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Synthesis of *N*-hydroxyenamide, a potential precursor of chartelline

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Abstract

In our synthetic plan for chartelline A–C, a compound including *N*-hydroxyenamide moiety was designed as an important intermediate. Synthesis of the required *N*-hydroxyenamide by N-acylation of a suitable oxime derivative has been developed using model compounds.

Keywords: *N*-Hydroxyenamide; Oxime; Chartelline; Imidazole

Chartelline A and its analogues are unique members of a marine alkaloid family isolated in the 1980s from a marine bryozoan, *Chartella papyracea*, by Christophersen and co-workers (Fig. 1).[1] Chartelline A, which includes indolenine, β-lactam, and imidazole (three biologically important heterocycles), linked together by an unsaturated 10-membered ring, has to date not been reported to have any significant biological activity. Nevertheless, the novel structure of the compound has made it a challenging synthetic target for organic chemists. Our attempts to synthesize this class of natural products has thus far resulted in the development of an efficient methodology for the preparation of spiro-β-lactam attached to an indolenine moiety, a core structure of chartelline A–C alkaloids.[2,3] The first total synthesis of chartelline C by Baran et al.[4] and extensive reports toward the synthesis of chartelline alkaloids from the Weinreb[5] and Magnus[6] group has prompted us to disclose our recent synthetic efforts directed toward the synthesis of these compounds.

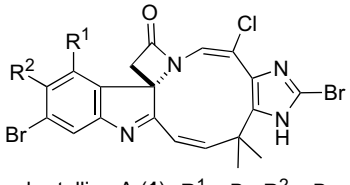
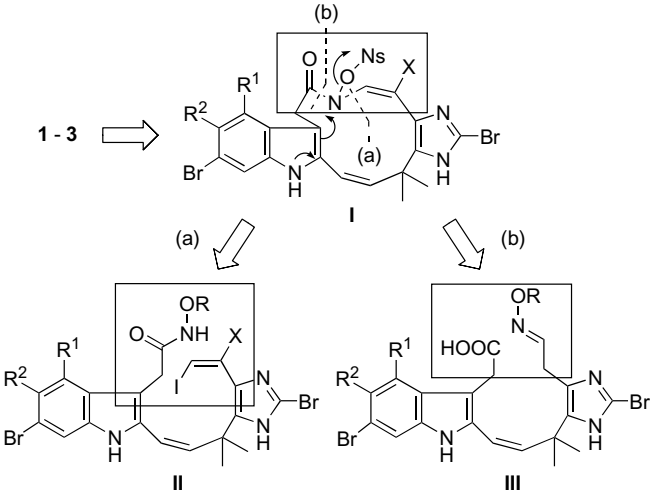


Fig. 1. Structure of chartelline alkaloids.

Scheme 1 outlines our strategies for the synthesis of chartelline A–C based on our previously reported



Scheme 1. Strategies for the synthesis of chartelline A–C.

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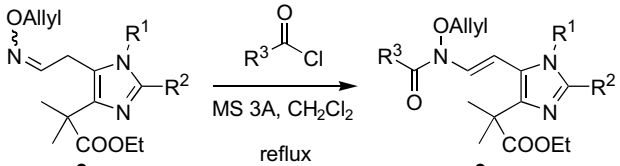
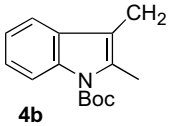
spiro-β-lactam chemistry. This methodology implements nucleophilic substitution at the amide nitrogen by the carbon atom at the 3 position of indole.[3] Employing this methodology for the formation of β-lactam in a trans-annular manner requires a 12-membered macrolactam containing a *N*-hydroxyenamide moiety, viz. compound **I**. However, there are few reports regarding the synthesis of *N*-hydroxyenamide.[7,8] Our retrosynthetic consideration led us to two disconnections that potentially could give the desired *N*-hydroxyenamide (compound **I**); (a) a direct intramolecular coupling between hydoroxamic acid and vinyliodide (compound **II**), or (b) N-acylation of alkyl-oxime (compound **III**). Since our preliminary experiments regarding route (a) were unsuccessful,[2,9] our attention was turned to route (b).

