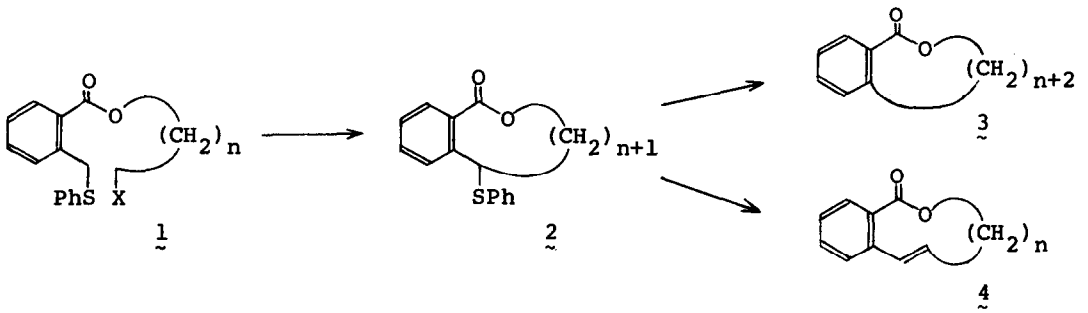
Tetrahedron Letters No. 49, pp 4917 - 4920.

0040-4039/78/1201-4917$02.00/0

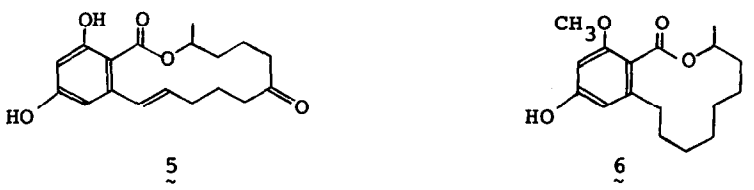
A NEW SYNTHETIC METHOD FOR AROMATIC TYPE MEDIUM AND LARGE MEMBERED LACTONES BASED ON INTRAMOLECULAR ALKYLATION OF ω-HALOALKYL 2-PHENYLTHIOMETHYLBENZOATE, AND ITS APPLICATION TO THE SYNTHESIS OF (±)LASIODIPLODIN USING A BUTADIENE TELOMER

Takashi TAKAHASHI, Kazuyuki KASUGA, and Jiro TSUJI*
Tokyo Institute of Technology, Meguro, Tokyo 152

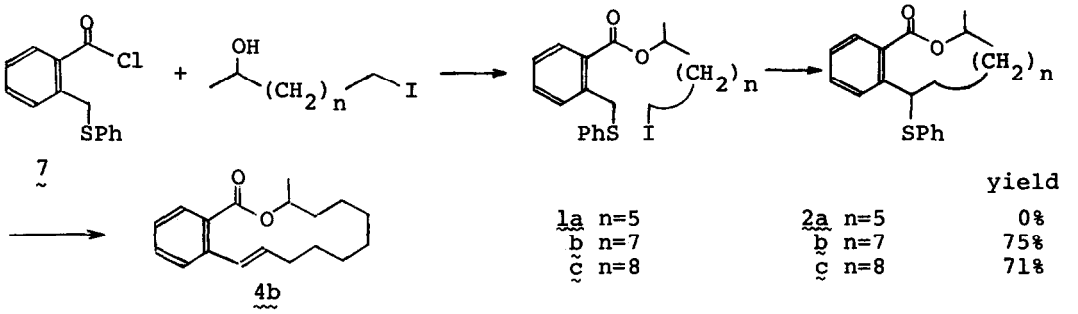
Synthesis of macrolides is a current problem of intensive research. Discovery of an efficient method of the cyclization is a major problem in the macrolide synthesis.[1] So far, the most widely used method of the lactone ring formation is intramolecular esterification of ω-hydroxy acids.[2] As another possibility, few attempts on the lactone formation by intramolecular carbon-carbon bond formation have been made.[3] One advantage of the carbon-carbon bond formation is that a functional group used for the cyclization can be transformed into another functional group in a target molecule. In this paper we wish to report the synthesis of aromatic type lactones based on the intramolecular alkylation of ω-haloalkyl 2-phenylthiomethylbenzoate (1) as shown by the following scheme. The lactone 2 can be converted to saturated or unsaturated lactones 3 and 4 by reductive or oxidative removal of the phenylthio group.



