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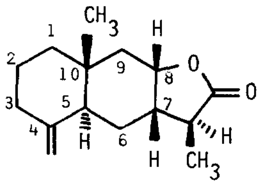
THE TOTAL SYNTHESIS OF *dl*-DIHYDROCALLITRISIN

Jollie D. Godfrey and Arthur G. Schultz*[1]

Department of Chemistry, Cornell University
Ithaca, New York 14853

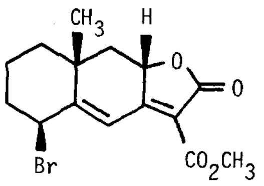
Bromodiene 2 is converted to *dl*-dihydrocallitrisin (1), a sesquiterpene lactone recently isolated from the heartwood of *Callitris columellaris*.

We wish to describe the total synthesis of *dl*-dihydrocallitrisin (1), a new sesquiterpene lactone isolated by Carman and Brecknell from the heartwood of *Callitris columellaris*.[2] The structure of dihydrocallitrisin is extremely interesting because of the novel stereochemical relationship between C(7), C(8) and C(10). Prior to the report of the isolation of 1, we were not aware of any natural eudesmane-like sesquiterpene which incorporated this relative stereochemistry. Structural confirmation by total synthesis of 1 is now provided.



1, $\delta_{C(10)CH_3}$ 0.74

Reductive debromination of 2[3] with Zn dust (10 equiv) in THF containing acetic acid (10 equiv)[4] affords the unconjugated diene lactone 3 (97% yield, mp 107-110°C).[5,6] Hydroboration of 3 with borane-methyl sulfide (BMS)[7] in ethyl acetate (20°C, 2 hr) followed by oxidation (sodium acetate, ethanol, 30% H_2O_2) gives *trans*-decalol 4a (32% isolated yield, mp 151-152°C), together with *cis*-decalol 5a (∿5%) and an isomeric tertiary alcohol (∿5%). Jones oxidation[8] of 4a gives the *trans*-fused keto lactone 4b in 93% yield (mp 188-189°C), IR 5.61, 5.75, 5.85μ).



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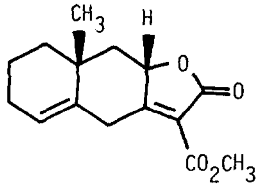

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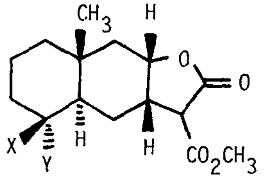
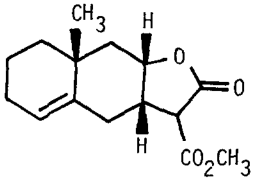


4a, X=H, Y=OH; δ_{CH_3} 0.85

b, X=Y=O; δ_{CH_3} 0.82



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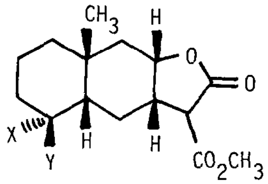
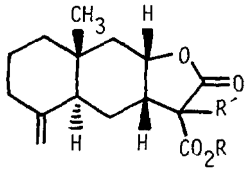


5a, X=H, Y=OH; δ_{CH_3} 1.05

b, X=Y=O; δ_{CH_3} 1.08



7a, R=CH_3; R′=H; δ_{CH_3} 0.74

b, R=R′=CH_3

While we were gratified to find that the major product of hydroboration of 3 was 4a, in which both carbon-carbon double bonds had undergone reduction, we nevertheless were disappointed in the low yield and necessity for a difficult separation of reaction products.[9] Thus, we developed a more efficient reaction sequence to 4b. Conjugate reduction[3] of 3 with sodium cyanoborohydride gives olefinic lactone 6 in 95% yield (mp 98-99°C, IR 5.62, 5.75μ).

Hydroboration-oxidation of 6 with BMS gives *cis*-fused alcohol 5a (61% isolated yield) and only a trace of the *trans*-fused alcohol 4a. Jones oxidation of 5a gives *cis*-fused keto lactone 5b (94%, mp 135-136°C, IR 5.63, 5.77, 5.88μ). Epimerization of 5b (or 4b) with sodium methoxide in refluxing methanol solution produces an equilibrium mixture of 4b and 5b (5:1, respectively) in quantitative yield.[10]

The stereochemistry of the decalin ring junction in these intermediates can be assigned with a high degree of confidence by consideration of the ^{1}H nmr chemical shift for the C(10) methyl resonance. Generally, the position of the angular methyl resonance in a *trans*-10-methyldecalin is at higher field (δ 0.73-0.9) than that of a *cis*-10-methyldecalin (1.05-1.20);[11] see formulae for relevant chemical shift data.

