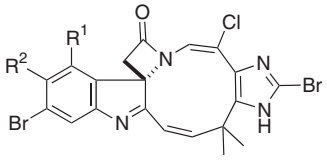
Synthesis of Model Compound Containing an Indole Spiro-β-lactam Moiety with Vinylchloride in Chartellines

Toshio Nishikawa,*[†,††] Shigeo Kajii,[†] and Minoru Isobe*[†]
[†]*Laboratory of Organic Chemistry, Graduate School of Bioagricultural Science, Nagoya University, Chikusa, Nagoya 464-8601*
[††]*PRESTO, Japan Science and Technology Agency*

(Received January 13, 2004; CL-040049)

A model compound containing an indole β-lactam moiety bearing vinylchloride in chartellines was synthesized from the Mannich reaction of isatin imine with ketene silyl acetal, β-lactam formation of the resulting β-amino ester, and copper(I)-mediated coupling with (*E*)-α-chloro-β-iodostyrene.

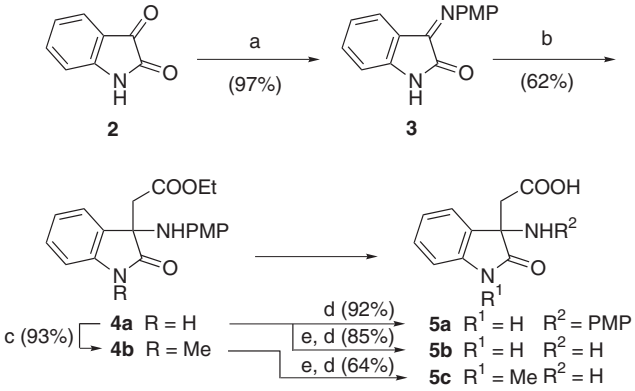
Chartelline A (**1**) and its analogs were isolated from the marine bryozoan, *Chratella papyracea*. The structure studies by X-ray crystallographic analysis and spectroscopic methods revealed an unusual structure including a 10-membered ring condensed with β-lactam, indoline and imidazole rings (Figure 1).[1] Despite the unique chemical architecture, few synthetic studies have been reported. Recently, Weinreb, and co-workers reported the synthesis of a model compound containing a spiro β-lactam and an unsaturated imine moiety,[2] which prompted us to disclose our preliminary result on model experiments of chartelline synthesis, focusing on the synthesis of the spiro β-lactam and its enamide moiety.



chartelline A (**1**) R^1 = Br R^2 = Br
chartelline B R^1 = Br R^2 = H
chartelline C R^1 = H R^2 = H

Figure 1. Structures of chartelline A–C.

With a view to the asymmetric synthesis of chartellines in the future, we planned to synthesize the spiro β-lactam from the corresponding β-amino acid, which would be prepared by the Mannich-type reaction of isatin imine with ketene silyl acetal. Generally, imine prepared from ketone is not suited as the substrate for the Mannich reaction owing to its low reactivity. However, we anticipated that an imine derived from isatin could serve as a good substrate, because the neighboring amide carbonyl group would enhance the electrophilicity of the imine. Thus, we examined the reaction of an imine **3**, readily prepared from isatin (**2**) and *p*-anisidine,[3] with ketene silyl acetal of ethyl acetate in the presence of a Lewis acid (Scheme 1). After some experiments, we found that the reaction proceeded with $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at −20 °C to give β-amino ester **4a** in 62% yield.[4] In this case, 2 equivalents of the Lewis acid was necessary to consume the imine **3**. Oxindole **4a** was treated with NaH and MeI to afford the corresponding *N*-methyl derivative **4b**. Deprotection of the PMP (*p*-methoxyphenyl) and ester of **4a** and **4b** was carried out under conventional conditions to give the precursors (**5a–5c**) for β-lactam formation.



Scheme 1. Reagents and Conditions, (a) *p*-anisidine, EtOH, reflux; (b) $CH_2{=}COEt(OTMS)$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, −20 °C; (c) NaH, MeI, DMF, rt; (d) aq 1 N NaOH, 2-PrOH, rt; (e) CAN, aq CH_3CN, 0 °C.

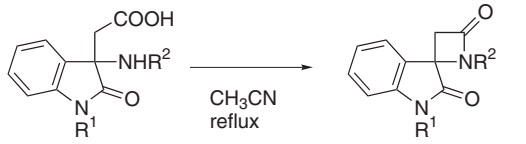
We next examined β-lactam formation of the β-amino acids (**5a–5c**) (Table 1). Under the conventional conditions employing $(PyS)_2/Ph_3P$ or 2-chloro-1-methylpyridinium iodide (**7**),[5] the substrates **5a** and **5b** gave the corresponding β-lactams **6a** and **6b** in low yields,[6] respectively (Entries 1, 2, 4, and 5). *N*-Methyl derivative **5c** also gave disappointing results under the same conditions (Entries 3 and 6). In this specific case, however, we found that β-lactam **6c**[7] was obtained in good yield when **5c** was treated with tris(2-oxo-3-benzoxazolinyl) phosphine oxide (**8**)[8] and Et_3N (Entry 9). These results indicate the importance of the substitution of the oxindole NH group as well as the reagent for this β-lactam formation.

