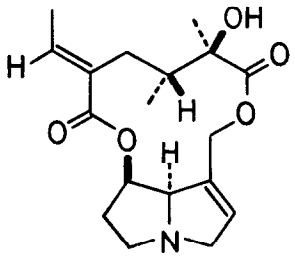
Tetrahedron Letters,Vol.27,No.38,pp 4601-4604,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

TOTAL SYNTHESIS OF OPTICALLY ACTIVE INTEGERRIMINE, A TWELVE-MEMBERED DILACTONIC PYRROLIZIDINE ALKALOID OF RETRONECINE TYPE. I. ENANTIOSELECTIVE SYNTHESIS OF THE PROTECTED (+)-INTEGERRINECIC ACID

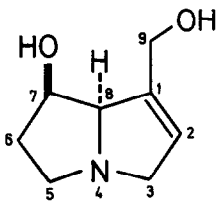
Haruki Niwa,* Yasuyoshi Miyachi, Youichi Uosaki, and Kiyoyuki Yamada*
Department of Chemistry, Faculty of Science, Nagoya University, Chikusa, Nagoya 464, Japan

Summary: For the total synthesis of optically active integerrimine, the twelve-membered dilactonic pyrrolizidine alkaloid, the necic acid component (+)-integerrinecic acid has been enantioselectively synthesized in the protected form.

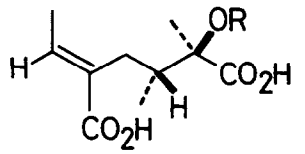
Pyrrolizidine alkaloids containing retronecine (2) or otonecine as the necine base exhibit remarkable hepatotoxicity and, in certain cases, antitumor activity and carcinogenicity.[1] The structural features necessary for strong toxicity of the alkaloids are, as shown in retronecine (2), the unsaturation between C-1 and C-2 and esterification of hydroxyl groups at C-7 and C-9 in the pyrrolizidine skeleton.[1b] Particularly, the greatest toxicity is shown by the macrocyclic dilactonic alkaloids such as integerrimine (1).[1b] Owing to the intriguing chemical structures and a wide range of biological activities, the macrocyclic pyrrolizidine alkaloids have attracted much attention as the challenging synthetic targets. While most of the synthetic work in pyrrolizidine alkaloids has been directed toward the necine base parts,[2] only a few reports[3] have so far been published on the total synthesis of the macrocyclic pyrrolizidine alkaloids. The total synthesis of racemic integerrimine (1) has recently been recorded by Narasaka.[3c,3e] Herein we wish to report the first enantioselective total synthesis of (-)-integerrimine (1),[4] a representative of 12-membered dilactonic pyrrolizidine alkaloids in this and accompanying papers.



1 (-)-integerrimine



2 (+)-retronecine

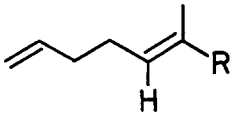


3 R = H
(+)-integerrinecic acid

4 R = CH_2SCH_3

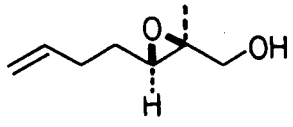
The total synthesis of (-)-integerrimine (1) involves the enantioselective synthesis of (+)-integerrinecic acid (3) and (+)-retronecine (2) and their regioselective coupling to elaborate the unsymmetrical 12-membered dilactone. As the first stage of the total synthesis of (-)-integerrimine (1), we describe in this communication the enantioselective synthesis of a protected (+)-integerrinecic acid 4, which has actually been employed in the synthesis of (-)-integerrimine (1).

