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A Formal Total Synthesis of (±)-Cephalotaxine Using Sequential *N*-Acyliminium Ion Reactions

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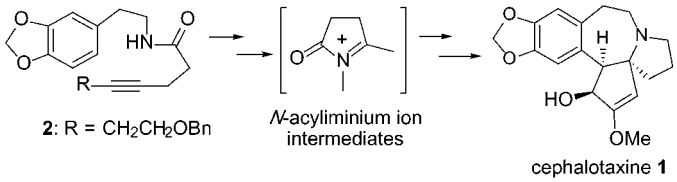
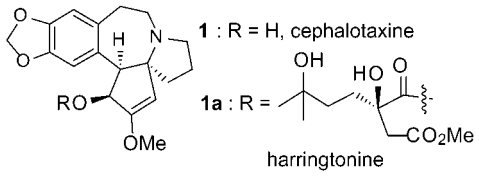
ABSTRACT



Novel synthesis of cephalotaxine 1 based on tertiary *N*-acyliminium ion chemistry starting from alkynylamide 2 was achieved. The key steps include the preparation of pyrroloisoquinoline 4 from alkynylamide 2, the ring expansion of pyrroloisoquinoline 4 to pyrrolobenzazepine 12, and the construction of cyclopentapyrrolobenzazepine ring system 6, all of which are derived from *N*-acyliminium ion intermediates.

Cephalotaxine **1**, a representative *Cephalotaxus* alkaloid,[1] possesses the unique structure of a pentacyclic ring system with a spiro-fused five-membered ring. Because of its unique structural features and the antileukemic activity of its 2-alkylhydroxysuccinates such as harringtonine **1a**,[2,3] many have reported[4] about the total synthesis of cephalotaxine **1**. However, it is known that cephalotaxine itself displays no significant antileukemic activity.



In our laboratory, the alkylidenelactams obtained by the AgOTf−$(TMS)_2$NLi-catalyzed cyclization of alkynylamides have been converted into *N*-acyliminium ion precursors for the synthesis of 5-substituted 2-pyrrolidinone derivatives.[5] Furthermore, the synthesis of isoindolobenzazepine alkaloids, such as lennoxamine and chilenine, utilizing the ring-expansion reaction of isoindoloisoquinoline to isoindolobenzazepine has also been reported.[6] The utility of these methods via *N*-acyliminium ion reactions[7] directed us to the

(1) For a first isolation of **1**, see: Paudler, W. W.; Kerley, G. I.; McKay, J. *J. Org. Chem.* **1963**, *28*, 2194.

(2) For reviews, see: (a) Huang, L.; Xue, Z. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1984; Vol. 23, p 157. (b) Hudlicky, T.; Kwart, L. D.; Reed, J. W. In *Alkaloids*; Pelletier, S. W., Ed.; John Wiley and Sons: New York, 1987; Vol. 5, p 639. (c) Miah, M. A. J.; Hudlicky, T.; Reed, J. W. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1998; Vol. 51, p 199. (d) Smith, C. R., Jr.; Mikolajczak, K. L.; Powell, R. G. In *Anticancer Agents Based on Natural Product Models*; Cassady, J. M., Douros, J. D., Eds.; Academic Press: New York, 1980; p 391.

(3) For an isolation of new alkaloids, cephalezomines, see: Morita, H.; Arisaka, M.; Yoshida, N.; Kobayashi, J. *Tetrahedron* **2000**, *56*, 2929.

(4) For recent total synthesis of **1**, see: (a) Ikeda, M.; El Bialy, S. A. A.; Hirose, K.; Kotake, M.; Sato, T.; Bayomi, S. M. M.; Shehata, I. A.; Abdelal, A. M.; Gad, L. M.; Yakura, T. *Chem. Pharm. Bull.* **1999**, *47*, 983. (b) Tietze, L. F.; Schirok, H. *J. Am. Chem. Soc.* **1999**, *121*, 10264 and references therein.

