SYNTHESIS OF AN OPTICALLY ACTIVE 1-AZASPIRO-[4.4]NON-8-EN-7-ONE

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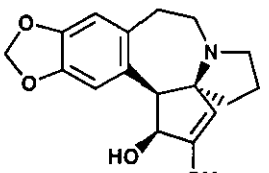
Abstract——The 1-azaspiro[4.4]non-8-en-7-one (**7**) and its (*R*)-9-(3,4-methylenedioxyphenyl)-substituted derivative (**12**) have been synthesized using an intramolecular aldol condensation of the pyrrolidine derivatives (**6**) and (**11**) as a key step.

There are considerable interests in the synthesis of cephalotaxine (**1**), the major constituent of the *Cephalotaxus* alkaloids,[1] because of its unique structural features and antileukemic activity of its ester derivatives. So far six total syntheses of **1** have been reported[2,3] but in a racemic form. In our own efforts to synthesize this alkaloid in an optically active form, we have seeked for a route to the synthesis of the optically active 1-azaspiro[4.4]non-8-en-7-one (**12**), which is considered to be a potential intermediate for the chiral synthesis of **1**. In this paper, we report our preliminary studies on the synthesis of the 1-azaspiro[4.4]non-8-en-7-one (**7**) and its (*R*)-9-(3,4-methylenedioxyphenyl)-substituted derivative (**12**) using an intramolecular aldol condensation reaction of the pyrrolidine derivatives (**6**) and (**11**).



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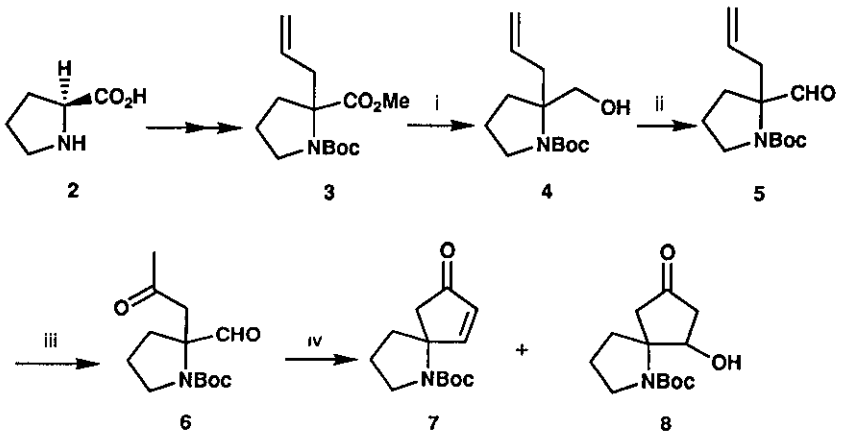
We first examined the aldol condensation of the keto aldehyde (**6**) which was prepared as follows. Thus, the pyrrolidine derivative (**3**),[4] readily available from L-proline (**2**), was reduced with lithium aluminum hydride in tetrahydrofuran at 0°C for 1 h to give the alcohol (**4**) in 88% yield. Other reducing reagents gave lower yields of

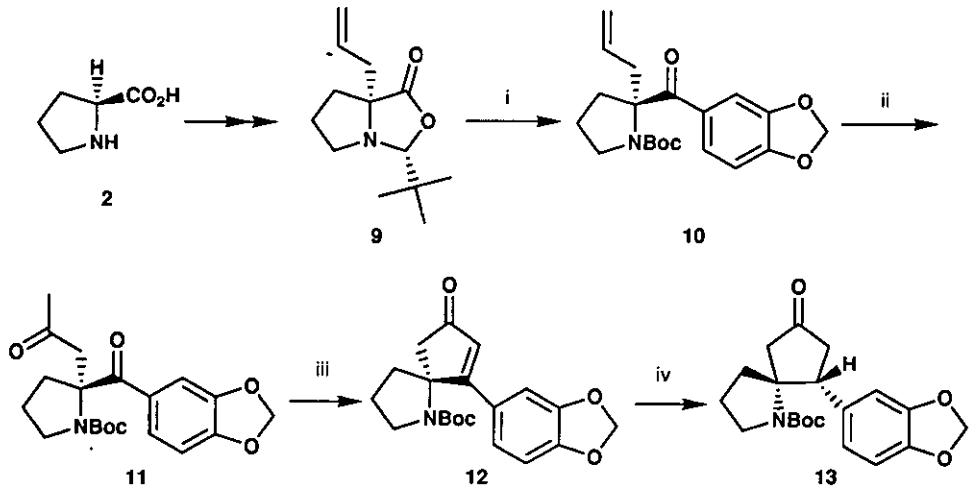
4 or only the unchanged starting material.[5] Swern oxidation of **4** followed by Wacker oxidation[6] of the resulting aldehyde (**5**) with oxygen, palladium chloride and copper(I) chloride in aqueous *N*,*N*-dimethylformamide, gave the desired keto aldehyde (**6**) in 72% overall yield from **4** [ir: 1735 (CHO), 1710 (COMe), 1690 cm^{-1} (*N*-Boc)].



Scheme 1. *Reagents and conditions:* i, $LiAlH_4$, THF, 0°C (88%); ii, DMSO, $(COCl)_2$, CH_2Cl_2, -60°C, then Et_3N; iii, O_2, $PdCl_2$ (cat.), CuCl, DMF-H_2O, room temperature (72% from **4**); iv, K_2CO_3, MeOH-H_2O, 70°C.

