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Asymmetric Synthesis of (−)-Adaline

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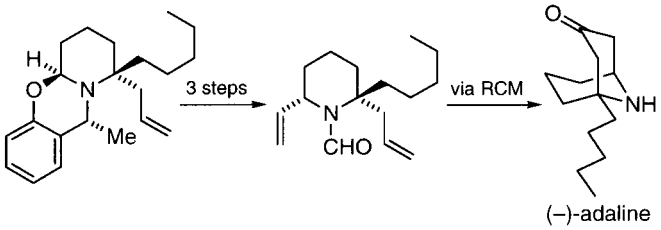
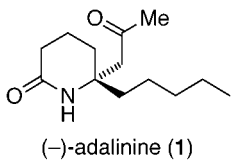
ABSTRACT

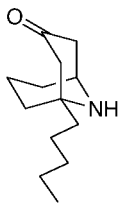


An enantioselective total synthesis of (−)-adaline has been achieved starting from a chiral 6,6-disubstituted piperidone derivative previously prepared by diastereoselective allylation of a chiral tricyclic *N*-acyl-*N*,*O*-acetal. The key steps include lithium ion-activated S_N2-type alkynylation of the tricyclic *N*,*O*-acetal leading to exclusive formation of the (6*S*)-ethynylpiperidine and ring-closing olefin metathesis of the (2*R*,6*S*)-*cis*-2,6-dialkenylpiperidine for constructing the bridged azabicyclononane.

We previously reported $TiCl_4$-mediated asymmetric allylation employing tricyclic *N*-acyl-*N*,*O*-acetals, in which enantiomeric 2-(1-aminoethyl)phenol (**3**) has been proven useful as a chiral auxiliary.[1] In connection with this investigation, most recently we have developed a convenient practical asymmetric synthesis of **3** via nucleophilic addition of methyllithium to a chiral oxime ether.[2] We have also demonstrated that this asymmetric allylation protocol is efficiently applicable to the total synthesis of various alkaloids,[1] and the first enantioselective synthesis of a new coccinellid alkaloid (−)-adalinine (**1**)[3,4] was achieved on the basis of a diastereoselective addition of allylsilane to an in situ generated



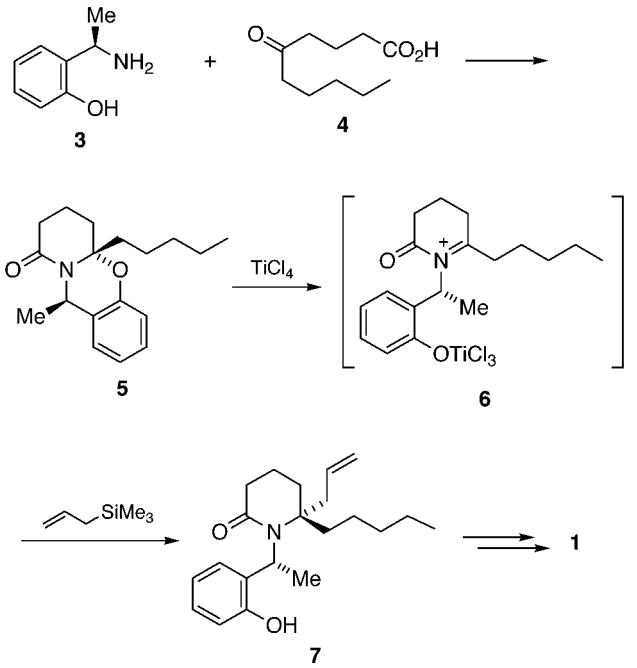
(−)-adalinine (**1**)



(−)-adaline (**2**)

N-acyliminium ion **6** to form the (*R*)-allylated piperidone **7** as shown in Scheme 1.[1a] We envisioned compound **7** utilized as the key synthetic intermediate in this scheme could be

Scheme 1



(1) (a) Yamazaki, N.; Ito, T.; Kibayashi, C. *Tetrahedron Lett.* **1999**, *40*, 739−742. (b) Yamazaki, N.; Ito, T.; Kibayashi, C. *Org. Lett.* **2000**, *2*, 465−467. (c) Yamazaki, N.; Dokoshi, W.; Kibayashi, C. *Org. Lett.* **2001**, *3*, 193−196.

