

Synthetic studies of salinosporamide A through the intramolecular hydroamidation of alkynes

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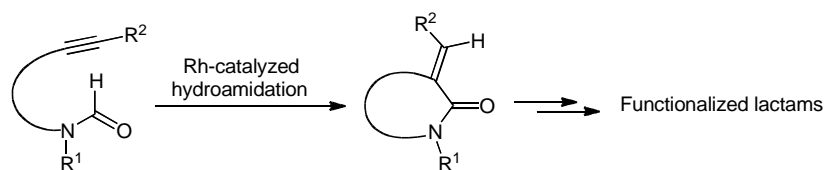
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Abstract:

Rhodium-catalyzed intramolecular hydroamidation of alkynes was carried out to construct the synthetic intermediates of a proteasome inhibitor, salinosporamide A. Several alkynyl formamides were synthesized and subjected to the hydroamidation reaction. Some derivatives with a methoxymethyl (MOM) or 2-methoxy-2-propyl (MOP) group near the reaction site were converted to the corresponding lactams in excellent yields.

1. Introduction

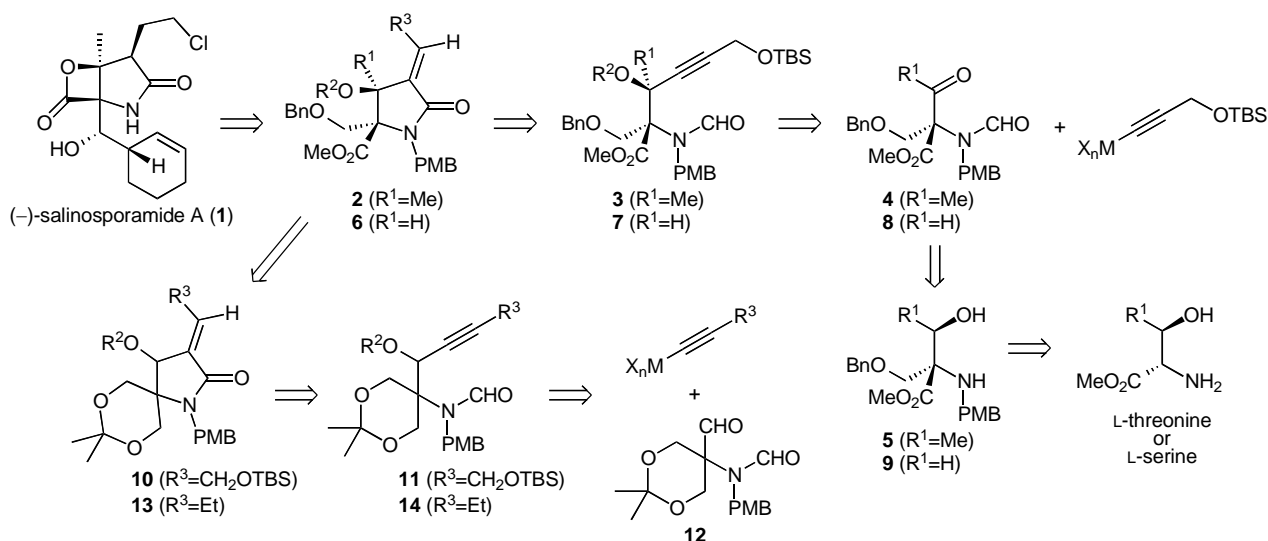
The synthesis of salinosporamide A (**1**) [1], a potent and selective proteasome inhibitor, has attracted much interest due to its important bioactivity and polysubstituted lactam structure [2–4]. In connection with our research on the synthesis of functionalized lactams through transition-metal-catalyzed reactions [5], we have launched a program directed toward the total synthesis of salinosporamide A. Our plan is based on the transition-metal-catalyzed hydroamidation of alkynes. By applying this reaction intramolecularly, we previously showed that α -alkylidene- γ -lactams can be synthesized from alkynyl formamides (Scheme 1) [6]. This approach has advantages for the synthesis of functionalized lactams in terms of ready access to cyclization precursors and neutral reaction conditions. Preceding studies [7] on hydroamidation were limited to simple substrates, and the reaction has rarely been applied to natural product synthesis [8].



Scheme 1.

