** and was in equilibrium with **17** under basic conditions. To further understand this interesting phenomenon, the reaction of (2*R*)-**13** was monitored over time. As mentioned above, formation of the two bicyclic aldol products **17** and its C-3 epimer **20** was very fast. The product ratio was constant over time and favored **17** (Figure 3c). [18] This result suggested that **17** might be the thermodynamic and kinetic product of the reaction of (2*R*)-**13**. Our density functional theory (DFT) calculations using simplified enolate **22** supported the experimental suggestion. As shown in Figure 3d, formation of the (2*R*,3*R*,4*R*)-isomer was favored both thermodynamically and kinetically. The energy differences calculated for products **P1** and **P2** correlated well with the diastereomeric ratios obtained in the aldol reaction. Considering the low activation barriers, the aldol adducts might be in rapid equilibrium with each other.

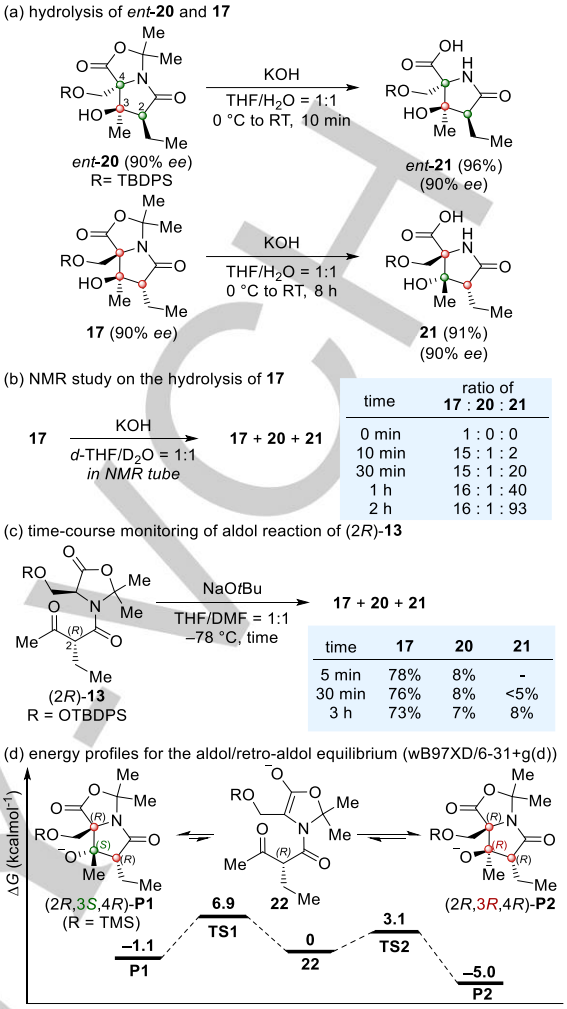


Figure 3. Hydrolysis of aldol products and mechanistic studies.

Based on the above experimental and computational studies, a hydrolytic C-3 epimerization mechanism of **17** was proposed, as shown in Scheme 5. Aldol product **17** is converted to its C-3 epimer **20** via a retroaldol–realdol process,[19] and the two are in fast equilibrium with one another. The minor aldol product **20** would experience more rapid hydrolysis because its C-3 hydroxyl group is *syn* to the adjacent oxazolidinone ring. This proximal C-3 hydroxyl group can cooperate or be involved in hydrolysis of the oxazolidinone ring, thus accelerating the rate of hydrolysis.[20] One possible route for participation is through intramolecular hydrogen-bond formation to promote hydrolysis.[20a,d] The other possible participation route for this proximal group is irreversible formation of the reactive *β*-lactone intermediate **23**. Although we could hardly detect it via NMR monitoring, we found that *β*-lactone **23**, which was obtained by intramolecular cyclization of **21**, was hydrolyzed extremely rapidly to afford **21** under the above basic conditions (see the Supporting Information for details). As a result of neighboring group participation by the C-3 hydroxyl group, the hydrolysis product distribution would not reflect the equilibrium distribution of the two aldol products, and the only hydrolytic product **21** arose from a minor component **20**. To the best of our knowledge, this type of substrate-driven hydrolytic DKR of diastereomers has not been reported thus far, although there are enzymatic or catalytic examples of hydrolytic DKR.[21]

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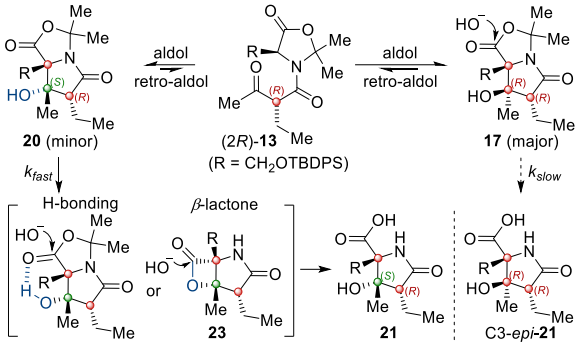


Scheme 5. Plausible hydrolytic epimerization mechanism of **17**.