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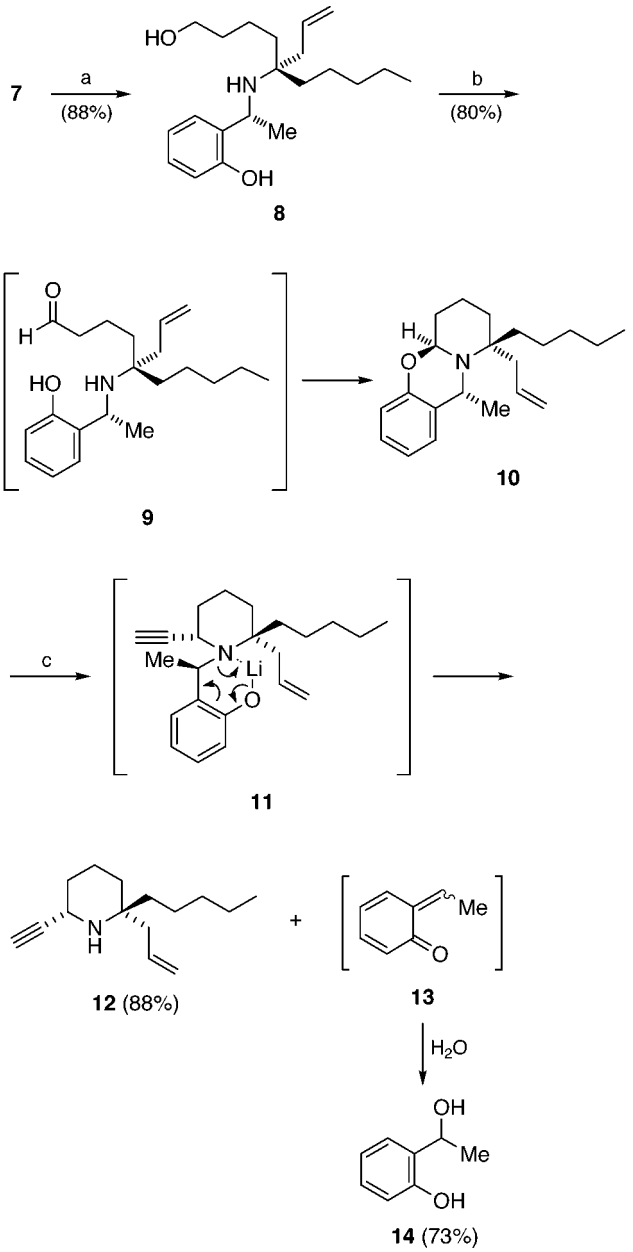
applicable to the synthesis of (−)-adaline (**2**),[4−6] which is the major defensive alkaloid from the European ladybug, *Adalia bipunctata*, and is suggested[7] to be biogenetically related to (−)-adalinine (**1**) isolated as a minor defensive alkaloid. In this paper, we describe the enantioselective total synthesis of (−)-adaline (**2**)[8] starting from the (6*S*)-piperidone **7** by an S_N2-like alkynylation using a tricyclic *N*,*O*-acetal as an extension of the previous *N*-acyl-*N*,*O*-acetal-based allylation, followed by ring-closing olefin metathesis.