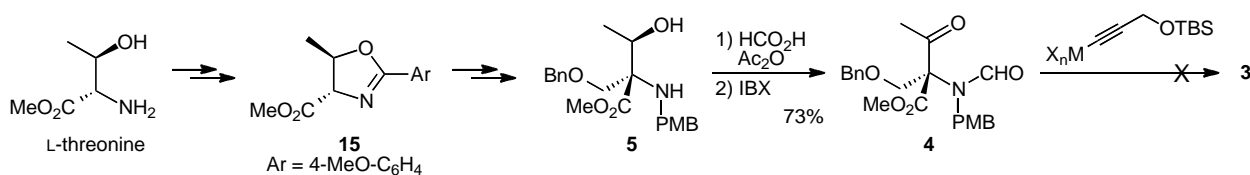
Our retrosynthetic analysis is shown in Scheme 2. To examine the key intramolecular hydroamidation, four cyclization precursors (**3**, **7**, **11**, and **14**) were designed. The targeted salinosporamide A (**1**) could be simplified by removing the cyclohexene moiety, opening the β -lactone, and introducing the exo-double bond in the lactam ring to yield γ -lactam **2**. This compound was envisioned to be formed by a key intramolecular hydroamidation that requires alkynyl formamide **3** as a precursor. Compound **3** could be obtained by the alkylation of keto amide **4**. Oxidation of known amino alcohol **5** [3a] derived from threonine will give ketone **4**. Formamide **7**, a cyclization precursor which lacks a methyl group at the propargylic position, could be prepared via synthetic intermediates **8** and **9** by a sequence similar to that for **3** from serine. Comparison of the hydroamidation of **7** with that of **3** may reveal the effect of steric hindrance near the alkynyl group. Another substrate for hydroamidation is acetal **11** which could be obtained from aldehyde **12**. For the total synthesis, differentiation of the two diastereotopic alkoxy groups

in the acetal moiety of **10** is required after the hydroamidation of **11**. We were also interested in formamide **14** with a simple alkyl group instead of a siloxymethyl group on the alkyne, since the bioactivities of salinosporamide A derivatives are known to strongly rely on the substituent at this position [9].

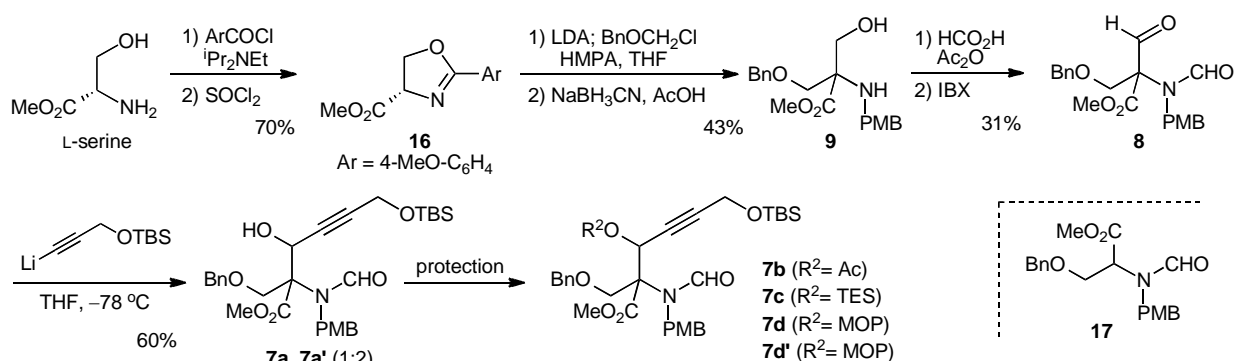


2. Results and discussion

The synthesis of **3** was attempted from amino alcohol **5** obtained from threonine through oxazoline **15** [3a] (Scheme 3). Alcohol **5** was converted to keto formamide **4** by formylation and oxidation. However, the alkylation of **4** did not proceed despite numerous and varied attempts; therefore, the cyclization precursor **3** was not available.

