

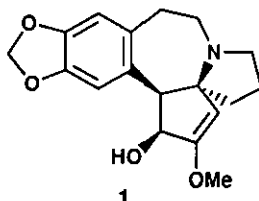
SYNTHESIS OF AN OPTICALLY ACTIVE 1-AZASPIRO-[4.4]NON-8-EN-7-ONE

Masazumi Ikeda,* Ken-ichiro Matsubayashi, Takayuki Imoto, Kaoru Kitao,
Hiroyuki Ishibashi, and Tatsunori Sato

Kyoto Pharmaceutical University, Misasagi, Yamashina, Kyoto 607, Japan

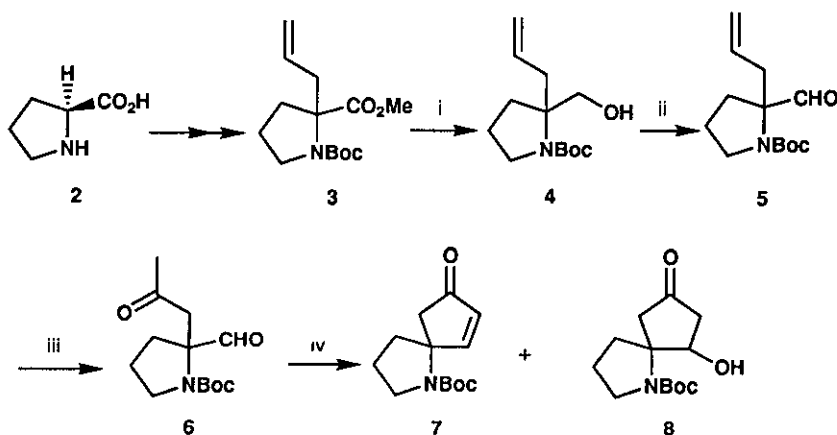
Abstract———The 1-azaspiro[4.4]non-8-en-7-one (**7**) and its (*R*)-9-(3,4-methylenedioxyphenyl)-substituted derivative (**12**) have been synthesized using an intramolecular aldol condensation of the pyrrolidine derivatives (**6**) and (**11**) as a key step.

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 sought 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**).



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

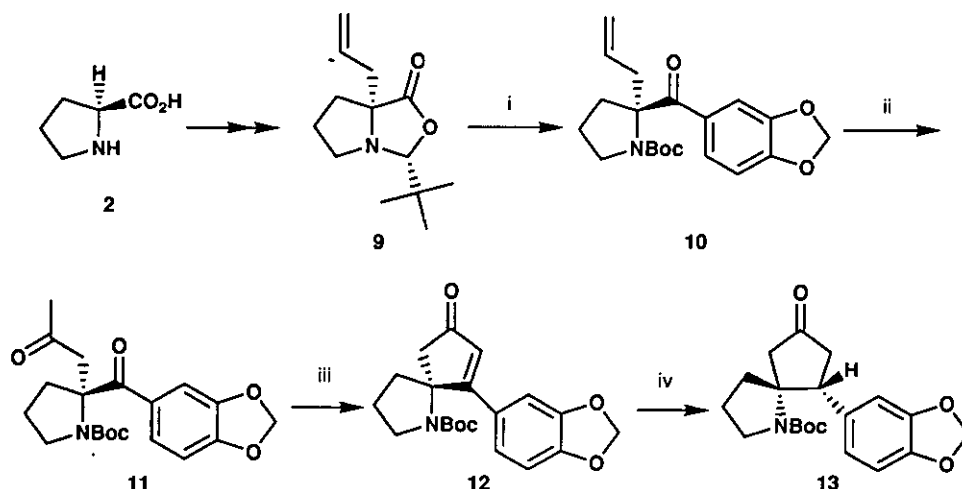
4 or only the unchanged starting material.⁵ Swern oxidation of 4 followed by Wacker oxidation⁶ of the resulting aldehyde (5) with oxygen, palladium chloride and copper(I) chloride in aqueous *N,N*-dimethylformamide, gave the desired keto aldehyde (6) in 72% overall yield from 4 [ir: 1735 (CHO), 1710 (COMe), 1690 cm^{-1} (*N*-Boc)].



