Tetrahedron Letters,Vol.28,No.6,pp 675-678,1987
Printed in Great Britain

0040-4039/87 $3.00 + .00
Pergamon Journals Ltd.

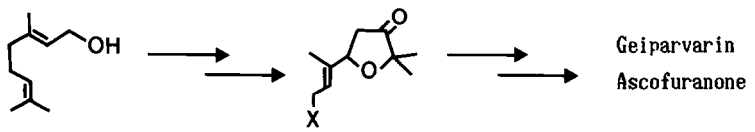
SIMPLE SYNTHETIC ROUTES TO GEIPARVARIN

S. H. Kang* and C. Y. Hong

Department of Chemistry, Korea Institute of Technology, Taejon, Korea

Summary: Starting from geranyl acetate, efficient routes to 3(2H)-furanone derivatives via allylic oxidation and cyclization are described which have been utilized in the synthesis of a naturally occurring antitumor agent, geiparvarin.

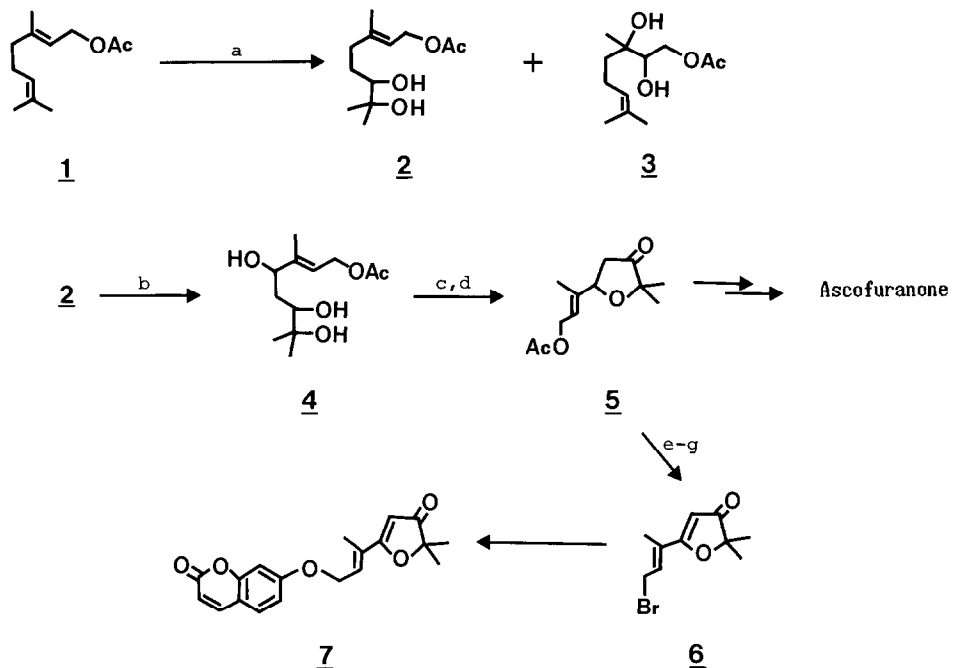
3(2H)-Furanone and 4,5-dihydro-3(2H)-furanone derivatives are central structural units in an increasing number of natural products including bullatenone, geiparvarin,[1] ascofuranone,[2] chilenone A,[3] jatrophone,[4] eremantholides,[5] lychnophorolides[6] etc. There have been several synthetic approaches[7] to them, which have been utilized in synthesizing mainly bullatenone, geiparvarin and ascofuranone. In these approaches, γ-hydroxyketones or their equivalents were constructed as the furanone precursors via alkylation, aldol or cycloaddition reactions. In planning of our studies of these compounds, we chose 1,4-diol or 4-hydroxyepoxide as the furanone precursor because it could be obtained from geraniol, without carbon-carbon bond formation, which has the necessary carbon skeleton, especially, for



geiparvarin. In order to realize this end, we considered that it is crucial to differentiate the two olefinic double bonds followed by allylic oxidation and to form a hydrofuran ring. Herein we report the synthesis of a novel antitumor agent, geiparvarin 7, and a possible synthetic intermediate for an antibiotic and hypolipidemic agent, ascofuranone, through the described strategy.

