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SYNTHESES OF (±)-CONFERTIFOLIN AND (±)-ISODRIMENIN

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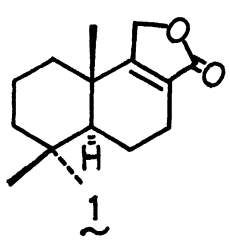
A large scale synthesis of (±)-confertifolin and (±)-isodrimenin was achieved starting from β-ionone via the tricyclic furan derivative. Oxidation of this common intermediate with $Pb(OAc)_4$ followed by pyrolysis afforded the former as a main product. The latter was prepared as a main product by $NaBH_4$ reduction of (±)-winterin derived from the same intermediate.

Confertifolin (1) and isodrimenin (2), isolated both from Drimys winteri Forst.,[1] are structurally related to warburganal (3)[2], an effective antifeedant against the African army worms. Taking into account of the structural similarity, we intended the synthesis of warburganal (3) starting from 1 and 2. Syntheses of 1 and 2 have already been published.[3] Quite recently, we also reported the transformation of dehydroabietic acid into 1 and 2.[4] However, in order to secure a sufficient amount of 1 and 2 for further synthetic work, another method should be developed. We now report a new synthetic route satisfying this requirement.



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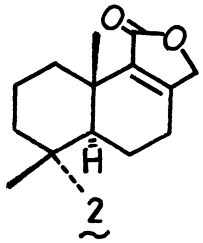

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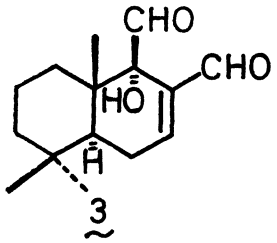

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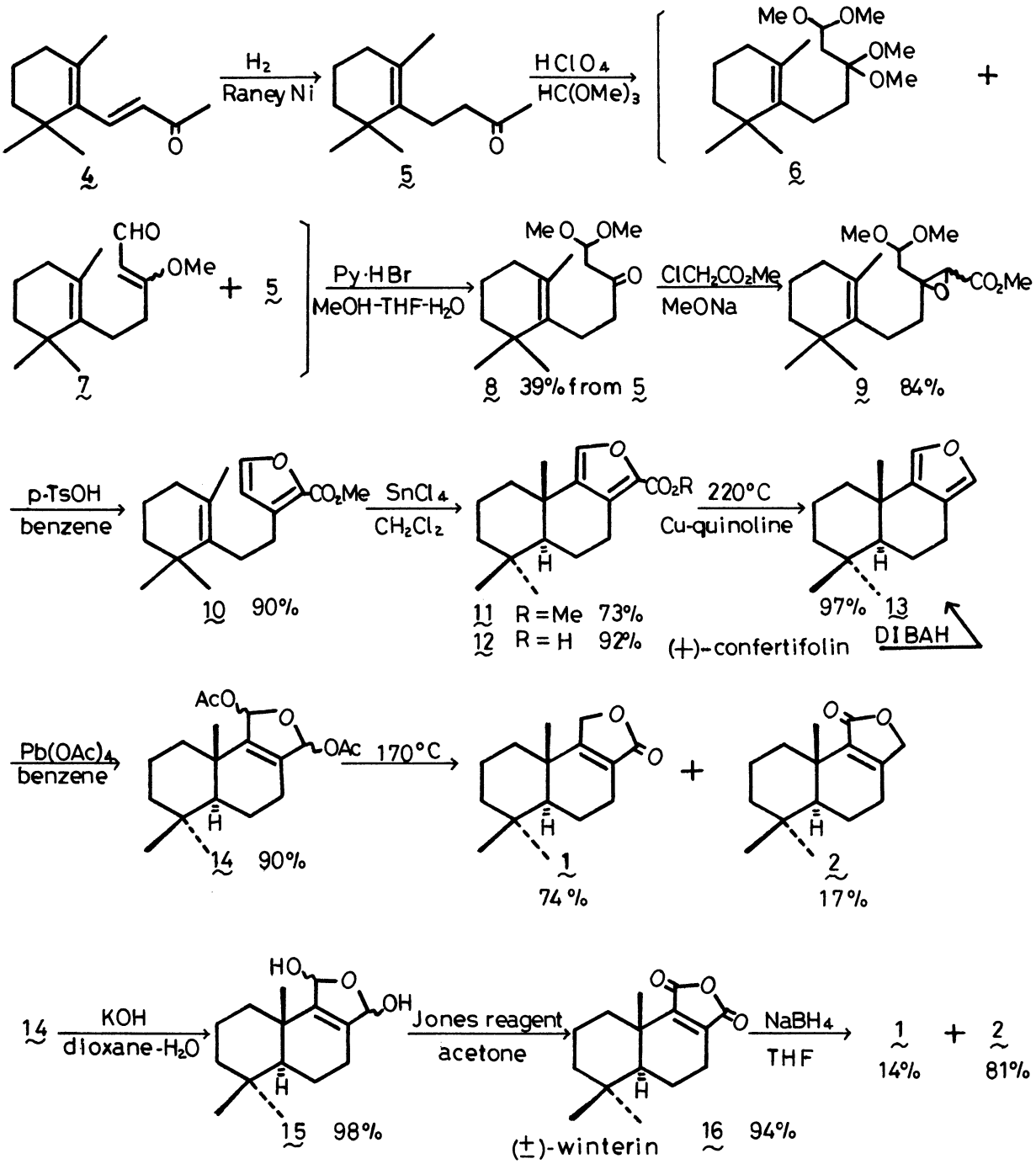
Dihydro-β-ionone (5)[5], readily obtainable from β-ionone (4) by partial reduction with Raney-Ni, was subjected to the reaction with trimethyl orthoformate in the presence of 70% $HClO_4$[6] to afford, after sat. $NaHCO_3$ treatment, the diacetal (6) and the alkoxy enal (7) along with the starting material (5)[7]. The oily