Scheme 1. Reagents and conditions: i, LiAlH₄, THF, 0°C (88%); ii, DMSO, (COCl)₂, CH₂Cl₂, -60°C, then Et₃N; iii, O₂, PdCl₂ (cat.), CuCl, DMF-H₂O, room temperature (72% from 4); iv, K₂CO₃, MeOH-H₂O, 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 ¹H-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*-butoxycarbonyl 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, $-78^{\circ}\text{C} \rightarrow \text{room temperature}$; (b) $(\text{tert-BuOCO})_2\text{O}$, 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 h⁹ to give the desired enone (**12**), mp $153\text{--}154^{\circ}\text{C}$, $[\alpha]_{\text{D}}^{21} -2.0^{\circ}$ (c 0.35, EtOH), in 43% yield. The structure of **12** was determined on the basis of spectroscopic¹⁰ and chemical evidence. Catalytic hydrogenation of **12** over PtO_2 gave the saturated ketone **13**, mp $119\text{--}121^{\circ}\text{C}$ [ir (CCl₄): 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

REFERENCES AND NOTES

1. For reviews of the *Cephalotaxus* alkaloids, see L. Huang and Z. Xue, "The Alkaloids—Chemistry and Pharmacology," Vol. 23, ed by A. Brossi, Academic Press, New York, 1984, Chapter 3; C. R. Smith, Jr., K. L. Mikolajczak, and R. G. Powell, "Anticancer Agents Based on Natural Product Models," ed. by J. M. Cassady and J. D. Douros, Academic Press, New York, 1980, Chapter 11.
2. a) S. M. Weinreb and J. Auerbach, *J. Am. Chem. Soc.*, 1975, **97**, 2503; b) M. F. Semmelhack, B. P. Chong, R. D. Stauffer, T. D. Rogerson, A. Chong, and L. D. Jones, *J. Am. Chem. Soc.*, 1975, **97**, 2507; c) S. Yasuda, T. Yamada, and M. Hanaoka, *Tetrahedron Lett.*, 1986, **27**, 2023; d) M. E. Kuehne, W. G.

- Bornmann, W. H. Parsons, T. D. Spitzer, J. F. Blount, and J. Zubieta, *J. Org. Chem.*, 1988, **53**, 3439; e) T. P. Burkholder and P. L. Fuchs, *J. Am. Chem. Soc.*, 1990, **112**, 9601.
3. H. Ishibashi, M. Okano, H. Tamaki, K. Maruyama, T. Yakura, and M. Ikeda, *J. Chem. Soc., Chem. Commun.*, 1990, 1436; M. Ikeda, M. Okano, K. Kosaka, M. Kido, and H. Ishibashi, *Chem. Pharm. Bull.*, 1993, **41**, 276.
4. P. N. Confalone, E. M. Huie, S. S. Ko, and G. M. Cole, *J. Org. Chem.*, 1988, **53**, 482.
5. LiI and NaBH₄ in ether under reflux for 24 h (64% yield); DIBALH in dichloromethane at room temperature for 24 h (60% yield); LiBH₄ in tetrahydrofuran under reflux for 2 days (0%).
6. J. Tsuji, *Synthesis*, 1984, 369.
7. Compound (7): Ir (CCl₄): 1720, 1690; ¹H-nmr (CDCl₃, 300 MHz) δ: (a major rotamer) 1.36 (s, *tert*-Bu), 1.80-2.18 (m, 3-H₂ and 4-H₂), 2.37 (d, *J*=18.0 Hz, 6-H), 2.77 (d, *J*=18.0 Hz, 6-H), 3.37-3.69 (m, 2-H₂), 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-H₂ and 4-H₂), 2.33 (d, *J*=17.3 Hz, 6-H), 2.95 (d, *J*=17.3 Hz, 6-H), 3.37-3.69 (m, 2-H₂), 6.15 (d, *J*=5.5 Hz, 8-H), 7.44 (d, *J*=5.5 Hz, 9-H).
8. D. Seebach, M. Boes, R. Naef, and W. B. Schweizer, *J. Am. Chem. Soc.*, 1983, **105**, 5390.
9. J. E. McMurry, A. Andrus, G. M. Ksader, J. H. Musser, and M. A. Johnson, *J. Am. Chem. Soc.*, 1979, **101**, 1330.
10. Compound (12): Ir (CHCl₃): 1680; ¹H-nmr (CDCl₃, 300 MHz) δ: (a major rotamer) 1.19 (s, *tert*-Bu), 1.79-2.06 (m, 3-H₂ 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, OCH₂O), 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-H₂ 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, OCH₂O), 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.

Received, 2nd March, 1994