Pergamon

Tetrahedron Letters, Vol. 37, No. 44, pp. 8037-8040, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01819-9

Diels-Alder Reaction of In-situ Generated p-Benzoquinones with Isoprenoidal Dienol Acetate: Novel Synthesis of 2-Isoprenoidal Naphthalene-5, 8-Quinols+

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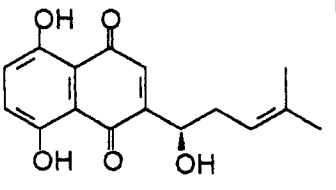
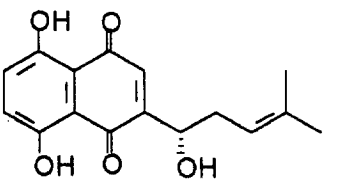
Abstract: Diels-Alder reaction of citral dienol acetate 3 with in-situ generated p-benzoquinones from **4 (a-d)** furnished cycloadducts **5 (a-d)** in quantitative yields. Brief exposure of **5b** towards activated silica gel furnished acyl migrated product **6a** in quantitative yield. Copyright © 1996 Published by Elsevier Science Ltd

Shikonin **1**[1], alkamin **2** and related isoprenoidal naphthaquinones[2], isolated from *Lithospermum erythrorhizon* and *Arnebia nobilis* and their racemate shikalkin display a high order of physiological activities such as anticancer[3], antiinflammatory[4], antibacterial[5] and immunostimulatory[6] activities. In view of their biological activities there has been considerable interest in the synthesis of these natural products[7-13]. With the hope to develop a synthetically viable method to **1, 2** and related natural products, we visualised a direct (4+2) cycloaddition approach of isoprenoidal dienol acetate **3** and in-situ generated p-benzoquinones from **4** (**a-d**) and the results are reported in the present communication[14].

FIG.1



1

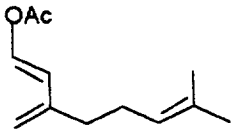


2

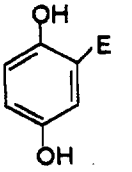
The citral dienol acetate 3 was prepared from commercially available citral[15]. The reaction of dienol acetate 3 with 2- methoxycarbonyl-p-quinol **4a** in the presence of silver oxide (40°C, 14 h) furnished **5a** in 55% yield as a pale yellow crystalline solid mp 90-92°C. The structure of **5a** was established on the basis of high resolution NMR spectroscopy[16]. The appearance of doublet of doublets at 3.45 (J=10.00, 6.00 Hz) for the H-8a proton, doublet at 5.75 (J=6.00Hz) for the H-4 proton and a doublet at 6.10 ppm (J=6.00Hz) for the H-3 proton. The

CDRI Communication No. 5249.

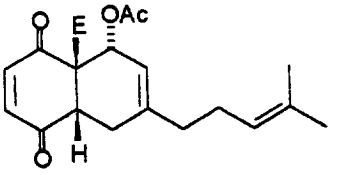
FIG. 2



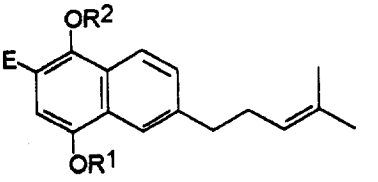
3



4 a) E=COOMe
4 b) E=COMe
4 c) E=CHO
4 d) E=H

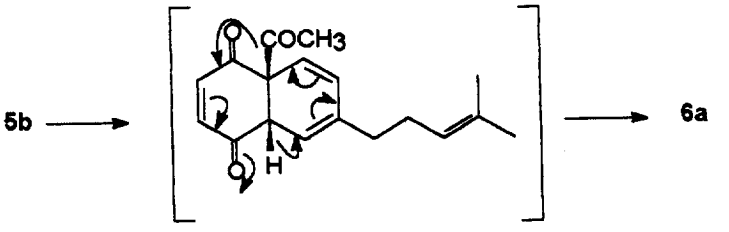


5a) E=COOMe
5b) E=COMe
5c) E=CHO
5d) E=H



6a) R^1 = R^2 = H, E=$COCH_3$
6b) R^1 = R^2 = E = $COCH_3$
6c) R^1 = R^2 = E = H
6d) R^1 = R^2 = $COCH_3$,E=H

SCHEME 1



^{13}C NMR of **5a** showed absorptions at 196.04 for C-5 and C-8 ketones, 169.26 and 165.90 for the methoxycarbonyl and acetate function, 64.67 and 44.38 ppm for the C-4a and C-8a carbon and it further confirmed the assigned structure. The citral dienol acetate 3 behaved differently with more reactive dienophiles generated from **4b**and **4c**. The reaction of citral dienol acetate 3 with 2-acetyl p-quinol **4b** (Ag_2O, 40°C, 24h) furnished **5b** in quantitative yield. The cycloadduct **5b** proved too labile towards SiO_2 column chromatography. The exposure of **5b** to SiO_2 (60-120 mesh, 14h) furnished acyl migrated product **6a** in quantitative yield as shown in Scheme-1. The reaction of **6a** (Ac_2O, Py, DMAP) cleanly furnished the diacetate **6b** in quantitative yield. The ^1H NMR of **6b**[16] showed a doublet of doublets at 7.40 for the H-7 proton (J=8.00, 2.00 Hz), a doublet at 7.52 for H-5 proton (J=2.00 Hz), a singlet at 7.54 for H-3 and a doublet at 7.85 for H-8 proton (J=8.00 Hz) and it confirmed the assigned structure.