Treatment of keto lactone 4b with methylene triphenylphosphorane (3.5 equiv) in THF:HMPA (2:1) solution at room temperature (17 hr) gives the tricyclic lactone 7a (86%, mp 113-114°C).[12] Alkylation of 7a (sodium hydride-methyl iodide in THF) results in a mixture of diastereoisomers 7b which is directly converted to *dl*-dihydrocallitrisin (1) in 85% overall yield by treatment with sodium cyanide in HMPA (80°, 1 hr).[13] The ^{1}H nmr ($CDCl_3$ and C_6D_6 solvents) and IR spectra together with the low resolution mass spectral fragmentation pattern (electron impact) for synthetic 1 (mp 125-126°C)[6] were identical to those of the natural material kindly supplied to us by Dr. R. M. Carman.[14] We note that the chemical shift for the C(10) methyl group in 1 is completely consistent with the presence of a *trans*-decalin ring fusion. Stereochemistry at C(7) and C(8) relative to C(10) is firmly established by crystallographic analysis of a related synthetic substance, *dl*-7,8-epialantolactone.[3] The overall isolated yield of *dl*-dihydrocallitrisin (1) from 2 is 36%.

Acknowledgement

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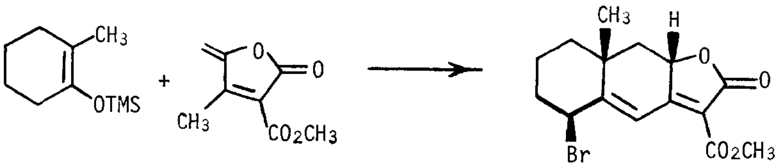
References

1. Address correspondence to this author at the Department of Chemistry, Rensselaer Polytechnic Institute, Troy, New York 12181.
2. D. J. Brecknell and R. M. Carman, Tetrahedron Letters, 73 (1978). In this note by Brecknell and Carman, stereochemistry at C(5,10) in the related elemane sesquiterpene lactone callitrin was established by chemical degradation and correlation with (-) elemol. Chemical evidence for C(5,10) relative stereochemistry in dihydrocallitrisin (1) was not obtained; however, mass spectral fragmentation and Eu(fod)$_3$ shift ^{1}H nmr studies with a series of sesquiterpenes provide evidence favoring identical stereochemistry at C(5,10); R. M. Carman, private communication. We thank Dr. Carman for providing us with this information prior to publication of a full account of the structural work.
3. Bromodiene 2 is prepared in 52% overall yield by the TiCl$_4$ promoted annelation of silyl enol ether A with butenolide B, followed by bromination with NBS. This annelation approach should be useful for rapid construction of a variety of eudesmane and elemane sesquiterpenes. We have already reported the preparation of 7,8-epialantolactone from 2; A. G. Schultz and J. D. Godfrey, J. Am. Chem. Soc., 101, 1276 (1979).



A B 2

4. Steroidal 6-bromo-1,4-diene-3-ones undergo reductive debromination to give 1,5-diene-3-ones; A. L. Nussbaum, G. B. Topliss, T. L. Popper and E. P. Oliveto, J. Am. Chem. Soc., 81, 4574 (1959). See C. E. Moppett and J. K. Sutherland, J. Chem. Soc. (C), 3040 (1968) for a related reaction with 6-bromodienoic esters.
5. Diene lactone 3 isolated from reaction of 2 with zinc is reproducibly contaminated with 3-4% of the fully conjugated diene lactone.
6. Compounds 1, 3, 4a, 4b, 5b, 6, 7a and 9 gave satisfactory elemental analysis.
7. C. F. Lane, J. Org. Chem., 39, 1437 (1974)
8. K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, J. Chem. Soc., 39 (1946).
9. Silica gel chromatography provides a good separation of 4a and 5a from the tertiary alcohol; however, 4a and 5a are rather difficult to separate by this method.
10. For the equilibration of a 10-methyl-1-decalone, see J. A. Marshall, M. T. Pike and R. D. Carroll, J. Org. Chem., 31, 2933 (1966).
11. (a) J. A. Marshall and A. R. Hochstetler, J. Am. Chem. Soc., 91, 648 (1969); (b) H. O. House and H. W. Thompson, J. Org. Chem., 26, 3729 (1961). See footnote 11 in R. K. Boeckman and S. M. Silver, Tetrahedron Letters, 3497 (1973) for a recent application of this principle.
12. It is clear from ^{1}H nmr data that 7a has the assigned trans-decalin ring fusion ($\delta_{C(10)\ CH_3}$ 0.74). The C(10) methyl resonance for 1-methylene-cis-10-methyldecalin is reported to be δ 0.87, while that for 1-methylene-trans-10-methyldecalin is 0.73; see ref 11a.
13. P. Muller and B. Siegfried, Tetrahedron Letters, 3565 (1973).
14. Synthetic and natural dihydrocallitrisin have identical retention times on three g.l.c. columns, namely SE 30 (180°C), DC 710 (220°C) and DEGS (190°C, R.T. ~50 min). We thank Dr. Carman for performing this experiment.

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