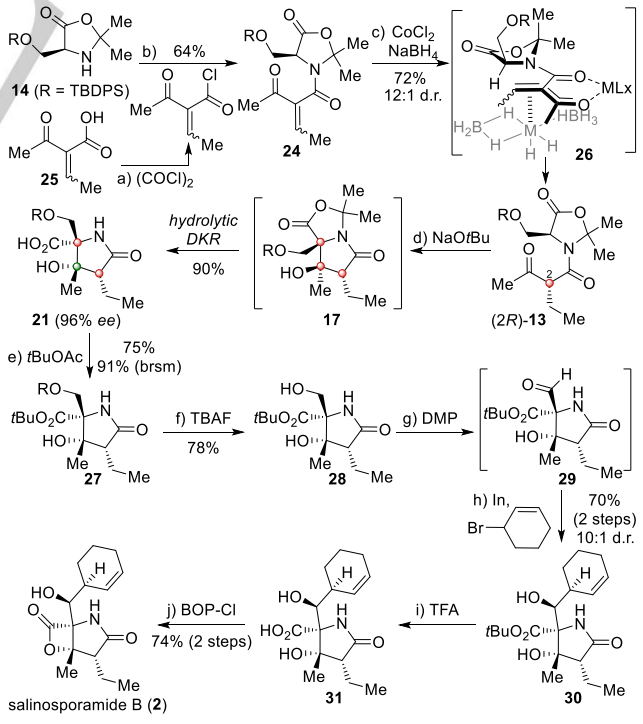
The initially envisioned MOC- and DKR-involved aldol approach with C-2 diastereomeric mixture **13** proved to be unsuccessful, especially with respect to the enantioselectivity; (2*R*)-**13** produced the desired stereomer **21** after aldol reaction and consequent hydrolysis, while (2*S*)-**13** afforded *ent*-**21**. Thus, we developed a new synthetic approach, as shown in Scheme 6. The endgame disconnections of our revised synthetic plan remained identical and would lead to pyrrolidinone **21**, which would be accessible via an intramolecular aldol reaction and hydrolysis of oxazolidinone **13**. Central to the new approach was selective installation of the C-2 stereocenter prior to the intramolecular aldol reaction. We envisioned that diastereoselective 1,4-reduction of α,β-unsaturated 1,3-dicarbonyl substrate **24** could be achieved with control by the stereocenter in the 5-oxazolidinone ring to afford either (2*S*)-**13** or (2*R*)-**13**. Although no precedent for this type of selective reduction has been reported, we deemed it possible based on Evans' oxazolidinone chemistry.[13]

The required substrate **24** was prepared as a 1:1.5 mixture of *E*/*Z* isomers by condensation of oxazolidinone **14** with the known β-ketoacid **25**.[22] This mixture was subjected to various 1,4-reduction conditions. Gratifyingly, we found that reduction with $NaBH_4$ in the presence of $CoCl_2$ in methanol proceeded with high diastereoselectivity (12:1) to afford (2*R*)-**13** as a major isomer.[23] Based on the stereochemical outcome at the C-2 center, we proposed that the reduction proceeded through **26** involving chelation and minimized allylic strain wherein a substituent on the oxazolidinone ring blocked the approach of the reductant from the *Re* face.

From our prior synthetic campaigns (Figure 3c),[18] it seemed that, under the appropriate conditions, the intramolecular aldol reaction of (2*R*)-**13** could occur in tandem with DKR hydrolysis. Thus, we sought reaction conditions for the one-pot tandem reaction. After some trials, we found that the reaction of (2*R*)-**13** with NaO*t*Bu in slightly wet *t*BuOH (~0.1% (v/v) water in *t*BuOH) at room temperature gave the desired pyrrolidinone **21** directly in 90% yield and with 96% *ee*. Increasing the water content was detrimental to the yield because excess water led to hydrolysis of the oxazolidinone ring prior to the aldol reaction.

