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STEREOSELECTIVE TOTAL SYNTHESES OF (±)-RECIFEIOLIDE AND (R)-(+)-RICINELAIDIC ACID LACTONE

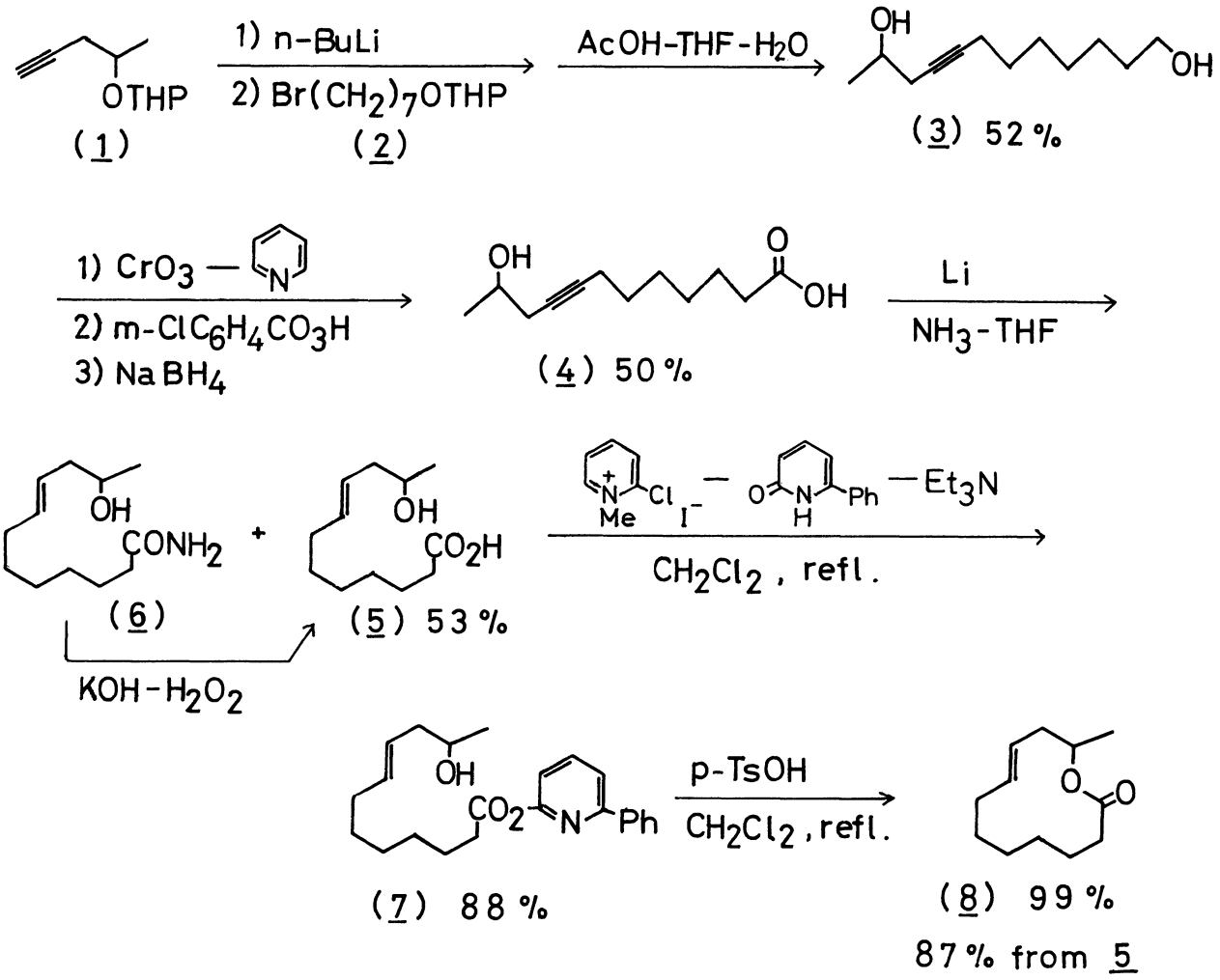
Koichi NARASAKA, Masahiko YAMAGUCHI, and Teruaki MUKAIYAMA
Department of Chemistry, Faculty of Science
The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

The naturally occurring macrolide, (±)-recifeiolide, was synthesized stereoselectively. (E)-11-Hydroxy-8-dodecenoic acid (5) was obtained stereoselectively from 11-hydroxy-8-dodecynoic acid by the reduction with lithium, and the acid (5) was cyclized to (±)-recifeiolide in excellent yield via its 6-phenyl-2-pyridyl ester. Similarly, (R)-(+)-ricinelaidic acid was lactonized to afford the corresponding lactone in high yield.

