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An Enantiocontrolled Synthesis of Pyrrolizidines, (-)-Platynecine and (-)-Hadinecine

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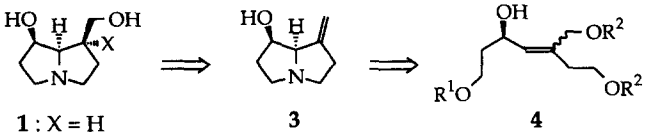
Abstract : Trisubstituted allylic alcohols **13** and **14** have been converted into a single isomeric *trans*-oxazoline **16** *via* an intramolecular iodoamidation of the corresponding trichloroacetimidates, which have been elaborated into (-)-platynecine **1** and (-)-hadinecine **2** *via* a common intermediate pyrrolizidine **3**. © 1997, Elsevier Science Ltd. All rights reserved.

The pyrrolizidine alkaloids are a class of the most prevalent naturally occurring compounds in flowering plant families.[1] The alkaloids are composed of necine bases and carboxylic acids by ester linkages, which display a variety of biological activities such as antitumor, carcinogenic, hepatotoxic, antiinflammatory, hypotensive, local anesthetic and antispasmodic property.[2] Necine bases, having the 1-azabicyclo[3. 3. 0]octane ring system as a common structural feature, comprise (+)-retronecine,[3] (-)-platynecine,[3b, 3d, 7c] (-)-hadinecine,[4] (+)-heliotridine,[3d, 3f, 3g, 5] (-)-turneforcidine,[3d] (+)-hastanecine[3d, 5b, 6, 7a] and so forth.[7] Their intriguing molecular structures and their potentially valuable pharmacological properties led us to be interested in their synthesis. In this paper we discolse our enantioselective synthetic route to (-)-platynecine **1** and (-)-hadinecine **2**.

On the basis of the retrosynthetic analysis toward **1** and **2**, the bicyclic pyrrolizidine with an exocyclic double bond **3** was chosen as a common key synthetic intermediate. Since **3** could be derived from a vicinal *threo* amino hydroxy derivative, we planned to secure the corresponding amino alcohol by employing an intramolecular iodoamidation[8] of trichloroacetimidate generated from allylic alcohol **4**.



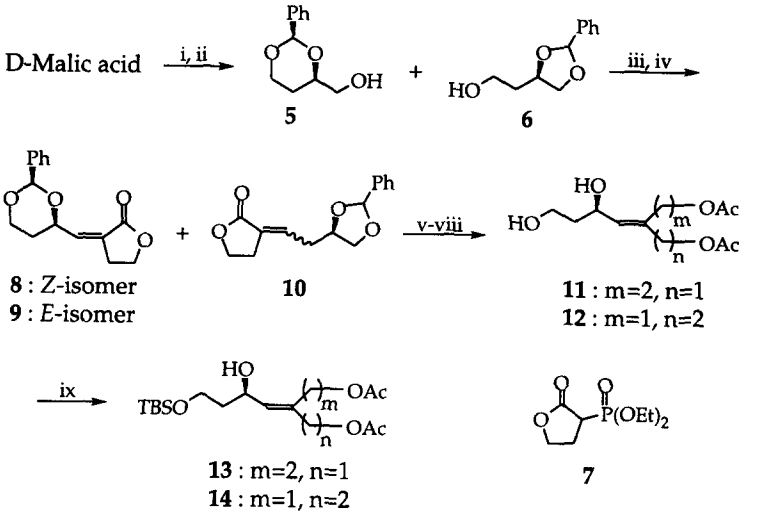
1 : X = H
2 : X = OH

3

4

A 7 : 1 inseparable mixture of benzylidenes **5** and **6** from D-malic acid[9] was oxidized under Swern conditions[10] and the resulting aldehydes were olefinated using phosphonate **7**,[11] which was prepared in 89% yield by Arbuzov reaction of α-bromo-γ-butyrolactone in triethylphosphite at 120°C (Scheme 1). The desired conjugated lactones **8**, $[\alpha]_D^{21}$ -35.9 (*c* 1.0, $CHCl_3$) and **9**, $[\alpha]_D^{21}$ -10.2 (*c* 1.0, $CHCl_3$) were produced in a ratio of 1.3 to 1 along with lactones **10** from 5-membered benzylidene **6** in 90% combined overall yield. After the mixture of **8-10** was reduced with DIBAL followed by sodium borohydride, the resulting diols were acetylated and then the remaining

