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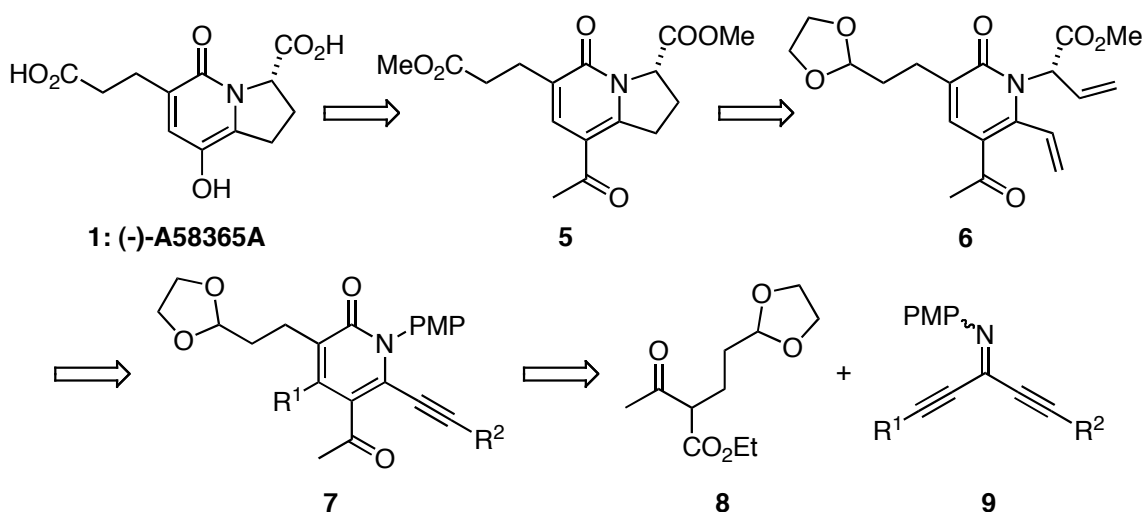
3,4,5,6-TETRASUBSTITUTED 2-PYRIDONE SYNTHESIS VIA NUCLEOPHILIC ADDITION OF ACTIVE METHINE COMPOUNDS TO DIALKYNYL IMINES DIRECTED TO THE SYNTHESIS OF (-)-A58365A

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Abstract—3,4,5,6-Tetrasubstituted-2-pyridone synthesis via nucleophilic addition of active methine compounds to dialkynyl imines directed to the synthesis of (-)-A58365A has been developed. The reaction of active methine compounds such as malonic esters or β -keto esters to dialkynyl imines provided 3,4,5,6-tetrasubstituted-2-pyridones in moderate to good yields.

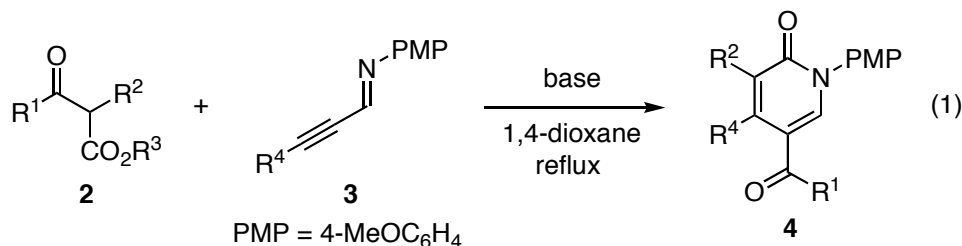
There are many biologically active compounds containing a 2-pyridone structure.¹ (-)-A58365A (**1**) having a 2-pyridone structure is one of them, which was obtained from a fermentation broth of the bacterium *Streptomyces chromofucus* in the Eli Lilly laboratories and found to be an angiotensin-converting enzyme inhibitors at nanomolar concentrations (Scheme 1).²



Scheme 1. Synthetic Plan for the Synthesis of (-)-A58365A

 This paper is dedicated to Professor Satoshi Omura on the occasion of his 70th birthday.

