Tetrahedron Letters,Vol.27,No.38,pp 4605-4608,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

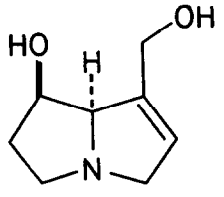
TOTAL SYNTHESIS OF OPTICALLY ACTIVE INTEGERRIMINE, A TWELVE-MEMBERED DILACTONIC PYRROLIZIDINE ALKALOID OF RETRONECINE TYPE. II. ENANTIOSELECTIVE SYNTHESIS OF (+)-RETRONECINE[1]

Haruki Niwa,* Yasuyoshi Miyachi, Osamu Okamoto, Youichi Uosaki, and Kiyoyuki Yamada*
Department of Chemistry, Faculty of Science, Nagoya University, Chikusa, Nagoya 464, Japan

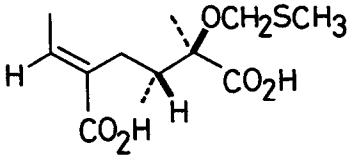
Summary: For the total synthesis of optically active integerrimine, the twelve-membered dilactonic pyrrolizidine alkaloid, the necine base component (+)-retronecine has been synthesized enantioselectively.

In the preceding letter,[1] we have achieved the enantioselective synthesis of (+)-integerrinecic acid methylthiomethyl ether (2), the necic acid component of the alkaloid (-)-integerrimine (3). As the second stage of the total synthesis of (-)-integerrimine (3), we describe herein the enantioselective synthesis of (+)-retronecine (1), the necine base component of (-)-integerrimine (3). Since the publication of the first synthesis of (+)-retronecine (1) by Geissman,[2a] many synthetic studies on racemic retronecine (1) including our synthesis[2g] have been reported.[2] However, the enantioselective synthesis of (+)-retronecine (1) has been a relatively recent development.[3]

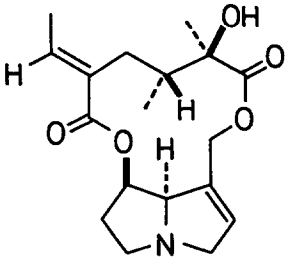
In our previous synthesis of racemic retronecine (1)[2g] the tricyclic lactone 16 was a key intermediate, which was efficiently converted into racemic 1. Thus our effort on the enantioselective synthesis of (+)-retronecine (1) in the present study was directed toward the construction of the optically active tricyclic lactone 16.



1 (+)-retronecine



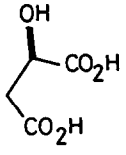
2



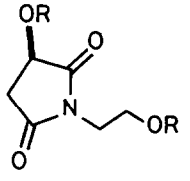
3 (–)-integerrimine

Our present synthesis started from (R)-(+)-malic acid (4). Sequential treatemnt of 4 with acetyl chloride (reflux, 3 h), ethanolamine in methylene chloride (reflux, 2 h), and then acetyl chloride again (reflux, 3 h) to give the cyclic imide 5[4] [colorless oil, $[\alpha]_D^{22}$ +16.5° (c 1.13, $CHCl_3$)] in 69% yield.[5] Acidic ethanolysis of 5 (dry HCl-EtOH, 50 °C, 3.5 h) afforded the diol imide 6[4] [hygroscopic solid, $[\alpha]_D^{25}$ +71.2° (c 1.08, acetone), 84% yield], which upon treatment with pivaloyl chloride and pyridine in ether (-30 °C, 3.5 h) provided monopivalate 7[4] [colorless oil, $[\alpha]_D^{23}$ +56.1° (c 0.60, $CHCl_3$), 66% yield]. Bromoacetylation of 7 under the controlled conditions (1.2 equiv of $BrCH_2COBr$ and 1.5 equiv of pyridine, ether,

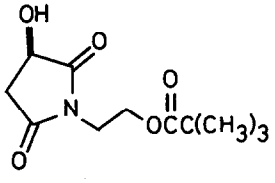
room temp., 30 min)[6] gave the bromoacetate 8[4] [colorless oil, $[\alpha]_D^{14}$ +9.4° (c 2.02, $CHCl_3$)] in 94% yield. A carbon-carbon bond formation between C-1 and C-8 (pyrrolizidine numbering) in 8 was a key step in the present synthesis and effected by utilizing a novel intramolecular Wittig reaction[7] of the imide carbonyl group in 8 in the one-pot procedure. Thus the bromoacetate 8 was first converted into the corresponding phosphonium salt 9 by reaction with triphenylphosphine in acetonitrile (50 °C, 4 h). The resulting reaction mixture containing 9 was then treated with 1.1 equiv of triethylamine (50 °C, 13 h), and the intramolecular Wittig reaction of the ylide 10 generated under the reaction conditions proceeded smoothly to yield the desired conjugated lactone 11[4] [mp 79.5-81 °C (hexane-benzene), $[\alpha]_D^{19}$ +62.5° (c 0.57, $CHCl_3$)] in 86% yield. Catalytic hydrogenation of 11 (H_2, 5% Rh/alumina, EtOAc, room temp., 3 h) afforded the lactone lactam 12[4] [mp 109-110 °C (benzene-hexane), $[\alpha]_D^{17}$ +48.8° (c 0.53, $CHCl_3$)] in 99% yield. The next problem was selective reduction of the lactam carbonyl group in 12 into the pyrrolidine derivative 14. Although the procedure of Borch [(i) $Et_3O{\cdot}BF_4$; (ii) $NaBH_4$][8a] proved to be unsatisfactory for this compound, the selective reduction of the lactam carbonyl group in 12 was achieved in high yield by using a modified procedure of Raucher.[8b] Thus, the lactone lactam 12 was converted into the thiolactam 13[9] (pale yellow solid) by treatment with the dimer of p-methoxyphenylthiophosphine sulfide (Lawesson's reagent)[10] in toluene (reflux, 1 h). The thiolactam 13 was then treated with triethyloxonium tetrafluoroborate in methylene chloride (room temp., 1 h) and subsequently with sodium cyanoborohydride[11] in methanol (0 °C, 2 h) to yield the desired 14[4] [colorless oil, $[\alpha]_D^{11}$ -8.6° (c 0.78, $CHCl_3$)] in 82% yield from 12. Conversion of the pyrrolidine derivative 14 into the



