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SYNTHESIS OF MACROCYCLIC TERPENOIDS BY INTRAMOLECULAR CYCLIZATION X. TOTAL SYNTHESIS OF METHYL CERIFERATE-I

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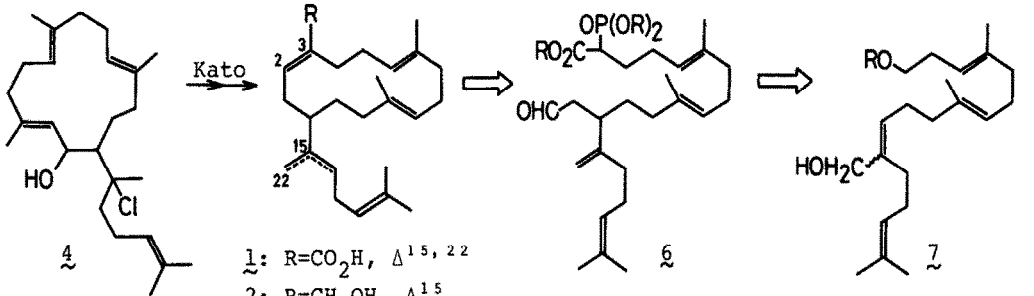
Abstract: The methyl ester of (±)-ceriferic acid-I, a 14-membered ring sesterterpene isolated from the wax of the scale insect Ceroplastes ceriferus, was synthesized by means of an intramolecular Wittig-type reaction.

Ceriferic acid-I (1) is a new fourteen-membered ring sesterterpene produced by the scale insect Ceroplastes ceriferus.[1] To date fifteen related substances have been isolated from the insect wax.[2] The structural studies on this class of sesterterpene have pursued a somewhat complicated course, the structures being established unequivocally by the synthesis of ceriferol (2) and ceriferol-I (3).[3] In the first synthesis of cembrane sesterterpenes, namely 2 and 3, Kato et al.[3] employed a route involving functionalization of the C-3 methyl group of the pre-formed fourteen-membered ring compound 4.

In a continuation of our studies on the synthesis of macrocyclic terpenoids,[4] we examined an intramolecular Wittig reaction approach to the synthesis of this class of sesterterpene. The successful synthesis of (±)-methyl ceriferate-I[5] (5) demonstrates the usefulness of this methodology.