This property makes it of potential value as a lead compound for the design of drugs to control blood pressure. In connection with the synthesis of (-)-A58365A (**1**), the development of the synthetic methods of functionalized 2-pyridone is important as a result of the large number of biologically active compounds containing a 2-pyridone structure and also as dienes in Diels-Alder cycloadditions.³⁻⁵ We have already reported 5-alkoxycarbonyl-2-pyridone and 5-acetyl-2-pyridone (**4**) synthesis via the nucleophilic addition of malonic esters or β -keto esters (**2**), respectively, to alkynyl imines (**3**) derived from 2-alkynals (Eq. 1).⁶



On the basis of these results, we planned a synthesis of (-)-A58365A (**1**) as shown in Scheme 1.⁷ Padwa group has already reported the total synthesis of (-)-A58365A via 2-pyridone intermediate (**5**),^{7b} and therefore, the preparation of the 2-pyridone (**5**) provides a formal synthesis of (**1**). 2-Pyridone intermediate (**5**) would be obtained from (**6**) via olefin metathesis. The 2-pyridone (**7**) would be synthesized using our 2-pyridone synthesis via nucleophilic addition of β -keto ester (**8**)⁸ to dialkynyl imine (**9**).

Table 1. 2-Pyridone (**7**) Synthesis via Nucleophilic Addition of (**8**) to (**9**)

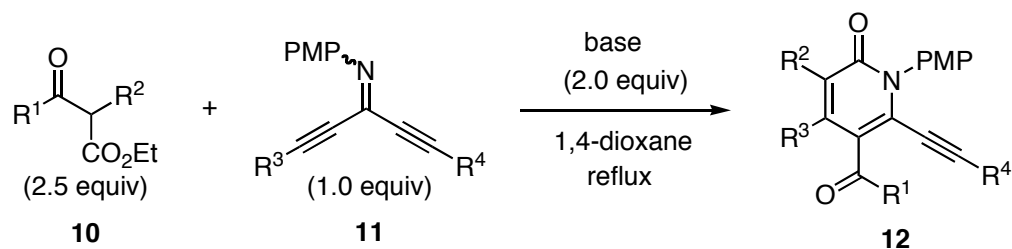
NaOEt
(2.0 equiv)
1,4-dioxane
reflux

8 (2.5 equiv)
9a: R¹ = R² = H
9b: R¹ = TMS, R² = TBDMS
9c: R¹ = H, R² = TBDMS
7a: R¹ = R² = H
7b: R¹ = TMS, R² = TBDMS
7c: R¹ = H, R² = TBDMS

Entry	Imine	Time (h)	Product	Yield (%)
1	9a	5.5	7a	8
2	9b	23.5	7b	7
3	9c	2.5	7c	9
4 ^a	9c	5.5	7c	51

^a The imine (**9c**) was added dropwise using a syringe pump to the solution of β -keto ester sodium salt (**8**) in 1,4-dioxane under reflux.

We investigated the effect of the substituents R¹ and R² of dialkynyl imine (**9**) (Table 1).⁹ When the reaction of β -keto ester (**8**) with imine (**9a**) was carried out in 1,4-dioxane in the presence of NaOEt under reflux, the desired 2-pyridone (**7a**) was obtained in 8% yield, because the imine (**9a**) decomposed under

Table 2. 2-Pyridone Synthesis Using Dialkynyl Imines

Entry	10	11	Base	Time (h)	12 , %yield ^a
1			NaOEt	6	 12a 66
2	10a		NaOEt	9	 12b 44
3		11a	NaOEt	14	 12c 52
4	10b	11b	NaH	14	 12d 56
5	10a		NaH	1	 12e 71
6			NaH	21	 12f 55
7	10b	11c	NaOEt	7	 12g 40 (28)
8	10b	11d	NaOEt	12	 12h 51 (31)
9		11d	NaH	21	 12i 42 (27) 12i' 12

