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SYNTHESIS OF CEMBRA-3E,7E,11E,15(17)-TETRAEN-cis-16,2-OLIDE[1)]

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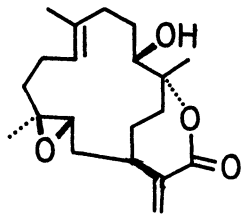
The titled natural product was synthesized from 3,7,11-trimethyl-cyclotetradeca-2E,6E,10E-trienone.

Recent interest in marine natural products has accumulated an increasing number of cembranolides, among which some have tumor inhibiting activity as exemplified by sinulariolide (1).[2)] In addition to its physiological activity, the highly oxygenated feature of 1 prompted us to explore the synthetic route through the lactonic intermediate (2), which is also a marine natural product isolated recently from a soft coral.[3)] This paper concerns with the exploration of the synthesis of the cembranolide (2).



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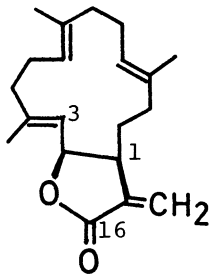
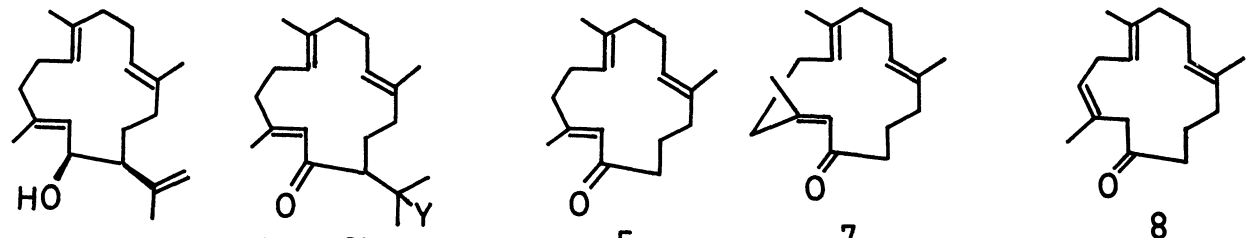


2

At the outset of our synthetic study, we intended to construct the α-methylene γ-lactone moiety from the alcohol (3) by selective oxidation of the isopropenyl group. 3 can be easily prepared from the chloroketone (4).[4)] However, all the trials we have done were unsuccessful and hence we were compelled to make the lactone group from cyclotetradecatrienone derivative (5), which may be available from the chloroketone (4). Treatment of 4 with ZnO (1 equiv.) in AcOH (45 °C, 3 h)[5)] afforded the corresponding acetate (6) in 71% yield, which was subjected to the reaction with LiOH in aq dioxane (75 °C, 5 h), resulting in the formation of a mixture of three isomeric ketones (5, 7, and 8) in 97% yield with the ratio of

8:1:4. After separation of each component by SiO_2 column chromatography, the mixture of 7 and 8 was treated with t-BuOK in t-BuOH (20 °C, 3 h), yielding three ketones in the same ratio, from which 5 was again isolated by the chromatography. By this procedure, 5 was furnished in 50% overall yield from the starting material (4).[6]