(5) (a) Koseki, Y.; Kusano, S.; Nagasaka, T. *Tetrahedron Lett.* **1998**, *39*, 3517. (b) Koseki, Y.; Kusano, S.; Ichi, D.; Yoshida, K.; Nagasaka, T. *Tetrahedron* **2000**, *56*, 8855.

(6) Koseki, Y.; Kusano, S.; Sakata, H.; Nagasaka, T. *Tetrahedron Lett.* **1999**, *40*, 2169.

(7) For reviews, see: (a) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (b) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 1047. (c) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367.

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synthesis of cephalotaxine **1** having a pentacyclopyrrolobenzazepine skeleton. In this paper, the synthesis of **1** based on tertiary *N*-acyliminium ions[8] from alkynylamide **2** is reported (Figure 1).

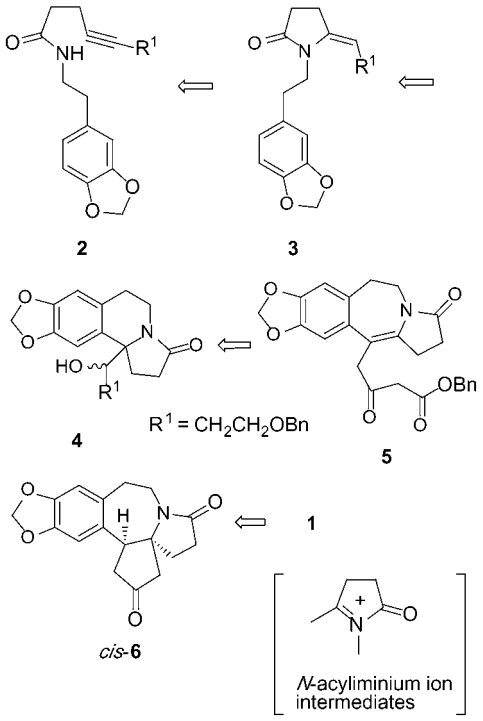


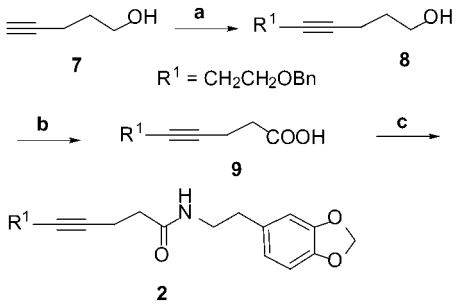
Figure 1. Retrosynthesis of cephalotaxine **1**.

Our synthetic plan relied on the construction of pentacyclopyrrolobenzazepine *cis*-**6** (*cis*-fused 7/5 ring system), an important intermediate in Hanaoka's synthesis,[9] from *β*-keto-ester **5**, which would be obtained by the ring expansion of **4** to the pyrrolobenzazepine skeleton (Figure 1).

Initially, we synthesized alkynylamide **2** from 4-pentyn-1-ol **7** (Scheme 1). Alkylation of the lithium salt of *O*-silylated **7** with 2-(benzyloxy)ethyl iodide proceeded in HMPA−THF and was followed by deprotection with 45% HF−CH_3CN to give alcohol **8**. Oxidation of **8** was carried out according to Zhao's method[10] to give carboxylic acid **9**, which was condensed with 2-(3,4-methylenedioxyphenyl)-ethylamine[11] by DEPC to alkynylamide **2**.

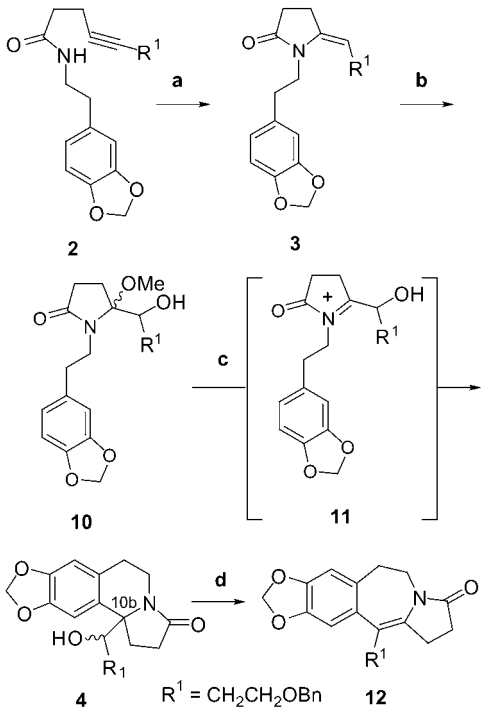
The synthesis of key building block **10** as a tertiary *N*-acyliminium ion equivalent from alkynylamide **2** was accomplished by utilizing successive methods previously reported by us (Scheme 2).[5b]

