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THE TOTAL SYNTHESIS OF (±)-COLORATA-4(13), 8-DIENOLIDE

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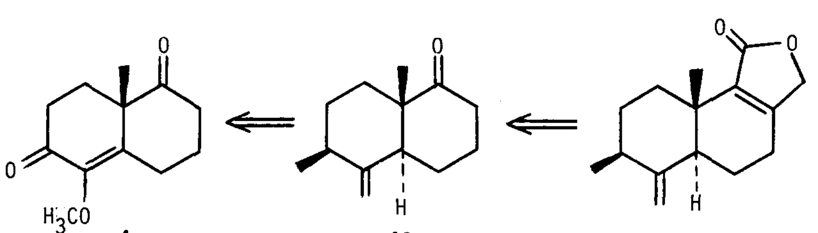
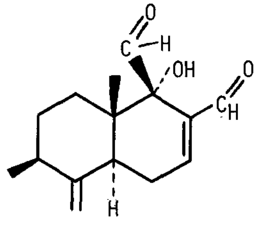
Summary: The total synthesis of (±)-colorata-4(13),8-dienolide (1), a sesquiterpene with a rearranged drimane skeleton, is described using 6β, 8aβ-dimethyl-5-methylene-3,4,4aα, 5,6,7,8,8a-octahydro-1(2H)-naphtalenone (10) as a key intermediate. A new annelation method for butenolides via hydrolysis of a thiophenyl furan is reported.

Only a few examples of sesquiterpenes possessing a rearranged drimane skeleton like colorata-4(13), 8-dienolide (1) and muzigadial (2) are isolated from natural products[1,2]. Fast growing interest in compounds with insect antifeedant activities like warburganal and other drimanes led to several new syntheses for drimane sesquiterpenes[3]. We now want to report on the first total synthesis of one of the rearranged drimanes e.g. 1 using the methylene ketone 10 as a key intermediate.



4 **10** **1** ;



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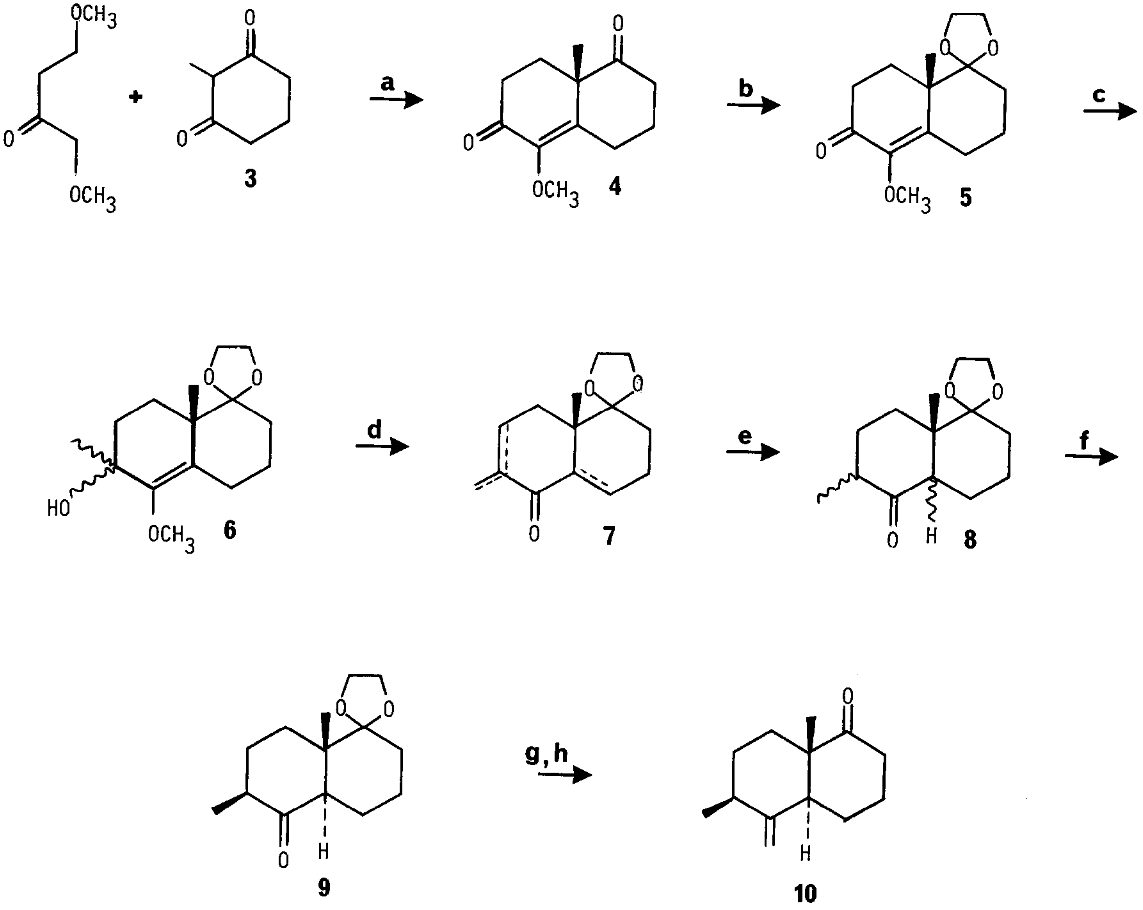
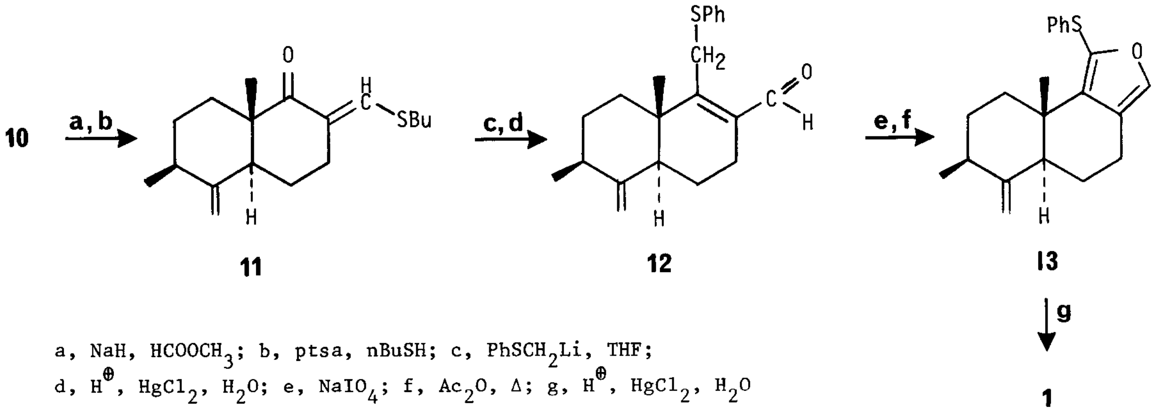
An efficient synthesis for methylene ketone 10 was developed starting from methoxy enone 4 which was obtained in 55% yield using tri-n-propylamine as a base[4,5].



