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Preparation of functionalised monobactams from pyridones

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ABSTRACT

A novel synthesis of functionalised monobactams in high isolated yields is described. The procedure involves photochemical cyclisation of commercially available 2-pyridones followed by ring-opening cross-metathesis.

The β-lactam skeleton is the common structural element in the penicillin family and is responsible for the observed biological activity. An alarming increase in bacterial resistance to β-lactam antibiotics has emerged which has stimulated research towards new antibiotic compounds.[1] As a result, several synthetic and semi-synthetic compounds containing the β-lactam ring have been prepared and subsequently tested.[2] The discovery of nocardicins **1** (Fig. 1) has demonstrated for the first time that β-lactams do not require a conformationally constrained bicyclic structure to have anti-bacterial properties, suggesting that a suitably functionalised 2-azetidinone ring as in **2** constitutes an adequate pharmacophore.[3]

It has been reported that monocyclic β-lactams are remarkably active, not only as antibacterials, but also as inhibitors of cytomegalovirus protease,[4] cholesterol absorption[5] and human tryptase.[6] These discoveries have encouraged the synthetic community towards finding alternative methods for their preparation allowing rapid construction of novel classes of monobactams.

As a part of our ongoing studies on the generation of chemical diversity using aromatic heterocycles,[7–12] we envisaged a novel synthesis of monobactams starting from commercially available 2-pyridones (Scheme 1). 2-Pyridones possess a low degree of aromaticity, and for this reason, they often have been employed as dienes in Diels-Alder reactions.[13] They have also been reported to undergo photochemical electrocyclisation to furnish bicyclic structures **4**.[14] The cyclisation is stereoselective and only cis-fused bicyclic compounds **4** were obtained. It was reasoned that if compounds **4** were metathesis active, their reaction with alkenes would furnish a novel means to produce monobactams **3**. Compounds **3** contain two alkene moieties that in turn could be employed to prepare libraries of monobactams for biological evaluation. As ring strain is the major driving force promoting ring-opening metathesis (ROM)/cross-metathesis (CM) sequences,[15] we were sufficiently confident on the viability of the reaction leading from **4** to **3** (Scheme 1). Importantly, in this synthesis, variation of the alkene component in the ROM/CM step or introduction of a substituent in the pyridone substrate would furnish an efficient means to generate libraries of compounds.

Herein, we report our preliminary results on the development of the synthetic strategy highlighted in Scheme 1. We started our investigation by submitting several commercially available 2-pyridones to photochemical-induced electrocyclisation (Table 1). A literature survey revealed the following facts:[14] (a) the cyclisation was faster when a methoxy substituent was present at position 4 of the 2-pyridone: typically, 4-methoxy-2-pyridone cyclised upon irradiation in 2–4 h, while the unsubstituted 2-pyridone required over 70 h; (b) while a large variety of solvents could be employed in this reaction, it appeared that each 2-pyridone required a specific solvent to ensure high conversion; (c) the yields of cycloadducts **4** were generally low, although quantitative conversions of **5** were often reported.[14a] With the aim of obtaining compounds **4a–e** in sufficient amounts for preparative studies, we studied the reaction of 2-pyridones **5a–e** in several solvents including toluene, CH_3CN, EtOH, EtOAc and MeOH (Table 1).

Irradiation of compounds **5a–d** always proceeded to quantitative conversion. However, the isolated yields of compounds **4a–d** after silica gel chromatography were never greater than 30–35%. It was also noticed that upon deposition of crude **4a–d** on silica gel several additional side products were formed. Further studies concluded that neutral alumina was the best medium for

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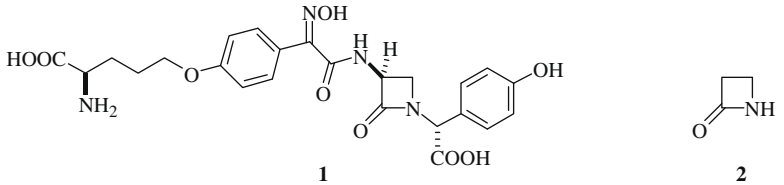
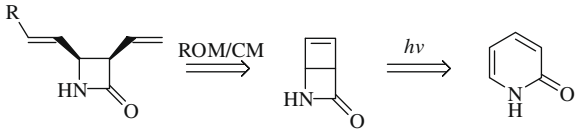
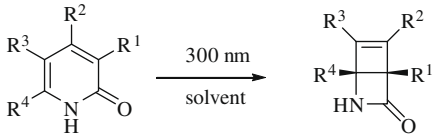


Figure 1.