With the desired β-lactam **6c** in hand, we then attempted direct coupling with vinyliodide for the enamide moiety of chartellines. Palladium- or copper-catalyzed enamide formations between amide and vinyl halides have been extensively developed by several groups.[9] Among them, we found the conditions recently reported by Buchwald[10] were fruitful. Thus, the β-lactam **6c** and (*E*)-α-chloro-β-iodostyrene (**9**)[11] as a model vinyl halide were heated with K_2CO_3, *N,N′*-dimethylethylenediamine and copper(I) iodide to give a 5:1 mixture of **10a** and **10b** in high yield (Scheme 2).[12]

This model study should provide an easy accessible route for simple analogs of chartellines. Further studies are in progress in our laboratory.

This work was financially supported by PRESTO, JST,

Table 1. β-Lactam formation

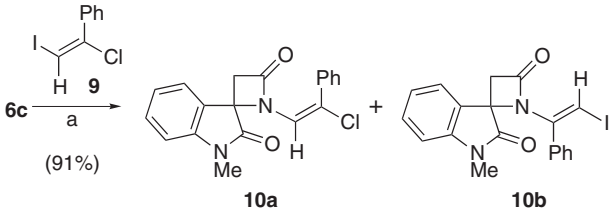


5a R^1 = H R^2 = PMP
5b R^1 = H R^2 = H
5c R^1 = Me R^2 = H

6a R^1 = H R^2 = PMP
6b R^1 = H R^2 = H
6c R^1 = Me R^2 = H

Entry	Substrate	Reagents[a]	Product	Yield/%
1	**5a**	$(PyS)_2$, Ph_3P	**6a**	15
2	**5a**	**7**, Et_3N	**6a**	20
3	**5a**	**8**, Et_3N	**6a**	26
4	**5b**	$(PyS)_2$, Ph_3P	**6b**	13
5	**5b**	**7**, Et_3N	**6b**	16
6	**5b**	**8**, Et_3N	**6b**	39
7	**5c**	$(PyS)_2$, Ph_3P	**6c**	13
8	**5c**	**7**, Et_3N	**6c**	16
9	**5c**	**8**, Et_3N	**6c**	70

[a] All reactions were carried out in [0.01 M] as a substrate concentration.



Scheme 2. Reagents and Conditions, (a) $(CH_2NHMe)_2$, CuI, K_2CO_3, toluene, reflux.

Grant-in-Aid for the 21st Century COE Program from the Ministry of Education, Culture, Sports, Science and Technology of Japan (MEXT).

References and Notes

1 a) L. Chevolot, A.-M. Chevolot, M. Gajhede, C. Lasen, U. Anthoni, and C. Christophersen, *J. Am. Chem. Soc.*, **107**, 4542 (1985). b) U. Anthoni, L. Chevolot, C. Larsen, P. H. Nielsen, and C. Christophersen, *J. Org. Chem.*, **52**, 4709 (1987).

2 a) X. Lin and S. M. Weinreb, *Tetrahedron Lett.*, **42**, 2631 (2001). b) C. Sun, X. Lin, and S. M. Weinreb, 19th International Congress of Heterocyclic Chemistry, Colorado, August, 2003, Abstr., p 324.

3 M. Rajopadhye and F. D. Popp, *J. Heterocycl. Chem.*, **21**, 289 (1984).

4 Mp 172–175 °C. IR (KBr) ν_{max} 3193, 1735, 1616, 1235 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.16 (3H, t, J = 7 Hz, OCH_2CH_3), 2.89 (1H, d, J = 15 Hz, $-CH_AH_B-$), 2.98 (1H, d, J = 15 Hz, $-CH_AH_B-$), 3.62 (3H, s, –OMe), 4.10 (2H, m, OCH_2CH_3), 4.91 (1H, br s, N*H*), 6.42 (2H, dt, J = 9, 3 Hz, PMP), 6.54 (2H, dt, J = 9, 3 Hz, PMP), 6.82 (1H, d, J = 8 Hz, indole), 7.04 (1H, dt, J = 8, 1 Hz, indole), 7.24 (1H, dt, J = 8, 1 Hz, indole), 7.34 (2H, d, J = 8 Hz, indole), 8.15 (1H, br s, N*H* of indole); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.9, 42.5, 55.3, 61.0, 64.0, 110.5, 114.2, 119.9, 123.0, 124.7, 129.4, 129.5, 138.0, 140.5, 154.3, 169.6, 179.0; Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23. Found: C, 67.05; H, 6.00; N, 8.13%.