Our studies commenced with a model experiment for N-acetylation of *O*-benzyl oxime **5a** prepared from phenyl-acetaldehyde (Table 1). The reaction proceeded smoothly in refluxing dichloromethane to afford benzyloxyenamide **6a** in 85% yield (Table 1, entry 1).[10] However, deprotection of the benzyl group by hydrogenolysis (H_2, Pd/C, AcOEt) failed due to preferential reduction of the C–C double bond. To find a suitable protective group for hydroxy-enamide, several oximes **5b–e**[11] were exposed to the same N-acetylation condition affording the corresponding *N*-alkoxyenamides **6b–e** (entries 2–5).[12] The low yields for the Dmb (3,4-dimethoxybenzyl)- and SEM-protected hydroxyenamide **6c** and **6d** may be caused by the labile nature of the protective group under acidic conditions. After conducting the deprotection experiments, we found that the allyl group in compound **6e** was smoothly deprotected with palladium(0) catalyst in the presence of morpholine affording the desired product in 68% yield (entry 5). The forgoing results encouraged us to synthesize *N*-allyloxyenamide indole **6f** (entry 6). In this specific case, the addition of molecular sieves (MS 3A) improved the yield.[13] Deprotection of the allyl group was carried out under the conditions mentioned above in good yield.

Based on the above results, we attempted to synthesize *N*-allyloxyenamide appended to an imidazole unit found in the chartelline alkaloids (Table 2).[14] Surprisingly, the oxime containing *N*-benzylimidazole **8a** did not react when treated with acetyl chloride at reflux in dichloromethane (entry 1), while the same conditions applied to compound

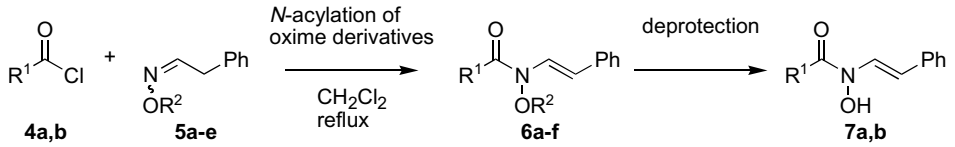
Table 2
Synthesis of *N*-allyloxyenamide containing imidazole

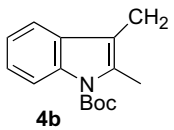


Entry	Oxime			Acid chloride		Product	Yield (%)
		R^1	R^2		R^3		
1	**8a**	Bn	H	**4a**	Me	**9a**	0
2	**8b**	Bn	Br		Me	**9b**	13[a]
3	**8c**	H	Br		Me	**9c**	47
4	**8c**	H	Br	**4c**	$PhCH_2$	**9d**	48
5	**8c**	H	Br	 **4b**		**9e**	39[b,c]

[a] Starting material was recovered in 74%.
[b] Starting material was recovered in 27%.
[c] After treatment with TsOH in aq. CH_3CN.

Table 1
N-Acylation of oxime derivatives



Entry	N-Acylation of oxime derivatives						Deprotection	
	R^1		R^2		Product	Yield (%)	Conditions	Result
1	**4a**	Me	**5a**	Bn	**6a**	85	H_2, Pd–C/EtOAc	See the text
2		Me	**5b**	PMB	**6b**	56	$DDQ/CH_2Cl_2–H_2O$ CAN/aq CH_3CN	Decomposed Decomposed
3		Me	**5c**	Dmb	**6c**	35	$DDQ/CH_2Cl_2–H_2O$	Decomposed
4		Me	**5d**	SEM	**6d**	30	TBAF/THF	**7a** 13%
5		Me	**5e**	Allyl	**6e**	78	$Pd_2[dba]_3$, Ph_3P, morpholine/THF	**7a** 68%
6	 **4b**		**5e**	Allyl	**6f**	45 (58)[a]	$Pd_2[dba]_3$, Ph_3P, morpholine/THF	**7b** 75%

[a] The yield was obtained in the presence of MS 3A.

8b gave a poor yield of the corresponding product **9b** along with a considerable amount of the starting material **8b** (entry 2). Interestingly, these results indicate that substitution of the imidazole ring might affect the reactivity of the oxime toward N-acylation. The *N*-benzylimidazole **8a** might rapidly react with acetyl chloride to form an acyl imidazolium cation, which prevents further N-acylation of the oxime through the high-energy dicationic intermediate.[15] On the other hand, the bromo substitution in compound **8b** decreases the nucleophilicity of the imidazole, which probably hinders the corresponding acyl imidazolium cation to be formed. We anticipated that debenzylated imidazole **8c** would react with acyl chlorides to form acyl imidazole, not acyl imidazolium cation, which might allow N-acylation of the oxime. As expected, N-acylation of compound **8c** with acetyl chloride and phenylacetyl chloride gave the corresponding allyloxyenamides **9c**[16] and **9d**, respectively, in moderate yields (entries 3 and 4). When the reaction was carried out using phenylacetyl chloride, an unstable less polar product was observed by TLC analysis.[17] Upon purification by silica gel chromatography this compound was converted to the desired product **9d**. When the same oxime **8c** was reacted with indoleacetyl chloride **4b**, the corresponding allyloxyenamide **9e**[18] could be obtained after treatment with TsOH in aqueous CH_3CN.[19] Compound **9e** has a structure similar to the one found in compound **I** depicted in Scheme 1 (Table 2, entry 5). Although these model experiments gave *E*-enamides exclusively, intramolecular cyclization would afford *Z*-enamide due to the strained structure of cyclic *E*-enamide.

