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AN EFFICIENT SYNTHESIS OF JOLKINOLIDE E INVOLVING THE BUTENOLIDE RING FORMATION BY INTRAMOLECULAR WITTIG REACTION†

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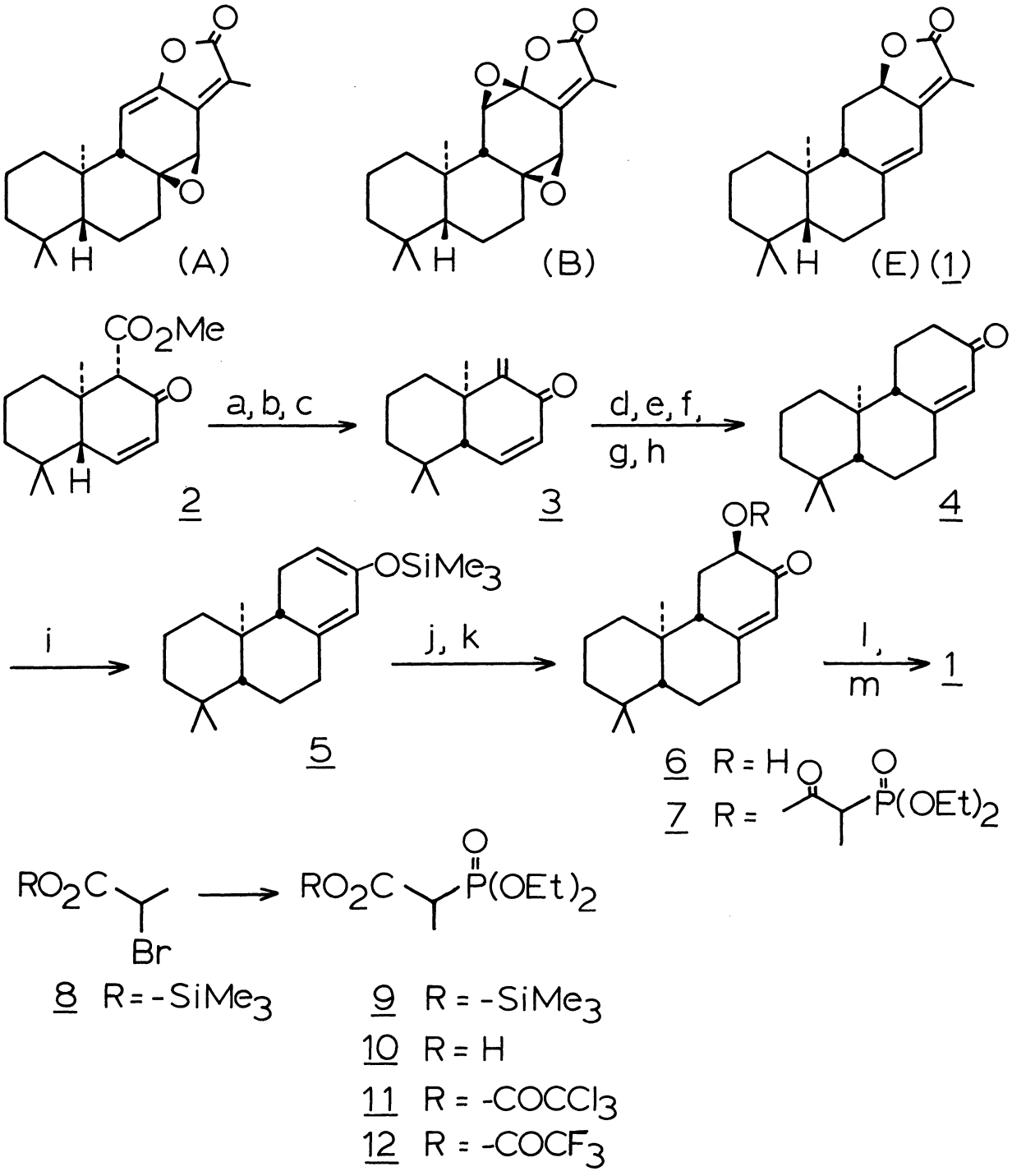
A synthesis of jolkinolide E from the bicyclic enone 3 using intramolecular Wittig reaction is described. In this synthesis a facile esterification method by means of a mixed anhydride of trichloroacetic acid catalyzed by DMAP, which culminates in the effective synthesis of the α,β,γ-trisubstituted butenolide ring, is also described.