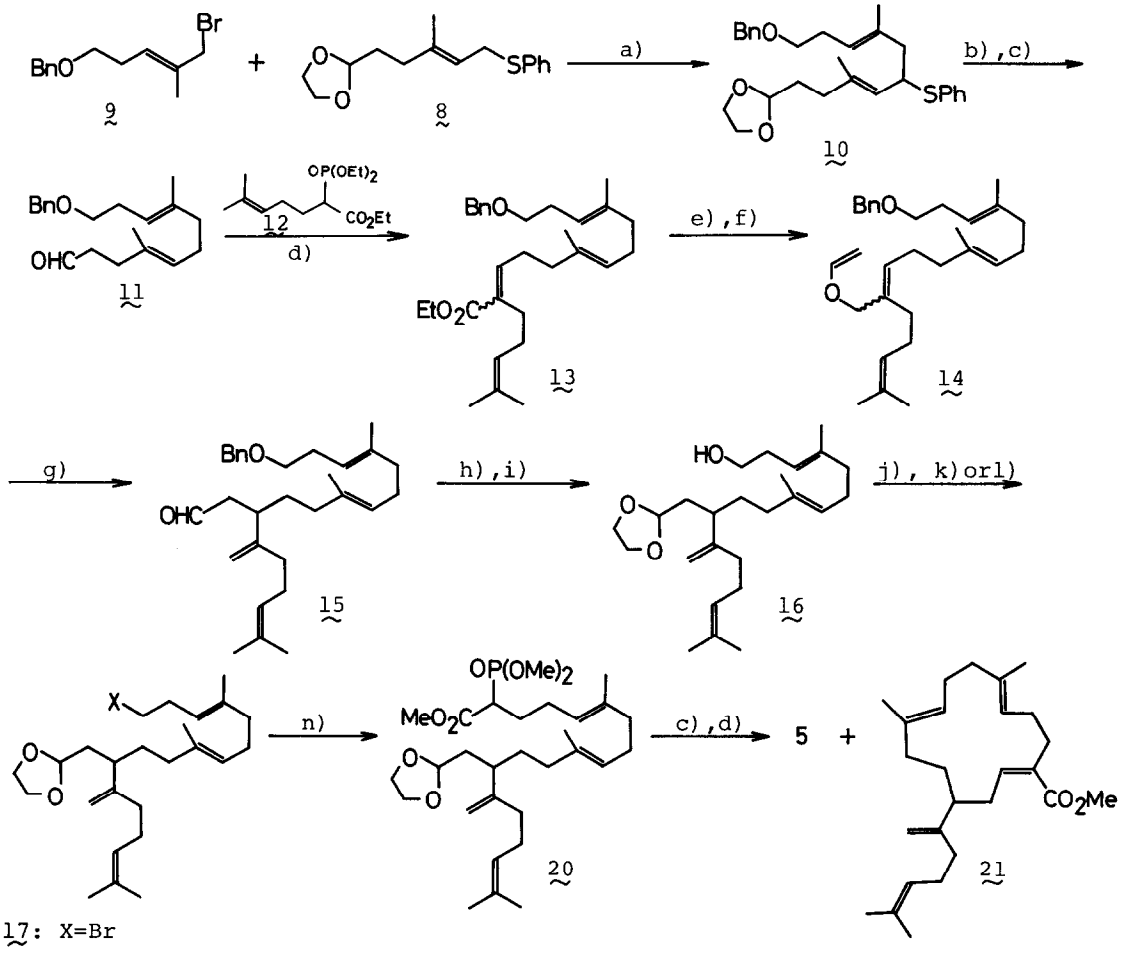
4

1: R=CO_2H, $\Delta^{15,22}$
2: R=CH_2OH, Δ^{15}
3: R=CH_2OH, $\Delta^{15,22}$
5: R=CO_2Me, $\Delta^{15,22}$

6 7

Our retrosynthetic analysis suggested that ring formation between C-2 and C-3 by means of a Wittig-type reaction would be highly effective for the synthesis of 5 since this method allows simultaneous construction of a macro ring and an α,β-unsaturated ester moiety. Thus, the immediate precursor to 5 in our route is the phosphonoacetate 6 which in turn should be accessible by the Claisen

rearrangement of an allylic alcohol of type 7 and subsequent modifications. In order to elaborate the sub-goal 7, the lithio derivative of the allyl sulfide 8[6] was first reacted with the bromide 9[7] at -78°C to yield 10[8] in 72% yield. After reductive removal of the phenyl sulfide group in 10 and subsequent hydrolysis of the acetal group (86%), the aldehyde 11 was subjected to Wadsworth-Emmons olefination using phosphonoacetate 12 (prepared from homoprenyl bromide and triethyl phosphonoacetate in 42% yield). The unsaturated ester 13, obtained in 85% yield as an approximately 1:1 mixture of cis and trans isomers, was reduced and the resulting alcohol was treated with excess ethyl vinyl ether in the presence of mercuric acetate to afford the vinyl ether 14 in 57% yield. The Claisen rearrangement was performed by heating 14 at 190°C without solvent, thereby yielding aldehyde 15[8] in 70% yield. By utiliz-



a) n-BuLi/DABCO,-78°C, b) Na/t-BuOH, c) p-TsOH, d) NaH/DME, e) $LiAlH_4$, f) CH_2=CHOEt/$Hg(OAc)_2$, g) 190°C, neat, h) $(CH_2OH)_2$/p-TsOH, i) Na/NH_3, j) MsCl/NEt_3, k) LiBr/DMF, l) NaI/DMF, m) $MePO(OMe)_2$/n-BuLi,-78°C, n) $ClCO_2Me$/n-BuLi,-78°C