Having achieved a selective route to **21**, the main task remaining for the total synthesis was attachment of the 2-cyclohexenyl group to the C-4 functional group with concomitant installation of the C-5 and C-6 stereogenic centers. We planned to achieve this goal by employing Corey's approach,[6a] which entailed the addition of a cyclohexenylzinc reagent to the C-4 aldehyde group. Corey's process is very commonly applied in syntheses of salinosporamides.[6a,b,d,e,i–k,m,o] However, success with this process required protection of the amide nitrogen, presumably due to the instability of the aldehyde intermediate and low diastereoselectivity.[6j,k] Only the Burton group has reported successful addition of the cyclohexenylzinc reagent to the unstable aldehyde substrate without a protecting group on the amide nitrogen, albeit in moderate yield.[6k] Encouraged by Burton's work, we proceeded to install the cyclohexene ring and stereocenters. To this end, the carboxylic acid in **21** was first converted to its *t*-butyl ester **27**, and the silyl protecting group was removed to afford **28**. Dess–Martin oxidation of **28** afforded the unstable aldehyde **29**, which was immediately subjected to the next reaction after filtration. The reaction of **29** with the cyclohexenylzinc reagent, which followed the Corey procedure,[6a] gave a mixture of two diastereomers (5:1 d.r.) with desired isomer **30** as the major component, albeit in modest yield (54%). Alternatively, we found that indium-mediated Barbier-type allylation, which greatly simplified the experimental operation, afforded the desired product with a much improved yield (70%) and selectivity (10:1 d.r.). The best outcome was obtained when THF was employed as the solvent and ammonium chloride as an additive.

With a route to **30** secured, we proceeded to construct β-lactone ring with two substituents at C-3 and C-4. Toward this end, *t*-butyl ester was hydrolyzed with trifluoroacetic acid (TFA) and the resulting crude acid **31** was treated with bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP–Cl) and triethylamine to give salinosporamide B (**2**) in good overall yield. The spectral data and optical rotations of **2** were in good agreement with those of natural salinosporamide B.[4] Overall, this asymmetric total synthesis was completed in only 11 steps from L-serine and 9% overall yield (9 steps from sily-protected serine **15** and 12% overall yield).

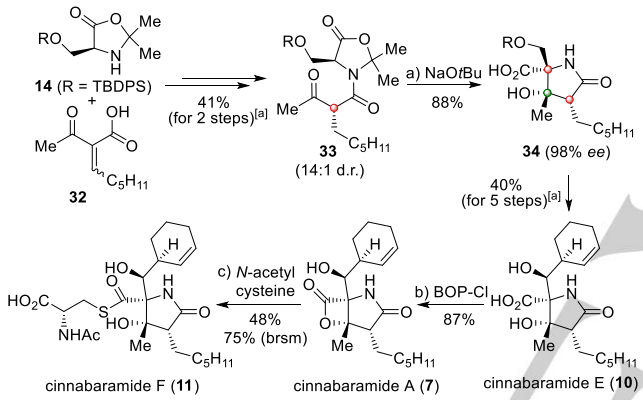


Scheme 6. Revised scheme for the total synthesis of salinosporamide B (**2**). Reagents and conditions: (a) $(COCl)_2$ (1.2 equiv), cat. DMF, CH_2Cl_2, 0 °C to rt, 2 h; (b) acid chloride of **25** (1.5 equiv), acetone, rt, 2 h, 64%; (c) $CoCl_2$ (4.0 equiv), $NaBH_4$ (5.0 equiv), MeOH, –78 °C to 0 °C, 1 h, 72% (12:1 d.r.); (d)

10.1002/anie.202210317

NaO*t*Bu (5.0 equiv), *t*BuOH, rt, 30 min, 90% (96% *ee*); (e) 50% $HClO_4$ (aq)/*t*BuOAc (1:50), rt, 16 h, 75% (91% brsm); (f) TBAF (2.0 equiv), AcOH (4.0 equiv), THF, 0 °C to rt, 12 h, 78%; (g) Dess–Martin periodinane (1.2 equiv), CH_2Cl_2, rt, 2 h; (h) In (5.0 equiv), 3-bromocyclohexene (3.0 equiv), NH_4Cl (5.0 equiv), THF, rt, 6 h, 70% (10:1 d.r.) for 2 steps; (i) TFA/CH_2Cl_2, rt, 2 h; (j) BOP-Cl (3.0 equiv), Et_3N (6.0 equiv), CH_2Cl_2, rt, 10 h, 74% for 2 steps. TBAF = tetrabutylammonium fluoride, DMP = Dess–Martin periodinane; TFA = trifluoroacetic acid, BOP-Cl = bis(2-oxo-3-oxazolidinyl)phosphinic chloride.