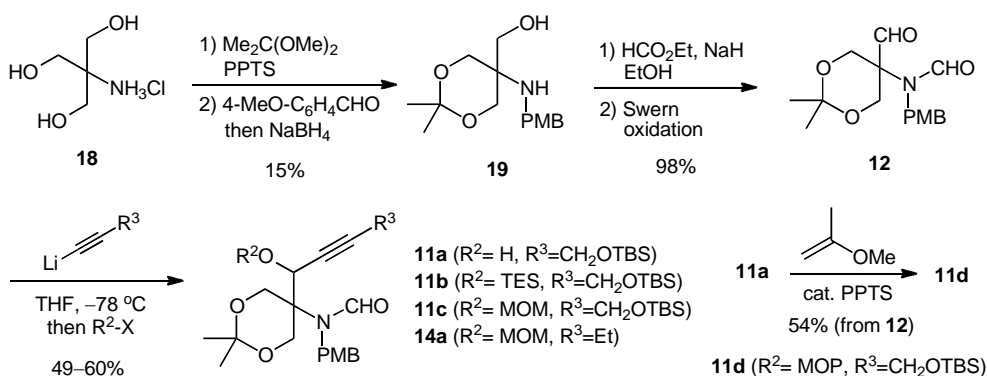


On the other hand, the syntheses of **7a-d**, **7a'**, and **7d'** were feasible (Scheme 4). Similar to **4**, aldehyde **8** was obtained in four steps from serine via **16** [10] and **9**. Addition of the lithium acetylide gave the desired alkynyl formamide as a 1:2 mixture of diastereomers, **7a** (less polar) and **7a'** (polar). During this addition process, the formation of retro-aldol product **17** was observed. This causes a moderate yield of **7**. Through appropriate protection of the hydroxy group in **7a** and **7a'**, formamides **7b-d** and **7d'** were obtained (**7b**: $R^2 = \text{Ac}$, **7c**: $R^2 = \text{TES}$, **7d** and **7d'**: $R^2 = \text{MOP}$).



Scheme 4.

Formamides **11a-d** and **14a** were synthesized in a straightforward manner (Scheme 5). Acetalization [11] of triol **18** followed by benzylation gave amino alcohol **19**. Selective *N*-formylation of this amino alcohol was accomplished with ethyl formate and sodium hydride in EtOH. Subsequent Swern oxidation gave aldehyde **12**, which was subjected to alkynylation with lithiated 3-siloxy-1-propyne or 1-butyne. Quenching of the alkoxides in situ with electrophiles such as water, TESCl, and MOMCl gave the corresponding formamides **11a-c** and **14a**. Compound **11d** was synthesized from **11a** by the reaction with 2-methoxypropene.



Scheme 5.

Hydroamidation was performed with Rh₄(CO)₁₂ (20 mol %) in xylene at 130 °C (Table 1) [6]. When **7a** with a free hydroxy group was subjected to the reaction, γ -lactam **6a** was obtained in 36% yield (entry 1). A significant amount of compound **17** (see Scheme 4) was also isolated (56%), which was probably formed by retro-aldol fragmentation. The corresponding diastereomer **7a'** gave similar results, which indicates that the stereochemistry at the propargylic position does not affect the reaction (entry 2). The same reaction of acetate **7b** and silyl ether **7c** did not give good results (entries 3, 4). However, 2-methoxy-2-propyl (MOP) derivatives **7d** and **7d'** underwent hydroamidation to give lactams **6a** and **6a'** in high yields after unexpected cleavage of the MOP group (entries 5, 6). It is likely that the MOP group was cleaved after cyclization because of the clear difference between the yields of entries 1 and 5. The reaction was also insensitive to the configuration of the starting materials **7d** and **7d'**. Similarly, hydroxy-free acetal **11a** gave lactam **10a** in 30% yield (entry 7). The reaction of **11b** (R²= TES) was also unsatisfactory (entry 8). Although the MOP group was cleaved during the reaction, compounds **11c** and **11d** with either a MOM or MOP group were converted to the corresponding lactams in acceptable yields (entries 9, 10). Since treatment of MOM **14** bearing an ethyl group instead of a siloxymethyl group under the same conditions furnished the desired product **13a** in a yield comparable to that of **11c** (entry 11), the acetylene can accommodate a simple alkyl group as an R³ substituent. The results in Table 1 show that substrates with acetal moieties such as MOM or MOP at the propargylic position gave better yields than others. The origin of this effect is under investigation in our laboratories.

