Tetrahedron Letters,Vol.25,No.4,pp 393-394,1984
Printed in Great Britain

0040-4039/84 $3.00 + .00

A SIMPLE SYNTHESIS OF GEIPARVARIN

Kau-Ming Chen and Madeleine M. Joullié*

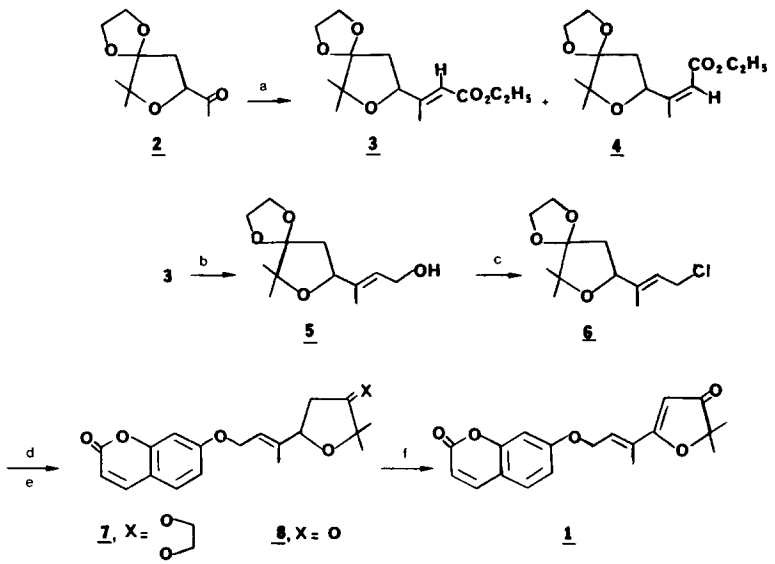
Department of Chemistry, University of Pennsylvania
Philadelphia, Pennsylvania 19104

Abstract: A simple, efficient (nine steps, 22% overall yield) synthesis of geiparvarin is described.

The naturally occurring antitumor agent geiparvarin (1) has been the subject of several synthetic investigations[1-3] since its isolation from the leaves of Geijera parviflora Lindl and characterization in 1967.[4] Geiparvarin has also been found in the extracts of the fruit of the same plant.[5] ^{1}H NMR studies confirmed the original structural assignments.[6]

Our continued interest in functionalized furanones[7-9] led us to devise a simple, efficient route to 1 from 6,6-dimethyl-1,4,7-trioxaspiro[4.4]non-8-yl methyl ketone (2) previously prepared in our laboratory by a three-step synthesis in overall yields of 75%.[8,9] This is the first synthesis of 1 with high isolated yields for each step from starting materials to products (Scheme 1).

Scheme 1



2 → 3 + 4; 3 → 5 → 6; 6 → 7 (X = ethylene ketal) → 8 (X = O) → 1

a: NaH, $(EtO)_2POCH_2CO_2Et$; b: 2.2 eq. DIBAL, CH_2Cl_2; c: 1.2 eq. TsCl, 2 eq. DMAP; d: 0.8 eq. 7-hydroxycoumarin, K_2CO_3/KI, DMF; e: $MeCO_2H$, H_2O; f: 2 eq. DDQ, C_6H_6.

Ketone 2 was added to a solution of the ylid of diethyl phosphonoacetate (generated from NaH in DME) to afford a 6:1 mixture of the corresponding trans and cis olefins 3 and 4 (63% overall yield for trans isomer).[10,11] After separation of the isomers by column chromatography, compound 3 was reduced with DIBAL in CH_2Cl_2 to the allylic alcohol 5.[12] Compound 5 was converted smoothly into the corresponding chloride (6) with p-toluenesulfonyl chloride and 4-N,N-dimethylaminopyridine in CH_2Cl_2 (72% yield).[13,14] Condensation of 6 with 7-hydroxycoumarin using K_2CO_3/KI in DMF and benzene afforded 7 in 93% yield.[15] Deprotection of the 1,3-dioxolane ring in 7 with aqueous acetic acid afforded the corresponding ketone 8 in 92% yield.[15] Dehydrogenation of 8 to 1 was accomplished with DDQ in 75% yield.[16,17]

Acknowledgements: We thank the University of Pennsylvania for support of this work and for a University Fellowship (1981-1982) and a Karcher Fellowship to K.-M. Chen.