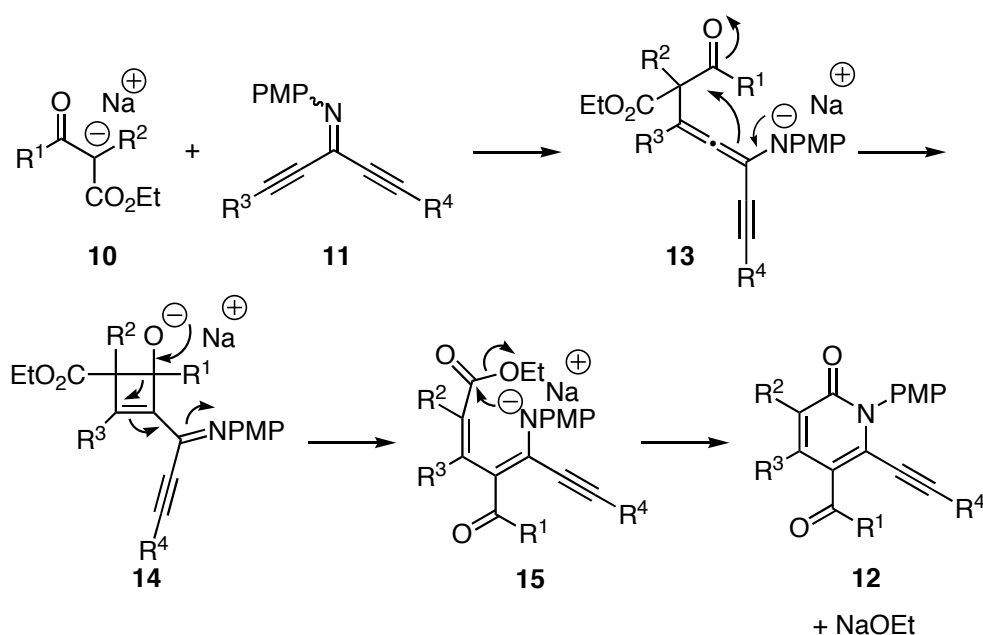
^a Isolated yields. Yields of the recovered imines in parentheses.

the reaction conditions (Entry 1). The reaction of imine (**9b**) gave the 2-pyridone (**7b**) in 7% yield along with the recovered imine (**9b**) in 84% yield since the initial 1,4-addition did not sufficiently proceed due to the steric bulk of the imine (**9b**). Use of imine (**9c**) afforded 2-pyridone (**7c**) in 9% yield (Entry 3). The reaction was very sensitive to the concentration of the imine (**9**). When the imine (**9c**) in 1,4-dioxane was added dropwise using a syringe pump to the solution of the sodium salt of β -keto ester (**8**) in 1,4-dioxane under reflux, 2-pyridone (**7c**) was obtained in 51% yield (Entry 4).

Next, we investigated the scope of substrates in a 3,4,5,6-tetrasubstituted-2-pyridone (**12**) synthesis via nucleophilic addition of active methine compounds (**10**) to dialkynyl imines (**11**). The results are summarized in Table 2.

First, we examined the reaction of a symmetrical dialkynyl imine with an active methine compound. The reaction of dialkynyl imine (**11a**) with the sodium salt of diethyl methylmalonate (**10a**) proceeded smoothly in 1,4-dioxane under reflux for 6 h to give the desired 2-pyridone (**12a**) in 66% yield (Entry 1).¹⁰ In the case of ethyl 2-methyl-3-oxobutanoate (**10b**), 2-pyridone (**12c**) was obtained in 52% yield (Entry 3). Not only an aromatic group but also an aliphatic counterpart as a substituent of imine (**11**) worked well (Entries 2 and 4). Next, we examined the reaction of an unsymmetrical dialkynyl imine.⁹ The 1,4-addition reaction of the sodium salt of diethyl methylmalonate (**10a**) to unsymmetrical dialkynyl imine (**11c**) proceeded regioselectively to give only 2-pyridone (**12e**) in 71% yield where the less hindered sp carbon reacted preferentially (Entry 5). Even increasing the steric bulk of the nucleophile as in the case with diethyl allylmalonate (**10c**), 2-pyridone (**12f**) possessing a double bond isomerized internally was obtained in 55% yield (Entry 6). The use of ethyl 2-allyl-3-oxobutanoate (**10d**) gave 2-pyridone (**12i**) in 42% yield accompanied by 2-pyridone (**12i'**) in 12% yield (Entry 9).