Reductive lactam ring opening of **7** was carried out by employing LiH_2NBH_3[9] (THF at 40 °C) to give the amino alcohol **8** in 88% yield (Scheme 2). This compound was cyclized by a one-pot procedure with TPAP−NMO in acetonitrile (4A MS, rt, 1 h) that involved oxidation to the aldehyde **9** followed by dehydrocondensation to afford the tricyclic *N*,*O*-acetal **10** (80% yield) as a single stereoisomer, where the chiral auxiliary **3** was incorporated. The 5a*S* configuration of **10** was confirmed by the NOESY interaction between 5a-H and the methyl group at C11 as depicted in Figure 1. Upon treatment of **10** using lithium acetylide ethylenediamine complex ($HC{\equiv}CLi{\cdot}H_2NCH_2CH_2NH_2$)[10] in THF at 40 °C, the nucleophilic alkynylation[11] proceeded with complete inversion of configuration at the reaction center and, unexpectedly, with concomitant removal of the 1-(2-hydroxyphenyl)ethyl function via C−N bond cleavage, leading to the (6*S*)-ethynylpiperidine **12** (88%) as a single diastereomer along with racemic 1-(2-hydroxyphenyl)ethanol (**14**) (73%).[12] The *S* absolute stereochemistry at C6 of **12** was determined by the NOESY experiment, which revealed the equatorial orientation of the C6-ethynyl group, syn to the C2-allyl group as shown in Figure 2. The exclusive formation of the (6*S*)-isomer **12** is a consequence of the coordination of the lithium ion to the oxygen of the *N*,*O*-acetal, activating the C−O bond for nucleophilic attack of the lithium acetylide to give the S_N2-type ring opening of the *N*,*O*-acetal.[13] In the second step, the generated lithium phenoxide **11** may form a tight six-membered chelate complex, facilitating the cleavage of the benzylic carbon−

Scheme 2[a]



[a] Key: (a) LiH_2NBH_3, THF, 40 °C; (b) TPAP, NMO, MeCN, 4A MS, rt; (c) $HC{\equiv}CLi{\cdot}H_2NCH_2CH_2NH_2$ (5 equiv), THF, 40 °C.

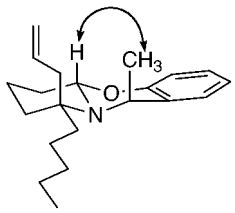


Figure 1. Selected NOESY correlation for **10**.

(2) Yamazaki, N.; Atobe, M.; Kibayashi, C. *Tetrahedron Lett.* **2001**, *42*, 5029−5032.

(3) For isolation and structure elucidation, see: Lognay, G.; Hemptinne, J. L.; Chan, F. Y.; Gaspar, C. H.; Marlier, M.; Braekman, J. C.; Daloze, D.; Pasteels, J. M. *J. Nat. Prod.* **1996**, *59*, 510−511.

(4) For a recent review of the coccinellid alkaloids, see: King, A. G.; Meinwald, J. *Chem. Rev.* **1996**, *96*, 1105−1122.

(5) For the isolation and structural determination of adaline, see: Tursch, B.; Braekman, J. C.; Daloze, D.; Hootele, C.; Losman, D.; Karlsson, R.; Pasteels, J. M. *Tetrahedron Lett.* **1973**, 201−202.

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(11) Treatment of **7** with vinylmagnesium bromide or vinyllithium in THF resulted in no reaction.

(12) Chiral HPLC (Chiralpak AD column) analysis of compound **14** showed two peaks with exactly equal integration for the both enantiomers.

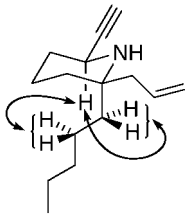
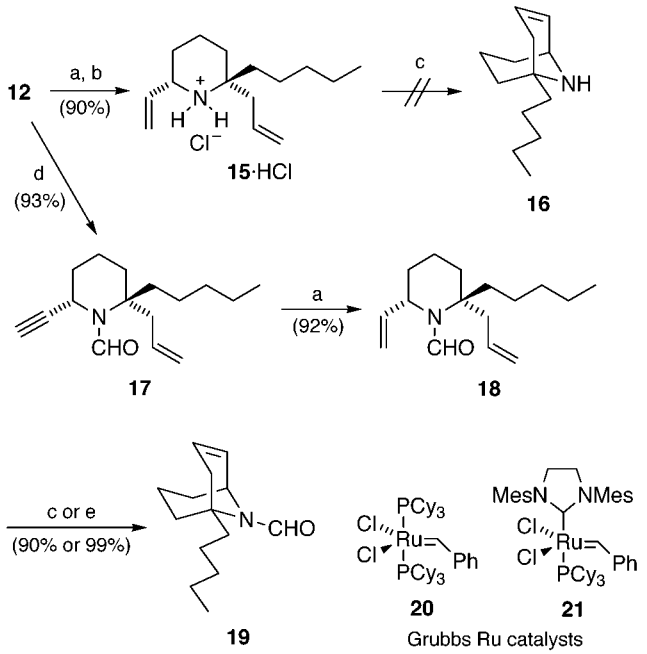


