Facile Total Synthesis of (±)-Adalinine

Naoki Yamazaki, Toshimasa Ito, and Chihiro Kibayashi*

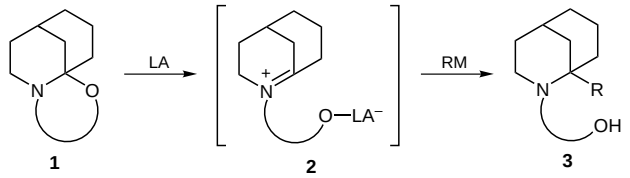
School of Pharmacy, Tokyo University of Pharmacy & Life Science, Horinouchi, Hachioji, Tokyo 192-0392, Japan
Fax +81(426)76-4475; E-mail: kibayasi@ps.toyaku.ac.jp

Revised 14 October 1998

Abstract: A useful construction of 6,6-disubstituted 2-piperidones has been developed based on allylation of the cyclic *N*-acyl-*N*,*O*-acetals using a combination of Lewis acid and allyltrimethylsilane, leading to the facile total synthesis of a new ladybird alkaloid adalinine in racemic form.

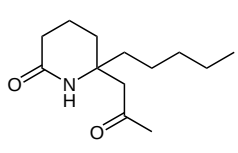
Key words: adalinine, piperidine alkaloid, cyclic N,O-acetals, Lewis acid induced allylation, nitrogenated quaternary center

We have recently recognized that Lewis acid treatment of the cyclic *N*,*O*-acetal **1** resulted in breaking of the C–O bond to generate a bridgehead iminium ion **2**, that served to effect construction of a quaternary center at the α position of the piperidine system to give **3** via subsequent treatment with organometallics (Scheme 1).[1]

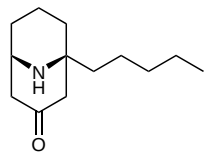


Scheme 1

In the course of this study, we were intrigued by the structure of a new piperidine alkaloid[2] with a quaternary center at the α position of the piperidine system, i.e., adalinine (**4**),[3] which has been isolated as a minor alkaloid from the European ladybird beetles *Adalia bipunctata* and *A. decempunctata* and suggested to be biosynthetically related to adaline (**5**), the major defensive alkaloid from the European ladybirds.[4] The synthesis of (±)-**4** has been reported by Braekman et al.[5] recently starting from cyclopentanone in five steps and 4.4% overall yield.

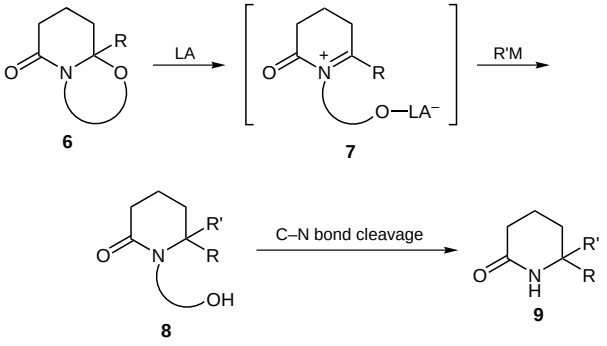


adalinine (**4**)



adaline (**5**)

We envisioned the use of the cyclic *N*,*O*-acetal-based methodology involving the creation of a nitrogenated quaternary center[6] for the synthesis of (±)-**4**. The protocol for the adalinine synthesis illustrated in Scheme 2 was based on the construction of the nitrogenated quaternary center via addition of a carbon nucleophile to the cyclic *N*-acyliminium intermediate **7**, followed by cleavage of the *N*-substituent of **8** to give **9**. In this paper, we report details of this sequence and provide an application of the process to the synthesis of adalinine (**4**).



Scheme 2

A series of the cyclic *N*-acyl-*N*,*O*-acetals **12a–d** were prepared according to the reported procedure[7] by dehydrocondensation of the hydroxy amines **10**, i.e., 2-aminopropanol, 2-(aminomethyl)benzyl alcohol, 2-aminophenol, and 2-hydroxybenzylamine, respectively, with 5-oxodecanoic acid (**11**)[8] in benzene at reflux (for yields of **12a–d**, see Table 1).