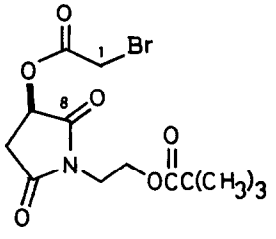
4



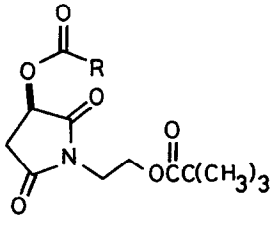
5 R = $COCH_3$
6 R = H



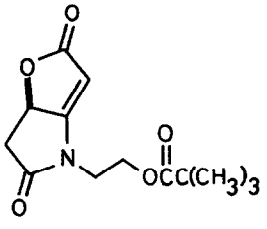
7



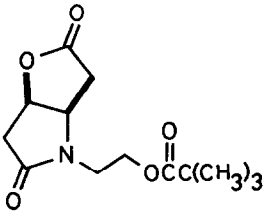
8



9 R = $CH_2\overset{+}{P}Ph_3\overset{-}{Br}$
10 R = $CH{=}PPh_3$

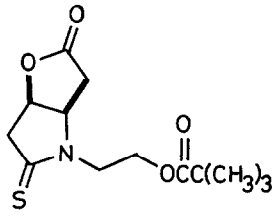


11

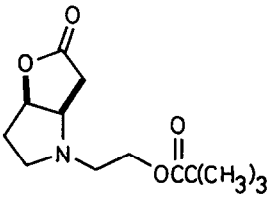


12

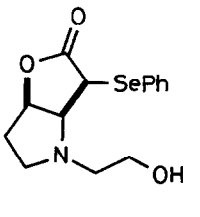
selenide alcohol 15[4,12] was achieved in 63% overall yield by a two-step sequence: (i) LDA-THF (-78 °C, 30 min), PhSeCl; (ii) 6 N HCl (50 °C, 17 h). The pivotal cyclization of 15 into the key intermediate 16 was effected by the three-step sequence in a one-pot procedure: (i) 1.5 equiv of n-BuLi in THF (-78 °C, 10 min); (ii) 1.1 equiv of TsCl (-78 °C, 1 h);[13] (iii) 2.0 equiv of LDA and 2.0 equiv of HMPA (-78 °C, 30 min and then -40 °C, 5 h). Extractive isolation and chromatographic purification gave the desired 16[4] (colorless oil) in 53% yield. Synthetic 16 was spectrally (IR, ^{1}H NMR, and mass) identical with racemic 16,[2g] and exhibited an optical rotation [$[\alpha]_D^{12}$ +50.9° (c 1.14, $CHCl_3$)] comparable to that of the authentic sample[14] [$[\alpha]_D^{19}$ +45.9° (c 0.54, $CHCl_3$)].



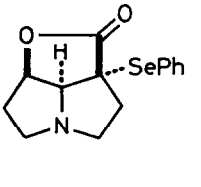
13



14



15



16

Finally, the key intermediate 16 was converted into (+)-retronecine (1) by our procedure previously reported[2g] in 66% overall yield: (i) reduction with $LiAlH_4$ (THF, -10 °C, 30 min); (ii) oxidation and elimination of the selenoxide (30% H_2O_2, AcOH, room temp., 3 h). Spectral (IR, ^{1}H NMR, and mass) and physical (mp and $[\alpha]_D$) properties of the synthetic 1 [mp 118-119 °C (acetone), $[\alpha]_D^{14}$ +50.5° (c 0.20, EtOH)] were completely identical with those of natural retronecine (1) [Lit.[3d,3e,15] mp 120-121 °C (acetone), 117-118 °C (acetone), 121-122 °C (acetone); $[\alpha]_D^{26}$+50.4° (c 0.29, EtOH), $[\alpha]_D^{20}$ +53.1° (EtOH), $[\alpha]_D$ +50.2° (c 1.83, EtOH)].