Figure 2. Selected NOE correlation for **12**.

nitrogen bond to furnish a transient trienone **13**, which can be immediately aromatized in the presence of water to the hydroxyphenol **14** with complete racemization.[12]

For ring-closing metathesis (RCM),[14] the enyne **12** was transformed to the *cis*-2,6-dialkenylpiperidine **15** by hydrogenation of the alkynyl moiety using Lindlar catalyst (Scheme 3). Since free bases are claimed to be ineffective

Scheme 3[a]



[a] Key: (a) Lindlar catalyst, H_2, MeOH; (b) HCl/MeOH; (c) Grubbs catalyst **20** (0.25 equiv), benzene, 50 °C; (d) HCl/MeOH, then $HC(OMe)_3$, TsOH; (e) Grubbs catalyst **21** (0.15 equiv), benzene, 50 °C.

for RCM mediated by Grubbs ruthenium catalyst due to poisoning of the catalyst by the amine functionality,[15] **15** was converted to the hydrochloride salt and the RCM reaction was applied to the construction of the Δ^3-homotropane **16**. However, attempts to induce the reaction using Grubbs catalyst **20**[16] failed, leading to recovery of the starting material. This failure is most probably due to diequatorial arrangement of the 2,6-dialkenyl substituents in **15** in a chair form as indicated by the NOESY correlation (Figure 3),

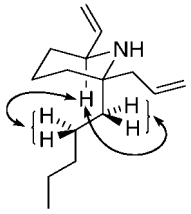
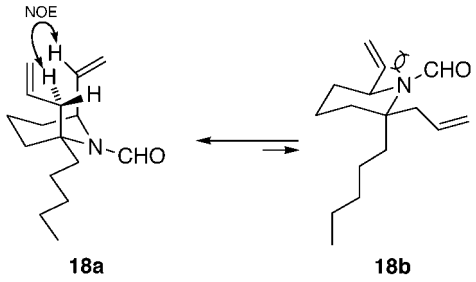


Figure 3. Selected NOE correlation for **15**.

which is inadequately disposed for the requisite ring closing to **16**. Indeed, it has been shown that RCM requires the substrate conformation constraining the olefins in close proximity.[17] We thus envisaged as a substrate for the RCM the use of the *N*-acyl derivative of **14**, wherein the 2,6-dialkenyl substituents would prefer the diaxial orientation required for the ring closure to avoid unfavorable $A^{(1,3)}$ strain[18] between the vinyl group at C6 and the *N*-acyl group. Thus, the hydrochloride salt of **12** was treated with trimethylorthoformate to give the formamide **17**, which was converted to the *cis*-2,6-dialkenylformamide **18** by Lindlar-catalyzed partial hydrogenation. The NOESY data revealed that **18** preferentially exists in the expected conformation **18a** having the diaxial disposition of the dialkenyl substituents. The RCM reaction applied to **18** smoothly proceeded with Grubbs catalyst **20** (25 mol %) in benzene at 50 °C for 6 h to give the Δ^3-homotropane **19** in high yield (90%).[19] When the second-generation Grubbs catalyst **21**[20] (15 mol %) was employed, the reaction proceeded more efficiently and was completed in 40 min affording **19** in almost quantitative yield.



The resulting homotropane **19** was subjected to dihydroxylation with OsO_4−NMO to form the diol **22** as the only product (97%) owing to an exclusive convex approach of

(13) For a review on the reactions and synthetic application of bicyclic lactams containing *N*,*O*-acetals, see: Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503−9569.

