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Synthetic studies toward macrocidins: an RCM approach for the construction of the central cyclic core

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Abstract—The central macrocyclic core of the macrocidins was constructed using RCM as the key reaction. A preliminary investigation dealing with the key reactions, that is, the Dieckmann cyclization and the RCM, revealed that RCM of the β-ketoamide is better than RCM of the corresponding acyltetramic acid.
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Macrocidins A (**1**) and B (**2**), the first representatives of a new family of cyclic tetramic acids, were recently isolated from the liquid cultures of *Phoma macrostoma* obtained from diseased Canada thistle growing in several geographically diverse regions.[1,2] The novel macrocyclic skeleton and the relative configuration of **1** were determined by extensive 2D NMR and by a single crystal X-ray structure. Biological testing of purified samples against different types of herbs revealed that these compounds have significant herbicidal activity on broadleaf weeds, but apparently not on grass weeds. The observed bleaching and stunting, primarily in the new growth of susceptible weeds, led to the conclusion that the macrocidins were phloem mobile. The combination of interesting herbicidal activity and novel chemical structures makes the macrocidins attractive targets for synthesis. Herein, we describe the synthetic studies toward *des*-methylmacrocidin A (**3**) (Fig. 1).

The retrosynthetic analysis is represented by two strategies, viz route-A and route-B, which differ the in order in which the critical structural elements—the tetramic acid

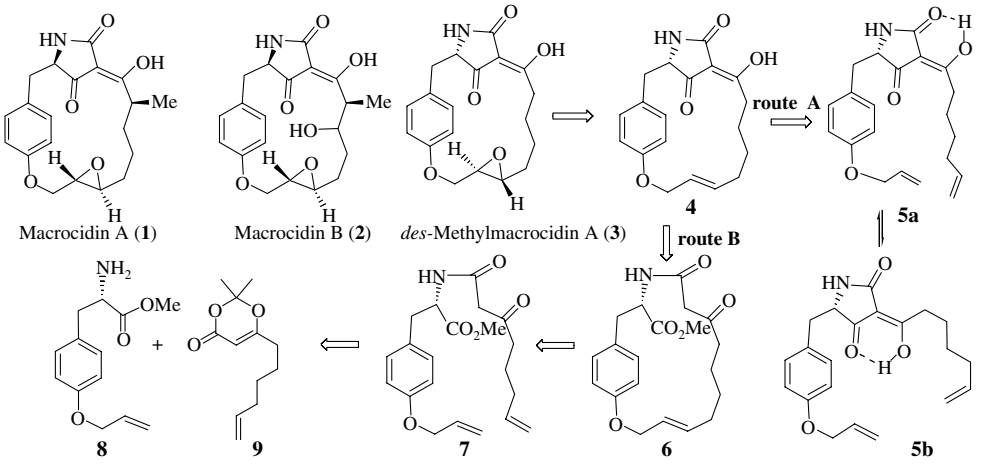

Figure 1. Macrocidins A and B and the retrosynthetic route for *des*-methylmacrocidin A (**3**).

Keywords: Macrocidins; Acyltetramic acid; Lacey–Dieckmann cyclization; Ring closing metathesis.
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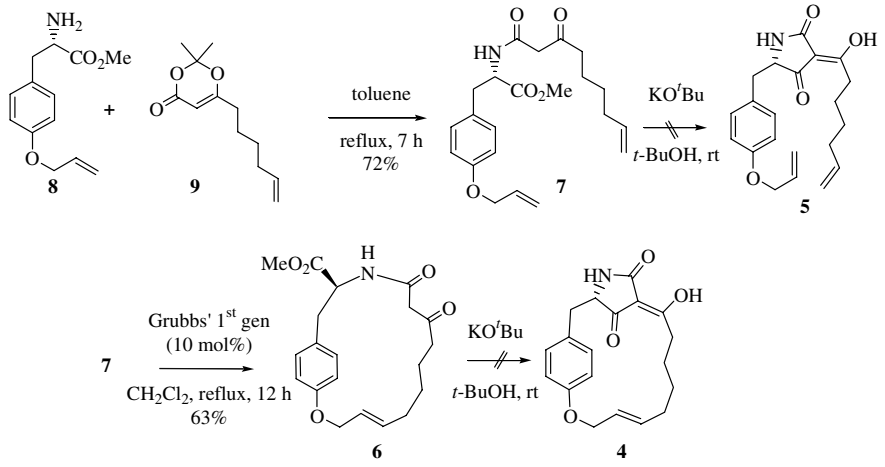
or the 18-membered macrocycle are formed. One issue in the case of route-A would be the effect of the tautomeric structures **5a** and **5b**.[3] The tautomeric structure represented by **5b** could prevent the RCM reaction from taking place. The surrogate of the epoxide present at C16–C17 of **3** would be the *E*-double bond. Condensation of a tyrosine derivative and a substituted [1,3]dioxin-4-one was envisaged to produce the key material **7**. Among the various synthetic methods[4] that could be utilized to construct acyltetramic acid units, the Lacey–Dieckmann cyclization[5] appeared to be the most appropriate in this context.