The above methodology, if successful, can offer a general synthetic method for a number of naturally occurring orsellinic acid type lactones such as zearalenone (5)[4] and lasiodiplodin (6).[5]



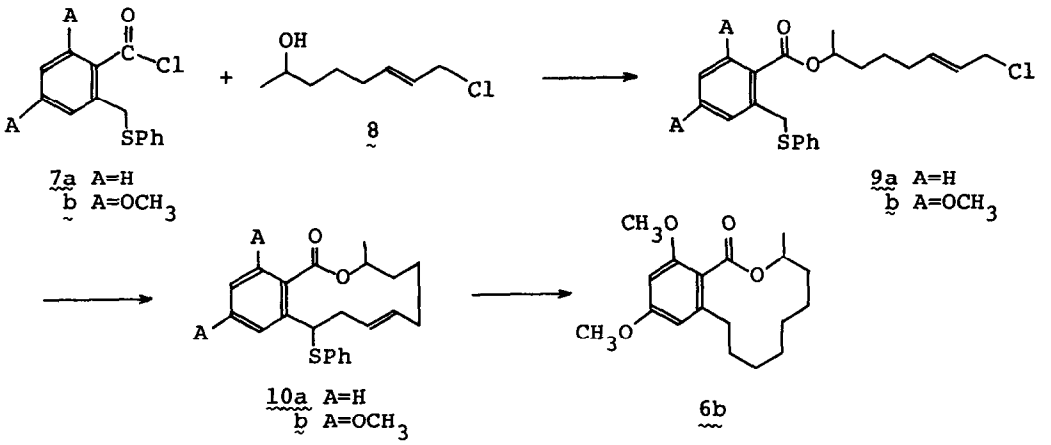
Based on the above scheme, we attempted to synthesize 12-, 14-, and 15-membered lactones. (n = 5, 7, and 8).



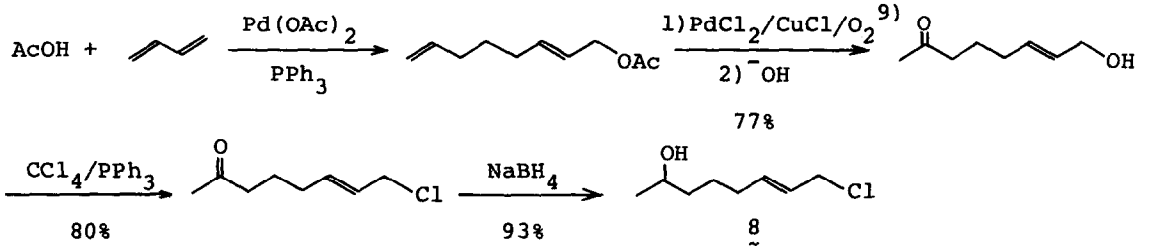
At first the 14-membered macrolide 4b was synthesized. The reaction of 10-iodo-2-dodecanol with 2-phenylthiomethylbenzoyl chloride (7) in dichloromethane afforded the desired ester 1b in 85% yield. NMR (CCl_4) δ 1.33 (d, J = 6.0 Hz, 3H, $-CH-CH_3$), 3.06 (t, J = 6 Hz, 2H, CH_2-I), 4.43 (s, 2H, $PhS-CH_2$), 4.85-5.25 (m, 1H, -O-CH-), 6.90-7.92 (m, 9H, aromatics); IR (film) 2920, 1710, 1260 cm^{-1}.
The cyclization was carried out by the following way. The ester 1b (0.684 mmol) in THF (13 ml) was added slowly in 2 h at 40° under nitrogen to two equiv. of potassium salt of hexamethyldisilazane in THF (18 ml). The reaction mixture was stirred additional 15 min and quenched. The 14-membered lactone 2b was isolated as an oil in 75% yield. NMR ($CDCl_3$) δ 1.36 (d, J = 6.0 Hz, 3H, $-CH-CH_3$), 5.15-5.55 (m, 1H, -O-CH-), 5.63 (t, J = 7.2 Hz, 1H, -CHSPh), 7.08-7.85 (m, 9H, aromatic); IR (film) 2920, 1710, 1260, 745 cm^{-1}.
The phenylthio group of 2b was oxidized with $NaIO_4$[6] and the product, without purification, was subjected to toluene reflux to give the unsaturated lactone 4b in nearly quantitative yield. NMR (CCl_4) δ 1.82 (d, J = 6.0 Hz, 3H, $-CH-CH_3$), 2.06-2.50 (m, 2H, $-CH_2-C=$), 4.90-5.33 (m, 1H, -CH-O-), 5.78 (dt, J = 7.2 and 15.6 Hz, 1H, olefin), 6.95-7.90 (m, 5H, aromatics and olefin). This is a model reaction for zearalenone,the synthesis of which is in progress in our laboratory.