ing this sequence, the $\Delta^{15,22}$-exo double bond in 5 was introduced regioselectively. In order to allow the modification of the homoallyl alcohol segment, the aldehyde group in 15 was first protected and the benzyl ether was reductively removed to afford 16.[8] Some difficulties were encountered in the next step, transformation of 16 into the phosphonoacetate 20. Thus, treatement of the bromide 17 or the iodide 18, prepared via the mesylate of 16, with triethyl phosphonoacetate under various basic conditions gave rise to none of the desired alkylated product 20. Indeed, most of the starting material was recovered unchanged.[9] These halides were unexpectedly stable in spite of their homoallyl nature.

This difficulty was overcome by employing a two step sequence; i) conversion of 18 into the phosphonate 19 by coupling with the lithio-anion of dimethyl methylphosphonate, and then ii) trapping the lithio-anion of 19 with ethyl chloroformate. Utilizing this method, the desired 20[8] was obtained in 49% yield. This two step synthesis would be generally applicable to the preparation of substituted phosphonoacetates. The protective group in 20 was readily hydrolyzed to the immediate precursor 6 (R=Me).[8]

When the phosphonoacetate 6 (R=Me) was treated with sodium hydride in dry DME at 80°C under high dilution conditions, the formation of two products was observed. These were separated by column chromatography. The more polar product obtained in 24% yield was found to be identical with methyl ceriferate -I (5) by the comparison of spectral data (^{1}H NMR and CMR) with those of an authentic specimen. The spectra of the less polar product (52% yield) were very similar to those of 5, except for the upfield shift of the signal due to H-2 in the ^{1}H NMR spectrum and some changes in the chemical shifts of the methylene carbons in the CMR spectrum.[8] These findings revealed that the less polar product was 21, the geometrical isomer of methyl ceriferate-I (5).

Thus, the second synthesis of a naturally occurring cembrane sesterterpene was achieved via an intramolecular Wittig reaction approach. Although the stereoselectivity in the macro ring formation was not high, the present work provides a methodology for the synthesis of functionalized macrocyclic terpenes.

We are grateful to Dr. Yoko Naya, Suntory Institute for Bioorganic Chemistry, for the spectra of an authentic sample of methyl ceriferate-I.

References and Notes

1) P.K. Pawlak, M. S. Tempest, T. Iwashita, K. Nakanishi, and Y. Naya, Chem. Lett., 1069 (1983).

2) F. Miyamoto, H. Naoki, T. Takemoto, and Y. Naya, Tetrahedron, 35, 1913 (1979); T. Kusumi, T. Kinoshita, K. Fujita, and H. Kakisawa, Chem. Lett., 1129 (1979); F. Miyamoto, H. Naoki, Y. Naya, and K. Nakanishi, Tetrahedron, 36, 3481 (1980); Y. Naya, F. Miyamoto, K. Kinoshita, T. Kusumi, H. Kakisawa, and K. Nakanishi, Chem. Lett., 883 (1980).

3) S. Fujiwara, M. Aoki, T. Uyehara, and T. Kato, Tetr. Lett., 25, 3003 (1984).

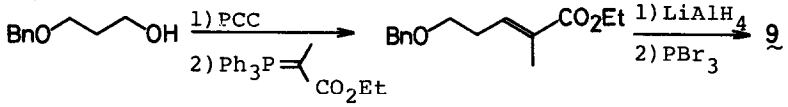
See also Y. Ikeda, M. Aoki, T. Uyehara, T. Kato, and T. Yokoyama, Chem., Lett., 1073 (1983).

4) For part IX in this series, see M. Kodama, K. Okumura, T. Kobayashi, T. Tsunoda, and S. Ito, Tetr. Lett., 25, 5781 (1984).

5) Since ceriferic acid-I was isolated as its methyl ester 5, we chose 5 as the synthetic target.

6) This compound was prepared from geranyl phenyl sulfide according to the procedure described in the literature [M. Kodama, T. Takahashi, T. Kojima, and S. Ito, Tetr. Lett., 23, 3397 (1982)].

