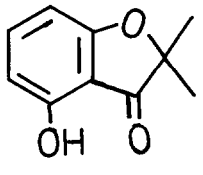
Tetrahedron Letters,Vol.25,No.48,pp 5585-5588,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

MYCORRHIZIN A: A SYNTHESIS OF TRICYCLIC ENONES EPIMERIC WITH AND IDENTICAL WITH THE KEY SYNTHETIC INTERMEDIATE OF KOFT AND SMITH

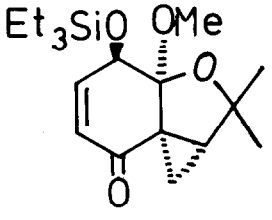
Roger F.C. Brown* and Peter Y.T. Teo
Department of Chemistry, Monash University,
Clayton, Victoria 3168, Australia

Summary: The benzofuranol (5) has been converted in eight steps to the epimeric (±)-tricyclic enones (12) and (2); the latter is the key intermediate in the Koft and Smith synthesis[2] of mycorrhizin A (3) and related substances.

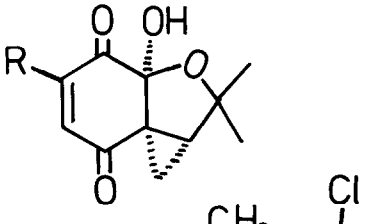
The first total synthesis of mycorrhizin A (3), an antifungal substance isolated by Trofast and Wickberg[1] from an unidentified mycorrhizal organism, was reported by Koft and Smith[2] in 1982. In this synthesis the hydroxybenzofuranone (1) was converted in about nine steps to the key tricyclic enone (2); a silylated side chain was then added with an alkenyl cuprate, and the product modified in three or four further steps to give racemic mycorrhizin A.

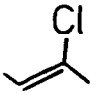


(1)



(2)

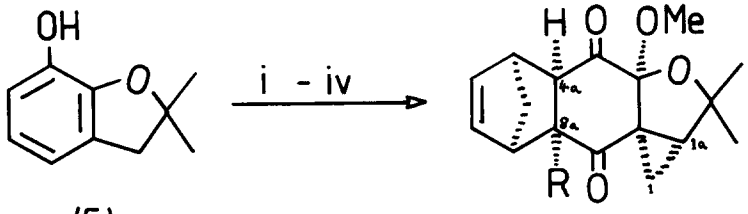


(3) R = 

(4) R = H

We have reported an alternative approach to substances of this class in which a commercial insecticide intermediate, the benzofuranol (5),[3] was converted in four steps into the cyclopentadiene adduct (6).[4] Flash vacuum pyrolysis (f.v.p.) of (6) yielded the O-methyl derivative of the parent system (4), but attempts to introduce a side chain early in the synthesis have been unsuccessful.[5] We now outline the conversion of adduct (6) into the epimeric enones (12) and (2), so that the two approaches converge.

Deprotonation of (6) with lithium diisopropylamide (LDA, 1.3 equiv., THF, -78°) occurred specifically at C8a, probably because approach to the C4a proton is hindered by the methoxyl group. Addition of allyl bromide then gave a single product (66%) shown by an X-ray study[6] to be (7), the 8a-allyl derivative of (6). No trace of 4a-alkylated or doubly alkylated product was detected.



(5)