The synthesis of the corresponding 15-membered lactone 2c was carried out in a similar way. The acid chloride 7 was esterified with 11-iodo-2-undecanol to give the ester 1c in 95% yield. The cyclization produced the lactone 2c in 71% yield.

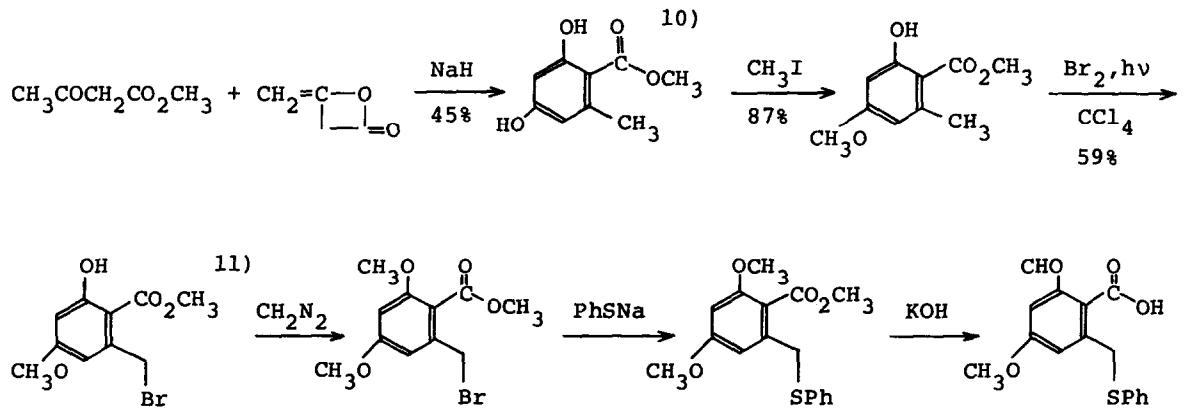
Then the synthesis of the 12-membered lactone 2a was attempted. Generally 10- and 12-membered lactones are regarded to be cyclized less efficiently than 15-membered lactone.[7] The attempted cyclization of the ester 1a under the same conditions produced no lactone, and only elimination of the terminal iodide to give terminal olefin took place. But this problem was solved by using allylic chloride 9a as the alkylating agent.



The ester 9a was prepared from 8-chloro-6-octen-2-ol (8) and 7a, and subjected to cyclization. The desired lactone 10a was obtained in 41% yield. Then the synthesis of the *o*-methyl derivative of lasiodiplodin 6b was attempted. The alcohol 8 was prepared in the following way from 8-acetoxy-1,6-octadiene[8] which is easily available by the palladium catalyzed telomerization of butadiene.



The synthesis of 2-phenylthiomethyl-4,6-dimethoxybenzoic acid was carried out by the following sequence of reactions.