Table 1. Rhodium-catalyzed intramolecular hydroamidation of alkynyl formamides.^a

entry	substrate	product	yield (%) ^b
1	7a (R ² = H)	6a (R ² = H)	36 ^c
2	7a' (R ² = H)	6a' (R ² = H)	24 ^d
3	7b (R ² = Ac)	6b (R ² = Ac)	-
4	7c (R ² = TES)	6c (R ² = TES)	18 (53)
5	7d (R ² = MOP)	6a (R ² = H)	quant
6	7d' (R ² = MOP)	6a' (R ² = H)	92
7	11a (R ² = H, R ³ = CH ₂ OTBS)	10a (R ² = H, R ³ = CH ₂ OTBS)	30
8	11b (R ² = TES, R ³ = CH ₂ OTBS)	10b (R ² = TES, R ³ = CH ₂ OTBS)	29 (22)
9	11c (R ² = MOM, R ³ = CH ₂ OTBS)	10c (R ² = MOM, R ³ = CH ₂ OTBS)	61
10 ^e	11d (R ² = MOP, R ³ = CH ₂ OTBS)	10a (R ² = H, R ³ = CH ₂ OTBS)	48
11	14a (R ² = MOM, R ³ = Et)	13a (R ² = MOM, R ³ = Et)	59

^a Reaction was carried out with Rh₄(CO)₁₂ (20 mol %) in xylene at 130 °C for 2 h. ^b The values in parentheses show the yield of recovered starting materials. ^c Compound **17** (see Scheme 4) was isolated in 56% yield. ^d Compound **17** was isolated in 70% yield. ^e 10 mol% of the catalyst was used.

In summary, we have developed concise synthetic routes to the key intermediates of salinosporamide A and its analogs. Hydroamidation was shown to be feasible even for functionalized substrates. It is worth noting that during the synthesis, the formyl group which initially acted as a protecting group, was incorporated into the molecular framework by its chemoselective activation with the rhodium catalyst. The results described herein are a progressive attempt to apply hydroamidation to total synthesis. Chemoselective activation of an inert functionality such as formamide with a transition metal catalyst was shown to be an effective and attractive synthetic strategy in a multistep synthesis. Further investigations directed toward the total synthesis of salinosporamide A are currently ongoing in our laboratories.

3. Experimental

3.1. General procedure for rhodium-catalyzed intramolecular hydroamidation

A mixture of formamide (0.0252 mmol) and Rh₄(CO)₁₂ (3.77 mg, 0.00504 mmol) in xylene (0.25 ml) was stirred at 130 °C for 2 h under Ar atmosphere. After cooling and evaporation of the volatile materials, the crude residue was purified by SiO₂ column chromatography to give lactam.

3.1.1 Analytical data for lactam **6a** ¹H NMR (500 MHz, CDCl₃, δ) 7.34–7.30 (m, 4H), 7.18–7.15 (m, 4H), 6.76 (d, 1H, *J* = 8.6 Hz), 6.74 (ddd, 1H, *J*₁ = *J*₂ = 4.8 Hz, *J*₃ = 2.1 Hz), 5.03 (dd, 1H, *J*₁ = 6.7 Hz, *J*₂ = 2.1 Hz), 4.62 (d, 1H, *J* = 15.3 Hz), 4.54 (dd, 1H, *J*₁ = 4.8 Hz, *J*₂ = 1.5 Hz), 4.53 (dd, 1H, *J*₁ = 4.8 Hz, *J*₂ = 1.5 Hz), 4.47 (d, 1H, *J* = 15.3 Hz), 4.27 (d, 1H, *J* = 11.9 Hz), 4.21 (d, 1H, *J* = 11.9 Hz), 3.87 (d, 1H, *J* = 10.4 Hz), 3.85 (d, 1H, *J* = 10.4 Hz), 3.76 (s, 3H), 3.54 (s, 3H), 3.45 (d, 1H, *J* = 6.7 Hz), 0.91 (s, 9H), 0.11 (s, 6H); ¹³C NMR (126 MHz, CDCl₃, δ) 171.1, 167.8, 158.8, 137.3, 136.5, 133.1, 129.6, 128.6, 128.5, 127.9, 127.6, 113.6, 73.3, 70.6, 67.8, 61.2, 55.2, 52.6, 44.7, 29.6, 25.8, -0.1, -5.5; IR (ATR) 3343, 1673 cm⁻¹; HRMS (FAB⁺) C₃₀H₄₁NO₇Si: (M⁺) 555.2652. Found 555.2657.

