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# Total synthesis of the coccinellid alkaloid (–)-adalinine and the assignment of its absolute configuration

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**Abstract**

The first asymmetric total synthesis of a new coccinellid alkaloid (–)-adalinine has been achieved, based on the construction of a 2-piperidone framework with an asymmetric quaternary center at the C-6 position, which was performed by Lewis acid-induced allylation of the cyclic *N*-acyl-*N,O*-acetal incorporating the chiral aminophenol auxiliary. This synthesis allowed the absolute stereostructure of natural (–)-adalinine to be assigned as *R*.

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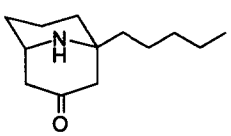
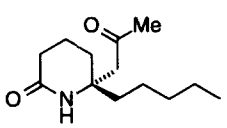
(–)-Adaline was originally isolated as a major alkaloid from the chemical defense secretion of the European two-spotted ladybird *Adalia bipunctata* and has been assigned structure **1** [1]. Upon subsequent single crystal X-ray and ORD spectral analyses, the absolute configuration of adaline has been established to be 1*R*,5*S* [2]. Recently, a reinvestigation of the secretion of this species led to the isolation and structure determination of a new piperidine alkaloid adalinine (**2**) as a minor component [3,4]. Synthesis of **2** in racemic form has been achieved by Braekman [5] and by us [6]. In the former synthesis, direct comparison of the synthetic sample with the natural compound confirmed the proposed structure, but the absolute configuration of the quaternary stereogenic center at the C-6 position was not assigned. Due to the fact that both adaline (**1**) and adalinine (**2**) occurred in *A. bipunctata* and also were found in *A. decempunctata*, adalinine has been speculated to be biogenetically derived from the major alkaloid adaline via a retro-Mannich reaction [3]. This suggests that the absolute configuration of **2** at C-6 is *R*, which is the same as that at C-1 of adaline. Based on this assumption, we have engaged in a synthetic approach to (*R*)-adalinine (**2**). In this paper, we report the first asymmetric synthesis of (–)-**2**, which allowed the first determination of the absolute configuration of the natural alkaloid to be *R* as shown.




(–)-adaline (**1**)




(–)-adalinine (**2**)

Our synthetic strategy for the asymmetric synthesis of adalinine entailed elaboration of an asymmetric quaternary center [7] at the C-6 position of the 2-piperidone ring system by utilizing the cyclic *N,O*-acetal-based methodology [8] (Scheme 1). Thus, Lewis acid treatment of a cyclic *N,O*-acetal **3** incorporating an appropriate chiral auxiliary would result in breaking of the C–O bond to

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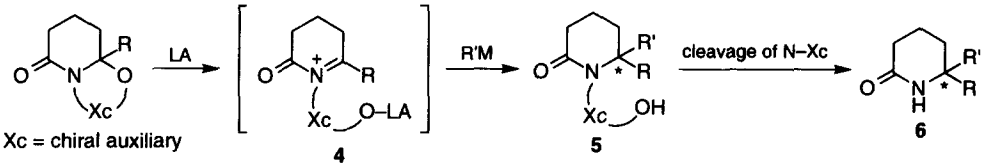
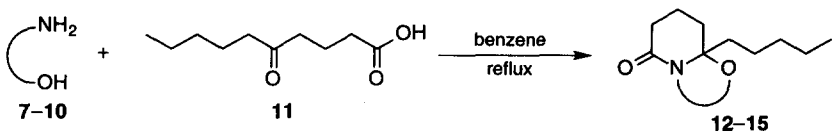
generate an acyliminium ion **4**, which would undergo diastereoselective alkylation onto the iminium ion [9], followed by cleavage of the chiral auxiliary, leading to enantiomeric formation of a 6,6-disubstituted 2-piperidone **6**.

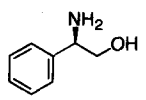
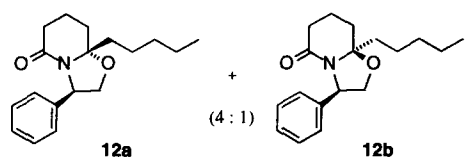
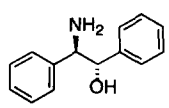
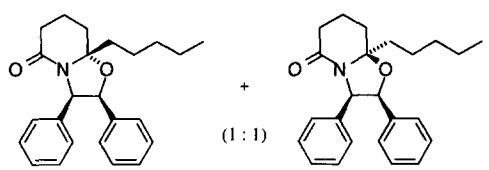
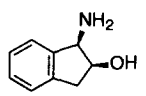
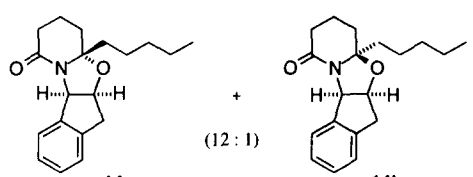
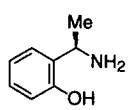
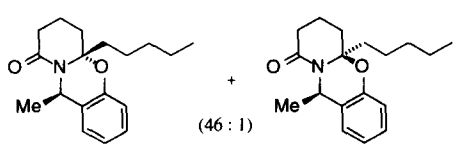
**Scheme 1**




