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An Efficient Total Synthesis of (±)-Methyl Jasmonate

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Summary: A short synthesis of Methyl dl-Jasmonate from bicyclo[4.3.0] nona-3,8-diene is described.

Methyl Jasmonate 1 is a major constituent of the essential oil of Jasmine.[1] Its fragrance properties are regarded in the perfume industry as finer than that of other members of the jasminoid family;[2] thus it has long been a target of synthetic efforts.[3]

We report here a synthesis of Methyl dl-Jasmonate that is clean, reasonably short (ten steps), and relatively inexpensive.

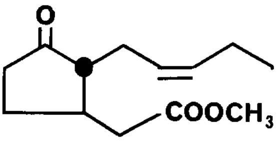
Treatment of the readily available bicyclo[4.3.0] nona-3,8-diene 2 with one-half equivalent of NBS in DMSO with water added gives a 56% yield (based on NBS) of bromohydrin mixture 3 in which addition has occured exclusively on the cyclohexene moiety. (Unusual selectivity has been observed in other bicyclo[4.3.0] nonadiene systems in these laboratories.)[4]

Distillation affords recovered diene (b.p. 30^0/.1 mm Hg.) which can be recycled and bromohydrins (b.p. 90^0/.1 mm Hg.) which on treatment with potassium t-butoxide in THF give a single epoxide 4 (b.p. 45^0/.1 mm Hg.) in 88% yield.

Our original scheme utilized dialdehyde 5 which is obtained in 80% yield upon treatment of epoxide 4 with periodic acid.[5] Reaction of 5 with either phenylseleneny1 bromide or phenylseleneny1 trifluoroacetate in CCl_4 with methanol and finely powdered sodium carbonate added[6] gives a mixture of products from which the desired acetal 6 is isolated via chromatography in 10% yield. Further conversions of this intermediate afforded compounds 7, 8 and 9. However, the low yield of the key cyclization prompted us to investigate other routes.

Treatment of epoxide 4 with 1.1 M CrO_3 in H_2SO_4-H_2O (Kiliani reagent[7]) with THF as co-solvent produced crystalline diacid 10 (m.p. 168-170^0) in 50% yield. Using standard Iodolactonization conditions (I_2, KI, $NaHCO_3$, H_2O) the crystalline Iodolactone 11 (m.p. 106-108^0) was obtained in 81% yield. 11 was also obtained in 60% yield by treatment of 10 with I_2 in ether, and in 34% yield using I_2 and acetonitrile.[8] Reduction of the Iodolactone with tri-n-butyl tin hydride in ether gave lactone 12 (m.p. 85-87^0) in 92% yield, which was in turn reduced to hemiacetal 13 (m.p. 83-85^0) in 84% yield using diisobutyl aluminum hydride in THF at -20^0.

The hemiacetal 13 was converted to hydroxyacid 14 via Wittig reaction (n-propyltriphenylphosphonium bromide, dimsyl sodium, DMSO, 80^0, 24 hrs.). Attempts to purify 14 via chromatography led to mixtures of 14 and lactone 15. Thus, after isolation, the crude hydroxyacid was treated with diazomethane to give the known ester 16[3i] in 80% yield from 14. Oxidation



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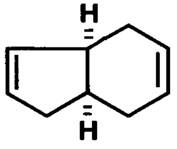

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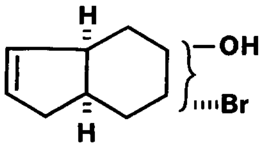

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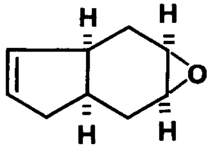

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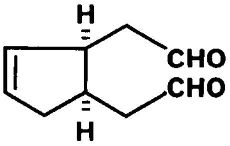

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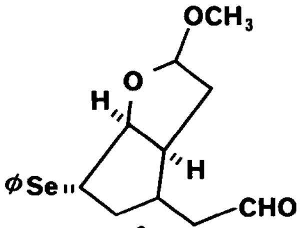

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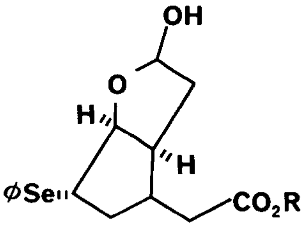