Scheme 1

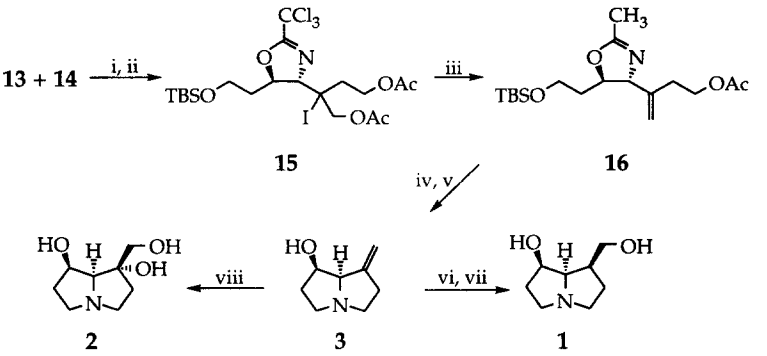


Reagents : i. $BH_3 \cdot SMe_2$, $B(OMe)_3$, THF, 0~20°C. ii. PhCHO, *p*-TsOH, PhMe, Dean-Stark trap, 140°C. iii. Swern ox. iv. **7**, DBU, LiCl, MeCN, 0°C. v. DIBAL, CH_2Cl_2, -78°C, then MeOH, $NaBH_4$, 0°C. vi. Ac_2O, DMAP, Et_3N, CH_2Cl_2, 0°C. vii. AcOH-H_2O (4:1), 20°C. viii. $NaIO_4$, MeOH-H_2O (4:1), 20°C. ix. TBSCl, imidazole, DMF, -40°C.

benzylidene groups were hydrolyzed in aqueous acetic acid to yield a mixture of 1,3- and 1,2-diols. For the facile purification, 1,2-diols were removed by treatment of the mixture with sodium periodate to afford the desired 1,3-diols **11**, $[\alpha]_D^{17}$ -16.0 (*c* 1.0, MeOH) and **12**, $[\alpha]_D^{20}$ -12.6 (*c* 1.0, MeOH) in 70% overall yield from the lactones. The regioselective silylation of **11** and **12** with *t*-butyldimethylsilyl chloride (TBSCl) furnished monosilyl ethers **13**, $[\alpha_D^{18}$ -14.4 (*c* 1.0, $CHCl_3$) and **14**, $[\alpha]_D^{16}$ -13.5 (*c* 1.0, $CHCl_3$) in 93% yield along with 4% of disilyl ethers.

After chromatographic separation of **13** and **14**, each was subjected to trichloroacetonitrile in the presence of DBU and then the generated allylic trichloroacetimidate was cyclized using iodine in the presence of potassium carbonate to give a 1:1 mixture of *trans*-oxazolines **15** in 76% and 89% yield from **13** and **14**, respectively (Scheme 2). It is worth noting that the identical *trans*-oxazolines **15** were formed from **13** and **14**, and that any appreciable amount of *cis*-oxazoline could not be isolated. Interestingly, it was ascertained that the isomeric positions of **15** were the carbons adjacent to iodine but not to nitrogen. More conveniently, the mixture of **13** and **14** was converted into **15** in 82% yield under the described iodoamidation conditions. When **15** reacted with zinc in the presence of ammonium chloride in aqueous *t*-butanol for the reductive elimination of its β-iodo acetate group,[12] its trichloromethyl group was concomitantly reduced to methyl group to provide a single olefinic *trans*-oxazoline **16**, $[\alpha]_D^{16}$ +81.1 (*c* 1.0, $CHCl_3$). Compound **16** was completely deprotected with methanolic HCl and the subsequent double cyclization of the resultant amino diol was effected using carbon tetrachloride and triphenylphosphine in the presence of triethylamine