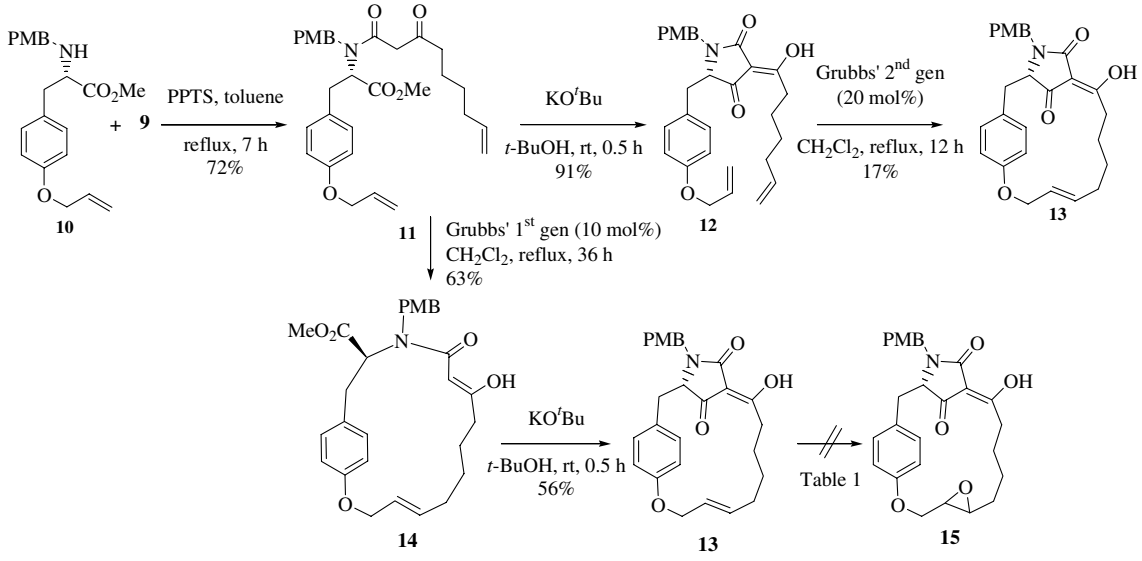
Methyl *O*-allyl-L-tyrosinate (**8**)[6] and [1,3]dioxin-4-one **9**[7] were heated under reflux in toluene in a Dean–Stark apparatus with continual removal of water to give β-ketoamide **7** (Scheme 1). Efforts to transform **7** into the corresponding tetramic acid derivative **5** were unsuccessful. The same observation was noted with the macrocycle **6**[8] derived by the RCM reaction of **7** with Grubbs' catalyst. However, the Lacey–Dieckmann cyclization of the corresponding *N*-PMB derivative **11** (Scheme 2) in the presence of KO^{t}Bu was successful in giving rise to the tetramic acid derivative **12**.

The critical RCM reaction of **12** with 1st and 2nd generation Grubbs' catalysts was unsatisfactory and only traces of macrocyclic derivative **13** were isolated. This suggested that the tautomeric structure **5b** was favored.

The RCM reaction of ketoamide **11** with the 1st generation Grubbs' catalyst was satisfactory and produced the 18-membered cyclic lactam derivative **14** in 63% yield. A Lacey–Dieckmann cyclization of **14** using KO^{t}Bu in *t*-butanol gave the core structure **13**. The spectral and analytical data of **13** were in accordance with the assigned structure.[9] The large coupling ($J =$ 15.6 Hz) in the ^{1}H NMR spectrum of **13** (which exists as an equilibrating 1:3 keto-enol mixture) indicated the required *E*-configuration of the cyclic olefin. A single



Scheme 1.



Scheme 2.

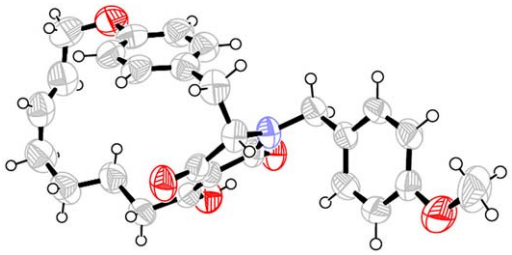


Figure 2. *ORTEP* structure of **13**.

Table 1. Attempted conditions for the epoxidation of **13**

Entry	Reagents and conditions	Result
1	MCPBA, CH_2Cl_2, −78 °C	No reaction
2	MCPBA, CH_2Cl_2, rt	Decomposition
3	Oxone®, acetone, EtOAc, rt	Decomposition
4	H_2O_2, $NaHCO_3$, THF–water	Decomposition
5	H_2O_2, $NaHCO_3$, $CHCl_3$–water	Decomposition
6	H_2O_2, $NaHCO_3$, PhCN–methanol	Decomposition
7	Diisopropyl tartarate, $Ti(O^iPr)_4$, THF, −78 °C, ^{t}BuOOH	Decomposition
8	$PhCO_2Ag$, I_2, Ph, reflux	No reaction

crystal X-ray structural analysis of **13** confirmed the structure (Fig. 2).[10]

However, the final endeavor to install the epoxide on the C16–C17 olefin, a reaction which looked to be straight forward, turned out to be difficult. Many reagents (Table 1) were utilized but the substrate **13** was unstable to the reaction conditions and gave intractable mixtures of compounds from which no pure product could be isolated in an appreciable yield. This study showed that the epoxide function would have to be installed by an another synthetic protocol because, under reaction conditions needed to epoxidize the olefin, the acyltetramic acid group rapidly decomposed,[11] at least in our hands.