Scheme 1.

Table 1



Entry	Substrate	R^1	R^2	R^3	R^4	Solvent[a]	Product	Yield[b] (%)
1	**5a**	H	H	H	H	CH_3CN	**4a**	65
2	**5b**	OCH_3	H	H	H	CH_3CN	**4b**	70
3	**5c**	H	CH_3	H	H	EtOAc	**4c**	75
4	**5d**	H	H	CH_3	H	EtOH	**4d**	70
5	**5e**	H	H	H	CH_3	EtOAc	**4e**	—

[a] Reactions carried out by irradiating with a monochromatic 300 nm lamp at a concentration of 10^{-3} M in a Hanovia chamber.
[b] Isolated yields after column chromatography on neutral alumina.

purification allowing compounds **4a–d** to be obtained in 65–75% isolated yields. Although previously reported,[14b] the conversion of **5e** into **4e** did not proceed in our hands. We next studied the ROM/CM of compounds **4a** and **4c** which were selected as examples of unsubstituted and substituted cyclobutenes. Reactions of **4a** and **4c** with ethylene were carried out using 0.1 equiv of Grubbs' catalyst I, Grubbs' catalyst II and Hoveyda catalyst II. The best results were obtained using Grubbs' catalyst I and dichloromethane as solvent. Initially, Grubbs' catalyst I was added in one portion at the onset of the reaction. Later it was found that cleaner and higher yielding reactions were obtained by dropwise addition of a freshly prepared solution of the ruthenium catalyst in dichloromethane. Reaction of **4a** and **4c** with ethylene in the presence of 0.1 equiv of Grubbs' I did not go to completion giving only 50% and 28% yields, respectively, of compounds **6** and **11** (Table 2, entries 1 and 4) together with recovered starting material. Addition of further amounts of ethylene did not improve the yields.

The reaction of **4a** and ethylene proceeded to full conversion after addition of a further 0.15 equiv of ruthenium catalyst to the reaction mixture, giving compound **6** in nearly 80% yield. Increasing the temperature did not lead to an improved yield. Reaction of **4a** with styrene or 1-hexene furnished the expected two regioisomers **7**, **8** and **9**, **10** in low yields (Table 2, entries 2 and 3). Reaction of **4c** and styrene or 1-hexene furnished only regioisomers **12** and **13** in low yields (Table 2, entries 5 and 6).

The following observations suggested that incomplete conversion in the experiments employing 0.1 equiv of catalyst (Table 2) can be attributed to deactivation of the metathesis catalyst: (a) the 2-azetidinone ring impedes delocalisation of the nitrogen lone pair, hence this could act as a ligand. (b) During the purification of compounds **6–13**, a discrete compound was repeatedly obtained containing monobactam and ruthenium; as yet we have not established the structure of this compound. (c) Free cyclohexylphosphine was obtained in the crude reaction mixture, indicating displacement of the ligand from the metal.

In order to obviate these problems, we decided to protect the nitrogen in compounds **4a** and **4c** prior to metathesis. Compounds **4a** and **4c** were protected as their *N*-Boc derivatives by reaction with $(Boc)_2O$ and triethylamine.[16] *N*-Boc protected **4a** and **4c** were subsequently reacted with ethylene and Grubbs' catalyst I. Unfortunately, this reaction did not produce the desired ROM/CM compounds and starting materials were recovered unreacted. The nitrogen of compounds **4a** and **4c** was instead protected using silicon-based protecting groups. This was achieved in DMF using an excess of TMSCl, TBDPSCl or TBDMSCl (1–2 equiv) and NEt_3 as the base (Table 3). While *N*-TMS and *N*-TBDPS monobactams **14–15** and **17–18** were obtained only in moderate yields (Table 3, entries 1, 2 and 4, 5), *N*-TBDMS monobactams **16** and **19** were obtained in excellent isolated yields.[14c]