7) F. E. Ziegler, S. I. Klein, U. K. Pati, and T. -F. Wang, J. Am. Chem. Soc., 107, 2730 (1985). We synthesized 9 by the following scheme in 41% overall yield;



8) Spectral data of some selected intermediates; 10: m/z 452(M^+) 73(b.p.), ν 1582 730 688 cm^{-1}, δ($CDCl_3$) 1.60(3H,s) 1.61(3H,s) 3.42(2H,t,J=7.3) 3.81(2H, m) 3.83(2H,m) 4.00(1H,ddd,J=10.1,9.3,5.7) 4.50(2H,s) 4.73(1H,t,J=4.9) 5.01 (1H,br.d,J=10.1) 5.18(1H,br.t,J=7.3) 7.22-7.40(10H,m), 15: m/z 436(M^+) 91 (b.p.), ν 1728 1640 888 cm^{-1}, δ 1.58(3H,s) 1.61(6H,s) 1.69(3H,s) 3.45(2H,t, J=7.3) 4.52(2H,s) 4.82(1H,br.s) 4.86(1H,br.s) 5.06-5.18(3H,m) 7.26-7.36(5H, m) 9.65(1H,t,J=2.5), 16: m/z 390(M^+) 73(b.p.), ν 3400 1638 882 cm^{-1}, δ 1.62 6H,s) 1.64(3H,s) 1.69(3H,s) 3.61(2H,t,J=6.6) 3.82(2H,m) 3.95(2H,m) 4.78-4.88(3H,m) 5.05-5.18(3H,m), 19: m/z 496(M^+) 73(b.p.), ν 1640 1235 1050 1025 880 cm^{-1}, δ 1.55(3H,s) 1.58(3H,s) 1.60(3H,s) 1.67(3H,s) 3.72(6H,d,J=11.0) 3.80(2H,m) 3.93(2H,m) 4.78-4.84(3H,m) 5.05-5.16(3H,m), 20: m/z 554(M^+) 73 (b.p.), ν 1740 1640 1256 1030 882 cm^{-1}, δ 1.57(6H,s) 1.62(3H,s) 1.69(3H,s) 3.01(1H,m) 3.76(3H,s) 3.78(3H,d,J=10.7) 3.80(3H,d,J=10.7) 3.82(2H,m) 3.95 (2H,m) 4.76-4.85(3H,m) 5.02-5.18(3H,m), 6(R=Me): m/z 510(M^+) 182(b.p.), ν 1740 1728 1642 1256 1050 1025 885 cm^{-1}, δ 1.58(3H,s) 1.60(3H,s) 1.62(3H,s) 1.69(3H,s) 3.00(1H,m) 3.76(3H,s) 3.78(3H,d,J=11.0) 3.79(3H,d,J=11.0) 4.83 (1H,br.s) 4.87(1H,br.s) 5.02-5.15(3H,m) 9.66(1H,t,J=2.4), 21: m/z 384(M^+) 135(b.p.), ν 1720 1640 880 cm^{-1}, δ 1.53(3H,s) 1.57(3H,s) 1.61(3H,s) 1.69 3H,s) 3.73(3H,s) 4.77(1H,br.s) 4.79(1H,br.s) 4.98(1H,br.t,J=7.2) 5.05(1H, br.t,J=6.3) 5.12(1H,br.t,J=7.2) 5.85(1H,t,J=7.7), CMR δ($CDCl_3$) 15.1(q) 17.7 (qx2) 23.7(t) 25.6(t) 25.7(q) 26.7(t) 29.0(t) 34.0(tx2) 34.2(tx2) 39.4(t) 44.2(d) 51.0(q) 108.7(t) 122.3(d) 124.3(d) 125.1(d) 130.9(s) 131.5(s) 133.7 (s) 134.6(s) 141.3(d) 152.8(s) 168.5(s).

9) In a model experiment, homofarnesyl iodide was treated under the same conditions and similar results were observed. The behavior of these long chain homoallyl halides seems to be quite different from that of simpler analogues such as homoprenyl bromide.

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