a, tri-n-propylamine; b, ptsa, MED; c, CH_3Li; d, ptsa, C_6H_6; e, H_2, Pd/C; f, $NaOCH_3/HOCH_3$; g, $H_2CP(Ph)_3$; h, $H^{\oplus}$, H_2O.

Treatment of 4 with methylethyldioxolan (MED) and p-toluenesulfonic acid at room temperature for seven days gave the best yield (97%) of the selectively protected ketal 5. Addition of methyllithium to 4 gave a nearly quantitative yield of the two diastereomeric alcohols 6. Acid catalyzed dehydration of 6 using waterfree p-toluenesulfonic acid in dry benzene afforded the one molecule of water necessary for the hydrolysis of the methoxy enol ether which resulted in a mixture of unsaturated ketones 7 with the double bonds in the indicated positions[6]. Hydrogenation of this crude mixture at atmospheric pressure gave a diastereomeric mixture of the saturated ketones 8 which could be equilibrated to pure 9 using sodium methanolate in methanol. Although it might not seem very satisfactory to continue the sequence from 5 to 9 without purification and thorough identification of all intermediates, it did give a good and reproducible yield of 73% of one single compound [7]. Reaction of 9 with an excess of methylene triphenyl phosphorane in DMSO at 50°C gave an 80% yield of methylene ketal which after hydrolysis gave the desired methylene ketone 10[8].

Starting from 10 a new procedure was developed for the construction of the butenolide. Formylation of 10 followed by protection of the aldehyde function as its n-butylthiomethylene derivative gave 11 in 84% yield.



a, NaH, $HCOOCH_3$; b, ptsa, nBuSH; c, $PhSCH_2Li$, THF;
d, $H^{\oplus}$, $HgCl_2$, H_2O; e, $NaIO_4$; f, Ac_2O, Δ; g, $H^{\oplus}$, $HgCl_2$, H_2O

Reaction of 11 with thiophenylmethyllithium followed by hydrolysis of the adduct gave 12 in 90% yield[9,10]. The hydrolysis of the adduct must be carried out at room temperature to prevent isomerisation of the exocyclic double bond. Under these circumstances it took about four weeks to achieve complete conversion of the adduct into 12. After one week the conversion was 65%. Oxidation of 12 with $NaIO_4$ in aqueous methanol gave the corresponding sulfoxide which was transformed into the thiophenyl furan 13 in 70% yield by heating it in acetic anhydride at 100°C for 1 hr. The hydrolysis of 13[11] to colorata-4(13),8-dienolide (1) again was performed at room temperature to avoid doublebond isomerisation. After one week a 60% yield of 1 was obtained[12].

References and Notes

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7. All new compounds gave satisfactory NMR, IR and mass spectra. Correct elemental analyses or exact mass measurements were obtained for compounds 10, 11, 12, DNPH of 12, 13 and 1.
8. 10, mp 47-48°C. ^{1}H NMR ($CDCl_3$): δ 0.97 (s, 3H); 1.05 (d, J = 6 Hz, 3H); 1.5-2.7 (m, 12H); 4.70 (s, J = 0.9 Hz, 1H); 4.82 (s, J = 0.9 Hz, 1H).
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10. 12, ^{1}H NMR ($CDCl_3$): δ 0.93 (s, 3H); δ 1.07 (d, J = 6 Hz, 3H); 1.5-2.6 (m, 10H); 3.95 (qAB, δ_A 3.75, δ_B 4.15, J_{AB} = 11 Hz, 2H); 4.63 (s, J = 0.9 Hz, 1H); 4.81 (s, J = 0.9 Hz, 1H); 7.31 (s, 5H); 10.21 (s, 1H).
11. 13, ^{1}H NMR ($CDCl_3$): δ 0.95 (s, 3H); 1.06 (d, J = 6 Hz, 3H); 1.2-2.9 (m, 10H); 4.52 (s, J = 0.9 Hz, 1H); 4.80 (s, J = 0.9 Hz, 1H); 6.8-7.1 (m, 5H); 7.22 (s, 1H).
12. The NMR and IR spectra of 1 were in complete agreement with those kindly provided by professor R.E.Corbett[1]. The mp of racemic 1 is 101-103°C.

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