We submitted compounds **14–19** to ROM/CM metathesis using Grubbs' catalyst I (0.1 equiv) and excess ethylene (Table 4). Delightfully, reaction of *N*-TBDPS protected bicyclic compounds **15** and **18** proceeded to completion and gave the expected alkenes **21** and **24** in good isolated yields (Table 4, entries 2 and 5). *N*-TBDMS-protected compounds **16** and **19** gave the corresponding ring-opened compounds **22** and **25** in excellent isolated yields (Table 4, entries 3 and 6). Reaction of *N*-TMS-protected **14** and **17** gave a complex reaction mixture (Table 4, entries 1 and 4).

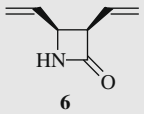
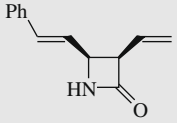
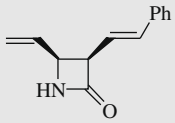
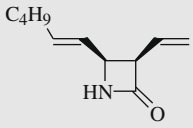
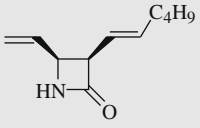
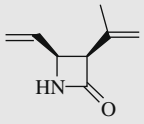
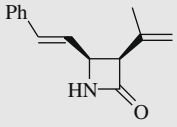
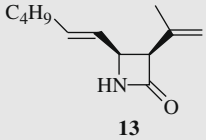
We have also demonstrated that the TBDMS group in compounds **22** and **25** can be removed by reaction with KF (1.1 equiv) in MeOH at −20 °C to give monobactams **6** and **11** in yields of over 80%. The cleavage of the silicon-protecting group was accompanied by partial isomerisation, resulting in formation of 5–8% of the more stable *trans*-**6** and *trans*-**11** isomers which were isolated and fully characterised (Scheme 2).

In conclusion, we have developed a novel route to alkene-functionalised monobactams. The synthesis made use of commercially available 2-pyridones and alkenes and furnished stereodefined monobactams in high yields. The methodology presented is modular in nature and allows introduction of diversity by variation of one component at a time. Studies on the use of compounds **6** and **11** in diversity-oriented synthesis and for the preparation of unnatural β-amino acids are in progress.

1. Preparation of 2-aza-bicyclo[2.2.0]hex-5-en-3-one 4a

1*H*-Pyridin-2-one **5a** (0.02 mol) in CH_3CN (500 mL) was irradiated with UV light (300 nm) at room temperature for 65 h using a Hanovia reactor. The crude product was purified by neutral Al_2O_3 column chromatography (eluent: petroleum ether/ethyl acetate, 1:1) to give compound **4a** as a pale yellow solid (65% yield). Mp = 65–66 °C, R_f = 0.10 (eluent: petroleum ether/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.59 (1H, m), 7.98 (1H, m),

Table 2
ROM/CM of compounds **4a** and **4c**

Entry	Reactant	Alkene[a]	Product	Yield[b] (%)
1	**4a**	Ethylene	 **6**	50
2	**4a**	Styrene	 **7**  **8**	**7** (7%)/**8** (5%)
3	**4a**	1-Hexene	 **9**  **10**	**9** (9%)/**10** (3%)
4	**4c**	Ethylene	 **11**	28
5	**4c**	Styrene	 **12**	15
6	**4c**	1-Hexene	 **13**	10

[a] Ethylene was used in large excess; 5 equiv of styrene and 1-hexene were used.
[b] Isolated yields after column chromatography.