Scheme 1[a]



[a] (a) (i) TBDMSCl, imidazole, DMF, rt, 95%; (ii) *n*-BuLi (1.1 equiv), THF, −5 °C, then $BnOCH_2CH_2I$ (1.3 equiv), HMPA, 0 °C; (iii) 45% HF−CH_3CN, rt, 79% in 2 steps; (b) $NaClO_2$, cat. NaClO, cat. TEMPO, pH 6.86 phosphate buffer−CH_3CN,[10] 35 °C, 84%; (c) 2-[3,4-(methylenedioxy)phenyl]ethylamine (1 equiv), DEPC (1 equiv), Et_3N (1.1 equiv), rt, THF, 88%.

Scheme 2[a]



[a] (a) LHMDS (0.3 equiv), AgOTf (0.15 equiv), toluene, 65−70 °C, 94%; (b) DMD (excess), MeOH, −78 to −30 °C; (c) $BF_3{\cdot}OEt_2$ (2.1 equiv), CH_2Cl_2, −45 to 0 °C, 80% (from **3**); (d) SO_2Cl_2 (2.1 equiv), Et_3N, (5 equiv), $CHCl_3$−Py (4:1), −78 to 0 °C, 76%.

Alkynylamide **2** was treated with a catalytic AgOTf−$(TMS)_2NLi$ (1:2) system[5a] to afford alkylidenelactam **3** in only a *Z*-form, which was oxidized with dimethyldioxirane (DMD) in the presence of MeOH[6] to give unstable methoxylactam **10** as a diastereomer mixture (1.8:1). When this crude material **10** was immediately treated with $BF_3{\cdot}OEt_2$, cyclization of **10** via acyliminium ion **11** proceeded smoothly to give pyrroloisoquinoline **4** in excellent yield as a diastereomer mixture (2:1).[12]