The reaction of citral dienol acetate with gentisaldehyde **4c** under identical reaction conditions furnished **5c** in quantitative yield. The cycloadduct **5c** proved too unstable towards SiO_2 on column chromatography.

The reaction of citral dienol acetate 3 with p-quinol **4d** (Ag_2O, 40°C, 24 h) furnished **5d** in quantitative yield. The reaction of **5d** (Ac_2O, PY, DMAP) furnished diacetate **6d**[16] in quantitative yield.

In conclusion the present methodology gives novel and efficient access to biologically important shikalkin analogs.

Acknowledgements: Financial support to AR from CSIR, New Delhi is gratefully acknowledged. We thank to Dr.Kamlakar Avasthi for useful discussions.

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16. The elemental analysis and spectral data for the new compounds were in accordance with the structures assigned and only selected data are listed.

5a: ^{1}H NMR (400 MHz, $CDCl_3$) 1.55 (s, 3H), 1.65 (s, 3H), 2.00 (s, 3H), 2.1 (m, 4H), 2.5 (m, 2H), 3.45 (dd, J=10.00, 6.00 Hz, 1H), 3.7 (s, 3H), 5.00 (m, 1H), 5.75 (d, J=6.00 Hz, 1H), 6.10 (d, J=6.00Hz, 1H), 6.75 (ABq, J=9.00 Hz, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz) 17.57 (q), 20.72 (q), 25.50 (q), 25.78 (t),26.72 (t), 36.83 (t), 44.38 (d), 53.36 (q), 64.67 (s), 66.99 (d), 117.88 (d), 122.86 (d), 132.08 (s), 137.76 (d), 142.08 (d), 143.89 (s), 165.90 (s), 169.26 (s), 190.42 (s), 196.04 (s); **6a:** ^{1}H NMR (400 MHz, $CDCl_3$) 1.50 (s, 3H), 1.65 (s,3H), 2.35 (m, 2H), 2.55 (s, 3H), 2.80 (m, 2H), 5.15 (m, 1H), 6.90 (s, 1H), 7.35 (dd, J=9.00, 2.00 Hz, 1H), 7.80 (d, J=2.00 Hz, 1H), 8.30 (d, J=9.00 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) 17.67 (q), 25.63 (q), 26.78 (q), 29.71 (t), 36.63 (t), 105.99 (d), 111.57 (s), 120.38 (d), 123.30 (d), 124.28 (s), 124.58 (d), 128.02 (d), 129.81 (s), 132.58 (s), 142.72 (s), 144.87 (s), 157.57 (s), 203.50 (s); **6b** : ^{1}H NMR (400 MHz, $CDCl_3$) 1.50 (s, 3H), 1.65 (s, 3H), 2.30 (m, 2H), 2.40 (s, 3H), 2.45 (s, 3H), 2.55 (s, 3H), 2.75 (m, 2H), 5.10 (m, 1H), 7.40 (dd, J=8.00, 2.00 Hz, 1H), 7.52 (d, J=2.00 Hz, 1H), 7.54 (s, 1H), 7.85 (d, J=8.00 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) 17.68 (q), 20.95 (q), 21.05 (q), 25.60 (q), 29.45 (q), 29.68 (t), 36.44 (t), 117.57 (d), 120.06 (d), 122.25 (s), 123.06 (d), 123.35 (d), 125.06 (s), 126.93 (s), 129.47 (d), 129.86 (s), 132.76 (s), 143.99 (s), 146.86 (s), 169.10 (s), 169.24 (s), 196.47 (s); **6d :** ^{1}H NMR (400 MHz, $CDCl_3$) 1.60 (s, 3H), 1.70 (s, 3H), 2.35 (m, 2H), 2.48 (s, 3H), 2.50 (s, 3H), 2.80 (m, 2H, 5.20 (m, 1H), 7.20 (ABq, J=10.00 Hz, 2H), 7.40 (dd, J=10.00, 2.00 Hz, 1H), 7.60 (d, J=2.00 Hz, 1H), 7.75 (d, J=10.00 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) 17.59 (q), 2x20.88 (q), 25.52 (q), 29.57 (t), 36.29 (t), 116.59 (d), 117.58 (d), 119.95 (d), 121.45 (d), 123.30 (d), 126.11 (s), 127.75 (s), 128.46 (d), 132.37 (s), 141.23 (s), 143.93 (s), 144.29 (s), 2x169.14 (s).

(*Received in UK* 12 *August* 1996; *accepted* 13 *September* 1996)