4.38 (1H, m), 4.11 (1H, m); ^{13}C NMR (106.6 MHz) δ_C 172.1, 142.5, 140.5, 59.6, 50.8; HRMS found: M^+ 95.0375, C_5H_5NO requires 95.0371, *m/z*: 95 (100%, M^+).[14b]

2. Preparation of 5-methyl-2-aza-bicyclo[2.2.0]hex-5-en-3-one 4c

4-Methylpyridone **5c** (0.5 mmol) in ethyl acetate (500 mL) was irradiated with UV light (300 nm) for 2 h at room temperature. The crude product was purified by neutral Al_2O_3 column chromatography (eluent: petroleum ether/ethyl acetate, 1:1) to give compound **4c** as a colourless solid (75% yield), MP = 55–56 °C, R_f = 0.15 (eluent: petroleum ether/ethyl acetate, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.12 (1H, m), 4.21 (1H, m), 3.99 (1H, m), 1.85 (3H, m); ^{13}C NMR (106.6 MHz, $CDCl_3$) δ_C 172.8, 151.7, 134.4, 61.0, 47.2, 16.5.[14b]

3. Procedure for the preparation of compounds 16 and 19[14c]

To a solution of compound **4a** or **4c** (1 mmol) in DMF (2 mL) at 0 °C were sequentially added triethylamine (1.3 mmol) and *tert*-butyldimethylsilyl chloride (1.3 equiv). The reaction was allowed to reach room temperature and stirred for 2 h, then extracted with diethyl ether (3 × 10 mL). The combined organic layer was washed with saturated NaCl (10 mL), then dried over Na_2SO_4 and evaporated in vacuo. The crude residue was purified by silica gel column chromatography (previously deactivated with NEt_3) (eluent: diethyl ether/petroleum ether, 1:5) to give compounds **16** and **19.**

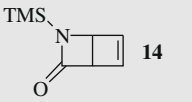
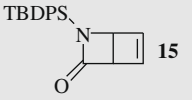
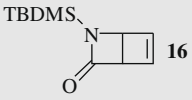
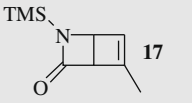
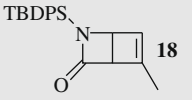
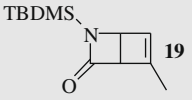
3.1. 2-(*tert*-Butyl-dimethylsilanyl)-2-aza-bicyclo[2.2.0]hex-5-en-3-one 16

Yellow oil, yield: 90%, R_f = 0.68 (eluent: diethyl ether/petroleum ether, 1:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.60 (1H, m), 6.49 (1H, m), 4.31 (1H, m), 4.14 (1H, m), 0.92 (9H, s), 0.20 (3H, s), 0.17 (3H, s); ^{13}C NMR (100.6 MHz) δ_C 175.3, 143.0, 141.2, 60.1, 52.0, 25.9, 18.2, −6.3, −6.7; HRMS found: M^+ 209.1237, $C_{11}H_{19}NOSi$ requires 209.1236, *m/z*: 209 (100%, M^+).[14c]

3.2. 2-(*tert*-Butyl-dimethylsilanyl)-5-methyl-2-aza-bicyclo[2.2.0]hex-5-en-3-one 19

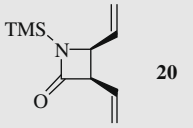
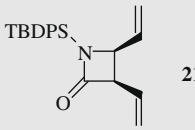
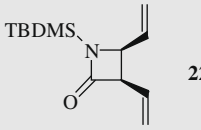
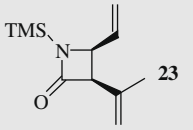
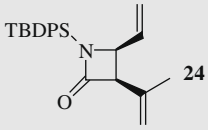
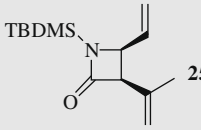
Yellow oil, yield: 90%, R_f = 0.63 (eluent: diethyl ether/petroleum ether, 1:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.15 (1H, m), 4.15 (1H, m), 4.03 (1H, m), 1.89 (3H, m), 0.92 (9H, s), 0.20 (3H, s), 0.16

Table 3
Protection of photoisomers **4a** and **4c**

Entry	Substrate	Reactant	Product	Yield[a] (%)
1	**4a**	TMSCl	 **14**	25
2	**4a**	TBDPSCl	 **15**	60
3	**4a**	TBDMSCl	 **16**	90
4	**4c**	TMSCl	 **17**	51
5	**4c**	TBDPCl	 **18**	28
6	**4c**	TBDMSCl	 **19**	90

[a] Isolated yields after column chromatography.