In summary, a new synthetic method for the formation of *N*-hydroxyenamide by N-acylation of oxime has been developed. The current method should be applicable to the synthesis of the 12-membered macrolactam **I**, a possible precursor of chartelline A–C. Further synthetic studies toward chartelline along the synthetic pathway outlined in Scheme 1 are currently underway in our laboratories.

Acknowledgements

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References and notes

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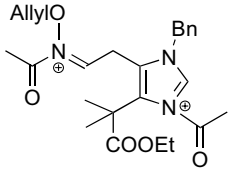
7. To the best of our knowledge, there is only one report regarding the synthesis of cycloalkoxy enamide, see: Lee, V. J.; Woodward, R. B. *J. Org. Chem.* **1979**, *44*, 2487–2491.
8. Enamide has been synthesized by N-acylation of oxime in the presence of iron as a reducing agent, see: (a) Barton, D. H. R.; Zard, S. Z. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2191–2192; (b) Laso, N. M.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1996**, *37*, 1605–1608.
9. We attempted copper-catalyzed coupling of hydroxamate with vinylhalide under the conditions developed for enamide synthesis. For example, see: (a) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. . *Org. Lett.* **2003**, *5*, 3667–3669; (b) Shen, R.; Lin, C. T.; Bowman, E. J.; Bowman, B. J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 7889–7901.
10. All reactions in Tables 1 and 2 gave *E* isomers exclusively. The geometry was determined by the coupling constant, $J = 14$–15 Hz.
11. O-Substituted hydroxylamines were prepared from *N*-hydroxylphthalimide by alkylation or Mitsunobu reaction with the corresponding alcohol. See Ramsay, S. L.; Freeman, C.; Grace, P. B.; Redmond, J. W.; MacLeod, J. K. *Carbohydr. Res.* **2001**, *333*, 59–71.
12. *Typical procedure of N-acylation of oxime*: To a solution of *O*-benzyl oxime **5a** (210 mg, 0.932 mmol) in CH_2Cl_2 (10.0 ml) at rt was added acetyl chloride (0.27 ml, 3.73 mmol). After refluxing the reaction mixture for 24 h, the reaction mixture was treated with saturated $NaHCO_3$ solution, and extracted with CH_2Cl_2 (×2). The combined organic extracts were washed with H_2O and brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (AcOEt–hexane = 1:9) to afford *N*-benzyloxyenamide **6a** (222 mg, 85%) as a colorless oil.
Compound **6a**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.19 (3H, s, –CH_3), 4.98 (2H, s, –CH_2–), 6.30 (1H, d, $J = 14.5$ Hz, –CH=C*H*–Ph), 7.17–7.46 (10H, m, aromatic), 7.76 (1H, d, $J = 14.5$ Hz, –C*H*=CH–Ph). HRMS (FAB) $(M+H)^+$ calcd for $C_{17}H_{18}NO_2$ 268.1338, found 268.1347.
Compound **6b**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.16 (3H, s, –CH_3), 3.84 (3H, s, –O–CH_3), 4.91 (2H, s, –CH_2–), 6.30 (1H, d, $J = 15$ Hz, –CH=C*H*–Ph), 6.96 (2H, d, $J = 9$ Hz, PMB), 7.17–7.42 (7H, m, aromatic), 7.76 (1H, d, $J = 15$ Hz, –C*H*=CH–Ph). HRMS (FAB) $(M+H)^+$ calcd for $C_{18}H_{20}NO_3$ 298.1443, found 298.1422.
Compound **6e**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.28 (3H, s, –CH_3), 4.50 (2H, d, $J = 6$ Hz, –C*H*$_2$–CHCH_2), 5.42 (1H, br d, $J = 11$ Hz, –CH=C*H*$_A$H$_B$), 5.48 (1H, dd, $J = 17$, 1.5 Hz, –CH=CH$_A$*H*$_B$), 6.05 (1H, ddt, $J = 17$, 11, 6 Hz, –C*H*=CH_2), 6.21 (1H, d, $J = 15$ Hz, –CH=C*H*–Ph), 7.16–7.39 (5H, m, –Ph), 7.71 (1H, d, $J = 15$ Hz, –C*H*=CH–Ph). HRMS (FAB) $(M+H)^+$ calcd for $C_{13}H_{18}NO_2$ 218.1181, found 218.1155.
Compound **6f**: IR (KBr) ν_{max} 2977, 1728, 1683, 1645, 1458, 1370, 1136 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.68 (9H, s, –Boc), 2.69 (3H, s, –Me), 3.96 (2H, s, –CH_2–), 4.55 (2H, d, $J = 6$ Hz, –C*H*$_2$–CHCH_2), 5.46 (1H, d, $J = 11$ Hz, –CH_2CH=C*H*$_A$H$_B$), 5.50 (1H, d, $J = 19$ Hz, –CH_2CH=CH$_A$*H*$_B$), 6.09 (1H, m, –CH_2–C*H*=CH_2), 6.24 (1H, d, $J = 14.5$ Hz, –CH=C*H*–Ph), 7.15–7.36 (7H, m, aromatic), 7.48 (1H, d, $J = 7$ Hz, indole), 7.69 (1H, br d, $J = 14.5$ Hz, –C*H*=CH–Ph), 8.10 (1H, d, $J = 7$ Hz, indole). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.4, 28.3, 28.8, 75.6, 83.7, 111.0, 111.1, 115.5, 117.9, 121.6, 122.6, 123.6, 125.9, 126.8, 128.7, 129.7, 130.5, 135.4, 135.7, 135.8, 150.6, 168.7. Anal. Calcd for $C_{27}H_{30}N_2O_4$: C, 72.62; H, 6.77; N, 6.27. Found: C, 72.63; H, 6.80; N, 6.23.
13. We assume that molecular sieves scavenge hydrochloric acid generated during the reaction. The acid is thought to cause decomposition of the product and/or substrate. On the other hand, when Et_3N or pyridine was added for the same purpose, the yield of the product decreased.