5 a) S. Kobayashi, T. Iimori, Y.-F. Wang, T. Izawa, and M. Ohno, *J. Am. Chem. Soc.*, **103**, 2405 (1981). b) H. Huang, N. Iwasawa, and T. Mukaiyama, *Chem. Lett.*, **1984**, 1465.

6 In the case of Entries 1–3, a small amount of amide derived from **5a** with *p*-anisidine was obtained, which suggested elimination of *p*-anisidine from the activated ester of **5a**.

7 Mp 234–237 °C; IR (KBr) ν_{max} 3279, 1783, 1690, 1618, 1475 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.24 (1H, dd, J = 14.5, 1 Hz, $-CH_AH_B-$), 3.25 (3H, s, NMe), 3.48 (1H, dd, J = 14.5, 2 Hz, $-CH_AH_B-$), 6.30 (1H, brs, –N*H*), 6.89 (1H, d, J = 8 Hz, indole), 7.15 (1H, dt, J = 8, 1 Hz, indole), 7.39 (1H, dt, J = 8, 1 Hz, indole), 7.46 (2H, d, J = 8 Hz, indole); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.6, 51.0, 55.9, 108.8, 123.3, 123.4, 126.6, 130.5, 143.6, 166.6, 175.0. HRMS (FAB) m/z calcd for $C_{11}H_{11}N_2O_2$ 203.0821, found 203.0822.

8 T. Nagamatsu and T. Kunieda, *Chem. Pharm. Bull.*, **36**, 1249 (1988).

9 For examples of Cu-mediated reaction, a) A. Klapars, J. C. Antilla, X. Huang, and S. L. Buchwald, *J. Am. Chem. Soc.*, **123**, 7727 (2001). b) K. Yamada, T. Kubo, H. Tokuyama, and T. Fukuyama, *Synlett*, **2002**, 231. c) R. Shen and J. A. Porco, Jr., *Org. Lett.*, **2**, 1333 (2000). For reviews of Pd-catalyzed reaction, d) B. H. Yang and S. L. Buchwald, *J. Organomet. Chem.*, **576**, 125 (1999). e) J. F. Hartwig, *Angew. Chem., Int. Ed. Engl.*, **37**, 2046 (1998).

10 L. Jiang, G. E. Job, A. Klapars, and S. L. Buchwald, *Org. Lett.*, **5**, 3667 (2003); The first report of Cu-mediated emamide formation: T. Ogawa, T. Kiji, K. Hayami, and H. Suzuki, *Chem. Lett.*, **1991**, 1443.

11 S. Uemura, H. Okazaki, A. Onoe, and M. Okano, *J. Chem. Soc., Perkin Trans. 1*, **1977**, 676.

12 **10a**: IR (KBr) ν_{max} 1776, 1727, 1617, 1470 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.87 (3H, s, NMe), 3.11 (1H, d, J = 15 Hz, $-CH_AH_B-$), 3.48 (1H, d, J = 15 Hz, $-CH_AH_B-$), 6.51 (1H, d, J = 8 Hz, indole), 6.78 (1H, s, vinyl), 6.98 (2H, d, J = 7.5 Hz, phenyl), 7.03–7.10 (3H, m, aromatic), 7.15 (1H, t, J = 7.5 Hz, Ph), 7.20 (1H, d, J = 7 Hz, indole), 7.27 (1H, dt, J = 8, 1.5 Hz, indole); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.5, 32.2, 50.8, 61.7, 108.9, 117.8, 121.7, 122.9, 123.1, 124.0, 127.5, 127.7, 128.7, 129.2, 130.3, 134.7, 143.2, 163.4, 172.8; HRMS (FAB) calcd for $C_{19}H_{16}N_2O_2Cl_1$ 339.0900, Found 339.0901. **10b**: IR (KBr) ν_{max} 1763, 1725, 1617, 1472 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.80 (3H, s, NMe), 3.13 (1H, d, J = 15 Hz, $-CH_AH_B-$), 3.40 (1H, d, J = 15 Hz, $-CH_AH_B-$), 6.46 (1H, d, J = 8 Hz, indole), 6.77 (2H, d, J = 7 Hz, Ph), 6.78 (1H, s, vinyl), 7.03–7.17 (4H, m, aromatic), 7.25 (1H, dt, J = 8, 1 Hz, indole), 7.35 (1H, d, J = 8 Hz, indole); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.1, 47.8, 50.5, 67.8, 108.4, 116.1, 123.1, 123.4, 125.3, 126.0, 127.5, 128.4, 128.8, 129.8, 130.5, 132.9, 142.4, 164.0, 173.2; HRMS (FAB) m/z calcd for $C_{19}H_{16}N_2O_2I_1$ 431.0257, found 431.0260.

Published on the web (Advance View) March 20, 2004; DOI 10.1246/cl.2004.440