Tetrahedron Letters No. 22, pp 1909 - 1912, 1978. 0040-4039/78/0522-1909$02.00/0

A FACILE ENTRY TO PSEUDOGUAIANES. TOTAL SYNTHESIS OF DAMSINIC ACID

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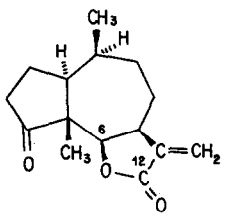
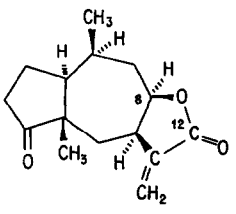
(Received in USA 17 February 1978; received in UK for publication 3 April 1978)

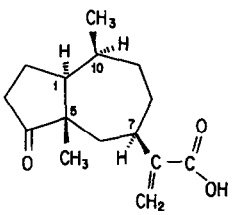
Among the various classes of sesquiterpene α-methylene-γ-butyrolactones, the pseudoguaianolides[1] are unparalleled as structural and stereochemical challenges[2] to the discriminating synthetic organic chemist. While several successful total syntheses of "6,12-olides" such as damsin(I), have recently been completed[3], the only synthesis of an 8,12-olide yet reported is Marshall's elegant, ring-expansion route[4] to confertin(II).



I



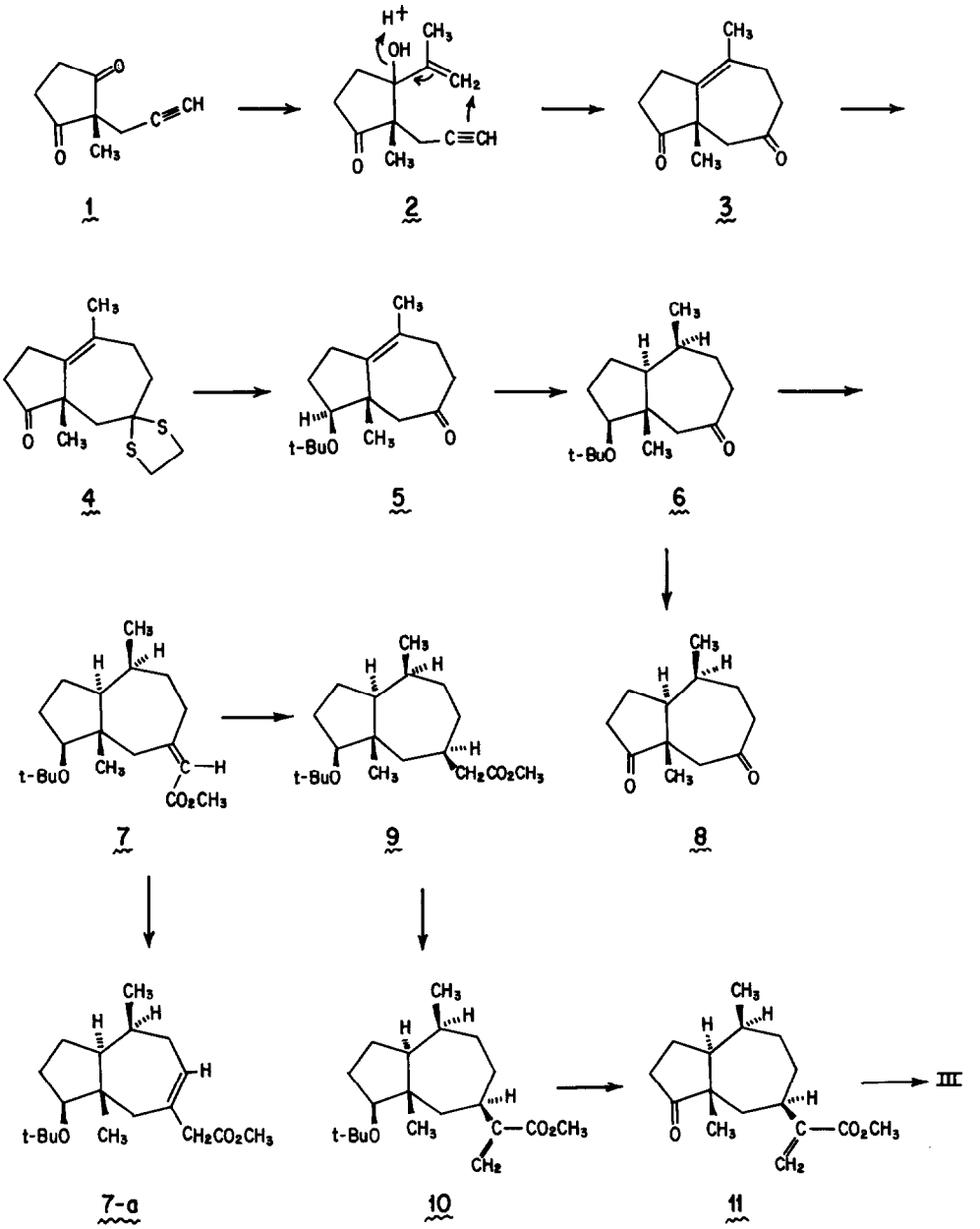
II



III

We herein report an extremely facile pseudoguaiane construction of potential value for total synthesis of 8,12-olides. The present sequence culminates with damsinic acid(III), a congener (and possible biosynthetic precursor) of damsin, which possesses the same relative configuration of I, II and other pseudoguaianolides at carbons 1,5,7 and 10, as well as most of their functionality.

