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DIELS-ALDER REACTION OF IN-SITU GENERATED 2-METHOXYCARBONYL-p-QUINONE WITH D-GLUCOSE BASED DIENES: A NEW APPROACH TO FORSKOLIN+

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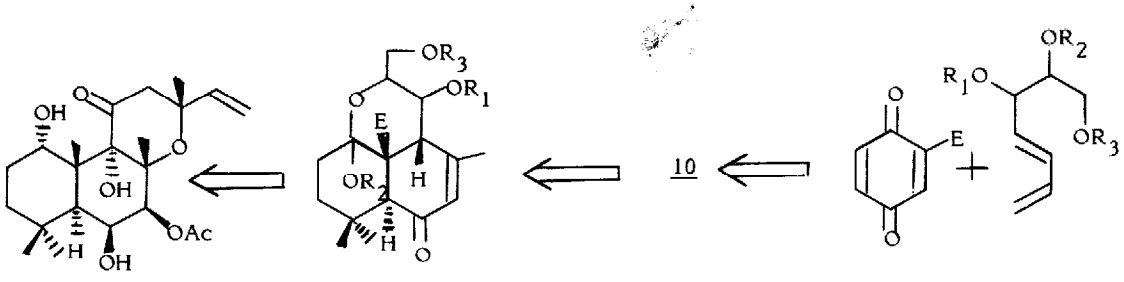
Abstract: *Diels-Alder reaction of 2-methoxycarbonyl-p-quinone 3 with D-glucose based dienes 4 (a-h) furnished cis-adducts 10 (a-h) in a stereo- and regiospecific manner. Chemical transformation of 10 afforded 11-15. Compounds 12, 13 and 15 are key intermediates in the proposed synthesis of forskolin.*

Forskolin (1), a highly oxygenated labdane diterpenoid isolated from Coleus forskohlii[1], displays a wide variety of physiological activities[2], such as branchospasmolytic, antihypertensive and inotropic activity. It also activates adenylate cyclase and reduces intraocular pressure in man[3].

The interesting biological properties coupled with the unique structural features of forskolin(1) have attracted much attention of synthetic chemists the worldover[4]. Three syntheses of forskolin (1) have been achieved[5-7]. Our new approach is to synthesize the AB ring skeleton of forskolin (1) by intermolecular (4+2) cycloaddition (scheme-1) of the diene 4 derived from D-glucose and in-situ generated 2-methoxycarbonyl-p-quinone 3.



1 2 3 4

Scheme - 1

The easily available 3-O-acetyl-4,6-O-benzylidene-D-allal 5[8] on a mercuration-demercuration reaction[9] affords the aldehyde 6, which on Wittig olefination gave diene 4a. Acetylation of 4a (Ac_2O, TEA, DMAP) furnished diene 4b. Mesylation (CH_3SO_2Cl,Py) and PTC alkylation (NaOH, MeI) of 4a furnished dienes 4c and 4d quantitatively. Diene 4e was made available from easily available 3,4,6-tri-O-acetyl-D-glucal 7[10] via Perlin transformation[11] followed by Wittig olefination and acetylation. PTC alkylation (NaOH, MeI) of 4e furnished diene 4g. Protection of hydroxyaldehyde 8 with DHP followed by Wittig olefination gave diene 4f, while PTC alkylation of 4f furnished diene 4h (scheme-II).

The Diels-Alder reaction of diene 4a with 2-methoxycarbonyl-p-quinol 9 in the presence of silver oxide[12] (RT, 24 h) furnished 10a[13] in 80% yield as a crystalline compound. Epimerization of 10a with basic alumina furnished 11a[13] in nearly quantitative yield. Examination of the

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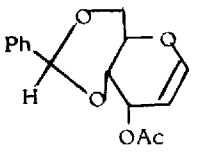

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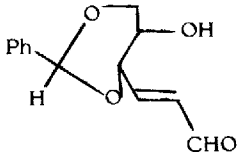

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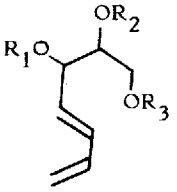

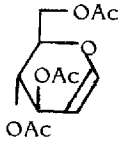

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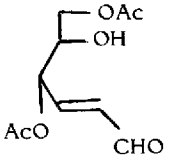