We propose a plausible reaction mechanism as shown in Scheme 2. Methalloallenamine (**13**) would be generated via a regioselective 1,4-addition reaction of the sodium salt of active methine compound (**10**) to dialkynyl imine (**11**) and undergoes an intramolecular cyclization to give cyclobutenoxide intermediate (**14**). The cyclobutenoxide intermediate (**14**) would be transformed into metalloenamine (**15**) via a ring-opening reaction, and the subsequent cyclization would give 3,4,5,6-tetrasubstituted 2-pyridone (**12**). In summary, we have found a 3,4,5,6-tetrasubstituted-2-pyridone synthesis via nucleophilic addition of active methine compounds to dialkynyl imines. Numerous methods for the synthesis of 2-pyridones have been reported. However, the present 2-pyridone synthesis is an attractive alternative method because substituted malonic esters, β -keto esters (**10**), and dialkynyl imines (**11**) are readily available, respectively and alkynyl groups in 2-pyridones can also be easily transformed into alkenyl and alkyl groups. The synthesis of (-)-A58365A from 2-pyridone (**7c**) is now in progress.



Scheme 2. Plausible Reaction Mechanism

ACKNOWLEDGEMENTS

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9. Unsymmetrical imines were geometrical mixtures of C=N bond.
10. A typical experimental procedure of the reaction of dialkynyl imines with active methine compounds: To NaOEt (27.2 mg, 0.400 mmol) was added a solution of diethyl methylmalonate (**10a**) (87.1 mg, 0.500 mmol) in 1,4-dioxane (2.0 mL) and a solution of dialkynyl imine (**11a**) (67.1 mg, 0.200 mmol) in 1,4-dioxane (2.0 mL) at room temperature. The reaction mixture was stirred under reflux for 6 h and then cooled to room temperature. Brine (10 mL) was added to quench the reaction. The mixture was extracted with CH₂Cl₂ (15 mL x 3). The combined organic layers were dried over sodium sulfate. The solvents were evaporated in vacuo and then the residue was purified by preparative TLC on silica gel (*n*-Hex/EtOAc = 1/1, as an eluent) to give 3,4,5,6-tetrasubstituted-2-pyridone (**12a**) (61.0 mg, 66%) as a light yellow solid. Mp 153.5-155.5 °C (white mica-like crystals, *n*-Hex-EtOAc). ¹H NMR (270 MHz, CDCl₃): δ = 7.38-7.47 (m, 3H), 7.20-7.36 (m, 7H), 7.01-7.08 (m, 4H), 3.96 (q, *J* = 7.3 Hz, 2H), 3.87 (s, 3H), 2.02 (s, 3H), 0.93 (t, *J* = 7.3 Hz, 3H). ¹³C NMR (67.8 MHz, CDCl₃): δ = 166.2, 162.6, 159.7, 146.8, 137.3, 132.1, 131.5, 129.5, 129.3, 129.2, 128.3, 128.3, 128.1, 128.1, 127.9, 121.1, 119.4, 114.4, 101.8, 81.2, 61.4, 55.5, 14.7, 13.6. IR (KBr): 3051, 2986, 2953, 2934, 2838, 2211, 1725, 1653, 1608, 1590, 1511, 1465, 1442, 1389, 1369, 1320, 1298, 1250, 1172, 1156, 1107, 1075, 1026, 1011, 832, 799, 764, 702, 691 cm⁻¹. MS (ESI) *m/z*: 464 (M+H)⁺.