To conclude, our synthetic strategy to build the macrocyclic structure and the acyltetramic acid of macrocidins was successful, although the macrocyclic intermediate **13** was found to be unstable to epoxidation conditions.

Acknowledgement

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8. Spectral data of compound **6**: $[\alpha]_D^{25}$15.3 (*c* 1.1, $CHCl_3$). IR ($CHCl_3$): υ 3340, 3019, 2931, 1727, 1973, 1611, 1511, 1217, 767 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.22–1.46 (m, 4H), 2.03 (d, $J = 12.0$ Hz, 1H), 2.04 (d, $J = 12$ Hz, 1H) 2.22 (ddd, $J = 5.2$, 9.3, 17.3 Hz, 1H), 2.40 (ddd, $J = 5.9$, 9.5, 17.3 Hz, 1H), 2.71 (dd, $J = 10.0$, 14.2 Hz, 1H), 3.18 (m, 2H), 3.35 (d, $J = 14.5$ Hz, 1H), 3.80 (s, 3H), 4.57 (dd, $J = 5.8$, 14.2 Hz, 1H), 4.62 (dd, $J = 5.5$, 14.2 Hz, 1H), 4.67 (m, 1H), 5.45 (dt, $J = 5.3$, 15.6 Hz, 1H), 5.59 (dt, $J = 6.9$, 15.6 Hz, 1H), 6.75 (d, $J = 8.2$ Hz, 2H), 6.94 (d, $J = 8.2$ Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.7 (t), 27.5 (t), 31.0 (t), 36.9 (t), 43.6 (t), 49.6 (t), 52.4 (q), 53.3 (d), 67.4 (t), 115.9 (d), 127 (d), 127.5 (s), 129.9 (d), 134.4 (d), 156.5 (s), 164.2 (s), 171.8 (s), 206.4 (s) ppm. ESI-MS: *m*/*z* 360.15 (51%, $[M+H]^+$), 382.12 (100%, $[M+Na]^+$). Anal. Calcd for $C_{20}H_{25}NO_5$: C, 66.83; H, 7.01; N, 3.90. Found: C, 66.66; H, 7.13; N, 3.72.
9. Spectral data of compound **13**: $[\alpha]_D^{25}$ − 36.2 (*c* 1.2, $CHCl_3$). IR ($CHCl_3$): υ 3400, 3019, 2932, 1708, 1613, 1511, 1461, 1433, 1246, 1215, 1034, 757 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.04–1.13 (m, 2H), 1.15–1.23 (m, 1H), 1.26–1.34 (m, 1H), 1.89–1.94 (m, 2H), 2.02–2.07 (m, 1H), 2.97 (dd, $J = 4.1$, 14.4 Hz, 1H), 3.04 (dd, $J = 2.7$, 14.4 Hz, 1H), 3.20 (dt, $J = 6.7$, 11.6 Hz, 1H), 3.79 (s, 3H), 4.14 (d, $J = 14.8$ Hz, 1H), 4.55–4.60 (m, 3H), 5.27–5.42 (m, 1H), 5.34 (d, $J = 14.8$ Hz, 1H), 5.52 (dt, $J = 7.4$, 15.6 Hz, 1H), 6.68 (br s, 2H), 6.76–6.78 (m, 1H), 6.87 (br d, $J = 8.0$ Hz, 2H), 6.95 (br s, 1H), 7.21 (br d, $J = 8.0$ Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 27.5 (t), 28.6 (t), 32.1 (t), 32.2 (t), 32.4 (t), 42.6 (t), 55.2 (q), 64.1 (d), 66.8 (t), 101.5 (s), 114.3 (d),

114.4 (d), 125.5 (d), 125.6 (s), 127.4 (s), 129.6 (d), 129.7 (d), 136.7 (d), 155.9 (s), 159.5 (s), 173.4 (s), 187.1 (s), 193.4 (s) ppm. ESI-MS: $m/z = 448.18$ (69%, $[M+H]^+$), 470.18 (100%, $[M+Na]^+$). Anal. Calcd for $C_{27}H_{29}NO_5$: C, 72.46; H, 6.53; N, 3.13. Found: C, 72.28; H, 6.45; N, 2.98.

10. The crystallographic data of compound **13** have been deposited with the Cambridge Crystallographic Data Centre as deposition No. CCDC 298644. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (1223)336033; e-mail: deposit@ccdc.cam.ac.uk].
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