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Scheme - II

4a R_1R_3 = CHPh, R_2 = H

4b R_1R_3 = CHPh, R_2 = $COCH_3$

4c R_1R_3 = CHPh, R_2 = SO_2CH_3

4d R_1R_3 = CHPh, R_2 = CH_3

4e R_1 = R_2 = R_3 = $COCH_3$

4f R_1 = R_3 = $COCH_3$, R_2 = THP

4g R_1 = R_2 = R_3 = CH_3

4h R_1 = R_3 = CH_3, R_2 = THP

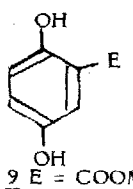
^1H and ^{13}C NMR spectra of 11a established the stereo- and regiochemical nature of the Diels-Alder reaction. The ^1H NMR spectrum of 11a displayed a doublet of doublets centered at 3.35 ppm ($J_{9,11}$ = 10.00, $J_{9,8}$ = 5.00 Hz) for the H-9 proton, and a doublet of doublets at 3.06 ppm ($J_{5,6'}$ = 10.00, $J_{5,6''}$ = 3.50 Hz) for the ring junction proton. Such a pattern is consistent only with the stereo- and regiochemistry of 11a. The ^{13}C NMR spectrum of 11a showed absorptions at 204 (carbonyl), 105 (hemiketal) and 56 ppm for the C-10 carbon. Further, an upfield shift of 5-6 ppm of C-10 carbon in the ^{13}C NMR is very much consistent with the ketal structures as in 11a, 11b and 13a as compared to free diketones 10a, 14e and 15e, also supported the assigned regiochemistry.

Acetylation (Ac_2O, TEA, DMAP) of 11a did not yield the expected acetate 14b. Instead, it gave an unexpected hemiketal acetate 11b. The ^{13}C NMR spectrum of 11b showed signals at 198 (single carbonyl), 93 (hemiketal) and 57 ppm for the C-10 carbon. The Diels-Alder reaction of 4b with 2-methoxycarbonyl-p-quinol 9 in the presence of silver oxide furnished compound 10b, which on epimerization over basic alumina provided a pale yellow crystalline compound 14b[13] (Table-1).

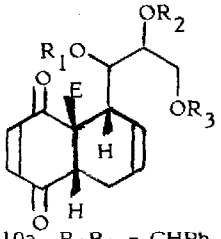
Table-1

Comp. No.	mp °C	$[\alpha]_D^{20}$ $CHCl_3$	Comp. No.	mp °C	$[\alpha]_D^{20}$ $CHCl_3$	Comp. No.	mp °C	$[\alpha]_D^{20}$ $CHCl_3$
(4a)	88-89	-106	(12)	137-38	-178	(15b)	170-71	-285
(4b)	78-80	- 58	(13a)	122-24	-122	(15c)	150-52	-305
(4c)	118-20	- 44	(11b)	128-30	-152	(15d)	138-40	-253
(4d)	40-42	- 72	(14b)	158-59	-222	(15e)	142-43	-206
(4e)	-	+ 25	(14c)	148-49	-154	(15f)	175-77	-162
(4f)	-	+ 53	(14d)	168-70	-218	(15g)	88-89	-212
(4g)	-	+ 18	(14e)	170-71	-209	(15h)	-	-233*
(4h)	-	+ 48*	(14f)	182-83	-247	(16)	186-88	- 30
(10a)	224-26	-346*	(14g)	119-20	-198			
(11a)	198-200	-220	(14h)	-	-184			

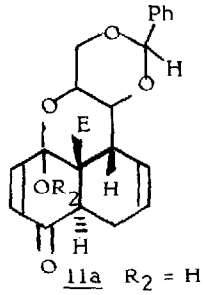
* Recorded in methanol



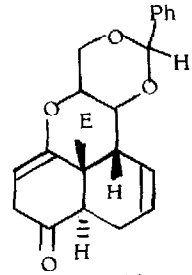
9 E = COOMe



10a R_1R_3 = CHPh, R_2 = H
10b R_1R_3 = CHPh, R_2 = $COCH_3$
10e R_1 = R_2 = R_3 = $COCH_3$



11a R_2 = H
11b R_2 = $COCH_3$



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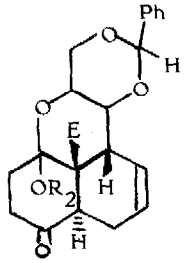
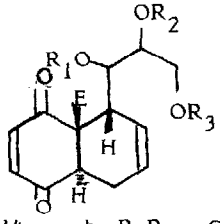
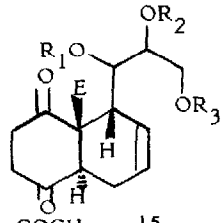