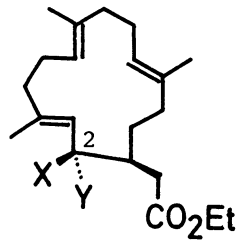


3 4 Y=Cl 5 7 8

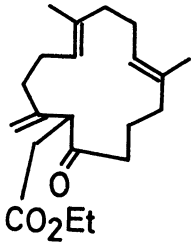
6 Y=OAc

The introduction of CH_2CO_2Et group at α-position of the ketone was achieved by admixing ICH_2CO_2Et at -78 °C with lithium enolate of 5, generated by the action of LDA (1.5 equiv.) in THF-HMPA (5:1) at -78 °C. The reaction led to the formation of a mixture of 9 and 10 in 66% yield with the ratio of 64:36, from which 9 was obtained by SiO_2 column chromatography. The alkylation of 5 was fairly complicated. When ICH_2CO_2Et in THF-solution was added at -78 °C to the lithium enolate of 5 prepared upon treatment with $LiN(TMS)_2$ in THF at -78 °C, an additional product (11) was formed, the ratio of 9, 10, and 11 being 4:53:43, respectively in 63% yield. None of the usual techniques, such as lower temperature, change of kinds of bases and solvents gave improved yield of 9. Reduction of 9 with $NaBH_4$ proceeded stereoselectively, giving hydroxy ester (12) and γ-lactone (13) in 68 and 28% yield, respectively. The relative configuration of the neighboring hydroxyl and CH_2CO_2Et groups of 12 was supported by a fully consistent PMR spectrum.[7] The coupling pattern of C_2-H of 12 was quite similar with that of cis alcohol (3). The hydroxy ester (12) was transformed quantitatively to the lactone (13) by the action of p-TsOH.Py in refluxing benzene for 10 min. Introduction of methylene unit into the lactone ring was carried out by the application of Grieco's procedure.[8] Deprotonation (LDA in THF, -78 °C) and reaction with gaseous HCHO at -20 °C provided the hydroxymethyl lactone (14) in 65% as a stereoisomeric mixture. 14 was transformed, without purification, to the objective (2) in 96% yield by successive treatments with $MsCl$ (3 equiv.) in CH_2Cl_2 containing catalytic amounts of dimethylaminopyridine and pyridine (6 equiv.)(rt, 6 h), and then by 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) in benzene (rt, overnight). Physical data of the synthetic

lactone (2) was identical with that of natural specimen except for the optical rotation.[9,10]



9 X, Y = O
12 X = OH, Y = H



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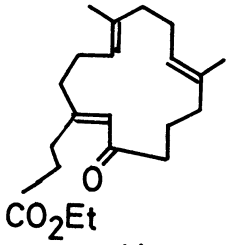

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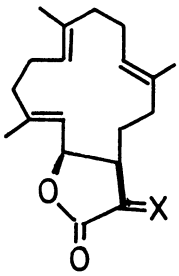

13 X = H_2
14 X = H, CH_2OH

References

1) This constitutes part 39 of the series of "Cyclization of Polyenes". Part 38, M. Aoki, T. Uyehara, T. Kato, K. Kabuto, and S. Yamaguchi, Chem. Lett., 1983, 1121.

2) A. J. Weinheimer, J. A. Matson, M. B. Hossain, and D. van der Helm, Tetrahedron Lett., 1977, 2923.

3) Y. Uchio, S. Eguchi, M. Nakayama, and T. Hase, Chem. Lett., 1982, 277.

4) T. Kato, M. Suzuki, T. Kobayashi, and B. P. Moore, J. Org. Chem., 45, 1126 (1980) and references cited therein.

5) S. Anandaraman, K. N. Gurudutt, C. P. Natarajan, and B. Ravindranath, Tetrahedron Lett., 21, 2189 (1980).

6) The structure of these ketones was established from the following physical data.

5: IR(CCl_4) 1685 and 1615 cm^{-1}; PMR(CCl_4) 1.52(3H), 1.58(3H), 2.03(3H, d, J = 1.2 Hz), 4.7-5.0(2H, m), and 5.77(1H, bs) ppm; CMR($CDCl_3$) 202.10(s), 155.55(s), 134.53(s), 133.30(s), 125.85 x 2(d), 124.94(d), 40.41(t), 39.49(t), 39.04(t), 37.34(t), 24.48(t), 24.22(t), 21.87(t), 19.26(q), 15.14(q), 14.95(q) ppm.

7: IR(CCl_4) 1690, 1655 and 1630 cm^{-1}; PMR(CCl_4) 1.55(6H), 1.82(3H, d, J = 1.5 Hz), 4.80(1H, t, J = 6.5 Hz), 4.88(1H, bt, J = 7.2 Hz), and 5.85(1H, bs) ppm; CMR($CDCl_3$) 201.50(s), 152.16(s), 134.47(s), 133.04(s), 128.34(d), 125.92(d), 122.91(d), 40.99(t), 39.36(t), 38.06(t), 32.38(t), 24.94(t), 24.54(t), 23.89 (q), 19.26(t), 15.34 x 2(q) ppm.

8: IR(CCl_4) 1715 cm^{-1}; PMR(CCl_4) 1.50(3H), 1.56(3H), 1.67(3H), 2.72(2H, t, J = 6.1 Hz), 2.91(2H, s), 4.78(1H, bt, J = 6.0 Hz), 4.97(1H, bt, J = 6.3 Hz), and 5.45(1H, bt, J = 8.3 Hz) ppm; CMR($CDCl_3$) 209.86(s), 133.82(s), 133.17(s), 129.