On the basis of this consideration, a series of the chiral 2-piperidones **12–15** incorporating the cyclic *N,O*-acetals were prepared according to the reported method [10] by dehydrocondensation of the chiral amino alcohols **7–9** and the chiral aminophenol **10** with 5-oxodecanoic acid (**11**) in refluxed benzene (Table 1). Stereochemical assignments of these diastereomeric products (chromatographically separable) were based on spectroscopic and X-ray crystallographic (for **13a**) analyses.

**Table 1. Preparation of Chiral *N,O*-Acetals (12–15) by Dehydrocondensation of Chiral Hydroxy Amines (7–10) and 5-Oxodecanoic Acid (11)**



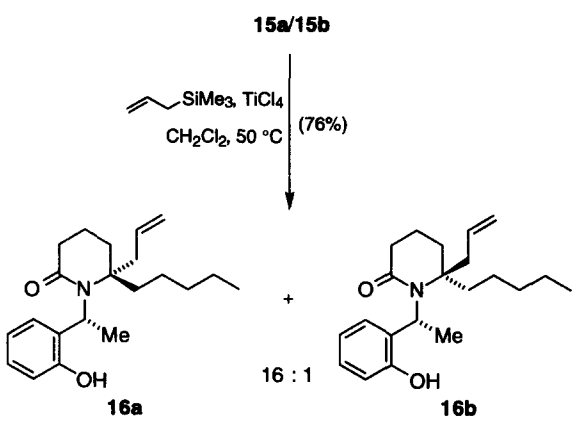

| entry | hydroxy amine | *N,O*-acetal (diastereomer ratio[a]) | % yield[b] |
|---|---|---|---|
| 1 |  **7** |  **12a** (4 : 1) **12b** | 83 |
| 2 |  **8** |  **13a** (1 : 1) **13b** | 85 |
| 3 |  **9** |  **14a** (12 : 1) **14b** | 92 |
| 4 |  **10** |  **15a** (46 : 1) **15b** | 88 |

[a]Determined by 400 MHz $^1$H NMR. [b]Isolated yield of the diastereomeric mixture.

We initially attempted to carry out nucleophilic allylation using **12a** and **12b** via exposure to allyltrimethylsilane (3 equiv) and $TiCl_4$ (3 equiv) in $CH_2Cl_2$ at room temperature; however, in both cases, no allylation took place even at elevated temperatures. This behavior is significantly different compared with the previously reported results [8] for a similar cyclic *N,O*-acetal-based allylation of the 2-pyrrolidone involving the same auxiliary (phenylglycinol); in the latter case, diastereoselective allylation occurred to produce 6,6-disubstituted 2-pyrrolidones. The allylations of **13a, b** and **14a, b** under the same conditions gave no reaction either.

In marked contrast, when used **15a** possessing the phenoxy moiety instead of the alkoxy moiety as in **12–14**, the $TiCl_4$–induced allylation reaction (50 °C in a sealed tube) occurred to afford **16a** with high diastereoselectivity (16:1) and full retention of the stereochemistry at the α carbon of the piperidine system. The use of the minor diastereomer **15b** under the same conditions gave almost the same yield and diastereoselectivity as that of **15a**. Thus, the diastereomeric mixture **15a/15b** obtained could be actually used without separation for the allylation reaction.

Such notable difference in the allylation reactivity between the acetal involving the phenoxy moiety (**15**) and the acetals involving the alkoxy moieties (**12–14**) is apparently due to that phenoxide ions are much better leaving groups than alkoxide ions in nucleophilic displacement reactions. These diastereomers **16a** and **16b** were easily separated by silica gel column chromatography and the configuration of the quaternary center for the major isomer **16a** was determined by X-ray crystallographic analysis to be *R* (Figure 1).



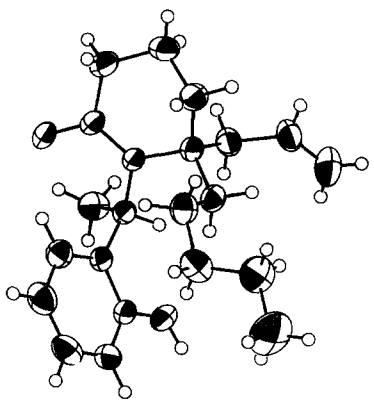
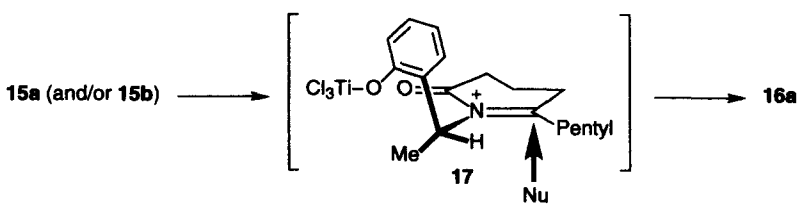