Treatment of geranyl acetate 1 with osmium tetroxide afforded diols 2 and 3 in 90% combined yield[8] (2:3 = 7:1) along with a trace amount of tetraol (Scheme 1). Allylic oxidation[9] of diol 2 with selenium dioxide in ethanol produced a diastereomeric mixture of triols 4 in 82% yield.[10] After chromatographic separation of 4 (the major:the minor = 65:35), their stereochemistry was unambiguously determined as follows (Scheme 2). Each of them was reacted with acetone in the presence of p-toluenesulfonic acid and then with acetic anhydride in triethylamine to give diacetoxy acetonide 8. The cleavage of the olefinic double bond in 8 was carried out with osmium tetroxide oxidation followed by sodium periodate oxidation to form a ketone, which was treated with methyllithium and then with 2,2-dimethoxypropane in the presence of p-toluenesulfonic acid to yield diacetonide 9. The ^{1}HNMR spectrum of the diacetonide from the major triol shows that the two protons at C_4 are not identical

Scheme 1



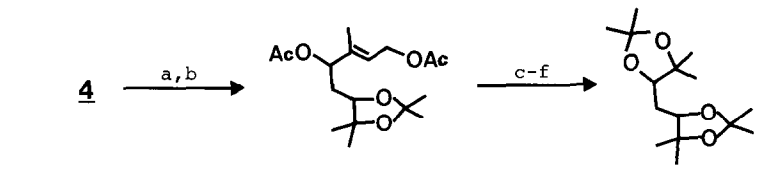
Reagents: a. OsO_4 (cat.)/NMO/acetone/5℃. b. SeO_2/Py/EtOH/reflux. c. p-TsOH (cat.)/PhH/reflux. d. PCC/molecular sieve 4Å/CH_2Cl_2/RT. e. NaOMe/MeOH/RT. f. CBr_4/PPh_3/CH_2Cl_2/0℃→RT. g. DDQ/dioxane/reflux.

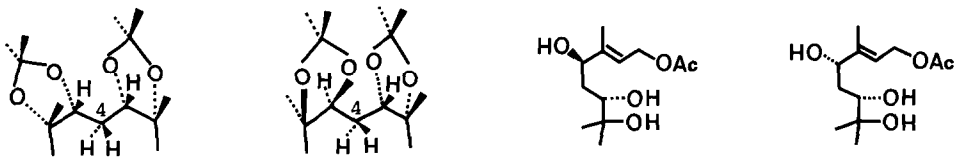
[δ1.57 (1H, td, J=6.1 and 13.9 Hz), 2.01 (1H, td, J=7.8 and 13.9 Hz)]; whereas, the diacetonide from the minor has two identical protons at C_4[δ 1.51 (2H, dd, J=5.6 and 7.0 Hz)]. The results prove that the diacetonide from the major is 9a and the diacetonide from the minor is 9b. Therefore, it is concluded that the major triol is 4a and the minor is 4b.

Triols 4 were heated at reflux in benzene in the presence of p-toluenesulfonic acid followed by PCC oxidation[11] to give dihydrofuranone derivative 5 in 81% yield, which might be utilized for the synthesis of ascofuranone. 5 was subjected to hydrolysis with sodium methoxide, bromination with carbon tetrabromide in the presence of triphenylphosphine[12] and DDQ oxidation in dioxane,[13] in sequence to afford 3(2H)-furanone derivative 6 in 76% overall yield, which was converted into geiparvarin by the known method.[1a, 14]

Another more efficient way to 5 was developed (Scheme 3). Geranyl acetate 1 was oxidized with MCPBA in the presence of sodium bicarbonate to produce monoepoxide 10 in 91% yield along with a trace amount of diepoxide. Treatment of 10 with selenium dioxide in dioxane in the presence of camphorsulfonic acid accomplished allylic oxidation and cyclization in one step. The resulting hydrofuran derivatives were subjected to PCC oxidation to yield 4,5-dihydro-3(2H)-furanone derivative 5 in 53% yield from 10.

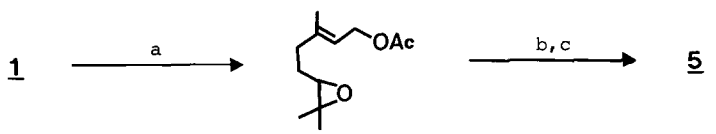
Scheme 2





Reagents: a. p-TsOH (cat.)/acetone/RT. b. Ac_2O/DMAP (cat.)/Et_3N/CH_2Cl_2/RT. c. OsO_4 (cat.)/NMO/acetone/RT. d. $NaIO_4$/MeOH-H_2O/RT. e. MeLi/THF/0℃→RT. f. $Me_2C(OMe)_2$/p-TsOH (cat.)/RT.