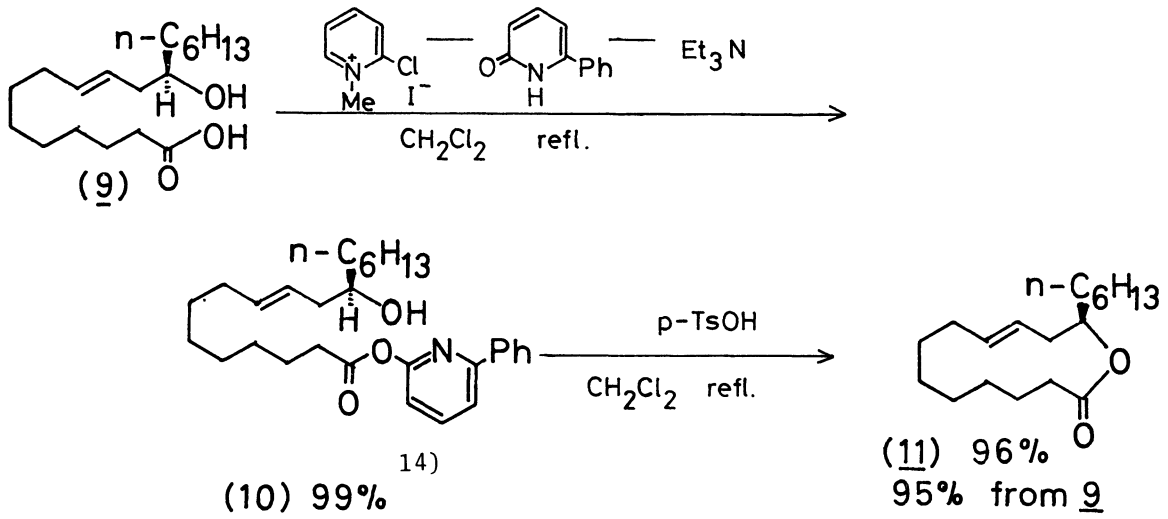
Recently, the efficient method for lactonization of long chain ω-hydroxycarboxylic acids was developed in our laboratory.[1] We now wish to report the use of this process in a stereoselective synthesis of (±)-recifeiolide, a naturally occurring macrolide isolated from the fungus Cephalosporium recifei,[2] and also in a synthesis of (R)-(+)-ricinelaidic acid lactone.

(±)-Recifeiolide was synthesized stereoselectively starting from the readily available acetylenic tetrahydropyranyl ether (1).[3] The acetylenic ether (1) was treated with butyllithium at -30°C, and successively with 7-bromoheptyl 2-tetrahydropyranyl ether (2)[4] in a mixture of THF and HMPA under refluxing for 12 h. Treatment of the resulting crude product with CH_3COOH-H_2O-THF (3:1:1) at 45-50°C for 4 h produced 8-dodecyne-1,11-diol[5] (3, 52% from 1). The acetylenic acid (4)[6] was obtained in 50% overall yield from the diol (3) by the oxidation with the Collins reagent (12 molar amounts)[7] in CH_2Cl_2 at r.t., and then with m-chloroperbenzoic acid (3 molar amounts)[8] in THF at r.t., followed by the reduction with $NaBH_4$. The isomerically pure (E)-olefinic acid was produced by the reduction of the acetylenic acid (4) with lithium. The acetylenic acid (4) was treated in an autoclave[9] with

lithium (12 molar amounts) in a mixture of liquid ammonia and THF at r.t. for 2 days to give (E)-11-hydroxy-8-dodecenoic acid (5) in 53% yield. During the reduction, small amount of (E)-11-hydroxy-8-dodecenamide (6) was sometimes produced as by-product which was converted to the acid (5) by alkaline hydrolysis.[10] The olefinic acid (5) thus obtained was submitted to lactonization. A mixture of 6-phenyl-2-pyridone (2.72 mmol), 2-chloro-1-methylpyridinium iodide (1.36 mmol) and triethylamine (2.72 mmol) in CH_2Cl_2 (28 ml) was stirred for 1 h at r.t. To this solution was slowly added a CH_2Cl_2 (41 ml) solution of the olefinic acid (5, 0.34 mmol) and triethylamine (0.34 mmol) under refluxing over a period of 6 h to give the 6-phenyl-2-pyridyl ester (7)[11] in 88% yield. A CH_2Cl_2 (73 ml) solution of the ester (7, 0.42 mmol) was added dropwise to a refluxing solution of p-toluenesulfonic acid (0.42 mmol) in CH_2Cl_2 (49 ml) over a period of 11 h, and after purification by column chromatography (silica gel), pure (±)-recifeiolide (8)[12] was obtained in 99% yield [87% overall yield from the olefinic acid (5)].