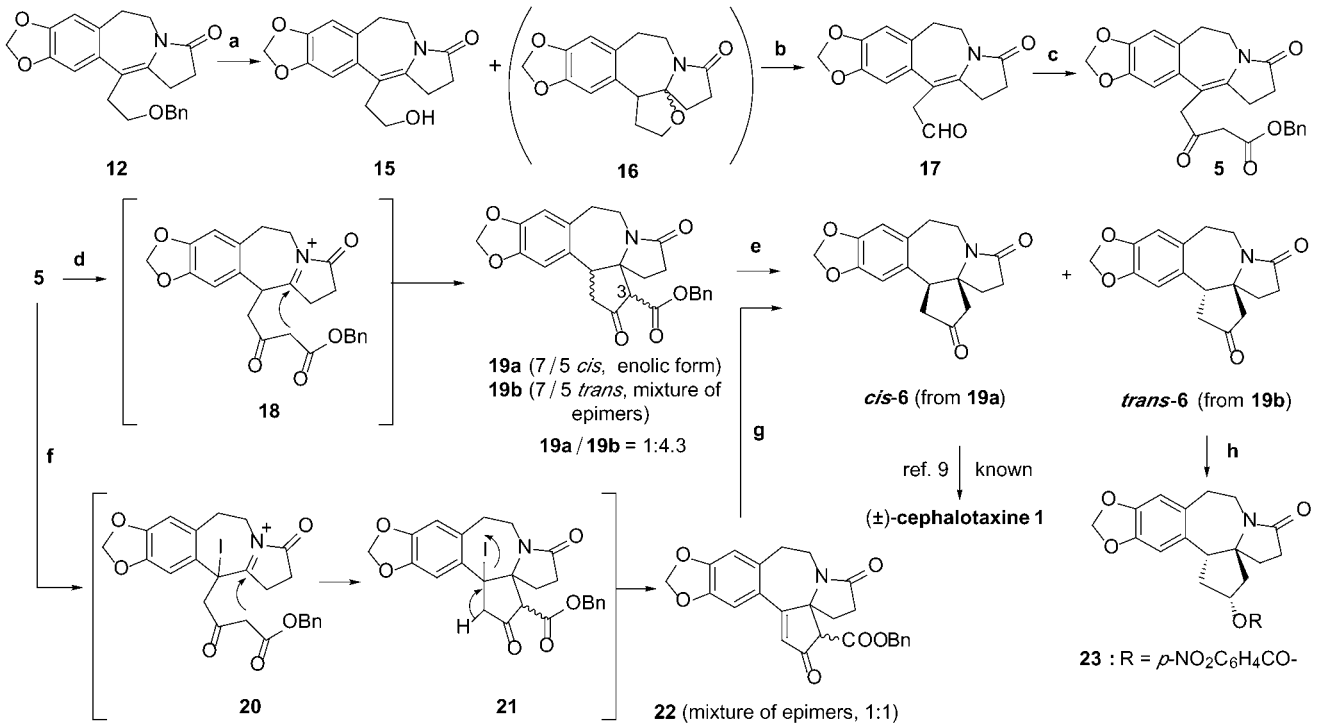
(8) (a) Ollero, L.; Mentink, G.; Rutjes, F. P. J. T.; Speckamp, W. N.; Hiemstra, H. *Org. Lett*. **1999**, *1*, 1331 and references therein. (b) Kim, S.-H.; Cha, J. K. *Synthesis* **2000**, 2113. (c) Kende, A. S.; Martin Hernando, J. I.; Milbank, J. B. J. *Org. Lett*. **2001**, *3*, 2505.

(9) Yasuda, S.; Yamamoto, Y.; Yoshida, S.; Hanaoka, M. *Chem. Pharm. Bull*. **1988**, *36*, 4229.

(10) Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem*. **1999**, *64*, 2564.

(11) (a) Ho, B. T.; McIsaac, W. M.; An, R.; Tansey, L. W.; Walker, K. E.; Englert, L. F., Jr.; Noel, M. B. *J. Med. Chem*. **1970**, *13*, 26. (b) Kihara, M.; Kobayashi, S. *Chem. Pharm. Bull*. **1978**, *26*, 155.

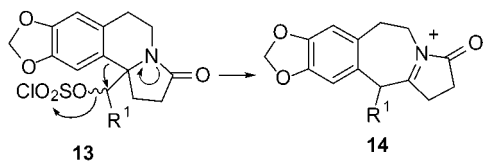
Scheme 3[a]



[a] (a) 5% Pd-C, H_2 (1 atm), THF−H_2O (**15**: 87%, **16**: 11%); (b) Dess−Martin periodinane, $CHCl_3$, rt, 80%; (c) (i) $LiCH_2COOBn$ (1.7 equiv), THF, −78 °C, 93%; (ii) Dess−Martin periodinane, $CHCl_3$, rt, 80%; (d) $TiCl_4$ (1.1 equiv), AcOH−CH_2Cl_2 (1:10), rt, 97% (**19a** + **19b**); (e) (i) 5% Pd-C, H_2 (1 atm), MeOH; (ii) 100 °C, toluene, 87% (from **19a** to *cis*-**6**), 95% (from **19b** to *trans*-**6**); (f) *N*-iodosuccinimide (3 equiv), $TiCl_4$ (1.2 equiv), MeOH−CH_2Cl_2 (1:30), rt, 71%; (g) (i) 5% Pd-C, H_2 (1 atm), THF−MeOH (1:1); (ii) 100 °C, toluene; (iii) 20% $Pd(OH)_2$, H_2 (1 atm), AcOEt, 73%; (h) (i) L-selectride (2 equiv), THF−CH_2Cl_2, −78 °C, quant; (ii) *p*-$NO_2C_6H_4COCl$ (2 equiv), Et_3N (2.2 equiv), Py, rt, 86%.