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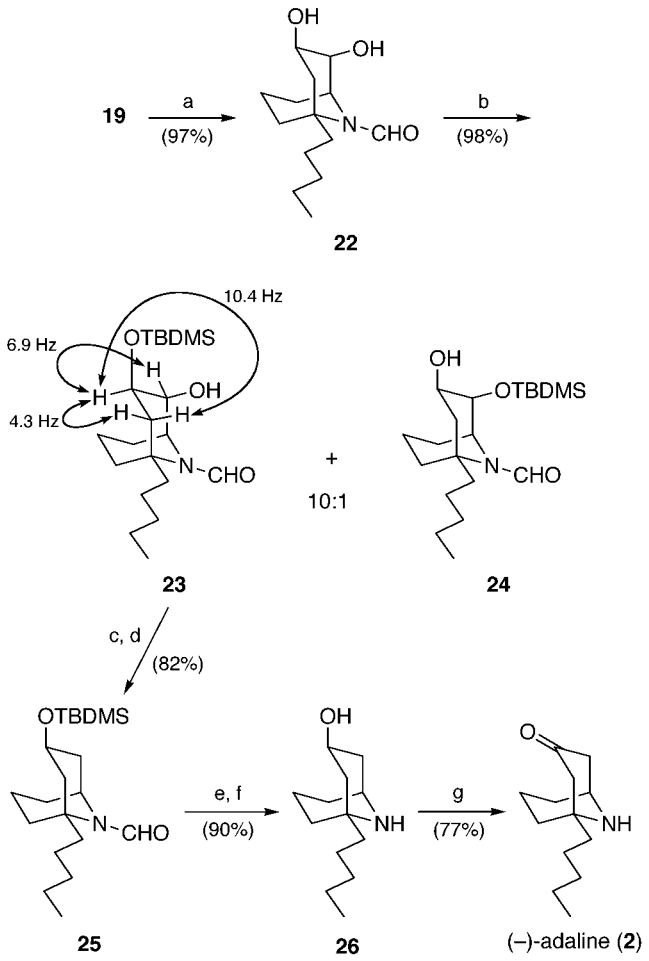
Scheme 4[a]



[a] Key: (a) OsO_4, NMO, $MeCN-H_2O$; (b) TBDMSOTf, Et_3N, CH_2Cl_2; (c) CS_2, NaH, MeI, THF; (d) AIBN, Bu_3SnH, benzene, reflux; (e) TBAF, THF; (f) $Li\cdot H_2NCH_2CH_2NH_2$; (g) PCC, CH_2Cl_2.

the oxidant (Scheme 4). The configuration of the C3 and C4 stereogenic centers newly generated by the dihydroxylation was assigned on the basis of the coupling constants observed for the vicinal protons in the ^{1}H NMR spectra of compound **23** (see below). Regioselective protection of **22** was achieved with TBDMSOTf and Et_3N to give a separable mixture of 3-siloxy alcohol **23** and 4-siloxy alcohol **24** with 10:1 chemoselectivity in a total yield of 98%. Conversion of **23** into **25** was accomplished by the Barton−McCombie radical-induced deoxygenation procedure.[21] Thus, **23** was converted to the methyl xanthate (CS_2, NaI, MeI), which was treated with AIBN and Bu_3SnH in refluxing benzene to give **25** in 82% yield. Removal of the TBDMS and formyl protecting groups in **25** was performed by treatment with TBAF in wet THF and Li−ethylenediamine complex,[22] respectively, to furnish the amino alcohol (dihydroadaline) **26**, which underwent PCC oxidation to provide (−)-adaline (**2**), $[\alpha]^{28}_D$ −11.4 (*c* 0.7, $CHCl_3$) [lit.[5] $[\alpha]^{20}_D$ −11 (*c* 2, $CHCl_3$)]. Spectral data (^{1}H NMR, ^{13}C NMR, and MS) of the synthetic material were identical to those reported[8b] for the natural adaline.

In conclusion, we have demonstrated the utility of 2-(1-aminoethyl)phenol as a chiral auxiliary on the highly diastereoselective S_N2-type alkynylation of the tricyclic *N*,*O*-acetal leading to exclusive formation of the (6*S*)-ethynylpiperidine. Using this reaction as well as ring-closing olefin metathesis for constructing the bridged azabicyclononane, the enantioselective total synthesis of (−)-adaline has been achieved.

Supporting Information Available: Experimental procedures and characterization data for all new compounds and adaline. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) After completion of our own work, a similar RCM approach to bridged azabicyclic structures was reported by Martin et al.; see: Neipp, C. E.; Martin, S. F. *Tetrahedron Lett.* **2002**, *43*, 1779−1782.

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