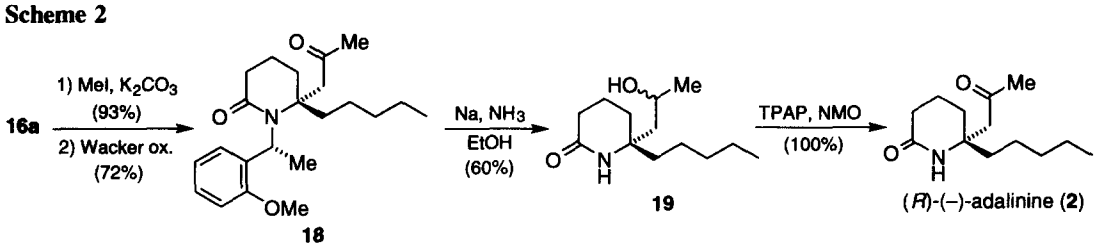
**Figure 1.** X-ray crystal structure of **16a** (ORTEP, 50% probability ellipsoids).

The stereochemical outcome of this allylation can be rationalized on the basis of $S_N1$-type nucleophilic addition with net retention. Accordingly, complexation of the *N,O*-acetal oxygen atom in **15a** (and/or **15b**) with the Lewis acid promotes C–O bond cleavage to form the *N*-acyliminium ion **17**, which preferably adopts the conformation with the hydrogen atom in the inside position to minimize the 1,3-allylic strain. Subsequent nucleophilic addition to **17** is expected to occur from the less hindered bottom face leading to the *R* configuration in the piperidone to give **16a**.



Having established the asymmetric quaternary center at the C-6 position of the piperidone system, effort was next focused on the transformation of the allyl group to the acetonyl group. Thus, after protection of the phenolic hydroxyl group in **16a** with iodomethane ($K_2CO_3$, acetone, 93% yield), Wacker oxidation ($PdCl_2$, CuCl, $O_2$, DMF–$H_2O$, 70 °C) was performed to give **18** in 72% yield. The cleavage of the chiral auxiliary was accomplished by Birch reduction ($Na^0$, $NH_3$, EtOH) to give a 1:1 mixture of the diastereomeric alcohols **19** in 60% yield. Finally, ruthenium oxidation was conducted to provide (*R*)-adalinine (**2**) in quantitative yield. The spectral data ($^1H$ and $^{13}C$ NMR, MS) of synthetic adalinine were identical to those reported [3] for the natural product. The optical purity of the synthetic material was determined to be 100% ee by HPLC analysis[1] and its optical rotation ($[\alpha]^{20}_{Hg578} = -29.2$ (*c* 1.1, $CH_2Cl_2$), $[\alpha]^{20}_{D} = -28.3$ (*c* 1.6, $CH_2Cl_2$)) was in good agreement with that reported for the natural product (lit. [3] $[\alpha]^{20}_{579} = -26$ (*c* 0.13, $CH_2Cl_2$)), thus establishing the absolute configuration of natural (–)-adalinine to be *R*.

**Scheme 2**




In summary, the facile asymmetric synthesis of (–)-(*R*)-adalinine has been achieved for the first time from readily available materials in six steps and 25% overall yield. An important feature of this synthesis is the efficient construction of an asymmetric quaternary center with the correct absolute stereochemistry, which was performed by Lewis acid-induced allylation of the cyclic *N*-acyl-*N*,*O*-acetal incorporating the chiral aminophenol auxiliary. This synthesis allowed the absolute configuration of natural (–)-adalinine to be established as *R*.

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[9] For our previous works on Lewis acid-mediated alkylation of cyclic *N*,*O*-acetals, see: (a) Yamazaki N, Suzuki H, Aoyagi S, Kibayashi C. Tetrahedron Lett. 1996;37:6161–6164. (b) Yamazaki N, Kibayashi C. Tetrahedron Lett. 1997;38:4623–4626. (c) Yamazaki N, Suzuki H, Kibayashi C. J. Org. Chem. 1997;62:8280–8281.

[10] Burgess LE, Meyers AI. J. Org. Chem. 1992;57:1656–1662.


[1] Separation conditions: Chiralpak OD column, 250 × 4.6 mm; eluent, hexane–*i*-PrOH (90:10, v/v); flow rate, 0.5 mL/min; column temperature, 20 °C; detection, UV (220 nm); retention times, $t_R$ = 24.2 min for (*S*)-**2**, $t_R$ = 27.4 min for (*R*)-**2**.