Scheme 3



Reagents: a. MCPBA/$NaHCO_3$/CH_2Cl_2/H_2O/0℃. b. SeO_2/CSA (cat.)/dioxane/50℃. c. PCC/molecular sieve 4Å/CH_2Cl_2/RT.

A synthetic route to another type of 4,5-dihydro-3(2H)-furanone derivative for eremantholides and lychnophorolides is currently under investigation.

Acknowledgement: Financial support from the Korea Science and Engineering Foundation and the Korea Institute of Technology is gratefully acknowledged.

References and Notes

1. a. T. Sakai, H. Ito, A. Yamawaki and A. Takeda, Tetrahedron Lett., 25, 2987 (1984). b. K. -M. Chen and M. M. Joullié, ibid., 25, 393 (1984). c. R. F. W. Jackson and R. A. Raphael, J. Chem. Soc., Perkin Trans. I, 535 (1984). d. A. B. Smith, III and P. J. Jerris, Tetrahedron Lett., 21, 711 (1980).
2. A. E. Guthrie, J. E. Semple and M. M. Joullié, J. Org. Chem., 47, 2369 (1982).
3. A. S. Martin, J. Rovirosa and O. Munoz, Tetrahedron Lett., 24, 4063 (1983).
4. S. M. Kupchan, C. W. Sigel, M. J. Matz, C. J. Gilmore and R. F. Bryan, J. Am. Chem. Soc., 98, 2295 (1976).
5. P. W. LeQuesne, S. B. Levery, M. D. Menachery, T. F. Brennan and R. F. Raffauf, J. Chem. Soc., Perkin Trans. I, 1572 (1978).
6. P. W. LeQuesne, M. D. Menachery, M. P. Pastore, C. J. Kelley, T. F. Brennan, K. D. Onan and R. F. Raffauf, J. Org. Chem., 47, 1519 (1982).
7. a. B. Tarnchompoo and Y. Thebtaranonth, Tetrahedron Lett., 25, 5567 (1984). b. P. G. Baraldi, A. Barco, S. Benetti, S. Manfredini, G. P. Pollini and D. Simoni, ibid., 25, 4313 (1984). c. D. P. Curran and D. H. Singleton, ibid., 24, 2079 (1983). d. S. H. Anderson, K. K. Sharma and K. B. G. Torssell, Tetrahedron, 39, 2241 (1983). e. H. Saimoto, T. Hiyama and H. Nozaki, J. Am. Chem. Soc., 103, 4975 (1981). f. A. B. Smith, III, P. A. Levenberg, P. J. Jerris, R. M. Scarborough, Jr. and P. M. Wovkulich, ibid., 103, 1501 (1983). g. J. E. Semple, A. E. Guthrie and M. M. Joullié, Tetrahedron Lett., 21, 4561 (1980).
8. The yield was based on recovered starting material. 21% of geranyl acetate was recovered after 48 hours at 5℃.
9. a. D. Arigoni, A. Vasella, K. B. Sharpless and H. P. Jensen, J. Am. Chem. Soc., 95, 7917 (1973). b. K. B. Sharpless and R. F. Lauer, ibid., 94, 7154 (1972). c. L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, John Wiley & Sons Inc., New York, N. Y., pp992-1000 (1967).
10. The yield was based on recovered starting material. 20% of diol 2 was recovered after reflux for 18 hours.
11. E. J. Corey and J. W. Suggs, Tetrahedron Lett., 16, 2647 (1975).
12. H. Hayashi, K. Nakanishi, C. Brandon and J. Marmur, J. Am. Chem. Soc., 95, 8749 (1973).
13. S. Matsuura, M. Iinuma, K. Ishikawa and K. Kagei, Chem. Pharm. Bull. Japan, 26, 305 (1978).
14. All new compounds showed satisfactory spectral data. The melting points, IR and ^{1}HNMR spectral data of bromide 6 and geiparvarin 7 are identical to those reported in the literatures.[1]

(Received in Japan 13 November 1986)