Using essentially the same chemistry described for the synthesis of **2**, we also accomplished the total syntheses of cinnabaramides, as briefly depicted in Scheme 7. The total synthesis of cinnabaramide A (**7**) was accomplished from **14** and **32** via the same process shown in Scheme 6. During this endeavor, cinnabaramide E (**10**) was obtained as a precursor to **7**, and cinnabaramide F (**11**) was derived from **7** by a reaction with *N*-acetylcysteine. The spectral data and optical rotations for the obtained cinnabaramides were in good agreement with those of the natural products,[5] thus confirming the structures of these natural products.



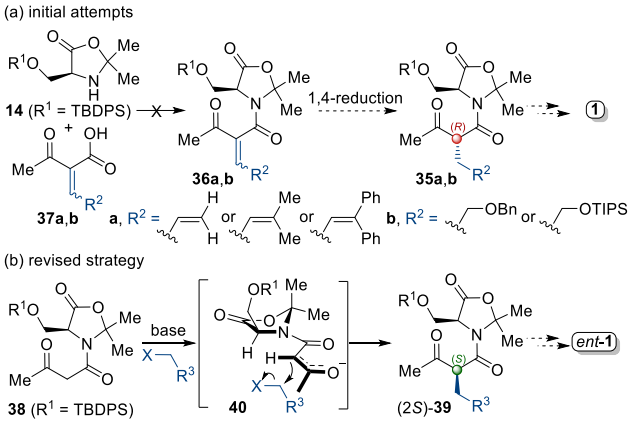
Scheme 7. Total syntheses of cinnabaramide A (**7**), E (**10**), and F (**11**). Reagents and conditions: (a) NaO*t*Bu (5.0 equiv), *t*BuOH, rt, 30 min, 88% (98% *ee*); (b) BOP-Cl (3.0 equiv), Et_3N (6.0 equiv), CH_2Cl_2, rt, 10 h, 87%; (c) *N*-Acetyl-L-cysteine (1.0 equiv), Et_3N (3.0 equiv), CH_2Cl_2, rt, 12 h, 48% (75% brsm). [a] The synthesis was performed with the same procedure as in Scheme 6. For details, see the supporting information.

Having established a concise route to salinosporamide B and cinnabaramides, we turned our attention to the total synthesis of salinosporamide A (**1**). We anticipated that the synthesis would be achieved by using basically the same chemistry, although it would require additional steps due to the presence of a reactive chlorine substituent. To this end, several attempts were first made to prepare the C-2 stereodefined aldol substrate **35** from **14** with the same 1,4-reduction protocol used for (2*R*)-**13** (Scheme 8a). However, all attempts were unsuccessful, mainly due to the instabilities of reduction substrate **36a** and the required *β*-ketoacids **37b**.

As an alternate strategy, we envisioned that the reaction of **38** with an alkylating reagent could selectively afford **39** (Scheme 8b). A related system that used Evans' 2-oxazolidinones has been reported.[24] However, a base-mediated alkylation of the Evans' auxiliary substituted *β*-ketoimides afforded very poor diastereoselectivity, probably because exposure of the products to basic conditions during the long reaction time led to epimerization at the stereocenter adjacent to the two carbonyl groups. In light of the notable configurational stability observed for C-2 of the 5-oxazolidinone **13** under basic conditions, we hypothesized that it could be possible to obtain **39** without substantial epimerization at C-2. Thus, we investigated the diastereoselective alkylation of 5-oxazolidinone-substituted *β*-ketoamide **38**.