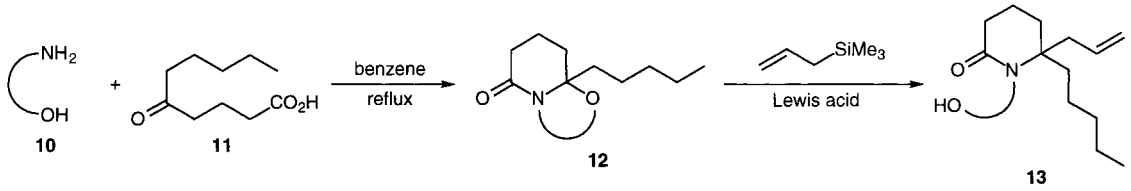
We initially attempted to carry out nucleophilic allylation with **12a** based on our previously developed procedure[9] with a combination of Et_2AlCl (2 equiv) and allylmagnesium bromide (2 equiv) in THF at room temperature; however, this reaction gave a complex mixture of products. The complexity in the reaction could be understood by the possibility that nucleophiles were both accepted at the iminium ion center and the carbonyl carbon of the amide moiety.

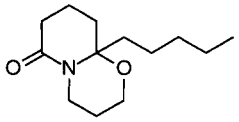
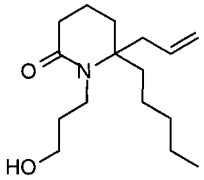
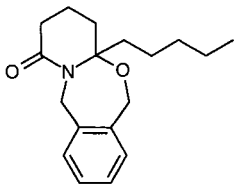
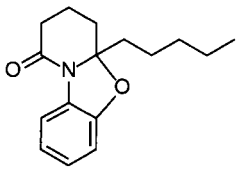
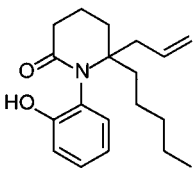
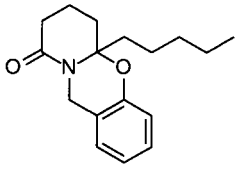
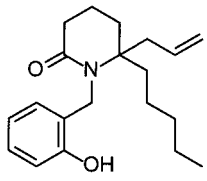
To avoid this, we decided to utilize nucleophilic alkenes which have been proven particularly useful for addition to *N*-acyliminium ions because of the greater electrophilicity of the *N*-acyliminium ion as compared with an ordinary iminium ion.[10] Thus, Lewis acid induced reaction of the series of the cyclic *N*-acyl-*N*,*O*-acetals **12a–d** using allyltrimethylsilane was next investigated. The results are

summarized in Table 1. When **12a** was treated with the allylsilane (3 equiv) in the presence of $TiCl_4$ or $HfCl_4$ (3 equiv) at room temperature, the allylation reaction occurred with rapid consumption of the substrate to afford the allylated product **13a** in 46% or 30% yield, respectively (entries 1, 2). Application of the same conditions to **12b**, however, led to the formation of an intractable complex mixture with no detection of the desired 2-allylated piperidone (**13b**) (entries 3, 4). The $TiCl_4$-induced allylation using **12c** involving the phenoxy moiety instead of the alkoxy moiety as in **12a** and **12b** resulted in the formation of the allylated product **13c** in low yield (26%), accompanied by a complex mixture of products (entry 5). In this reaction, change of the Lewis acid from $TiCl_4$ to $HfCl_4$ and $ZrCl_4$ remarkably increased the yields of **13c** up to 72% and 70%, respectively (entries 6, 7). When the $TiCl_4$-induced allylation was carried out using **12d** with the phenoxy moiety, it successfully gave the allylated product **13d** in high yield (92%), although prolonged reaction time (96 h) was needed (entry 8). In this case, the Lewis acids $HfCl_4$ and $ZrCl_4$, however, did not work well with **12d** and produced mostly recovered starting material with very low yield (1–2%) of **13d**. Higher temperatures and extended reaction times caused the destruction of the substrate.