(6) R = H

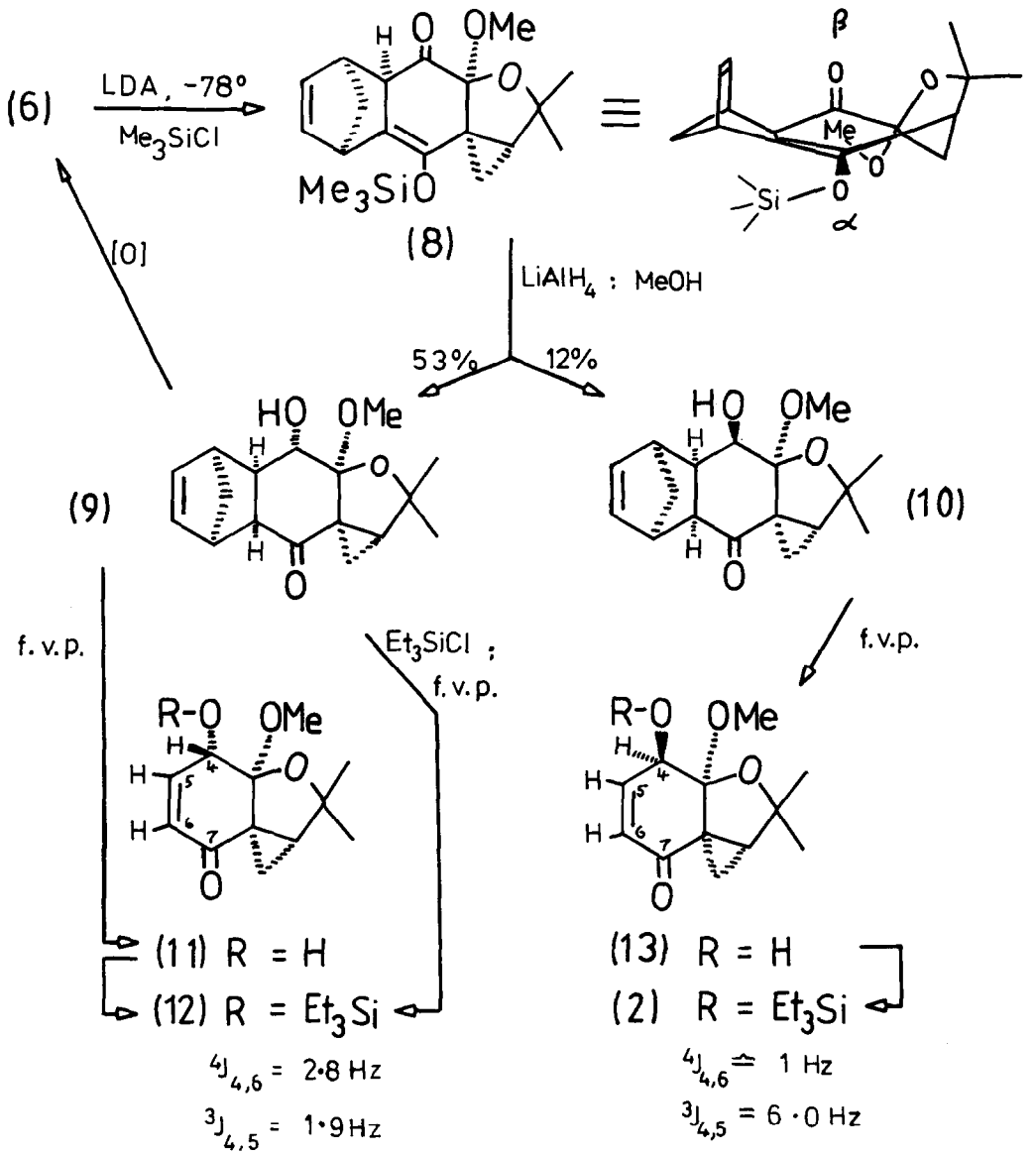
(7) R = CH_2=CH-CH_2

(i) $\cdot ON(SO_3K)_2$ (ii) NBS/CCl_4; Ag_2O/MeOH; C_5H_6 (iii) CH_2N_2, $-78^0 \rightarrow 0^0$ (iv) hν, Et_2O, -78^0.

This alkylative approach, which would ultimately place a C_3 side chain on the wrong position of (4), was abandoned, but similar silylation of the specific enolate of (6) gave in quantitative crude yield the trimethylsilyl enol ether (8). Reduction of (8) with $LiAlH_4$ (3 mol equiv., Et_2O, -20°) followed by methanolysis of the silyl ether function gave a mixture of the epimeric alcohols (9) and (10) which could be separated by flash chromatography (EtOAc/light petroleum, 2:3). The major product (53%) was (9) formed by attack of hydride at C4 from the concave β-face; attack from the convex α-face leading to (10) (12%) must be hindered by the methoxyl group. Alcohol (9) retained the stereochemistry of (6) at other positions, as shown by its slow re-oxidation to (6) (9 equiv. of pyridinium dichromate, CH_2Cl_2, 20°, 120 h; 29% conversion, 66% recovery).