Aldol condensation of **6** was effected by treatment with potassium carbonate in aqueous methanol at 70°C for 40 min. The reaction mixture was separated by flash column chromatography on silica gel [hexane-AcOEt; 5:1] to give the desired enone (**7**)(50% yield), mp 76-77°C, the unchanged starting material (**6**)(8%), and the alcohol (**8**)(23%). The structure of the enone (**7**) was confirmed by the ^{1}H-nmr spectrum which indicated two doublets due to two olefinic protons at δ 6.10 and 7.35 (*J*=5.5 Hz). Its ir spectrum showed two carbonyl absorption bands at 1720 (an α,β-unsaturated five-membered ketone) and 1690 cm^{-1} (*N*-Boc).[7] Use of potassium hydroxide as base gave almost the same results. Prolonged reaction time resulted in the decrease of the yield of **7**. Treatment of the alcohol (**8**) under the aldol reaction conditions gave essentially the same mixture of three compounds.

Encouraged by the success of the synthesis of the enone (**7**), we next turned our attention to the synthesis of the (*R*)-9-(3,4-methylenedioxyphenyl)-1-azaspiro[4.4]non-8-en-7-one (**12**). The chiral azabicyclic compound (**9**), prepared from L-proline (**2**) according to the Seebach's procedure,[8] was treated with 3,4-methylenedioxyphenyllithium in tetrahydrofuran at -78°C and then at room temperature for 3 h to give the oily amino ketone which was protected with *tert*-butyloxycarbonyl group to afford the *N*-Boc derivative (**10**) in 86% overall yield from **9**. The Wacker oxidation of **10** gave the diketone (**11**) as an oil in 72% yield.



Scheme 2. *Reagents and conditions:* i, (a) 3,4-methylenedioxyphenyllithium, THF, -78°C→room temperature; (b) (*tert*-BuOCO)$_2$O, AcOEt, room temperature (86% from **9**); ii, O_2, $PdCl_2$ (cat.), CuCl, DMF-H_2O, room temperature (72%); iii, 2-methyl-2-butanol (cat.), NaH, benzene, reflux (43%); iv, PtO_2, H_2, EtOH (84%).

In contrast to **6**, considerable difficulty was encountered in finding conditions suitable for the base catalyzed aldol condensation of **11**. Among the conditions examined, the most effective was the use of a catalytic amount of sodium 2-methyl-2-butanolate in refluxing benzene for 2 h[9] to give the desired enone (**12**), mp 153-154°C, $[\alpha]_D^{21}$ -2.0° (c 0.35, EtOH), in 43% yield. The structure of **12** was determined on the basis of spectroscopic[10] and chemical evidence. Catalytic hydrogenation of **12** over PtO_2 gave the saturated ketone **13**, mp 119-121°C [ir (CCl_4): 1745 and 1690] as a single isomer in 84% yield, whose stereochemistry was assigned on the basis of the assumption that hydrogen would attack from the less hindered side of the double bond of **12**.

We are now studying the conversion of the azaspiro heterocycle (**12**) to optically active cephalotaxine (**1**).[11]

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5. LiI and $NaBH_4$ in ether under reflux for 24 h (64% yield); DIBAH in dichloromethane at room temperature for 24 h (60% yield); $LiBH_4$ in tetrahydrofuran under reflux for 2 days (0%).
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7. Compound (**7**): Ir (CCl_4): 1720, 1690; ^{1}H-nmr ($CDCl_3$, 300 MHz) δ: (a major rotamer) 1.36 (s, *tert*-Bu), 1.80-2.18 (m, 3-H_2 and 4-H_2), 2.37 (d, *J*=18.0 Hz, 6-H), 2.77 (d, *J*=18.0 Hz, 6-H), 3.37-3.69 (m, 2-H_2), 6.10 (d, *J*=5.5 Hz, 8-H), 7.35 (d, *J*=5.5 Hz, 9-H); (a minor rotamer) 1.44 (s, *tert*-Bu), 1.80-2.18 (m, 3-H_2 and 4-H_2), 2.33 (d, *J*=17.3 Hz, 6-H), 2.95 (d, *J*=17.3 Hz, 6-H), 3.37-3.69 (m, 2-H_2), 6.15 (d, *J*=5.5 Hz, 8-H), 7.44 (d, *J*=5.5 Hz, 9-H).
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10. Compound (**12**): Ir ($CHCl_3$): 1680; ^{1}H-nmr ($CDCl_3$, 300 MHz) δ: (a major rotamer) 1.19 (s, *tert*-Bu), 1.79-2.06 (m, 3-H_2 and 4-H), 2.42 (td, *J*=12.8, 7.2 Hz, 4-H), 2.55 (d, *J*=17.6 Hz, 6-H), 2.94 (d, *J*=17.6 Hz, 6-H), 3.53 (td, *J*=11.1, 7.0 Hz, 2-H), 3.69-3.87 (m, 2-H), 6.04 (s, OCH_2O), 6.36 (s, 8-H), 6.86 (d, *J*=8.3 Hz, 5'-H), 7.05 (d, *J*=1.7 Hz, 2'-H), 7.13 (dd, *J*=8.3, 1.7 Hz, 6'-H); (a minor rotamer) 1.38 (s, *tert*-Bu), 1.79-2.06 (m, 3-H_2 and 4-H), 2.25-2.47 (m, 4-H), 2.44 (d, *J*=17.1 Hz, 6-H), 3.14 (d, *J*=17.1 Hz, 6-H), 3.40-3.58 (m, 2-H), 3.69-3.87 (m, 2-H), 6.02 (s, OCH_2O), 6.39 (s, 8-H), 6.84 (d, *J*=8.3 Hz, 5'-H), 7.03 (d, *J*=1.7 Hz, 2'-H), 7.11 (dd, *J*=8.3, 1.7 Hz, 6'-H).
11. It should be noted that the absolute configuration of **12** corresponds to the enantiomer of naturally occurring (-)-cephalotaxine.

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