Table 4
ROM/CM of compounds **14**–**19** with ethylene

Entry	Substrate	Product	Yield[a] (%)
1	**14**	 **20**	–
2	**15**	 **21**	60
3	**16**	 **22**	89
4	**17**	 **23**	–
5	**18**	 **24**	53
6	**19**	 **25**	90

[a] Isolated yields after column chromatography.

(3H, s); ^{13}C NMR (106.6 MHz, $CDCl_3$) δ_C 175.8, 152.3, 134.9, 61.5, 48.3, 25.9, 18.2, 16.7, −6.3, −6.7; HRMS found: M^+ 223.1402, $C_{12}H_{21}NOSi$ requires 223.1392, *m/z*: 223 (100%, M^+).[14c]

4. Procedure for the preparation of compounds 22 and 25

To a solution of compound **16** or **19** (1 mmol) in dry CH_2Cl_2 (7 mL), were added Grubbs' I catalyst (10% mol) dissolved in dry CH_2Cl_2 (7 mL) and ethylene under pressure (300 psi). This reaction was carried out using a Parr 5500 series bench-top compact reactor. After 4 h the reaction was filtered, the organic layer was evaporated in vacuo and the crude residue was purified by silica gel column chromatography (eluent: diethyl ether/petroleum ether, 1:5) to give compound **22** or **25**. It was important to deactivate the silica gel using NEt_3 prior to chromatography.

4.1. 1-(*tert*-Butyl-dimethylsilanyl)-3,4-divinyl-azetidin-2-one 22

Yellow oil, yield 89%, R_f = 0.85 (eluent: diethyl ether/petroleum ether, 1:1), IR: ν_{max} (neat)/cm^{-1}: 3241, 2932, 1765; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.81–5.66 (2H, m), 5.33–5.19 (4H, m), 4.15–4.04 (2H, m), 0.93 (9H, s), 0.20 (3H, s), 0.16 (3H, s); ^{13}C NMR (100.6 MHz) δ_C 173.1, 137.3, 129.6, 119.7, 119.1, 59.0, 56.8, 26.4, 18.4, −5.3, −5.5; HRMS found: M^+ 237.1555, $C_{13}H_{23}NOSi$ requires 237.1549, *m/z*: 237 (100%, M^+).

4.2. 1-(*tert*-Butyl-dimethylsilanyl)-3-isopropenyl-4-vinyl-azetidin-2-one 25

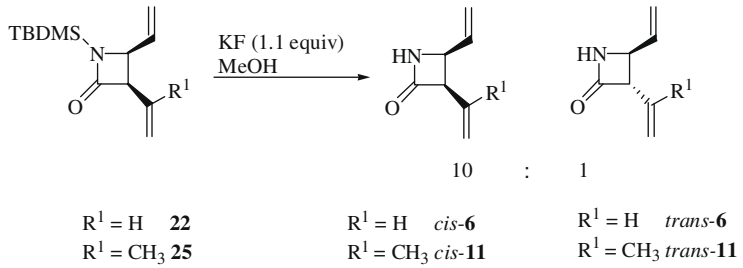
Dark oil, yield 90%, R_f = 0.83 (eluent diethyl ether/petroleum ether, 1:1), IR: ν_{max} (neat)/cm^{-1}: 3080, 1758, 1415, 891; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.69 (1H, dt, *J* = 17.2, 10.0 Hz), 5.20 (1H, dd, *J* = 17.2, 1.4 Hz), 5.12 (1H, dd, *J* = 10, 1.4 Hz), 4.99 (1H, s), 4.89 (1H, s), 4.01 (1H, dd, *J* = 10, 6 Hz), 3.93 (1H, d, *J* = 6 Hz), 1.51 (3H, s), 0.85 (9H, s), 0.10 (3H, s), 0.09 (3H, s); ^{13}C NMR (106.6 MHz, $CDCl_3$) δ_C 173.0; 137.39; 136.82; 119.3; 114.5; 61.6; 56.6; 26.3; 22.2; 18.3; −5.2; −5.59; HRMS found: M^+ 251.1704, $C_{14}H_{25}NOSi$ requires 251.1705, *m/z*: 251 (100%, M^+).