The lactonization of optically active ricinelaidic acid, (R)-(+)-(E)-12-hydroxy-9-octadecenoic acid (9), was also successfully achieved according to the above mentioned procedure, and the desired (R)-(+)-lactone (11)[13] was obtained in 95% as shown in the following scheme.



It is noted that the present method for the lactonization of hydroxy acid (5 and 9) employing the onium salt of azaaromatic compound proceeded under mild conditions to afford the corresponding lactones in higher yields as compared with the previously reported methods.[10, 15]

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References and Notes

1) T. Mukaiyama, K. Narasaka, and K. Kikuchi, Chem. Lett., 1977, 441.

2) R. F. Vensonder, F. H. Stodola, L. J. Wickerham, J. J. Ellis, and W. K. Rohwedder, Can. J. Chem., 49, 2029 (1971).

3) This acetylenic ether was prepared as follows : Lithium acetylide was treated with propylene oxide in a mixture of THF and HMPA at r.t. to give 4-pentyn-2-ol (76%), which was converted to the tetrahydropyranyl ether (1) according to the usual procedure.[10]

4) Methyl 7-bromoheptanoate[16] was reduced with $LiAlH_4$ at -30°C in THF, and the resulting bromo alcohol was converted to the tetrahydropyranyl ether (2).

5) NMR($CDCl_3$) δ 1.28 (3H, d, J=7Hz), 1.2-1.9 (10H, m), 1.9-2.4 (4H, m), 2.53 (2H, s), 3.62 (2H, t, J=7Hz), 3.92 (1H, m); IR(neat) 3330 cm^{-1}.

6) NMR($CDCl_3$) δ 1.25 (3H, d, J=9Hz), 1.1-1.9 (8H, m), 2.0-2.5 (6H, m), 3.93 (1H, m), 8.08 (2H, s); IR(neat) 1705 cm^{-1}.

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11) NMR($CDCl_3$) δ 1.16 (3H, d, J=8Hz), 1.2-2.4 (13H, m), 2.61 (2H, t, J=8Hz), 3.74 (1H, m), 5,3-5.6 (2H, m), 6.9-8.1 (8H, m); IR(neat) 3360 and 1760 cm^{-1}; Found: C, 74.96; H, 8.14; N, 3.88%. Calcd for $C_{23}H_{29}N_1O_3$: C, 75.17; H, 7.95; N, 3.81%.

12) The NMR and IR spectra well agreed with the literatures.[10), 15)] NMR($CDCl_3$) δ 1.16 (3H, d, J=8Hz), 1.1-1.8 (8H, m), 1.8-2.4 (6H, m), 4.8-5.0 (1H, m), 5.0-5.3 (2H, m); IR(neat) 1714 cm^{-1}; MS $^m/_e$ 196 (M^+), 152 (M^+-CO_2); Found: C, 72.90; H, 10.59%. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.20%.

13) The NMR and IR spectra and optical rotation well agreed with the data of the literature.[15)] NMR($CDCl_3$) δ 0.6-1.0 (3H, br), 1.1-1.8 (20H, m), 1.8-2.3 (6H, m), 4.6-5.0 (1H, m), 5.2-5.4 (2H, m); IR(neat) 1730 cm^{-1}; $[\alpha]_D^{25}$= +45.7° (c=1. $CHCl_3$); MS $^m/_e$ 280 (M^+); Found: C, 76.71; H, 12.00%. Calcd for $C_{18}H_{32}O_2$: C, 77.09; H, 11.50%.

14) NMR($CDCl_3$) δ 0.8-1.1 (3H, m), 1.1-1.8 (20H, m), 1.64 (1H, s), 1.8-2.3 (4H, m), 2.64 (2H, t, J=8Hz), 3.4-3.7 (1H, m), 5.3-5.6 (2H, m), 6.9-8.1 (8H, m); IR(KBr) 3270 and 1750 cm^{-1}; MS $^m/_e$ 451 (M^+), 337; Found: C, 76.89; H, 9.33, N, 2.94%. Calcd for $C_{29}H_{41}N_1O_3$: C, 77.12, H, 9.15, N, 3.10%.

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