Although several research groups reported on the synthesis of racemic integerrinecic acid (3),[3e,5] there seems to be no report on the enantioselective synthesis of the acid 3. The present synthesis started from readily available (E)-2-methylhepta-2,6-dienoic acid (5).[6] Reduction of 5 with lithium aluminum hydride in tetrahydrofuran (room temp., 3 h) afforded the allylic alcohol 6[7,8] (colorless oil, 69% yield[9]), which was subjected to Sharpless asymmetric epoxidation[10] [t-BuOOH/(+)-DET/(i-PrO)$_4$Ti, CH_2Cl_2, -25 °C, 3.5 h] to give the (-)-epoxy alcohol 7[7] [colorless oil, $[\alpha]_D^{11}$ -18.1° (c 1.92, $CHCl_3$), 96% ee,[11] 71% yield]. Regioselective ring opening of 7 with trimethylaluminum[12] in hexane (0 °C, 1.5 h) furnished the desired 1,2-diol 8[7] [colorless oil, $[\alpha]_D^{16}$ +34.2° (c 0.98, $CHCl_3$), 78% yield] together with the isomeric 1,3-diol (11%). The primary hydroxyl group in 8 was selectively esterified with 3,5-dinitrobenzoyl chloride and pyridine (0 °C, 1 h) to give the monobenzoate 9[7] [mp 88-89.5 °C (hexane-ether), $[\alpha]_D^{19}$ +16.0° (c 0.85, $CHCl_3$), 88% yield]. Oxidation of 9 with ruthenium tetraoxide generated in situ[13] [$RuCl_3/NaIO_4$, CCl_4-CH_3CN-pH 7 phosphate buffer (1:1:1.5), room temp., 2 h] and subsequent treatment[14] of the resulting crude product with a catalytic amount of p-toluenesulfonic acid (benzene, reflux, 1 h) provided the lactone benzoate 10[7] [colorless oil, $[\alpha]_D^{20}$ +19.0° (c 0.94, $CHCl_3$), 99% overall yield]. Methanolysis of 10 with sodium methoxide in methanol (room temp., 30 min) followed by treatment[14] of the resulting crude product with a catalytic amount of p-toluenesulfonic acid (50 °C, 15 min) afforded the lactone alcohol 11[7] [mp 85-86 °C (benzene-hexane), $[\alpha]_D^{13}$ +49.1° (c 0.59, $CHCl_3$), 96% ee,[11] 76% overall yield]. Although attempts were made to convert the 1,2-diol 8 directly into the lactone alcohol 11 by ozonization, a complex mixture was formed, from which the desired product 11 was obtained in low yield (ca. 30% yield). Oxidation of 11 with the Jones reagent and PDC afforded the undesired products, 18 and 19, respectively. The ruthenium tetraoxide oxidation under the conditions[13] described above (room temp., 1.5 h) was the method of choice for the conversion of 11 into the corresponding carboxylic acid, which was esterified with diazomethane to give the lactone ester 12[7] [colorless oil, $[\alpha]_D^{19}$ +6.5° (c 0.56, $CHCl_3$), 85% overall yield].

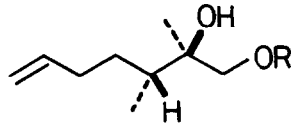


5 R = CO_2H

6 R = CH_2OH



7

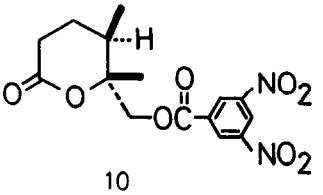


8 R = H

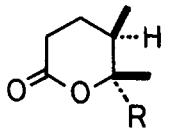
9 R = CO-(3,5-dinitrophenyl)

Spectral (IR and ^1H NMR) properties of synthetic (+)-12 were identical with those reported for racemic 12.[3e] Conversion of (+)-12 into (+)-integerrinecic acid lactone methyl ester (15) was achieved by a modification of the Narasaka's route.[3e,5f] The aldol reaction of the lactone enolate generated from 12 (LDA, THF, -78 °C, 1 h) with acetaldehyde (-30 °C, 2 h) provided the adduct 13 as a mixture of the diastereomers. Without purification, the adduct 13 was converted with methanesulfonyl chloride and pyridine (room temp., 1 h) into the mesylate 14, which was treated with DBU (benzene, reflux, 2 h) to yield the desired (+)-15[7] [mp 92.5-93.5 °C (benzene-hexane), $[\alpha]_D^{12}$ +48.0° (c 0.63, $CHCl_3$), 34% unoptimized yield from 12] along with a small amount of the geometrical isomer of 15 (3%). The spectral (IR, ^1H NMR, and mass) and