In a key step concerning the approach to pyrrolobenzazepine, our successful ring-expansion reaction of the six-membered ring (isoindoloisoquinoline) to a seven-membered ring[6,13] was applied to **4**, which possessed the secondary hydroxy group at the 10b-position of the pyrroloisoquinoline ring. When compound **4** was submitted to 2.1 equiv of SO_2Cl_2 in a mixed solvent ($CHCl_3$−pyridine = 4:1) containing 5 equiv of Et_3N, pyrrolobenzazepine **12** was isolated in 76% yield.

A plausible mechanism for this ring-expansion reaction is shown below. At the first step, chlorosulfonylation of a hydroxy group with SO_2Cl_2 afforded **13**,[14] which underwent the migration of an aromatic ring to give **12** via acyliminium ion **14**.



Next, we examined the removal of the benzyl protecting group of **12** by catalytic hydrogenation in order to create the β-keto-ester moiety in **5** (Scheme 3).

Initially, use of 5%Pd−C under atmospheric pressure hydrogen in MeOH for 1 day afforded the desired product **15** in low yield (5%<).

In 10%Pd−C under 2 atm of pressure for 8 h, the undesired product **16** was the major product.[15] The use of aqueous THF (1:5) solvent containing 5%Pd−C led to dramatic improvement of the isolated yield of **15** (87%, along with **16** in 11%), even under atmospheric pressure for 5 h. Oxidation of alcohol **15** with Dess−Martin periodinane afforded aldehyde **17** followed by an aldol reaction with the lithium enolate of benzyl acetate in THF, and oxidation of the resulting alcohol with Dess−Martin periodinane again afforded β-keto-ester **5**.

In the final key step, the cyclization of β-keto-ester **5** via acyliminium ion **18** to pentacyclic compound **19** was examined.[8] For the intramolecular cyclization of **5** to **19**, some acidic conditions were attempted, e.g., BF_3·OEt_2,

(12) For a similar intramolecular cyclization via an *N*-acyliminium ion, see for some examples: (a) García, E.; Arrasate, S.; Ardeo, A.; Lete, E.; Sotomayor, N. *Tetrahedron Lett*. **2001**, *42*, 1511. (b) Cid, M. M.; Domínguez, D.; Castedo, L.; V.-López, E. M. *Tetrahedron* **1999**, *55*, 5599. (c) Heancy, H.; Simcox, M. T.; Slawin, A. M. Z.; Giles, R. G. *Synlett* **1998**, 640. (d) Collado, M. I.; Manteca, I.; Sotomayor, N.; Villa, M. J.; Lete, E. *J. Org. Chem*. **1997**, *62*, 2080.

(13) Recently, synthesis of pyrrolo[3]benzazepines utilizing Stevens [1,2]-rearrangement of tetrahydroisoquinilines has been reported, see: (a) Padwa, A.; Beall, L. S.; Eidell, C. K.; Worsencroft, K. J. *J. Org. Chem*. **2001**, *66*, 2414. For reviews on other ring expansion reactions, see: (b) Weinstock, J.; Hieble, J. P.; Wilson, J. W. *Drugs Future* **1985**, *10*, 645. (c) Kametani, T.; Fukumoto, K. *Heterocycles* **1975**, *3*, 931.

(14) Yamauchi, T.; Hattori, K.; Nakao, K.; Tamaki, K. *Bull. Chem. Soc. Jpn*. **1987**, *60*, 4015.

(15) For example, the similar result has been obteined by Kende et al., see: ref 8c.