5. Procedure for the preparation of compounds 6 and 11

To a solution of *N*-TBDMS-protected azetidinone **22** or **25** (1 mmol) in methanol (10 mL) at −20 °C was slowly added solid potassium fluoride (1.1 mmol). The reaction mixture was stirred for 50 min, and the solvent was evaporated in vacuo. The crude residue was purified by flash column chromatography (eluent: petroleum ether/ethyl acetate, 1:1) to afford compound **6** or **11**.

5.1. *cis*-3,4-Divinyl-azetidin-2-one 6

Brown oil, yield 81%, R_f = 0.54 (eluent: petroleum ether/ethyl acetate, 1:1), IR: ν_{max} (neat)/cm^{-1}: 3241, 2932, 1765; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.80–5.70 (1H, m), 5.68–5.61 (1H, m), 5.30–5.18 (4H, m), 4.24 (1H, t, *J* = 5.6 Hz), 3.95 (1H, t, *J* = 6.4 Hz); ^{13}C NMR (100.6 MHz) δ_C 168.6, 134.9, 129.1, 120.4, 118.5, 58.75,



Scheme 2.

54.3; HRMS found: M^+ 123.0689, C_7H_9NO requires 123.0684, *m/z*: 123 (100%, M^+).

5.2. *trans*-3,4-Divinyl-azetidin-2-one 6

Brown oil, yield 9%, $R_f = 0.44$ (eluent: petroleum ether/ethyl acetate, 1:1), IR: ν_{max} (neat)/cm^{-1}: 3239, 2930, 1765; ^1H NMR (400 MHz, $CDCl_3$) δ_H 5.93–5.81 (2H, m), 5.25–5.14 (4H, m), 3.90–3.88 (1H, m) 3.47 (1H, d, $J = 6.4$ Hz); ^{13}C NMR (100.6 MHz) δ_C 168.3, 136.5, 130.7, 119.4, 117.4, 62.1, 56.8. HRMS found: M^+ 123.0679, C_7H_9NO requires 123.0684, *m/z*: 123 (100%, M^+).

5.3. *cis*-3-Isopropenyl-4-vinyl-azetidin-2-one 11

Brown oil, yield 75%, $R_f = 0.53$ (eluent: petroleum ether/ethyl acetate, 1:1), IR: ν_{max} (neat)/cm^{-1}: 3235, 2927, 1755; ^1H NMR (400 MHz, $CDCl_3$) δ_H 5.75 (1H, ddd, $J = 17.2$, 10.0, 7.6 Hz), 5.26 (1H, d, $J = 17.2$ Hz) 5.20 (1H, d, $J = 10.0$ Hz), 5.01 (1H, s), 4.96 (1H, s), 4.21–4.18 (1H, m), 3.91 (1H, d, $J = 5.6$ Hz), 1.59 (3H, s); ^{13}C NMR (100.6 MHz) δ_C 168.4, 138.1, 136.9, 119.2; 115.1, 61.5, 54.5, 22.2. HRMS found: M^+ 137.0846, $C_8H_{11}NO$ requires 137.0841, *m/z*: 137 (100%, M^+).

5.4. *trans*-3-Isopropenyl-4-vinyl-azetidin-2-one 11

Brown oil, yield 8%, $R_f = 0.47$, (petroleum ether:,ethyl acetate 1:1), IR: ν_{max} (neat)/cm^{-1}: 3232, 2928, 1754; ^1H NMR (400 MHz, $CDCl_3$) δ_H 5.97 (1H, ddd, $J = 17.2$, 10.4, 7.2 Hz), 5.34 (1H, d, $J = 17.2$ Hz), 5.22 (1H, d, $J = 10.4$ Hz), 5.00 (1H, s) 4.96 (1H, s), 4.00 (1H, dd, $J = 7.2$, 2 Hz), 3.52 (1H, m, $J = 2$ Hz), 1.82 (3H, s); ^{13}C NMR (100.6 MHz) δ_C 168.2, 138.1, 137.0, 117.4; 114.1, 65.2, 55.7, 29.7. HRMS found: M^+ 137.0846, $C_8H_{11}NO$ requires 137.0841, *m/z*: 137 (100%, M^+).

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