13a R_2 = H
13b R_2 = $COCH_3$



14 b R_1R_3 = CHPh, R_2 = $COCH_3$
c R_1R_3 = CHPh, R_2 = SO_2CH_3
d R_1R_3 = CHPh, R_2 = CH_3
e R_1 = R_2 = R_3 = $COCH_3$
f R_1 = R_3 = $COCH_3$, R_2 = THP
g R_1 = R_2 = R_3 = CH_3
h R_1 = R_3 = CH_3, R_2 = THP



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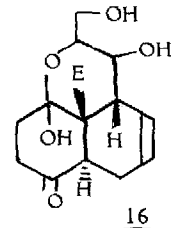

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Treatment of 11b with Zn-AcOH gave an unexpected compound 12. The ^{13}C NMR spectrum of 12 had signals at 206 (single carbonyl), 149 and 101 ppm (C_1-C_2 double bond). Reduction (Zn-AcOH) of 11a gave the expected hemiketal 13a in good yield.

The Diels-Alder reactions of 2-methoxycarbonyl-p-quinol 9 with dienes 4 (c-h) with suitable protecting groups for further manipulations were then studied. Diels-Alder reaction of diene 4e with 2-methoxycarbonyl-p-quinol 9 in the presence of silver oxide (RT, 8 days) provided 10e, which on epimerization over basic alumina furnished pale yellow crystalline compound 14e[13]. The ^1H NMR spectrum of 14e displayed a doublet of doublets centered at 3.65 ppm ($J_{9,8}$ = 5.00, $J_{9,11}$ = 2.00 Hz) for the H-9 proton, and a doublet of doublets at 3.02 ppm ($J_{5,6'}$ = 10.00, $J_{5,6''}$ = 8.00 Hz) for the ring junction proton. The ^{13}C NMR spectrum of 14e showed absorptions at 193 and 196 for two carbonyl groups and absorption at 65 ppm for the C-10 carbon. Reduction (Zn-AcOH) of 14e furnished 15e in nearly quantitative yield. Similarly, dienes 4 (f-h) on Diels-Alder reaction with 9 in the presence of silver oxide (RT, 5-8 days) followed by epimerization over basic alumina provided crystalline compounds 15 (f-h) in nearly quantitative yield (Table-1).

Deprotection (70% aq AcOH, 80°, 6 h) of 13a provided a crystalline compound 16[13]. The ^{13}C NMR spectrum of 16 showed absorptions at 208 (single carbonyl), 93 (hemiketal) and 57 ppm for the C-10 carbon. Alkaline hydrolysis of 15e (methanolic $NaHCO_3$) also provided the same compound 16, thereby indicating same stereo- and regiochemistry of the compounds 13a and 15e.

Compounds 12, 13 and 15 are key compounds in the proposed synthesis of forskolin and their further transformations are in progress.

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References

1. a) S.V. Bhat, B.S. Bajwa, H. Dornauer, N.J. de Souza and H.W. Fehlhaber, Tetrahedron Lett., 1669 (1977).
   b) J.S. Tandon, M.M. Dhar, S. Ramakumar and K. Venkatesan, Ind. J. Chem., **15B**, 880 (1977).
2. a) N.J. de Souza, A.N. Dohadwala and Reden, J. Medicin. Res. Rev., **3**, 201 (1983).
   b) K.B. Seamon, Ann. Rep. Medicin. Chem., **19**, 293 (1984).
3. J. Caprioli, and M. Sears, The Lancet, **1**, 958 (1983).
4. a) P.R. Jenkins, K.A. Minear, P. Barraclough, and M.S. Nobbs, J. Chem. Soc., Chem. Commun., 1423 (1984).
   b) K.C. Nicolaou and W.S. Li, ibid, 421 (1985).
   c) F.E. Ziegler, B.H. Jaynes, and M.T. Saindance, Tetrahedron Lett., 3307 (1985).
   d) G. Bold, S. Chao, R. Bhide, S.H. Wu, D.V. Patel, and C.J. Shih, ibid, 1973 (1987).
   e) B.G. Baraldi, A. Barco, S. Benetti, G.P. Pollini, E. Polo, and D. Simoni, J. Chem. Soc., Chem. Commun., 757 (1986).
   f) J.H. Hutchinson, G. Pattenden, and P.L. Myers, Tetrahedron Lett., 1313 (1987).
   g) E.R. Koft, A.S. Kotnis, T.A. Broadent, Tetrahedron Lett., 2799 (1987).
   h) S. Hashimoto, M. Sonegawa, S. Sakata, and S. Ikegami, J. Chem. Soc., Chem. Commun., 24 (1987).
   i) J.A. Oplinger, and L.A. Paquette, Tetrahedron Lett., 5441 (1987).
   j) A.P. Kozikowski, S.H. Jung, and J.P. Springer, J. Chem. Soc., Chem. Commun., 167 (1988).
5. F.E. Ziegler, B.H. Jaynes, and M.T. Saindane, J. Am. Chem. Soc., **109**, 8115 (1987).
6. S. Hashimoto, S. Sakata, M. Sonegawa, and S. Ikegami, J. Am. Chem. Soc., **110**, 3672 (1988).
7. E.J. Corey, P.S. Jardine, and J.C. Rohloff, J. Am. Chem. Soc., **110**, 3672 (1988).
8. a) M. Sharma, and R.K. Brown, Can J. Chem., **44**, 2825 (1966).
   b) T. Nobuo, Y. Sumio, K. Takashi, and M. Oyo, Chem. Lett., **3**, 289 (1983).
9. A. Mukhopadhyay, S.N. Suryawanshi, and D.S. Bhakuni, Ind. J. Chem. , **27B**, 1009 (1988).
10. W. Roth, and W. Pigman, Methods Carbohydr. Chem., **2**, 406 (1963).
11. F. Gonzalez, S. Lesage, and A.S. Perlin, Carbohydr. Res., **42**, 267 (1975).
12. G.A. Kraus, M.J. Taschner, J. Org. Chem., **45**, 1175 (1980).
13. The elemental analyses and spectral data for the new compounds were in accordance with the structures assigned, and only selected data are listed.