Having established that the Lewis acid induced allylation at the C-6 position in the 6-pentyl-2-piperidone occurred with the use of **12c** and **12d** with the phenoxy moieties, the remaining transformation necessary for obtaining adalinine was construction of the 2-oxopropyl moiety at the

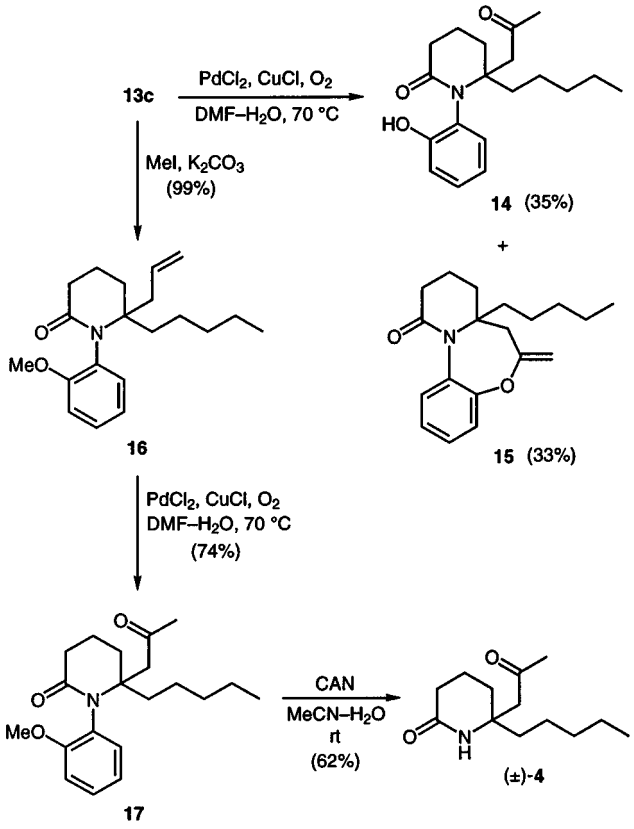
Table 1. Lewis Acid-Induced Nucleophilic Allylation of *N,O*-Acetals **12** with Allylsilane[a]



entry	*N,O*-acetal **12**[b] (% yield[c])	Lewis acid	time (h)	allylated product **13**	% yield[d] of **13**
1	 **12a** (62)	$TiCl_4$	1	 **13a**	46
2		$HfCl_4$	1		30
3	 **12b** (26)	$TiCl_4$	1	complex mixture	
4		$HfCl_4$	1	complex mixture	
5	 **12c** (99)	$TiCl_4$	20	 **13c**	26
6		$HfCl_4$	18		72
7		$ZrCl_4$	18		70
8	 **12d** (81)	$TiCl_4$	96	 **13d**	92

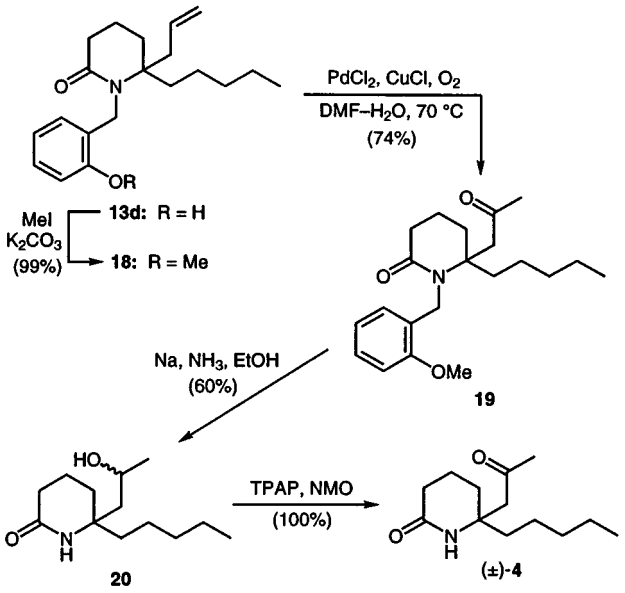
[a]All reactions were carried out using CH_2Cl_2 as a solvent at rt. [b]Obtained by condensation of the amino alcohol or aminophenol **10** with the δ-keto acid **11** in refluxing benzene. [c]Isolated yield of **12** obtained by the reaction of **10** with **11**. [d]Isolated yield

C-6 position and cleavage of the N-substituent group. To this end, Wacker oxidation was performed with **13c**; however, the formation of the desired oxo compound **14** (35%) was accompanied by the formation of the cyclization product **15** (33%). The formation of **15** was understood by internal attack of phenolic OH group to the intermediacy of the π-allylpalladium species instead of H_2O as in a usual Wacker process. Thus, to prevent the formation of **15**, **13c** was converted to the methyl ether **16** (MeI, K_2CO_3, 99% yield), which was subjected to Wacker oxidation to afford the oxo compound **17** in 74% yield.[11] Oxidative cleavage of the *N*-(*o*-methoxyphenyl) group was performed using ceric ammonium nitrate (CAN)[12] to provide (±)-adalinine (**4**) in 62% yield (Scheme 3). The spectral data (^1H and ^{13}C NMR, MS) of synthetic material were identical to those reported[3] for the natural product.