14. Oximes **8a**–**c** were prepared from the corresponding aldehydes. The synthesis of these aldehydes will be reported elsewhere.
15. Dicationic intermediate referred to in the text.



16. Compound **9c**: IR (KBr) ν_{max} 3172, 2982, 1727, 1652, 1550, 1437, 1388, 1258, 1143 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 1.19 (3H, t, $J = 7$ Hz, –OCH_2–CH_3), 1.58 (6H, s, dimethyl), 2.44 (3H, s, –Ac), 4.13 (2H, q, $J = 7$ Hz, –O–CH_2–CH_3), 4.47 (2H, d, $J = 7$ Hz, –CH_2–CH=CH_2), 5.47 (1H, d, $J = 10$ Hz, –CH=CH_AH_B), 5.53 (1H, d, $J = 17$ Hz, –CH=CH_AH_B), 6.09 (1H, m, –CH=CH_2), 6.20 (1H, d, $J = 14.5$ Hz, –CH=CH–), 7.77 (1H, d, $J = 14.5$ Hz, –CH=CH–). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.2, 20.8, 26.3, 43.5, 60.9, 75.8, 100.0, 114.9, 118.7, 122.4, 125.3, 129.8, 143.9, 169.9, 176.6. HRMS (FAB) $(M+H)^+$ calcd for $C_{16}H_{23}BrN_3O_4$ 402.0851, found 402.0889.
17. The structure of the less polar product is assumed to be the corresponding enamide, which has an *N*-phenylacetyl group attached to the imidazole ring.
18. Compound **9e**: IR (KBr) ν_{max} 3203, 2978, 1729, 1652, 1460, 1358, 1257, 1137 cm^{-1}. ^1H NMR (CD_3OD, 400 MHz): δ 1.20 (3H, t, $J = 7$ Hz, –OCH_2–CH_3), 1.56 (6H, br s, dimethyl), 1.72 (9H, s, Boc), 2.58 (3H, s, –CH_3), 4.01 (2H, br s, –CH_2–), 4.15 (2H, q, $J = 7$ Hz, –O–CH_2–CH_3), 4.62 (2H, br s, –CH_2–CH=CH_2), 5.50 (1H, br d, $J = 10.5$ Hz, –CH=CH_AH_B), 5.60 (1H, br d, $J = 17$ Hz, –CH=CH_AH_B), 6.19 (1H, br d, $J = 14.5$ Hz, –CH=CH–), 6.20 (1H, br s, –CH=CH_2), 7.20 (1H, t, $J = 7$ Hz, indole), 7.24 (1H, t, $J = 7$ Hz, indole), 7.47 (1H, d, $J = 7$ Hz, indole), 7.51 (1H, br d, $J = 14.5$ Hz, –CH=CH–), 8.12 (1H, d, $J = 8$ Hz, indole). HRMS (FAB) $(M+H)^+$ calcd for $C_{30}H_{38}BrN_4O_6$ 631.1954, found 631.1928.
19. Before the acid treatment, the product was an allyloxyenamide containing *N*-indoleacetyl imidazole, which could be isolated by silica gel TLC.