(10a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.10 (dq, J = 20.00, 10.00, 6.00, 4.00 Hz, 1H), 2.80 (m, J = 20.00, 6.00, 4.00, 2.00 Hz, 1H), 3.45 (dd, J = 12.00, 2.00 Hz, 1H), 3.50 (d, J = 12.00 Hz, 1H), 3.65 (m, 2H), 3.70 (s, 3H), 3.90 (six line pattern, J = 10.00, 6.00 Hz, 1H), 4.25 (dd, J = 12.00, 6.00 Hz, 1H), 5.15 (s, 1H), 5.85 (m, 2H), 6.62 (AB q, J = 10.00 Hz, 2H), 7.65 (m, 2H), 7.75 (m, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 19.76 (t), 37.02 (d), 44.90 (d), 52.86 (q), 60.67 (d), 61.50 (s), 70.86 (t), 80.79 (d), 100.21 (d), 122.70 (d), 126.14 (d), 126.38 X 2 (d), 127.37 X 2 (d), 128.37 (d), 136.30 (s), 137.17 (d), 141.66 (d), 170.10 (s), 192.91 (s), 197.52 (s).

(11a): ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (dq, J = 20.00, 10.00, 5.00, 2.50 Hz, 1H), 2.60 (dt, J = 20.00, 7.00, 2.50 Hz, 1H), 3.06 (dd, J = 10.00, 3.50 Hz, 1H), 3.35 (dd, J = 10.00, 5.00 Hz, 1H), 3.70 (s, 3H), 3.75 (s, 2H), 4.30 (m, 2H), 5.55 (s, 1H), 5.80 (dt, J = 10.00, 7.50 Hz, 1H), 5.95 (m, 1H), 6.25 (AB q, J = 12.00 Hz, 2H), 7.50 (m, 5H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 23.39 (t), 37.10 (d), 41.17 (d), 51.96 (q), 56.24 (s), 63.05 (d), 67.97 (t), 80.03 (d), 92.83 (s), 100.87 (d), 125.85 (d), 126.04 X 2 (d), 126.59 (d), 127.92 X 2 (d), 128.69 (d), 137.64 (s), 143.64 (d), 170.45 (s), 196.76 (s).

(14e): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.92 (s, 3H), 2.05 (s, 3H), 2.10 (s, 3H), 2.40 (m, 2H), 3.02 (dd, J = 10.00, 8.00 Hz, 1H), 3.60 (s, 3H), 3.65 (dd, J = 5.00, 2.00 Hz, 1H), 4.15 (dd, J = 10.00, 6.00 Hz, 1H), 4.25 (dd, J = 10.00, 4.00 Hz, 1H), 5.20 (dd, J = 6.00, 2.00 Hz, 1H), 5.35 (m, 1H), 5.70 (m, 1H), 5.80 (dt, J = 8.00, 4.00 Hz, 1H), 6.70 (dd, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 20.53 (q), 20.72 (q). 20.75 (q), 23.83 (t), 38.33 (d), 44.95 (d), 53.55 (q), 62.09 (t), 64.99 (s), 70.67 (d), 71.64 (d), 123.25 (d), 128.55 (d), 138.17 (d), 141.88 (d), 167.86 (s), 169.83 (s), 170.10 (s), 170.43 (s), 192.57 (s), 195 (s).

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