3.1.2 Analytical data for lactam **6a'**

¹H NMR (500 MHz, CDCl₃, δ) 7.34–7.31 (m, 3H), 7.21 (d, 2H, *J* = 7.0 Hz), 7.16 (d, 1H, *J* = 8.6 Hz), 6.74 (d, 2H, *J* = 8.6 Hz), 6.64 (dd, 1H, *J*₁ = 6.4 Hz, *J*₂ = 3.1 Hz), 5.11 (m, 1H), 4.63–4.52 (m, 3H), 4.39–4.30 (m, 3H), 3.90 (d, 1H, *J* = 10.7 Hz), 3.82 (d, 1H, *J* = 10.7 Hz), 3.74 (s, 3H), 3.39 (s, 3H), 0.91 (s, 9H), 0.13 (s, 3H), 0.13 (s, 3H); ¹³C NMR (126 MHz, CDCl₃, δ) 169.8, 168.6, 158.9, 137.5, 134.0, 132.8, 130.3, 128.8, 128.4, 127.9, 127.8, 113.5, 73.2, 71.4, 69.4, 66.6, 62.3, 55.2, 52.0, 44.3, 25.8, 18.4, –0.1, –5.7; IR (ATR) 3366, 1670 cm⁻¹; HRMS (FAB⁺) C₃₀H₄₂NO₇Si: (MH⁺) 556.2731. Found 556.2731.

3.1.3 Analytical data for lactam **10c**

¹H NMR (500 MHz, CDCl₃, δ) 7.25 (d, 2H, *J* = 8.8 Hz), 6.88 (dd, 1H, *J*₁ = *J*₂ = 6.4 Hz), 6.84 (d, 2H, *J* = 8.8 Hz), 4.84 (s, 1H), 4.65 (s, 2H), 4.56 (d, 2H, *J* = 5.2 Hz), 4.06 (d, 1H, *J* = 12.2 Hz), 3.93 (d, 1H, *J* = 12.2 Hz), 3.79 (s, 3H), 3.53 (d, 1H, *J* = 11.9 Hz), 3.38 (s, 3H), 3.10 (d, 1H, *J* = 11.9 Hz), 1.36 (s, 6H), 0.92 (s, 9H), 0.10 (s, 3H), 0.098 (s, 3H); ¹³C NMR (126 MHz, CDCl₃, δ) 168.0, 159.1, 139.4, 128.9, 114.1, 98.8, 94.0, 71.0, 62.8, 62.2, 60.3, 55.6, 55.2, 43.2, 26.4, 25.8, 20.5, 18.2, –5.35, –5.39; IR (ATR) 1692 cm⁻¹; HRMS (FAB⁺) C₂₇H₄₃NO₇Si: (M⁺) 521.2809. Found 521.2789.

3.1.4 Analytical data for lactam **13a**

¹H NMR (500 MHz, CDCl₃, δ) 7.25 (d, 2H, *J* = 8.9 Hz), 6.84 (d, 2H, *J* = 8.9 Hz), 6.83 (t, 1H, *J* = 14.7 Hz), 4.83 (s, 1H), 4.66 (s, 2H), 4.55 (s, 2H), 4.09 (d, 1H, *J* = 12.2 Hz), 3.94 (d, 1H, *J* = 12.2 Hz), 3.79 (s, 3H), 3.53 (d, 1H, *J* = 12.2 Hz), 3.41 (s, 3H), 3.07 (d, 1H, *J* = 12.2 Hz), 2.40 (dq, 2H, *J*₁ = 14.7 Hz, *J*₂ = 7.4 Hz), 1.37 (s, 3H), 1.36 (s, 3H), 1.01 (t, 3H, *J* = 7.4 Hz); ¹³C NMR (126 MHz, CDCl₃, δ) 168.4, 159.0, 143.0, 128.8, 114.0, 98.8, 93.6, 70.6, 62.7, 62.0, 60.2, 55.6, 55.2, 43.0, 26.4, 22.5, 20.5, 13.5; IR (ATR) 1685 cm⁻¹; HRMS (FAB⁺) C₂₂H₃₁NO₆: (M⁺) 405.2151. Found 405.2149.

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