Scheme 3

Similarly, allylated compound **13d** was converted to the oxo compound **19** in 73% yield via O-methylation (to form **18**) followed by Wacker oxidation. Subsequent removal of the *N*-(*o*-methoxybenzyl) group from the molecule was first attempted according to the previously described method[13] for oxidative removal of the *N*-(*p*-methoxybenzyl) group with CAN; however, it led to a complex mixture of products. Thus, reductive cleavage of the *N*-benzyl moiety was conducted under the Birch conditions to give a 1:1 mixture of the diastereomeric alcohols **20** (60% yield), which without separation underwent



Scheme 4

TPAP (tetrapropylammonium perruthenate) oxidation[14] to furnish (±)-**4** in quantitative yield (Scheme 4).

In conclusion, we have developed a useful approach for the elaboration of the nitrogenated quaternary center based on Lewis acid induced allylation of the cyclic *N*-acyl-*N*,*O*-acetals to afford the 6,6-disubstituted 2-piperidones **13c** and **13d**, which allowed facile two entries to (±)-adalinine (**4**) via oxidative de-*N*-arylation and reductive de-*N*-benzylation in 32% (5 steps) and 33% (6 steps) overall yields, respectively, from the known δ-keto acid **11**.

References and Notes

(1) Yamazaki, N.; Suzuki, H.; Kibayashi, C. *J. Org. Chem.* **1997**, *62*, 8280.
(2) For a review of the piperidine alkaloids, see: (a) Fodor, G. B.; Colasanti, B. In *Alkaloids: Chemical and Biological Perspective*, Vol. 3; Pelletier, S. W., Ed.; Wiley: New York, 1985; Ch. 1, pp. 1–90. (b) Schneider, M. J. In *Alkaloids: Chemical and Biological Perspective*, Vol. 10; Pelletier, S. W., Ed.; Elsevier Science: Oxford, 1996; Ch. 2, pp. 155–299.
(3) Lognay, G.; Hemptinne, J. L.; Chan, F. Y.; Gaspar, CH.; Marlier, M.; Braekman, J. C.; Daloze, D.; Pasteels, J. M. *J. Nat. Prod.* **1996**, *59*, 510.
(4) For a recent review of the coccinellid alkaloids, see: King, A. G.; Meinwald, J. *Chem. Rev.* **1996**, *96*, 1105.
(5) Broeders, F.; Braekman, J. C.; Daloze, D. *Bull. Soc. Chim. Belg.* **1997**, *106*, 377.
(6) For the enantioselective construction of a quaternary center at the α position of the pyrrolidine system by Lewis acid–allylsilane alkylation of cyclic *N*-acyl-*N*,*O*-acetals, see: Burgess, L. E.; Meyers, A. I. *J. Am. Chem. Soc*. **1991**, *113*, 9858.
(7) Burgess, L. E.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 1656.
(8) (a) Jpn. Kokai Tokkyo Koho JP 81,161,348; *Chem. Abst.* **1982**, *96*, 142275z. (b) Fréville, S.; Célérier, J. P.; Thuy, V. M.; Lhommet, G. *Tetrahedron: Asymmetry* **1995**, *6*, 2651.

(9) (a) Yamazaki, N.; Suzuki, H.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **1996**, *37*, 6161. (b) Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **1997**, *38*, 4623.
(10) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*, Vol. 2; Heathcock, C. H., Ed.; Pergamon Press: Oxford, 1991; Ch. 4.5, pp. 1047–1082.
(11) The oxo compound **17** was actually isolated as a 1:1 mixture of two atropisomers i and ii, which were easily separated by silica gel chromatography and assigned their relative stereochemistry as shown based on NOESY data. In this work, this mixture was used without separation in the next reaction.
(12) Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765.
(13) Yoshimura, J.; Yamaura, M.; Suzuki, T.; Hashimoto, H. *Chem. Lett.* **1983**, 1001.
(14) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.