Tetrahedron Letters No. 32, pp 3375 - 3378, 1972. Pergamon Press. Printed in Great Britain.

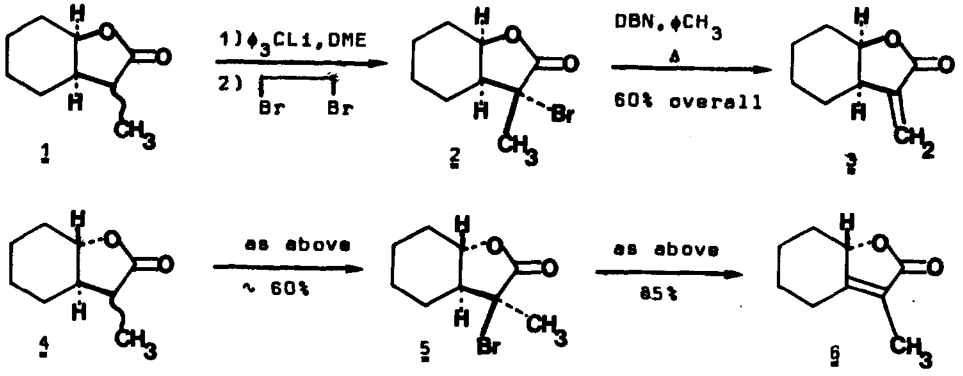
A NEW APPROACH TO α-METHYLENE-γ-BUTYROLACTONES. II.
SYNTHESIS OF (+)-ARBUSCULIN-B.

A.E. GREENE, J.-C. MULLER and G. OURISSON

Laboratoire Associé au C.N.R.S., Institut de Chimie,
Université Louis Pasteur, 67008 STRASBOURG, France.

(Received in UK 26 June 1972; accepted for publication 6 July 1972)

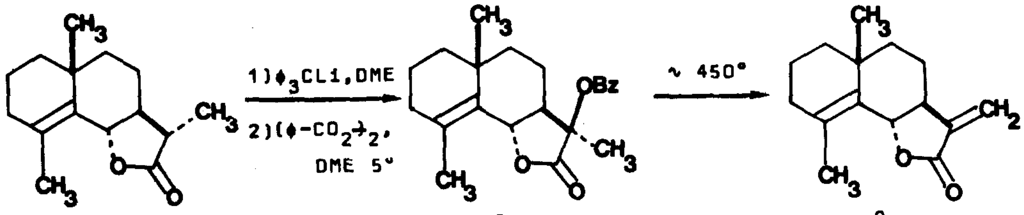
In a previous paper[1] we described an efficient synthesis of α-methylene-γ-butyrolactones which involves bromination and subsequent dehydrobromination of the corresponding α-methyllactones. The latter are particularly attractive precursors due to their general availability[2a-b,3]. Unfortunately, this method is limited to <u>cis</u>-fused lactones (<u>e.g.</u>, **1** → **3**). <u>Trans</u>-fused bromolactones undergo a facile <u>trans</u> elimination of HBr to afford, in contrast, exclusively endocyclic olefins in excellent yields (<u>e.g.</u>, **5** → **6**).



(No exocyclic olefin **11**)

We now describe a successful method for achieving the α-methyl→α-methylene conversion for <u>trans</u>-fused lactones based on a pyrolytic (<u>cis</u>) elimination[4] and demonstrate its utility in the synthesis of (+)-arbusculin-B, an allergenically active[2b] sesquiterpene isolated[5] from <u>Artemisia arbuscula</u> Nutt. ssp. <u>arbuscula</u>.

The known[6] lactone 7 was secured in 70% overall yield from α-santonin[7] by hydrogenation ($(\phi_3P)_3RhCl$, ϕH-EtOH), thioketalization (ethanedithiol, BF_3-Et_2O, AcOH, 15°), and reduction[8] (Raney-Ni, EtOH or MeOH, 25°, 15 min.).