physical (mp and $[\alpha]_D$) properties of synthetic (+)-15 were completely identical with those of an authentic sample[15] of (+)-15 [mp 92.5-94 °C (benzene-hexane), $[\alpha]_D^{21}$ +47.3° (c 0.68, $CHCl_3$); Lit.[5c] mp 93-94 °C, $[\alpha]_D^{27}$ +42.0° (c 0.23, EtOH)]. Since transformation of (+)-15 into (+)-3 is the known procedure,[4,5f] the first enantioselective synthesis of (+)-integerrinecic acid (3) was formally accomplished.

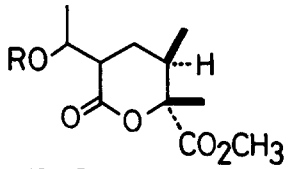


10



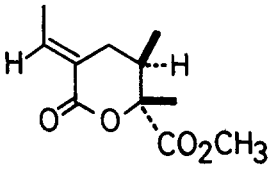
11 R = CH_2OH

12 R = CO_2CH_3

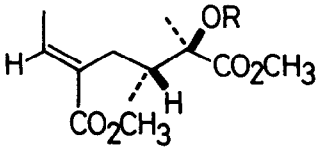


13 R = H

14 R = SO_2CH_3

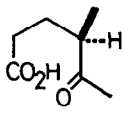


15

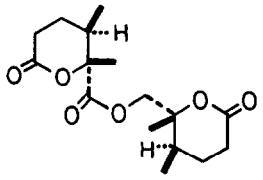


16 R = H

17 R = CH_2SCH_3



18



19

For the total synthesis of (-)-integerrimine (1), the lactone methyl ester (+)-15 was further converted into the protected (+)-integerrinecic acid 4. Thus, methanolysis of 15 (NaOMe, MeOH, room temp., 2.5 h) and subsequent methylthiomethylation[16] of the resulting hydroxyl ester 16 (DMSO-Ac_2O, 40 °C, 24 h) gave the methylthiomethyl ether derivative 17[7] (colorless oil, $[\alpha]_D^{25}$ +34° (c 0.64, $CHCl_3$), 75% yield from 15]. Finally, saponification of 17 (KOH-MeOH, reflux, 1 h) furnished the protected (+)-integerrinecic acid 4[7] [mp 125-128 °C (benzene-hexane), $[\alpha]_D^{11}$ +52.2° (c 0.59, $CHCl_3$), 89% yield].

Thus, the protected (+)-integerrinecic acid 4 has been synthesized from the starting compound 5 in 4.6% overall yield.

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. Reviews: a) L. B. Bull, C. C. J. Culvenor, and A. T. Dick, "The Pyrrolizidine Alkaloids", North-Holland Publishing Co., Amsterdam, 1968. b) A. R. Mattocks, "Phytochemical Ecology", ed. J. B. Harborne, Academic Press Inc., New York, 1972, p 179. c) L. W. Smith and C. C. J. Culvenor, J. Nat. Prod., 44, 129 (1981).

2. Reviews: a) "The Alkaloids", Specialist Periodical Reports, The Royal Society of Chemistry, London, 1978-1983, Vols. 8-13. b) D. J. Robins, Adv. Heterocycl. Chem., 24, 247 (1979). c) D. J. Robins, Fortschr. Chem. Org. Naturst., 41, 115 (1982). d) D. J. Robins, Nat. Prod. Rep., 1, 235 (1984). e) D. J. Robins, Nat. Prod. Rep., 2, 213 (1985). f) J. T. Wróbel, "The Alkaloids", ed. A. Brossi, Academic Press Inc., London, 1985, Vol.

26, p 327. g) K. Narasaka, J. Synth. Org. Chem. Jpn., 43, 464 (1985).