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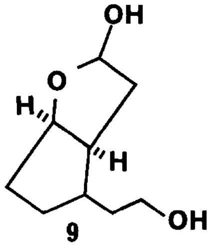
8 R = CH_3



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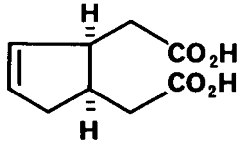

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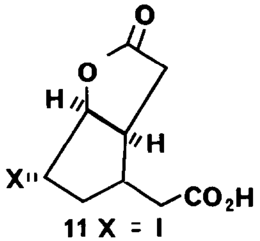
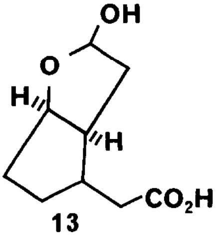


11 X = I

12 X = H



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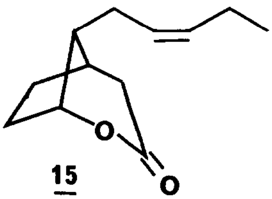

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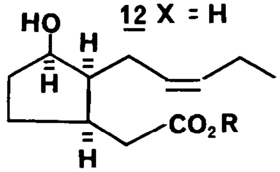
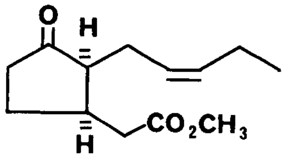


14 R = H

16 R = H



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of this compound using the same Kiliani reagent and CH_2Cl_2 as co-solvent afforded a mixture of Methyl dl-Jasmonate 1 and epi-Methyl Jasmonate 17, in 80% yield.

Utilizing previously established procedures,[3i] this mixture was heated in triethylamine in a sealed tube at 135° for 24 hrs. to effect complete conversion to the more thermodynamically stable Methyl dl-Jasmonate 1, whose spectral data are in agreement with those reported in the literature.[3,10] Overall yield of 1 from epoxide 4 is 20%.

Advantages of this synthesis include the ready availability and low cost of starting material, and ease of purification of intermediates. (Only a single chromatography is required throughout; all intermediates are distillable liquids or crystalline.)

Acknowledgements

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9. E. J. Corey, R. Greenwald and M. Chaykovsky, *J. Org. Chem.*, **28**, 1128 (1963). This successful result is in contrast to an earlier report (3i).

10. Selected spectral data: (NMR: $CDCl_3$, TMS internal standard; IR: neat film unless otherwise noted.)

4: δ 5.6(m, 2H, olefinic), 3.7-1.2(m,10H); ν 3060-2870, 1435, 970.

5: δ 9.93(t, 2H, ald.), 6.1-5.7(m, 2H, olefinic, 3.6-1.3(m, 8H). ν 3020-2800, 2720, 1720.

6: δ 9.73(t, 1H, ald.), 7.65-7.15(m, 5H, Ar.), 4.96(d, J = 4 Hz., OCHO), 4.55(d, J = 6 Hz. 1H, CHO), 3.7(m, 1H, CHSe), 3.2(s, 3H, CH_3O), 2.65-2.3(m, 6H). ν 3040-3080, 3000-2800, 2720, 1725.

10: δ 10.5(br., 2H, $-CO_2H$), 5.85-5.6(m, 2H, olefinic), 2.95-1.4(m, 8H).

11: δ 10.33(br., 1H, $-CO_2H$), 5.35(d, J = 6 Hz., 1H, CHO), 4.5(d, J = 6 Hz., 1H, CHI), 3.6-1.2(m, 8H). ν 3600-2400, 1775, 1700 (KBr pellet.)

12: δ 9.4(br., 1H, $-CO_2H$), 5.07(t, 1H, CHO), 3.2-1.2(m, 10H). ν 1770, 1700 (KBr).

15: δ 5.6-5.3(m, 2H, olefinic), 4.2(m, 1H, CHO), 3.66(s, 3H, CH_3O), 2.6-1.3(m, 13H), 0.97 (t, J = 7 Hz., 3H, CH_3). ν 3600-3240, 3020-2800, 1730.

1: δ 5.5-5.3(m, 2H, olefinic, 3.65(s, 3H, CH_3O), 3.0-1.2(m, 12H), 0.97(t, J = 7 Hz., 3H, CH_3). ν 3080-3020, 1735, 1650.

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