Jolkinolide E (1) was isolated from Euphorbia Jolkini Boiss together with jolkinolide A, B, C, D and its structure was determined except the stereochemistry at C-12[1]. In this communication, we would like to report an efficient synthesis of jolkinolide E. In the course of the synthetic study of jolkinolides we developed the synthetic method of an α,β,γ-trisubstituted butenolide using intramolecular Wittig reaction, and we found that the mixed anhydride of trichloroacetic acid with an appropriate carboxylic acid was very effective for esterification catalyzed by 4-dimethylaminopyridine (DMAP).

Our basic strategy for 1 is the effective use of the versatile intermediate, carbomethoxy enone 2 whose simple and unique synthetic method has been established from β-ionone by our group[2]. 2 was reduced, oxidized selectively, and dehydrated with acid yielding exomethylene enone 3[3] in 88 % overall yield. Michael addition of methyl acetoacetate to 3 followed by hydrolysis with 1 % aq NaOH (1.3 equiv. in MeOH), decarboxylation, hydrogenation, and cyclization with 1 % aq NaOH in methanol at 100°C afforded tricyclic enone 4 in 70.5 % overall. α-Hydroxyenone 6 was prepared as follows[4]. Thus 4 was derived to silyl enol ether 5 (LDA, Me_3SiCl) which was followed by epoxidation with 1 equiv. MCPBA in hexane at -15°C and a

treatment with n-tetrabutylammonium fluoride in CH_2Cl_2 yielding 6 (mp 133-134°C)[5] in 71 % yield. The stereoisomer of 6 could not be recognized in the nmr spectrum. From the study of a molecular model the α-face of the C-ring in 5 is crowded owing to the α-methyl group at C-10. MCPBA must attack from the β side exclusively to give β-hydroxy group. This assignment was also supported by nmr[5] of both 6 and 7 which was obtained in the following step. Next we attempted the synthesis of butenolide block straightforward by intramolecular Wittig reaction. α-Bromopropionic acid trimethylsilylester (8) was heated with triethylphosphite at 160°C for 6 h to give 9 (bp 92-94°C/107Pa) which was treated with dil HCl yielding α-(diethylphosphono)propionic acid (10)[7),8)] in 60 % yield from 8. Esterification of 6 with 10 was achieved by mixed anhydride method. 10 was treated with trichloroacetyl chloride in the presence of triethylamine in THF for 30 min at room temperature and the mixed anhydride 11 generated was reacted with 6 in the presence of DMAP[9)]. The reaction proceeded very smoothly (benzene, room temp, 10 min) and the desired ester 7[5)] was obtained in 92 % yield. On the other hand trifluoroacetyl derivative 12[6c)] in the absence of DMAP gave 7 in only 54 % yield and 20 % of the starting material was recovered[10)]. The above results indicated that in mixed anhydride of phosphonopropionic acid with trifluoroacetic acid 12 the low selectivity of the attack by the hydroxy group of 6 was attributed to the steric hindrance of the methyl group in propionic acid because the high selectivity was reported in that of phosphonoacetic acid, and also indicated that the larger steric hindrance of trichloromethyl group enhanced the selective attack of DMP to the propionyl carbonyl. Surprisingly we could not find any precedent of the rapid and mild esterification method using trichloroacetyl group as a counterpart of mixed anhydride in combination with DMAP in the literature[11)]. Finally the synthesis of jolkinolide E (1) was achieved by a treatment of 7 with 1.1 equiv. of NaH in DME (room temp, 30 min) in 70 % yield. The synthesized 1 (mp 154-155°C) was identical with the natural compound (ir, nmr, uv, mass, and TLC behavior)[12)]. Thus the stereochemistry at 12 position of jolkinolide E is depicted as formula 1. Further study toward the synthesis of jolkinolide A and B is in progress.