The ester 9b was subjected to cyclization and the lactone 10b NMR (CCl_4) δ 1.30 (d, J = 7.2 Hz, 3H, -CH-CH_3), 1.90-2.86 (m, 4H, -CH_2-C=C), 3.72 (s, 3H, -OCH_3), 3.75 (s, 3H, -OCH_3), 4.73 (dd, J = 4.2 and 10.8 Hz, 1H, -CH-SPh), 5.0-5.76 (m, 3H, -CH-O and olefin), 6.28 (d, J = 2.1 Hz, 1H, aromatic), 6.94 (d, J = 2.1 Hz, 1H, aromatic) was obtained in 40% yield. Removal of the phenylthio group and the reduction of the double bond were achieved by refluxing in ethanol with an excess of Raney nickel to give *o*-methyl derivative of lasiodiplodin in 70% yield. NMR ($CDCl_3$) δ 1.31 (d, J = 7.2 Hz, 3H, -CH-CH_3), 2.44-2.83 (m, 2H, -CH_2-Ph), 4.76 (s, 6H, -OCH_3), 5.00-5.48 (m, 1H, -O-CH-), 6.28 (s, 2H, aromatics); IR (KBr) 2930, 1715, 1605, 1590 cm^{-1}; MS, Found: *m/e* 306.1831. Calcd for $C_{18}H_{26}O_4$: M, 306.1827.

References

1. For review (a) K. C. Nicolau, Tetrahedron, 33, 683 (1977). (b) S. Masamune, G. S. Bates and J. W. Corcoran, Angew. Chem. Int. Ed. Engl., 16, 585 (1977). (c) T. G. Back, Tetrahedron , 33, 3041 (1977).
2. (a) E. J. Corey and K. C. Nicolaou, J. Am. Chem. Soc., 96, 5614 (1974). (b) S. Masamune, Y. Hayase, W. Shilling, W. K. Chan, and G. S. Bates ibid., 99, 6756 (1977). (c) K. Narasaka, M. Yamaguchi, and T. Mukaiyama, Chem. Lett., 959 (1977). (d) T. Kurihara, Y. Nakajima, and O. Mitsunobu, Tetrahedron Lett., 2455 (1976).
3. (a) B. M. Trost and T. R. Verhoeven, J. Am. Chem. Soc., 99, 3867 (1977) and Tetrahedron Lett., 2275 (1978). (b) E. J. Corey and H. A. Krist, J. Am. Chem. Soc., 94, 667 (1972). (c) R. N. Hurd and D. H. Shah, J. Org. Chem., 38, 390 (1973). (d) K. Maruoka, S. Hashimoto, Y. Kitagawa, H. Yamamoto, and H. Nozaki, J. Am. Chem. Soc., 99, 7705 (1977).
4. (a) Isolation; W. H. Urrz, H. L. Wehrmeister, E. B. Hodge, and P. H. Hidy, Tetrahedron Lett., 3109 (1966). (b) Synthesis; D. Taub, N. N. Girotra, R. D. Hoffoommer, C. H. Kuo, H. L. Slates, S. Weber, and N. L. Wendler, Tetrahedron, 24, 2443 (1968). I. Vlattas, I. T. Harrison, L. Tokes, J. H. Fried, and A. D. Cross, J. Org. Chem., 33, 4176 (1968).
5. Isolation; D. C. Aldridge, S. Galt, D. Giles, and W. B. Turner, J. Chem. Soc. (c), 1623 (1971). Synthesis; H. Gerlach and A. Thalmann, Helv. Chim. Acta., 60, 2866 (1977).
6. B. M. Trost, T. N. Sulzmann, and K. Hiroi, J. Am. Chem. Soc., 98, 4887 (1976).
7. E. J. Corey, D. J. Brunelle, and P. J. Stork, Tetrahedron Lett., 3405 (1976).
8. S. Takahashi, T. Shibano, and N. Hagihara, ibid., 2451 (1967).
9. J. Tsuji, I. Shimizu, and K. Yamamoto, ibid., 2975 (1976).
10. T. Kato and T. Hozumi, Chem. Pharm. Bull., 20, 1574 (1972).
11. W. R. Allison and G. T. Newbold, J. Chem. Soc., 3335 (1959).

(Received in Japan 9 September 1978)