Our present approach for the synthesis of (+)-retronecine (1) proved efficient (5.5% overall yield from the starting compound 4).

Acknowledgment: Financial support from the Ministry of Education, Science, and Culture (Grant-in-Aid for Special Project Research, Innovative Studies on Highly Selective Synthesis) is gratefully acknowledged.

References and Notes

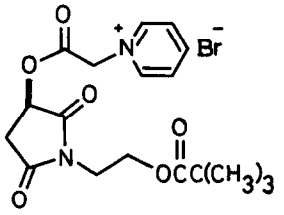
1. Part I: H. Niwa, Y. Miyachi, Y. Uosaki, and K. Yamada, Tetrahedron Lett., preceding papaer.
2. a) T. A. Geissman and A. C. Waiss, Jr., J. Org. Chem., 27, 139 (1962). b) J. J. Tufariello and G. E. Lee, J. Am. Chem. Soc., 102, 373 (1980). c) G. E. Keck and D. G. Nickell, J. Am. Chem. Soc., 102, 3632 (1980). d) E. Vedejs and G. R. Martinez, J. Am. Chem. Soc., 102, 7993 (1980). e) K. Narasaka, T. Sakakura, T. Uchimaru, K. Morimoto, and T. Mukaiyama, Chem. Lett., 1982, 455. f) T. Ohsawa, M. Ihara, K. Fukumoto, and T. Kametani, Heterocycles, 19, 2075 (1982). g) H. Niwa, A. Kuroda, and K. Yamada, Chem. Lett., 1983, 125. h) T. Ohsawa, M. Ihara, K. Fukumoto, and T. Kametani, J. Org. Chem., 48, 3644 (1983). i) K. Narasaka, T. Sakakura, T. Uchimaru, and D. Guédin-Vuong, J. Am. Chem. Soc., 106, 2954 (1984). j) E. Vedejs, S. Larsen, and F. G. West, J. Org. Chem., 50, 2170 (1985).

3. a) H. Rüeger and M. Benn, Heterocycles, 19, 23 (1982). b) H. Rüeger and M. Benn, Heterocycles, 20, 1331 (1983). c) J. G. Buchanan, G. Singh, and R. H. Wightman, J. Chem. Soc., Chem. Commun., 1984, 1299. d) A. R. Chamberlin and J. Y. L. Chung, J. Org. Chem. 50, 4425 (1985). e) Y. Nishimura, S. Kondo, and H. Umezawa, J. Org. Chem., 50, 5210 (1985).

4. Satisfactory spectral (IR, ^{1}H NMR, and mass) and analytical (microanalyses or high resolution mass spectra) data were obtained for this compound.

5. All chemical yields refer to the materials purified by column or preparative layer chromatography on silica gel.

6. Use of a large excess of pyridine should be avoided in this reaction, otherwise the yield of 8 was dramatically decreased owing to the formation of the pyridinium salt i.



i

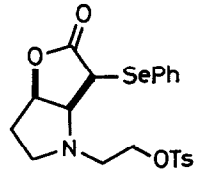
7. The related studies on intramolecular Wittig reaction of the imide carbonyl group was reported: J. M. Muchowski and P. H. Nelson, Tetrahedron Lett., 21, 4585 (1980); W. Flitsch and P. Wernsmann, Tetrahedron Lett., 22, 719 (1981).

8. a) R. F. Borch, Tetrahedron Lett., 1968, 61. b) S. Raucher and P. Klein, Tetrahedron Lett., 21, 4061 (1980).

9. Separation by flash column chromatography on silica gel afforded the thiolactam 13 slightly contaminated with the materials resulting from the Lawesson's reagent, which was used for the next reaction without further purification. Satisfactory spectral (IR, ^{1}H NMR, and mass) data were obtained for the partially purified thiolactam 13.

10. S. Scheibye, B. S. Pedersen, and S. O. Lawesson, Bull. Soc. Chim. Belg., 87, 229 (1978). The execellent review for this reagent: M. P. Cava and M. I. Levinson, Tetrahedron, 41, 5061 (1985).

11. Reduction of the generated iminium salt was examined with $NaBH_4$ in the various solvents (MeOH, DME, or i-PrOH) or with $LiAlH(O\text{-}t\text{-}Bu)_3$ in THF, resulting in the formation of 14 in low yield (40-60%).



ii

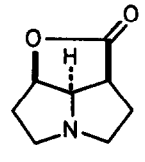
12. This material was a 9:1 mixture of the diastereomers as to the phenylselenenyl group.

13. Attempted isolation of the intermediate ii failed owing to its instability.

14. The authentic specimen of (-)-16 was prepared by the phenylselenenylation[2g] of the tricyclic lactone iii[16] derived from natural (+)-retronecine (1).

15. G. Barger, T. R. Seshadri, H. E. Watt, and T. Yabuta, J. Chem. Soc., 1935, 11.

16. A. J. Aasen and C. C. J. Culvenor, Aust. J. Chem., 22, 2657 (1969).



iii

(Received in Japan 24 June 1986)