a: LAH, b: MnO_2, c: H^+, d: $CH_3COCH_2CO_2CH_3$/NaOMe,
e: 1 % NaOH, MeOH-H_2O, f: H^+, g: H_2/Pd-C, DME, h: 1 % NaOH, MeOH-H_2O,
i: LDA, Me_3SiCl, DME, j: MCPBA, hexane, k: Bu_4NF, CH_2Cl_2,
l: 11/DMAP, benzene, m: 1.lequiv. NaH, DME

References

†) Dedicated to Emeritus Professor Takeo Sakan on the occation of his 70th birthday.

1) D. Uemura and Y. Hirata, Tetrahedron Lett., 1974, 819; 1972, 1387; 1977, 283.

2) Compound 2 was synthesized by two methods from β-ionone. The key step of one of them is the direct photocyclization of 10-carbomethoxy-β-ionone enolate and the other is the thermal electrocyclic reaction of 7,8-cis-10-carbomethoxy-β-ionone enolacetate followed by methanolysis. The details will be reported elsewhere.

3) Satisfactory spectral data (ir, ^{1}H-nmr, and uv) and elemental analysis for 3 were obtained. ^{1}H-NMR; (CCl_4) δ 1.00 (3H, s), 1.03 (3H, s), 1.12 (3H, s), 2.18 (pair of d, J=3,2Hz), 4.99 (1H, d, J=2Hz), 5.72 (1H, d, J=2Hz), 6.06 (1H, dd, J=10,3Hz), 6.85 (1H, dd, J=10,2Hz).

4) G. M. Rubottom and J. M. Gruber, J. Org. Chem., 43, 1599 (1978).

5) 6 gave satisfactory elemental analysis. ^{1}H-NMR: 6 ($CDCl_3$): δ 0.87 (3H,s), 0.92 (3H, s), 1.02 (3H, s), 3.42 (1H, br, OH), 4.2 (1H, dd, J=12,7Hz), 5.83 (1H, s).
7 (CCl_4): δ 0.87 (3H, s), 0.93 (6H, s), 1.27 (3H, t, J=7Hz), 1.32 (6H, t, J=7Hz), 4.1 (4H, quint, J=7Hz), 5.17 (1H, br. t, J=7Hz, half-band width; 10Hz), 5.80 (1H, s).

6) a) W. S. Wadsworth, Jr., Org. Reac., 25, 73 (1977). b)K. B. Becker, Tetrahedron, 36, 1717 (1980). c) S. F. Donovan, M. A. Avery, and J. E. McMurry, Tetrahedron Lett., 1979, 3287 and references cited terein.

7) G. Stork and R. Matthews, J. Chem. Soc. Chem. Commun., 1970, 445.

8) L. Lombardo and R. J. K. Taylor, Synthesis, 1978, 131; P. Coutrot, M. Snoussi, and P. Savignac, ibid., 1978, 133.

9) 2,4,6-Trichlorobenzoyl has been reported as a counterpart of the mixed anhydride in combination with DMAP. J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, and M. Yamaguchi, Bull. Chem. Soc. Jpn., 52, 1989 (1979) and references cited therein.

10) The TLC analysis of this reaction product showed that the both carbonyl groups of trifluoroacetyl and phosphonopropionyl were attacked by the hydroxy of 6.

11) E. Haslam, Tetrahedron, 36, 2409 (1980) and reference 9).

12) We are indebted to Dr. D. Uemura for his kind gifts of natural jolkinolide E and the copies of its spectral charts.

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