Scheme 2



Reagents : i. Cl_3CCN, DBU, MeCN, 0°C. ii. I_2, K_2CO_3, MeCN, 0~20°C. iii. Zn, NH_4Cl, *t*-BuOH-H_2O (4:1), 0~20°C. iv. 6N HCl-MeOH (1:5), 20°C. v. CCl_4, Ph_3P, Et_3N, DMF, 20°C. vi. BH_3•THF, THF-CH_2Cl_2 (2:1), 0°C, then basic H_2O_2, EtOH, 50°C. vii. 6N HCl-MeOH (1:1), 50°C. viii. OsO_4, NMO, acetone-H_2O (4:1), 0°C.

in DMF[13] to produce the bicyclic pyrrolizine **3**,[4] $[\alpha]_D^{16}$ -96.5 (*c* 0.52, $CHCl_3$) in 51% overall yield from **15**. Treatment of **3** with borane•THF followed by basic hydrogen peroxide furnished platynecine-borane complex, which was decomplexed with hot methanolic HCl to afford (-)-platynecine **1**, mp 147-148°C, $[\alpha]_D^{18}$ -60.3 (*c* 0.30, $CHCl_3$) in 79% yield. On the other hand, dihydroxylation of **3** with a catalytic amount of osmium tetroxide in the presence of N-methyl-morpholine N-oxide (NMO)[4, 14] gave (-)-hadinecine **2**, $[\alpha]_D^{18}$ -67.8 (*c* 0.39, MeOH) in 80% yield.

For the identification of the synthetic materials, (-)-platynecine **1** and the olefinic pyrrolizidine **3** were prepared from the commercially available crotaline by the known procedures.[4, 15] While **1** and **3** from our synthesis were identical with those from crotaline in all aspects,[14] the spectroscopic data of our synthetic (-)-hadinecine **2** were quite different from those in the literature.[16, 17] When the synthetic (-)-hadinecine **2** was converted into (-)-hadinecine•HCl salt, mp 154-156°C, $[\alpha]_D^{18}$ -69.1 (*c* 0.48, MeOH), its spectroscopic data matched with the reported.[1]

To sum up, we have established an efficient synthetic route to pyrrolizidine alkaloids exemplified by (-)-platynecine and (-)-hadinecine, which has culminated in the enantiospecific intramolecular amidation of trichloroacetimidates from trisubstituted allylic alcohols **13** and **14**.

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17. All new compounds showed satisfactory spectral data. *Spectroscopic data* for **2** and **3** : **2** : ^{1}H NMR (300MHz, Py-d_5) δ 1.94-2.19(3H, m), 2.65(1H, td, *J* 10.6, 12.0Hz), 3.08(1H, br t, *J* 9.7Hz), 3.19-3.30(1H, m), 3.72-3.78(1H, m), 3.94(1H, dt, *J* 7.0, 10.7Hz), 4.09(1H, br s), 4.41(1H, d, *J* 11.0Hz), 4.53(1H, d, *J* 11.0Hz) and 4.74(1H, br s) ; ^{13}C NMR (75.5MHz, Py-d_5) δ 35.9, 37.2, 54.6, 54.9, 65.7, 70.0, 80.4 and 82.3 ; IR ν_{max}/cm^{-1}(neat) 3337, 2942, 1418, 1318, 1174, 1117, 1030 and 832. **3** : ^{1}H NMR (300MHz, $CDCl_3$) δ 1.84-2.07(2H, m), 2.47-2.55(2H, m), 2.60-2.68(1H, m), 2.77(1H, ddd, *J* 6.5, 10.9, 9.8Hz), 3.03-3.16(2H, m), 3.88-3.92(1H, m), 4.11-4.15(1H, m), 4.86(1H, td, *J* 2.1, 1.8Hz) and 5.16(1H, td, *J* 1.9, 1.9Hz) ; ^{13}C NMR (75.5MHz, $CDCl_3$) δ 34.6, 35.6, 52.9, 54.9, 72.1, 73.9, 107.8 and 148.0 ; IR ν_{max}/cm^{-1}(neat) 3292, 3076, 2915, 1663, 1434,1332, 1175, 1128, 1093, 1016, 886 and 833.

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