REFERENCES AND NOTES

1. A. B. Smith III and P. J. Jerris, Tetrahedron Lett., 1980, 711.
2. H. Saimoto, T. Hiyama, and H. Nozaki, J. Am. Chem. Soc., 1981, 103, 4975.
3. R. F. W. Jackson and R. A. Raphael, Tetrahedron Lett., 1983, 2117.
4. F. N. Lakey and J. K. MacLeod, Aust. J. Chem., 1967, 20, 1943.
5. D. L. Dreyer and A. Lee, Phytochemistry, 1972, 11, 763.
6. R. M. Carman, F. N. Lakey, and J. K. MacLeod, Aust. J. Chem., 1967, 20, 1957.
7. Z. Lysenko, F. Ricciardi, J. E. Semple, P. C. Wang and M. M. Joullié, Tetrahedron Lett., 1978, 2679.
8. J. E. Semple, A. E. Guthrie and M. M. Joullié, Tetrahedron Lett., 1980, 4561.
9. A. E. Guthrie, J. E. Semple, and M. M. Joullié, J. Org. Chem., 1982, 47, 2369.
10. All new compounds gave satisfactory C and H combustion analysis within 0.3% and/or appropriate parent ion identification by high resolution mass spectrometry. Selected spectral data is given. All ^{1}H NMR spectra are in $CDCl_3$, 250 MHz.
11. (3, IR (neat) 2920, 2850, 1730, 1620, 1440, 1460, 1370, 1360, 1320, 1230, 1150, 1040, 952, 900 and 875 cm^{-1}); ^{1}H NMR δ 1.24 (d, 6H), 1.26 (m, 3H), 1.96 (dd, 1H); 2.08 (d, 3H, J = 1.2), 2.28 (dd, 1H), 3.95 (m, 4H), 4.16 (q, 2H), 4.44 (dd, 1H), 6.05 (m, 1H), 4, ^{1}H NMR δ 1.24 (s, 6H), 1.24 (m, 3H), 1.87 (dd, 1H), 1.96 (d, 3H, J = 1.1), 2.54 (dd, 1H), 3.95 (m, 4H), 4.12 (dd, 2H), 5.67 (m, 1H), 5.67 (m, 1H)
12. 5, IR (neat) 3400, 2980, 2880, 1660, 1460, 1440, 1380, 1365, 1300, 1145, 1030, 1000, 950, 880; ^{1}H NMR δ 1.23 (d, 6H), 1.32 (t, 1H), 1.67 (s, 3H), 2.07 (2dd, 2H), 3.94 (m, 4H), 4.20 (t, 2H), 4.40 (dd, 1H), 5.74 (t, 1H, J = 6.6).
13. We thank Professor K. C. Nicolaou and his coworkers, W. S. Li and C.-K. J. Hwang for sharing this methodology with us before its publication.
14. 6, ^{1}H NMR δ 1.23 (d, 6H), 1.71 (d, 3H, J = 1.1), 2.10 (2dd, 2H), 3.95 (m, 4H), 4.10 (d, 2H, J = 8.1) 4.41 (dd, 1H), 5.79 (t, 1H, J = 8.0).
15. 7, ^{1}H NMR δ 1.23 (d, 6H), 1.75 (s, 3H), 2.10 (2dd, 2H), 3.95 (m, 2H), 4.45 (dd, 1H), 4.64 (d, 2H, J = 6.3), 5.84 (t, 1H, J = 6.3), 6.24 (d, 1H, J = 9.4), 6.81 (dd, 1H, J = 2.4), 6.85 (d, 1H, J = 2.4), 7.35 (d, 1H, J = 8.4), 7.63 (d, 1H, J = 9.5).
16. ^{1}H NMR δ 1.25, 1.33 (2s, 6H), 1.81 (s, 3H), 2.44 (dd, 1H), 2.65 (dd, 1H), 4.63 (m, 1H), 4.68 (d, 2H, J = 6.3), 5.91 (t, 1H, J = 6.2), 6.26 (d, 1H, J = 9.5), 6.82 (dd, 1H, J = 2.3), 6.86 (d, 1H, J = 2.3), 7.38 (d, 1H, J = 8.3), 7.64 (d, 1H, J = 9.5).
17. 1, mp 156-157°C ^{1}H NMR δ 1.41 (s, 6H), 2.03 (d, 3H, J = 1.0), 4.84 (d, 2H, J = 5.9), 5.63 (s, 1H), 6.28 (d, 1H, J = 9.4), 6.75 (t, 1H, J = 5.85), 6.85 (dd, 1H, J = 2.4), 6.90 (d 1H, J = 2.5), 7.41 (d, 1H, J = 8.5) 7.66 (d, 1H, J = 9.5). IR ($CHCl_3$) 3009, 1728, 1699, 1653, 1616, 1562, 1508, 1475, 1406, 1381, 1365, 1279, 1232, 1201, 1174, 1159, 1124, 1016, 837, 804; MS (HRCI) M^+ Calcd. 326.1154; Found: 326.1157.

(Received in USA 7 November 1983)