Alcohol (9), m.p. 108-110°,[7] was converted to the triethylsilyl ether and this was subjected to flash vacuum pyrolysis (f.v.p.; 560°/0.1 mm) to give in essentially quantitative yield the silylated tricyclic enone (12) as an oil which proved to be different from the enone (2) of Koft and Smith.[2] Most notably the ^1H n.m.r. spectrum of (12) at 90 MHz showed pronounced allylic coupling (^4J 2.8 Hz) between the pseudo-axial H4 and the α-proton, H6, of the enone system; in the case of (2),[7] in which both H4 and H6 must be nearly coplanar with the enone system, this coupling was much smaller and was not visible in a routine 90 MHz FT spectrum.

Direct f.v.p. of the alcohol (9) was less clean, but gave in 65% yield the hydroxyenone (11), m.p. 75-76°, which could be silylated (81%) to the triethylsilyl ether (12) in lower overall yield.


(6)
LDA, -78°
Me3SiCl
Me3SiO
(8)
β
α
[O]
LiAlH4 : MeOH
53%
12%
(9)
(10)
f. v. p.
Et3SiCl ;
f. v. p.
f. v. p.
(11) R = H
(12) R = Et3Si
(13) R = H
(2) R = Et3Si
4J4,6 = 2·8 Hz
3J4,5 = 1·9 Hz
4J4,6 ≏ 1 Hz
3J4,5 = 6·0 Hz

In contrast to the slow but complete silylation of alcohol (9) (Et_3SiCl, Et_3N, DMAP, CH_2Cl_2, 20°, 18 h) the minor product of hydride reduction (10), m.p. 119-120°, with the same reagents (20°, 42 h) failed to undergo silylation of the hydroxyl group on the hindered concave β-face of the molecule. Direct f.v.p. of (10), however, gave the hydroxy-enone (13) as a viscous oil (>95%). Triethylsilylation of (13) then proceeded quantitatively to give the (±)-tricyclic enone (2) as an oil which proved indistinguishable (infrared spectra; ^1H n.m.r. spectra; t.l.c. on silica, EtOAc/light petroleum, 1:5) from a sample of (2) kindly provided by Professor A.B. Smith, III.[8]

Although this synthesis is marginally shorter than that of Koft and Smith[2], the photochemical step (iv) in the conversion of (5) to (6) is not easy to scale up beyond 1 g of diazomethane adduct, and the utility of the epimeric enone (12) in that synthesis[2] has not been demonstrated. Attempts to invert the stereochemistry of alcohol (11) through a Mitsunobu reaction[9] gave instead the product of an apparent hydride shift which will be discussed elsewhere.

References and Notes

1. J. Trofast and B. Wickberg, Tetrahedron, 33, 875 (1977).
2. E.R. Koft and A.B. Smith, J. Am. Chem. Soc., 104, 2659 (1982).
3. We thank FMC Corporation, Agricultural Chemicals Division, for a generous supply of benzofuranol (5), and the Australian Research Grants Scheme for general maintenance.
4. R.F.C. Brown, G.D. Fallon, B.M. Gatehouse, C.M. Jones and I.D. Rae, Aust. J. Chem., 35, 1665 (1982).
5. R.F.C. Brown, G.L. Edwards, C.M. Jones, I.D. Rae, and P.Y.T. Teo, Aust. J. Chem., 36, 1263 (1983).
6. B.M. Gatehouse and K.B. Caldwell, unpublished, 1983; K.B. Caldwell, B.Sc. Honours report, Monash University, 1983.
7. All crystalline products gave satisfactory elemental analyses; all products gave infrared, n.m.r., and high or low resolution mass spectra consistent with structures proposed.
8. We thank Professor A.B. Smith, III for several infrared and n.m.r. spectra, and for a substantial sample of the (-)-enone (2).
9. O. Mitsunobu, Synthesis, 1, (1981).

(Received in UK 6 September 1984)