mixture was, without purification, treated with pyridine hydrobromide in MeOH-THF (2 : 3)(70 °C, 30 min, then 50 °C, 50 min after addition of a small amount of H_2O) to produce the β-keto acetal (8)[8] [IR(CCl_4) 1715 cm^{-1}; NMR($CDCl_3$) δ 2.69(2H, d, J=6 Hz), 3.36(6H, s), 4.77(1H, t, J=6 Hz)] in 39% yield from 5. An appreciable amount (14%) of 5 was recovered unchanged. Condensation of 8 with methyl chloroacetate (3 equiv) using NaOMe (3 equiv) as a base in ether afforded the epoxy ester (9) [84% yield; IR(CCl_4) 1760, 1735 cm^{-1}; NMR($CDCl_3$) δ 3.32(6H, s), 3.73 (3H, s)], which was refluxed for 1 h in benzene in the presence of a catalytic amount of p-TsOH·H_2O while distilling off benzene and MeOH gradually to afford the methoxycarbonyl furan (10)[9]: 90% yield; IR(CCl_4) 1715 cm^{-1}; NMR($CDCl_3$) δ 3.86 (3H, s), 6.39(1H, d, J=2 Hz), 7.40(1H, d, J=2 Hz). Cyclization of 10 with $SnCl_4$ (2 equiv) in CH_2Cl_2 (1 h under ice cooling, then 4 h at room temp.) produced the tricyclic compound (11) [mp 96-7 °C; IR(CCl_4) 1708 cm^{-1}; NMR($CDCl_3$) δ 3.85(3H, s), 7.20(1H, s)] in 73% yield. Refluxing of 11 with an excess of KOH in H_2O-MeOH (1 : 10) for 2 h afforded the carboxylic acid (12) [92% yield; mp 185-6 °C; IR (KBr) 1670 cm^{-1}; NMR($CDCl_3$) δ 7.30(1H, s)] after acidification with 10% HCl. Decarboxylation was then effected by heating 12 for 1 h at 220-230 °C (bath temp.) in quinoline in the presence of copper powder under nitrogen to yield the furan (13): 97% yield; oil; NMR($CDCl_3$) δ 7.02(2H, s). The compound (13) was found to be identical in every respect with an authentic sample prepared by the reduction (DIBAH-THF) of (+)-confertifolin, which showed that 13 involved the same trans-decalin moiety as confertifolin. Treatment of 13 with $Pb(OAc)_4$ (1 equiv) in benzene (3 h, room temp.) afforded the diacetoxy derivatives (14): 90% yield; mp 124-6 °C; NMR($CDCl_3$) δ 2.10(6H, s). On heating 14 for 1 h at 170 °C (bath temp.) and subsequent repeated recrystalization of the resulting solid from CH_2Cl_2-hexane, (±)-confertifolin (1), mp 116-7 °C, was obtained in 74% yield. The filtrate was subjected to chromatography using Lobar column to afford (±)-isodrimenin (2): 17% yield; mp 89-90 °C. Spectral data (NMR, IR, GC-MS) of 1 and 2 were identical in every respect with those of the authentic (+)-confertifolin and (+)-isodrimenin, respectively.