Given that the 5-oxazolidinone moiety in **38** effectively acts as a chiral auxiliary, the alkylation reaction would proceed via transition state **40**, and thus, the major product would have the 2*S* stereochemistry (Scheme 8b). Because the 2*S* stereoisomer would lead to synthesis of the enantiomer of natural **1**, D-serine-derived oxazolidinone *ent*-**14** was employed as the precursor to (–)-**1**. (Scheme 9). Condensation between *ent*-**14** and the known *β*-ketoacid chloride **41**[25] in the presence of pyridine provided *β*-ketoamide *ent*-**38** without epimerization at the C-4 position. Gratifyingly, the reaction of *ent*-**38** with allyl bromide afforded the C-2 allylated product (2*R*)-**42** in good yield and with high diastereoselectivity (>16:1 d.r.). Notably, the diastereo-selectivity reported for alkylation of Evans' auxiliary substituted *β*-ketoimide with allyl halide was very low (up to 2:1 d.r.),[24a,c] which suggested the potential utility of the 4-substituted 5-oxazolidinone moiety in asymmetric synthesis.

The one-pot tandem aldol reaction and hydrolysis protocol was also successfully applied to (2*R*)-**42** to give the desired pyrrolidinone **43** (96% *ee*) via intermediate **44**. After conversion of the carboxylic acid moiety in **43** to the *t*-butyl ester, ozonolysis followed by reductive work-up yielded **45**. The primary hydroxyl group in **45** was protected with a Boc group, and the silyl protecting group was removed to afford **46**. Dess–Martin oxidation of **46** and a subsequent indium-mediated Barbier-type allylation afforded **47** with a good two-step yield (73%) and high diastereoselectivity (10:1 d.r.). After removal of the two acid-labile protective groups, lactonization with BOP-Cl followed by chlorination with Ph_3PCl_2 afforded (–)-**1** in good overall yield. The spectral data and optical rotation obtained for **1** were in good agreement with those of natural salinosporamide A.[1,6]



Scheme 8. Synthesis of the C-2 stereodefined aldol substrate for total synthesis of salinosporamide A (**1**).

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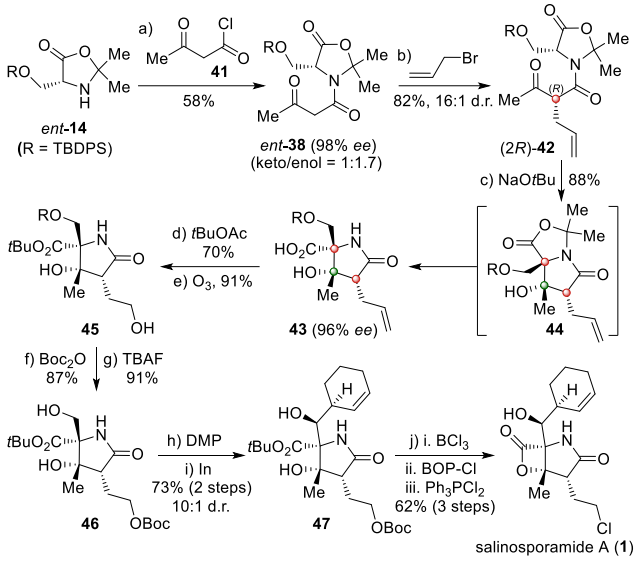

Scheme 9. Total Synthesis of Salinosporamide A (**1**). Reagents and conditions: (a) 3-oxobutanoyl chloride (1.5 equiv), pyridine (2.5 equiv), acetone, rt, 2 h, 58% (98% *ee*); (b) allyl bromide (5.0 equiv), NaH (1.1 equiv), DMF, 0 °C, 30 min, 82% (16:1 d.r.); (c) NaO*t*Bu (5.0 equiv), *t*BuOH, rt, 30 min, 88% (96% *ee*); (d) 50% $HClO_4$ (aq)/*t*BuOAc (1:50), rt, 16 h, 70%; (e) O_3, CH_2Cl_2/MeOH (1:1), –78 °C, 10 min, then $NaBH_4$ (10 equiv), 0 °C, 2 h, 91%; (f) Boc_2O (5.0 equiv), VOF_3 (0.1 equiv), CH_2Cl_2, reflux, 48 h, 87%; (g) TBAF (2.0 equiv), AcOH (4.0 equiv), THF, 0 °C to rt, 12 h, 91%; (h) Dess–Martin periodinane (1.2 equiv), CH_2Cl_2, rt, 2 h; (i) In (5.0 equiv), 3-bromocyclohexene (3.0 equiv), NH_4Cl (5.0 equiv), THF, rt, 6 h, 73% (10:1 d.r.) for 2 steps; (j) i. BCl_3 (3.0 equiv), CH_2Cl_2, 0 °C, 1 h; ii. BOP-Cl (3.0 equiv), CH_2Cl_2/pyridine (2:1), rt, 8 h; iii. Ph_3PCl_2 (2.0 equiv), CH_3CN/pyridine (1:1), rt, 4 h, 62% for 3 steps.

