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TOTAL SYNTHESIS OF OPTICALLY ACTIVE INTEGERRIMINE, A TWELVE-MEMBERED DILACTONIC PYRROLIZIDINE ALKALOID OF RETRONECINE TYPE. III. REGIOSELECTIVE ELABORATION OF THE UNSYMMETRICAL TWELVE-MEMBERED DILACTONE AND TOTAL SYNTHESIS OF (-)-INTEGERRIMINE[1]

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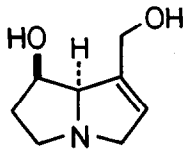
Summary: The first enantioselective synthesis of optically active integerrimine, the twelve-membered dilactonic pyrrolizidine alkaloid has been achieved.

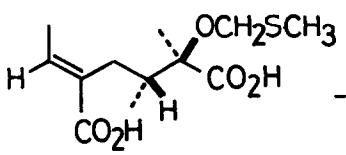
While the macrocyclic pyrrolizidine alkaloids are challenging synthetic targets from the viewpoints of novel structures and a wide range of biological activities,[2] only a few reports on the total synthesis[3] have appeared recently: the total synthesis of racemic integerrimine (7) has been accomplished by Narasaka.[3c,3e] Enantioselective synthesis of macrocyclic pyrrolizidine alkaloids has not yet been achieved to date. In the preceding letters,[1] we have completed the enantioselective synthesis of (+)-retronecine (1) and (+)-integerrinecic acid methylthiomethyl ether (2), the two components necessary for the total synthesis of optically active integerrimine (7). Herein, we wish to describe the first enantioselective synthesis of (-)-integerrimine (7)[4] by virtue of the regioselective coupling of the two components, (+)-retronecine (1) and (+)-integerrinecic acid methylthiomethyl ether (2).

The central problem in the final stage of the total synthesis of (-)-integerrimine (7) is regioselective elaboration of the unsymmetrical dilactone moiety by coupling the unsymmetrical diol 1 with the unsymmetrical diacid 2. This synthetic problem was solved by utilizing the reaction of the cyclic anhydride 3 with the cyclic stannoxane 4. Thus, treatment of (+)-2 with 1 equiv of dicyclohexylcarbodiimide (CH_2Cl_2, room temp., 2 h) provided 3[6] (colorless oil), which was used for the next reaction without purification. On treatment of (+)-1 with 1.1 equiv of dibutyltin oxide[5] (benzene, reflux, 24 h), a solution of the cyclic stannoxane 4[7] in benzene was obtained. Regioselective monoesterification was effected by the addition of a solution of 3 in benzene to the solution of 4 (0 °C to room temp., 3 h) to yield the desired monoester 5[6] [colorless oil, $[\alpha]_D^{15}$ +51.4° (c 0.66, $CHCl_3$)] in 98% yield after purification by column chromatograohy on silica gel.

Lactonization of 5 was achieved by the procedure reported by Yamaguchi:[8] (i) formation of the mixed anhydride (1.1 equiv of 2,4,6-trichlorobenzoyl chloride and 4 equiv of Et_3N, THF, room



1 (+)-retronecine



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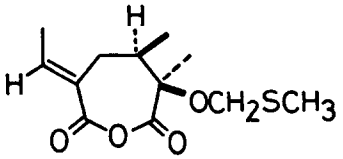

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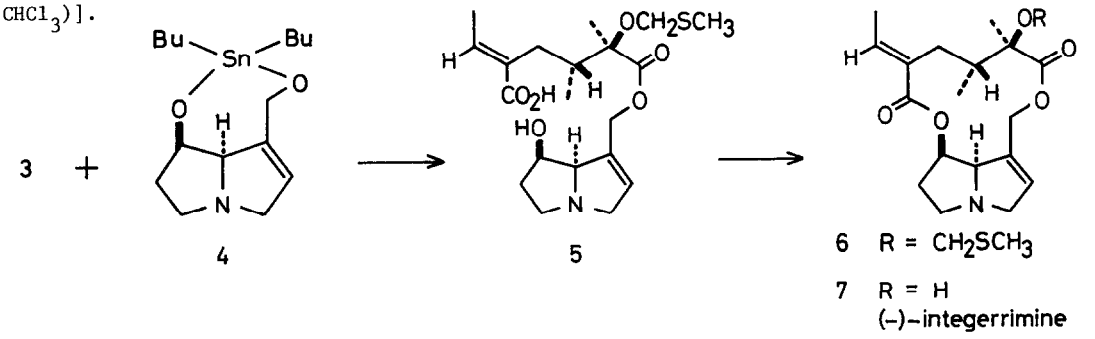
temp., 2 h); (ii) slow addition of the solution containing the mixed anhydride to a refluxing solution containing 6 equiv of 4-DMAP in toluene (over 1.5 h) followed by refluxing for additional 2 h. Extractive isolation and chromatographic purification by preparative TLC on silica gel provided integerrimine methylthiomethyl ether (6)[6] [colorless oil, $[\alpha]_D^{24}$ +51.2° (c 0.52, $CHCl_3$)] in 75% yield. Finally, deprotection of 6 was effected by treatment with 1.2 equiv of triphenylcarbenium tetrafluoroborate[9] (CH_2Cl_2, room temp., 1.5 h) to furnish (-)-integerrimine (7) [mp 169-170.5 °C (acetone): Lit.[10] mp 168-169 °C (acetone), 171-172 °C (EtOH)] in 81% yield after purification by column chromatography on silica gel. Synthetic (-)-7 was spectrally (IR, ^{1}H NMR, and mass) and chromatographically identical with natural integerrimine in all respects, exhibiting an optical rotation [$[\alpha]_D^{17}$ -19.5° (c 0.15, $CHCl_3$)] comparable to the literature values[10][$[\alpha]_D$ -21.4° (c 9.00, $CHCl_3$), $[\alpha]_D^{23}$ -22.1° (c 5.12, $CHCl_3$)].



It is worthy of note that the present method for the regioselective elaboration of the unsymmetrical dilactone is operationally simple and requires no protecting groups to distinguish each of the two carboxyl groups in the necic acid 2, as well as each of the two hydroxyl groups in the necine base 1.

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References and Notes

1. Part I: H. Niwa, Y. Miyachi, Y. Uosaki, and K. Yamada, Tetrahedron Lett., preceding paper. Part II: H. Niwa, Y. Miyachi, O. Okamoto, Y. Uosaki, and K. Yamada, Tetrahedron Lett., preceding paper.
2. See references 1 and 2 in Part I.[1]
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. Guédin-Vuong, J. Am. Chem. Soc., 106, 2954 (1984). f) E. Vedejs and S. D. Larsen, J. Am. Chem. Soc., 106, 3030 (1984).
4. See reference 4 in part I.[1]
5. A. Shanzer, J. Libman, H. Gottlieb, and F. Frolow, J. Am. Chem. Soc., 104, 4220 (1982).
6. Satisfactory spectral (IR, ^{1}H NMR, and mass) and analytical (microanalyses or high resolution mass spectra) data were obtained for this compound.
7. Although the actual structure of this compound could not be clarified, the structure of this intermediate was tentatively depicted as the formula 4.
8. J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, and M. Yamaguchi, Bull. Chem. Soc. Jpn., 52, 1989 (1979).
9. P. K. Chowdhury, R. P. Sharma, and J. N. Baruah, Tetrahedron Lett., 24, 4485 (1983).
10. a) E. Gellert and C. Måtė, Aust. J. Chem., 17, 158 (1964). b) K. Hayashi, A. Natorigawa, and H. Mitsuhashi, Chem. Pharm. Bull., 20, 201 (1972).

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