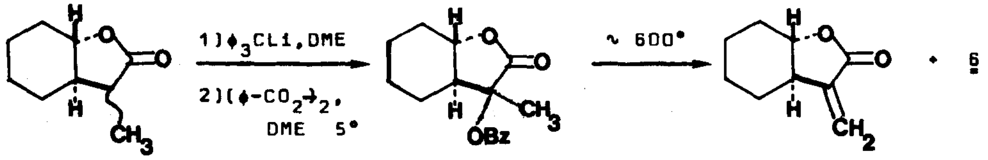
7 8 9

(+)-arbusculin-B

Treatment of 7 with triphenylmethyllithium (5 equiv.) in dimethoxyethane (DME) at 5° for 2 hr gave the corresponding enolate which was added to a stirred solution of dibenzoylperoxide[9] (6 equiv.) in DME at 5°. After 1 hr, the excess peroxide was destroyed (KI, AcOH, H_2O) and the benzoxylactone 8 was isolated in ~ 50% yield (~ 70% based on consumed 7) by silica gel chromatography : mp 139-140° (hexane) ; $[\alpha]_D$ = +17° ($CHCl_3$) ; IR $\nu_{max}^{CHCl_3}$ 1780 and 1725 cm^{-1} ; NMR $\delta_{TMS}^{CDCl_3}$ 8.00 (m, 2H), 7.50 (m, 3H), 5.10 (d, J=10 Hz, 1H), 1.79 (s, 3H), 1.68 (s, 3H) and 1.01 ppm (s, 3H) ; $M^{+\cdot}$ = 354 (calc. 354) ; Anal. Calc. for $C_{22}H_{26}O_4$: C 74.55, H 7.39 ; Found : C 74.63, H 7.56.

Pyrolysis[4] of 8 (~ 450°, 30 ml N_2/min) by dropwise addition of an ethereal solution onto a vertical column (30 cm packed with 4 mm diameter glass beads) gave, after silica gel chromatography, (+)-arbusculin-B (mp 86-88° $[\alpha]_D$ = +46° ($CHCl_3$)) in 35% yield. The spectroscopic[5] and chromatographic[10] properties were in full agreement with those of the authentic material.

In the preliminary model experiments, similar treatment of trans-lactone[11] 4 afforded the benzoate 10 (50%) which upon pyrolysis (~ 600°, 20 ml N_2/min) gave a readily separated 3:1 mixture of the known α-methylene-γ-butyrolactone[11] 11 and lactone[12] 6 in 60% yield.



4 10 11

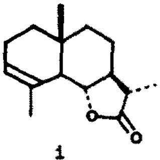
In summary, both cis-[1] and trans-fused α-methylene-γ-butyrolactones – widely occuring[2a-c] and often biologically active[2b,c] compounds – can now be synthesized from the corresponding methyllactones. Furthermore, a high yield synthesis of endocyclic olefin-lactones is now also available.

We wish to thank Messrs. Roure-Bertrand et Justin-Dupont (Grasse) and F.Hoffmann-La Roche (Basle) for partial support of this work and the C.N.R.S. for a temporary fellowship awarded one of us (A.E. Greene).

References

1. A.E. Greene, J.-C. Muller and G. Ourisson, Tetrahedron Letters, 2489 (1972).
2. Cf. a) G. Ourisson, S. Munavalli and C. Ehret, "Données relatives aux sesquiterpénoïdes", Pergamon Press, Paris, 1966. b) J.C. Mitchell and G. Dupuis, Br. J. Derm., **84**, 139 (1971) and references cited. c) S.M. Kupchan, M.A. Eakin and A.M. Thomas, J. Med. Chem., **14**, 1147 (1971) and references cited.
3. For examples of various high yield synthetic procedures leading to α-methylbutyrolactones see : a) E.W. Colvin, R.A. Raphaël and J.S. Roberts, Chem. Comm., 858 (1971). b) E.I. Heiba and R.M. Dessau, J. Amer. Chem. Soc., **93**, 995 (1971). c) D.H.R. Barton and A.J.L. Beckwith, Proc. Chem. Soc., 335 (1963). d) F.D. Gunstone and R.M. Heggie, J. Chem. Soc., 1354 (1952). e) Y. Abe and M. Sumi, J. Pharm. Soc. Japan, **72**, 652 (1952).
4. Cf. C.H. De Puy and R.W. King, Chem. Reviews, **60**, 431 (1960) and references cited.
5. M.A. Irwin and T.A. Geissman, Phytochemistry, **8**, 2411 (1969). Also from A. tridentata : F. Shafizadeh, N.R. Bhadane, M.S. Morris, R.G. Kelsey and S.N. Khanna, Phytochemistry, **10**, 2745 (1971).
6. D.H.R. Barton, G.P. Moss and J.A. Whittle, J. Chem. Soc. (C), 1813 (1968).
7. Purchased from Coopérative Pharmaceutique Française, S.A. Meulun. $[\alpha]_D = -176°$ ($CHCl_3$).

8. *Cf.* reference 6. A second product tentatively identified as lactone i was formed in ∿ 10% yield.



i

9. *Cf.* D.J. Rawlinson and G. Sosnovsky, *Synthesis*, 1, 1 (1972).

10. We thank Dr. J. Connolly (Glasgow) for a sample of arbusculin-B for chromatographic comparison.

11. J.A. Marshall and N. Cohen, *J. Org. Chem.*, 30, 3475 (1965).

12. W.G.Dauben and P.D.Hance, *J. Amer. Chem. Soc.*, 75, 3352 (1953).