3. a) J. A. Devlin and D. J. Robins, J. Chem. Soc., Chem. Commun., 1981, 1272. b) J. Huang and J. Meinwald, J. Am. Chem. Soc., 103, 861 (1981). c) K. Narasaka, T. Sakakura, T. Uchimaru, K. Morimoto, and T. Mukaiyama, Chem. Lett., 1982, 455. d) K. Brown, J. A. Devlin, and D. J. Robins, J. Chem. Soc., Perkin Trans. I, 1983, 1819. e) K. Narasaka, T. Sakakura, T. Uchimaru, and D. Guèdin-Vuong, J. Am. Chem. Soc., 106, 2954 (1984). f) E. Vedejs and S. D. Larsen, J. Am. Chem. Soc., 106, 3030 (1984).
4. Isolation and structure: a) R. H. F. Manske, Can. J. Res., 17B, 1 (1939). b) R. Adams and B. L. Van Duuren, J. Am. Chem. Soc., 75, 4631 (1953). c) M. Kropman and F. L. Warren, J. Chem. Soc., 1950, 700. d) M. D. Nair and R. Adams, J. Am. Chem. Soc., 82, 3786 (1960). The $[\alpha]_D$ value of integerrimine (1) was initially reported to be +4.3° in MeOH, and later found to be -21.4° in $CHCl_3$ (see; K. Hayashi, A. Natorigawa, and H. Mitsuhashi, Chem. Pharm. Bull., 20, 201 (1972) and references cited therein). We have chosen the prefix (-) for representing natural integerrimine (1).
5. a) C. C. J. Culvenor and T. A. Geissman, J. Am. Chem. Soc., 83, 1647 (1961). b) N. K. Kochetkov, A. E. Vasil'ev, and S. N. Levchenko, Zh. Obshch. Khim., 34, 2202 (1964) [Chem. Abstr., 61, 9399d (1964)]. c) J. D. Edwards, Jr., T. Hase, C. Hignite, and T. Matsumoto, J. Org. Chem., 31, 2282 (1966). d) U. Pastewka, H. Wiedenfeld, and E. Röder, Arch. Pharm. (Weinheim, Ger.), 313, 846 (1980). e) S. E. Drewes and N. D. Emslie, J. Chem. Soc., Perkin Trans. I, 1982, 2079. f) K. Narasaka and T. Uchimaru, Chem. Lett., 1982, 57.
6. P. M. Savu and J. A. Katzenellenbogen, J. Org. Chem., 46, 239 (1981).
7. Satisfactory spectral (IR, ^{1}H NMR, and mass) and analytical (microanalyses or high resolution mass spectra) data were obtained for this compound.
8. The ^{1}H NMR spectral analysis indicated that this material contained a small amount (7%) of 2-methylhept-6-en-1-ol resulting from overreduction. This material was used for the next reaction without further purification.
9. All chemical yields refer to the materials purified by column or preparative layer chromatography on silica gel.
10. T. Katsuki and K. B. Sharpless, J. Am. Chem. Soc., 102, 5974 (1980).
11. The enantiomeric excess of this compound was determined by analyzing the ^{1}H NMR spectrum of the derived MTPA ester: See, J. A. Dale, D. L. Dull, and H. S. Mosher, J. Org. Chem., 34, 2543 (1969).
12. T. Suzuki, H. Saimoto, H. Tomioka, K. Oshima, and H. Nozaki, Tetrahedron Lett., 23, 3597 (1982).
13. P. H. J. Carlsen, T. Katsuki, V. S. Martin, and K. B. Sharpless, J. Org. Chem., 46, 3936 (1981).
14. Without this procedure, the yields of the desired lactones (10 and 11) were somewhat decreased owing to the formation of the products with the lactone ring opened.
15. The authentic sample of (+)-15 was prepared by methylation (CH_2N_2) of (+)-integerrinecic acid lactone, which was obtained by acidic hydrolysis of natural senkirkine.[17]
16. K. Yamada, K. Kato, H. Nagase, and Y. Hirata, Tetrahedron Lett., 1976, 65.
17. L. H. Briggs, R. C. Cambie, B. J. Candy, G. M. O'Donovan, R. H. Russell, and R. N. Seelye, J. Chem. Soc., 1965, 2492.

(Received in Japan 24 June 1986)