38(s), 127.22(d), 126.31(d), 123.57(d), 47.65(t), 39.04(t), 38.58(t), 38.38(t), 27.55(t), 24.94(t), 23.83(q), 19.06(t), 15.27(q), and 14.95(q) ppm.

7) The structure of the intermediates was confirmed by the following physical evidence.

9: IR($CHCl_3$) 1730, 1680, and 1610 cm^{-1}; PMR(CCl_4) 1.23(3H, t, J = 7.1 Hz), 1.56 (3H, s), 1.63(3H, s), 2.06(3H, d, J = 1.2 Hz), 2.48(1H, dd, J = 15.9 and 7.3 Hz), 4.03(2H, q, J = 7.1 Hz), 4.8-5.1(2H, bs), and 5.89(1H, bs) ppm; CMR($CDCl_3$) 203.14(s), 172.26(s), 157.71(s), 134.53(s), 133.49(s), 125.26 x 2(d), 124.61 (d), 60.38(t), 46.09(d), 39.56(t), 38.97(t), 37.01(t), 36.03(t), 29.57(t), 24. 35(t), 23.96(t), 19.71(q), 15.41(q), 15.27(q), and 14.17(q) ppm.

10: IR($CHCl_3$) 1730, 1710, and 1640 cm^{-1}; PMR($CDCl_3$) 1.24(3H, t, J = 7.2 Hz), 1.5 3(3H, s), 1.60(3H, s), 2.31(1H, dd, J = 16.4 and 5.0 Hz), 2.88(1H, dd, J = 16. 4 and 9.3 Hz), 3.50(1H, dd, J = 9.3 and 5.0 Hz), 4.08(2H, q, J = 7.2 Hz), 4.83 (1H, s), 4.96(1H, s), and 4.7-5.1(m) ppm; CMR($CDCl_3$) 208.75(s), 172.40(s), 14 4.72(s), 134.99(s), 133.23(s), 125.66(d), 123.96(d), 114.10(t), 60.45(t), 53. 46(d), 39.10 x 2(t), 37.86(t), 35.32(t), 35.05(t), 24.81(t), 24.09(t), 19.39 (t), 15.67(q), 15.47(q) and 14.17(q) ppm.

11: IR($CHCl_3$) 1725, 1680, and 1610 cm^{-1}; PMR(CCl_4) 1.26(3H, t, J = 7.1 Hz), 1.5 3(3H, s), 1.60(3H, s), 4.39(2H, q, J = 7.1 Hz), 4.7-5.0(2H, bs), and 5.79(1H, s) ppm; CMR($CDCl_3$) 201.38(s), 173.18(s), 158.30(s), 134.73(s), 133.30(s), 125. 33(d), 125.07(d), 124.68(d), 60.38(t), 40.34(t), 39.04(t), 37.34 x 2(t), 33.0 3(t), 28.20(t), 24.54(t), 24.22(t), 21.80(t), 15.14(q), 14.95(q), and 14.30 (q) ppm.

12: IR($CHCl_3$) 3300-3650, and 1720 cm^{-1}; PMR(CCl_4) 1.25(3H, t, J = 7.1 Hz), 1.57 (9H, bs), 2.46(1H, dd, J = 15.5 and 8.2 Hz), 4.06(2H, q, J = 7.1 Hz), 4.40(1H, dd, J = 8.1 and 1.7 Hz), 4.7-5.1(2H, m), and 5.23(1H, d, J = 8.1 Hz) ppm.

13: IR($CHCl_3$) 1770 and 1670 cm^{-1}; PMR(CCl_4) 1.58(6H), 1.68(3H), 4.7-5.1(2H, m), and 5.33(2H, bs) ppm; CMR($CDCl_3$) 15.05, 15.06, and 16.17(C_{12}-, C_8-, and C_4-Mes), 79.99(d, C_2), and 39.13(d, C_1) ppm.

8) P. A. Grieco and K. Hiroi, Chem. Commun., 1972, 1317.

9) Trans isomer of 2 was synthesized by S. Ito's group. K. Kodama, T. Takahashi, and S. Ito, Tetrahedron Lett., 23, 5175 (1982).

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