BF_3·2AcOH,[16] and catalytic or stoichiometric amount of $TiCl_4$, but these conditions afforded no pentacyclic ring system compounds. Conversely, on exposure to 1.2 equiv of $TiCl_4$ in the presence of AcOH in CH_2Cl_2 at room temperature, the intramolecular cyclization of **5** proceeded smoothly through the formation of acyliminium ion **18** to give the pentacyclic system compound **19** as a diastereomer mixture of *cis*- and *trans*-fused 7/5 ring system in the ratio of 1:4.3 (**19a**-*cis*:**19b**-*trans*)[17] in 18% and 79% isolated yield, respectively. The debenzylation of **19a** (enolic form) and **19b** (as a 2:1 mixture of two epimers at the 3-position) on 5% Pd−C followed by heating at 100 °C in toluene afforded the target compound **6**, respectively. However, both the ^{1}H NMR spectra and the melting point (268−271 °C) of the major isomer **6** were not identical with those of an authentic sample *cis*-**6** (*cis*-fused 7/5 ring system, mp 192−193 °C).[18]

The stereochemistry of major isomer **6** in this study was confirmed to be a *trans*-fused 7/5 ring system by X-ray analysis of nitrobenzoate **23** derived from ketone **6** in two steps.

Next, the iodonium-mediated generation of *N*-acyliminium ion **20** from enamide **5** for the construction of the *cis*-fused 7/5 ring was examined. When **5** was treated with 3 equiv of *N*-iodosuccinimide (NIS) in a $TiCl_4$−MeOH system, the iodocarbocyclization via an *N*-acyliminium ion intermediate proceeded to afford iodospiro-ketone **21**, which was easily converted into enone **22** as a 1:1 mixture of two epimers in 71% yield under these reaction conditions. In this cyclization of **5** to **19** or **22**, the absence of cosolvents (AcOH or MeOH, respectively) caused the cleavage of methylenedioxy function on aromatic rings. The decarbobenzyloxylation of **22** followed by catalytic reduction afforded spiro-ketone *cis*-**6**[9,18] in 73% isolated yield.

In summary, a formal total synthesis of cephalotaxine **1** using the sequential *N*-acyliminium ion reactions, the oxidation of alkylidenelactam to *N*-acyliminium ion precursors, and the ring expansion of a six-membered ring to a seven-membered ring via *N*-acyliminium ions was achieved. The synthetic method reported herein was done in many steps (17 steps from **7** to *cis*-**6**) compared with those described by other authors.[4b] However, in the final key step, this result shows that the cyclization of the β-keto-ester moiety to the enamide through the formation of tertiary *N*-acyliminium ion intermediate by the combined use of a $TiCl_4$−AcOH or $TiCl_4$−NIS−MeOH system is an efficient method for the construction of *N*-heterocyclic rings. Investigation of the enantiotopic face-selective cyclization against the double bond of enamide of compound **5** for the asymmetric synthesis of **1** is now underway.

Acknowledgment. The authors are grateful to Professor M. Hanaoka of Kanazawa University for kindly providing spectral data of compound *cis*-**6**.

Supporting Information Available: Experimental procedure of **3**, **4**, **12**, **15**, **19a**,**b**, **22**, and *cis*-**6**; full characterization data for compounds **3**, **12**, **15**, **17**, **5**, *cis*-/*trans*-**6**, **22**, and **23**; and X-ray data for **23** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Brodney, M. A.; Padwa, A. *J. Org. Chem*. **1999**, *64*, 556.

(17) The intermolecular nucleophilic addition of silyl enol ether to the enamide through the formation of *N*-acyliminium ion by HCl−$TiCl_4$ was reported; see: (a) Wanner, K. T.; Kärtner, A.; Wadenstorfer, E. *Heterocycles* **1988**, *27*, 2549. The examples of the β-keto-ester ring closure to *N*-acyliminium ion imtermediate, see: (b) Mori, M.; Watanabe, Y.; Kagechica, K.; Shibasaki, M. *Heterocycles* **1989**, *29*, 2089. (c) Tsuda, Y.; Ishiura, A.; Hosoi, S.; Isobe, K. *Chem. Pharm. Bull*. **1992**, *40*, 1697. (d) Kigoshi, H.; Hayashi, N.; Uemura, D. *Tetrahedron Lett*. **2001**, *42*, 7469.

(18) The ^{1}H NMR spectra data and melting point (mp 204−205 °C) of minor isomer **6** was identical with those of *cis*-**6** in the literature (mp 192−193 °C); see ref 9.