Key elements of our synthesis are: 1) intramolecular carbonium ion attack on a terminal alkyne group[6] to generate hydroazulenedione 3 in only three steps; 2) protection of the less-hindered 7-carbonyl group while introducing the desired chirality at carbons 1, 5 and 10, (3 → 6), and 3) introduction of carbons 11-13 by initial nucleophilic attack at C_7 = O (6 → 7), instead of more typical electrophilic alkylation of endocyclic enolates[3,4]. Propargylation of 2-methyl-1,3-cyclopentanedione in aqueous sodium bicarbonate affords 1[7], mp 71.5-72°, in 85% yield. Treatment of 1 with two equivalents of 2-lithiopropene (prepared by lithium-halogen exchange of 2-bromopropene with t-butyllithium[8] gives carbinol 2 (separable epimers); heating (80°/1 hr) in 90% formic acid affords oily diketone 3[7] (ν_{film} 1740, 1700 cm^{-1}) in ∿50% yield. Diketone 3 reacted preferentially at the cycloheptanoid carbonyl group with a


1
2
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7-a
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11
III

variety of nucleophiles, e.g. enamine formation with pyrrolidine, p-tosylhydrazine,. and, even excess methyl α-lithiotrimethylsilylacetate[9] (cf. 6 → 7). Thioketalization of 3 proceeded in 75% yield to crystalline 4[7], (ν_{film} 1728 cm^{-1}), mp. 110.5-111°, thus providing a convenient isolation procedure[10] for 3 as well as a means to effect the required α-side hydrogenation of C_1-C_{10}. After 4 was reduced with methanolic sodium borohydride, the crystalline thioketal-alcohol[7], mp 127-127.5°, was hydrolyzed (Hg^{+2} in aqueous acetonitrile) and the resulting ketol[7] (97% yield) converted to the t-butyl ether[7] 5, mp 51.5-52°, in 80% yield. Hydrogenation of 5 (Pt, ethyl acetate) gave pure 6, mp 64-64.5° (methanol) after recrystallization to remove ca. 10-15% of epimeric product from β-hydrogenation[11]. The homogeneity of 6 was further established by ether cleavage and oxidation (TFA, then Jones reagent) to pure diketone 8[7] (not achievable when 3 was reduced directly). Side chain construction now began by addition of the lithium salt derived (LDA) from methyl trimethylsilylacetate[12] to 6, giving E and Z isomers[7] of 7 in 97% yield. Hydrogenation of 7 afforded 9 (93%), which contained ca. 15-20% of unremovable C_7-side chain epimer (observable only in 100 mHz nmr spectrum: methyl ester, δ 3.616, shoulder on major band at δ 3.605). The $C_{11,13}$-α-methylene group was introduced (→ 10) by the familiar[13] ester enolate-formaldehyde route, followed by deblocking and oxidation at C_4, giving (±)-methyl damsinate (11), which checked[14] (by glc, ir and nmr) with (+)-ester prepared by diazomethane treatment of naturally-derived (+)-damsinic acid. Likewise saponification[15] of 11 gave III, whose solution ir and nmr spectra[14] were undistinguishable from spectra of authentic (+)-damsinic acid.

This basic route, when optimized and modified[16] to improve hydrogenation at C_7-C_{11} inter alia, is expected to provide access to a number of biologically-active pseudoguaian-8,12-olides. We have already demonstrated that kinetic enolization of 7 occurs at position 8, as required for further elaboration (e.g. → 7a) toward such goals[15].

ACKNOWLEDGMENT

We are grateful to the Donors of the Petroleum Research Fund, administered by the American Chemical Society for support of this research. Special thanks go to Professor Raymond W. Doskotch, College of Pharmacy, The Ohio State University, for a sample of damsinic acid and spectra of 11 and III.

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7. Satisfactory elemental analyses and confirmatory infrared, nmr and mass spectra were obtained for this compound.
8. E. J. Corey and D. J. Beames, J. Amer. Chem. Soc., 94, 7210 (1972).
9. However, this regiospecific carbanion addition in 3 required postponement to 6 so that the C_1-C_{10} tetrasubstituted double bond could be slowly but stereospecifically reduced first before the otherwide more reactive acrylic ester side chain (cf. as in 7 → 9) reduces with less overall stereospecificity at both sites.
10. 4 was readily obtained in 25% overall yield from 1, without extensive purification of intermediates, a sequence which can probably be optimized in future work.
11. Some reduction of the carbonyl also occurred on occasion, thus necessitating careful "back oxidation" with pyridinium chlorochromate.
12. a. H. Yamamoto et al, J. Am. Chem. Soc., 96, 1620 (1974).
b. S. L. Hartzell, D. F. Sullivan and M. W. Rathke, Tet. Letters, 1403 (1974).
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14. Our 11 contained ca. 15-20% C_7-epimer (cf. 7 → 9), which was fortunately not present in high enough concentration to obscure the clear-cut correspondence of the solution ir and nmr spectra of synthetic and natural methyl damsinate (or the acids).
15. These experiments were performed by J. E. Hengeveld; kinetic hydrolysis of the dienolate from 7, revealed the vinyl proton in 7a as a triplet (δ 5.69, $J \simeq 6$ Hz).
16. Both 2-methyl-2-(β-chloroallyl)-1,3-cyclopentanedione and 2-methyl-2-allenyl-1,3-cyclopentanedione were also synthesized, via Claisen rearrangements of enol ethers, and cyclized to 3 in formic acid; initial yields are no better than those encountered with 1.