Conclusion

In this article, we have described the evolution of an asymmetric total synthetic strategy for preparing salinosporamide natural products. Given the challenging structural features and significant biomedical properties, salinosporamides have attracted great interest from the synthetic community, and many elegant synthetic strategies have been reported. However, there is still room for more efficient and selective synthetic routes. Our endeavors resulted in a 11-step concise total synthesis of salinosporamide B (**2**) and a 14-step route to salinosporamide A (**1**) with excellent stereoselectivities from the natural amino acid L-serine (or total 9 steps and 12 steps from **15**, respectively). In addition, the total syntheses of several natural congeners, including cinnabaramides A (**7**), E (**10**), and F (**11**) were achieved with the same chemistry, and this confirmed their structures. Initially, we focused on an approach that would implement a combination of MOC and DKR principles in the intramolecular aldol reaction of a 5-oxazolidinone aldol substrate for rapid access to the highly decorated pyrrolidinone core. However, unlike our previous studies with oxazolidine-4-carboxylate, MOC and DKR did not operate with the 5-oxazolidinone substrate. Throughout this study, efforts were made to explore and exploit the innate properties of the 5-oxazolidinone moiety as a stereochemical controller. Indeed, we have found that the 5-oxazolidinone moiety acts as in a manner similar to that of Evans' 2-oxazolidinone chiral auxiliary, and we utilized this moiety for selective installation of the C-2 stereocenter. In the revised synthetic approach, the C-2 stereocenter was installed prior to the intramolecular aldol reaction and was used to determine the stereochemical outcome of the aldol reaction. During our use of pyrrolidinone aldol products to synthesize the target products, we observed an interesting and unexpected hydrolytic DKR during hydrolyses of 5-oxazolidinone/pyrrolidinone bicyclic aldol products. This type of substrate-driven hydrolytic DKR with diastereomers has not been reported thus far and was utilized to prepare the pyrrolidinone core with excellent efficiency. Because of both the conciseness and potential modularity of this synthetic sequence, we anticipate that various analogs, including stereoisomers and congeners, will be easily accessible; this will provide a chance to achieve a greater understanding of the biomedical properties of salinosporamide natural products and lead to new drug discovery. In addition, given the excellent stereochemical induction observed, we believe that the 4-substituted 5-oxazolidinone moiety might serve as an effective chiral auxiliary or substrate in asymmetric synthesis. Such investigations are underway in our laboratory.

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Keywords: total synthesis • salinosporamides • kinetic resolution • natural products • heterocycles

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[15] The compound *ent*-**20** was rapidly converted to **19** through the oxazolidinone ring opening reaction with NaOEt in EtOH, while **17** was unreactive under the same conditions.

[16] The absolute stereochemistry of *ent*-**20** was determined by the synthesis of salinosporamide B (**2**) from *ent*-**20**. The sign of the optical rotation ($[\alpha]^{20}_D$= +49.4 (*c* 0.3, MeOH)) for the obtained **2** was opposite that of the optical rotation reported for the natural product ($[\alpha]^{25}_D$= –54.5(*c* 0.286, MeOH)).

[17] The stereochemistry of (2*S*)-**13** was determined by X-ray crystallographic analysis. Deposition Number 2179295 (for (2*S*)-**13**) contains supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

[18] As the reaction time was prolonged, **21** was formed, albeit in small amounts, presumably due to the presence of inadvertent moisture.

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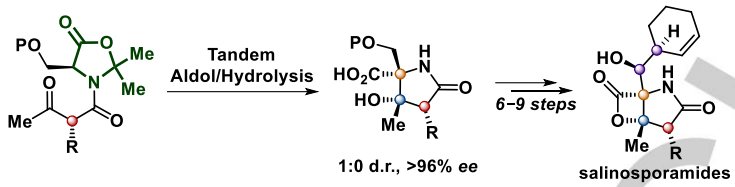

Described herein are the total syntheses of salinosporamides and cinnabaramides via a strategy involving rapid construction of the highly decorated pyrrolidinone core of the natural products from the simple amino acid serine. The key to the success of this synthesis was to exploit the innate properties of the serine-derived 5-oxazolidinone as a stereochemical controller and unprecedented substrate-driven hydrolytic dynamic kinetic resolution.