For the purpose of obtaining isodrimenin in quantity, another route starting from 14 was sought. Hydrolysis of 14 with 20% KOH-dioxane (1 : 4)(40 min, room temp.) produced 15: 98% yield; mp 134-7 °C; IR(KBr) 3350, 3250 cm^{-1}. Jones oxidation of 15 in acetone (15 min under ice cooling, then 45 min at room temp.)

yielded (±)-winterin (16) [94% yield; mp 144-7 °C; IR(CCl_4) 1845, 1775 cm^{-1}], $NaBH_4$ reduction of which proceeded selectively in THF affording (±)-isodrimenin (2) in 81% yield along with a small amount of 1 (14%).

Every step in the above synthesis can be carried out on large scale under a standard procedure. The preparative method for the syntheses of (±)-confertifolin and (±)-isodrimenin was thus established.



Acknowledgement

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References and Notes

1) H. H. Appel, J. D. Connolly, K. H. Overton, and R. P. M. Bond, J. Chem. Soc., 1960, 4685.

2) I.Kubo, Y.-W. Lee, M. J. Pettei, F. Pilkiewicz, and K. Nakanishi, J. Chem. Soc. Chem. Commun., 1976, 1013.

3) a) E. Wenkert and D. P. Strike, J. Am. Chem. Soc., 86, 2044(1964). b) Y. Kitahara, T. Kato, T. Suzuki, S. Kanno, and M. Tanemura, J. Chem. Soc. Chem. Commun., 1969, 342. c) H. Yanagawa, T. Kato, and Y. Kitahara, Synthesis, 1970, 257. d) A. Matsukawa, H. Shintani, and A. Ohsuka, the 22nd Symposium on the Chemistry of Terpenes, Essential Oils, and Aromatics, Yokohama, 1978. Abstructs of Papers, p. 231. e) A. Kimura, and S. Isoe, ibid., p. 233. f) S. P. Tanis and K. Nakanishi, J. Am. Chem. Soc., 101, 4398 (1979).

4) H. Akita and T. Oishi, Tetrahedron Lett., 1978, 3733.

5) a) R. Poul and G. Hilly, Bull. Soc. Chim. France, 3, 2330(1936). b) J. Kandel, Ann. Chim., 11, 73(1939). c) J. Kandel, Comt. rend., 205, 994(1937).

6) a) J. P. Dusza and J. P. Joseph, J. Am Chem. Soc., 86, 3908(1964). b) E. Yoshii, T. Oribe, T. Koizumi, I. Hayashi, and K. Tumura, Chem. Pharm. Bull., 25, 2249 (1977).

7) The compounds 6 [NMR($CDCl_3$) δ 3.20(6H, s), 3.32(6H, s)] and 7 [NMR($CDCl_3$) δ 3.69(3H, s), 5.36(1H, d, J=8.4 Hz), 9.84(1H, d, J=8.4 Hz); IR(CCl_4) 1665, 1610 cm^{-1}] can be isolated by silica gel chromatography from the mixture in 25% and 14% yields, respectively.

8) Satisfactory elemental analytical data were obtained for all new compounds.

9) cf. D. M. Burness, Org. Syn., Coll. Vol. 4, 649(1963).

10) (±)-Isodrimenin (2) has been successfully converted to (±)-warburganal (3) [T. Nakata, H. Akita, T. Naito, and T. Oishi, J. Am. Chem. Soc., 101, 4400(1979)] Other synthesis of 3, see ref. 3f; A. Ohsuka and A. Matsukawa, Chem. Lett., 635 (1979); A. Kimura and S. Isobe, the 22nd Symposium on the Chemistry of Natural Products, Fukuoka, 1979. Abstracts of papers, p. 198.

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