Reductive Elimination of Vicinal Oxygen Functions with Palladium(0). Applications in the Withanolide Series

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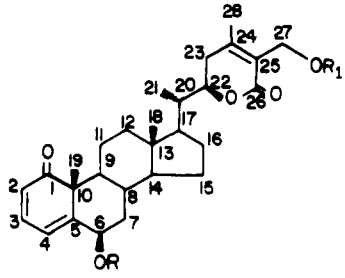
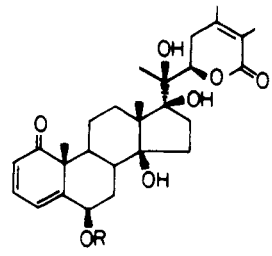
A high-yielding, chemoselective approach to the steroidal 6β-hydroxy 2,4-dien-1-one system is described by starting from the 4β-acetoxy-5β,6β-epoxy 2-en-1-one derivative. The method allows some useful interconversions in the withanolide series such as the conversion of 4β-acetoxywithanolide E into withaperuvin C and the conversion of withaferin A into jaborosalactone. The transformation involves a palladium-mediated reductive elimination of two vicinal oxygen functions one of which is allylic. A plausible reaction mechanism is suggested on the basis of ^{1}H NMR studies, aided by observed spin-saturation-transfer phenomena (path B in Scheme I). It involves initial complexation of Pd(0) to the C_2 olefin to give η^2 complex I, followed by formation of (π-allyl)palladium complex II, which then undergoes trans deoxypalladation leading to the final dienone product.

Due to their biological activities as antitumor[1] and insect antifeedant[2] agents, highly oxygenated ergostane-type steroids such as withanolides[3] are of growing interest. Since total or even partial synthesis of most withanolides must involve the positioning of a complex array of oxygen functions, it is not surprising that few synthetic efforts in this field have been recorded to date.[4]

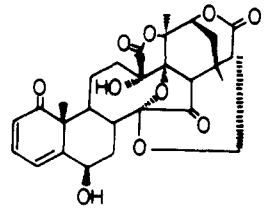
The synthesis of ergostane-type steroids with a dienone functionality in ring A (e.g., compound **1–3**) has been long desired for the following reasons: (a) there is a growing number of recently discovered natural products with this functionality including jaborosalactone B[5] (**1a**), withaperuvin C[6] (**2a**), and physalin G[7] (*3*); (b) steroidal derivatives containing this dienone system are important intermediates that have already been used in several approaches to synthesize naturally occuring[4] and modified withanolides[8].



1a: R=R$_1$=H
1b: R=H; R$_1$=Ac
1c: R=R$_1$=Ac



2a: R=H
2b: R=Ac



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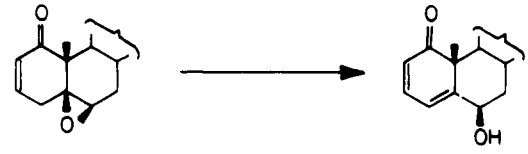
The only approach used so far leading to this A ring dienone has involved a dehydration-type process (eq 1), requiring rather harsh basic[4c,d,5b,9] or acidic[4e,10] conditions.



(1)

This method was proved successful in a limited number of relatively simple compounds but was incompatible with the functional groups present in complex molecules such as withanolide E. Since we desired to produce the dienone derivative of withanolide E,[8] a much more chemoselective approach has been sought. We present herein a highly effective approach for achieving this goal using organopalladium chemistry.

In one synthesis, 4β-acetoxywithanolide E[11] (**4**) was treated with 1 equiv of tetrakis(triphenylphosphine)palladium [$Pd(PPh_3)_4$] in benzene for 30 mn at room temperature, followed by flash chromatography on silica gel. This procedure (eq 2) afforded withaperuvin C (**2a**) in essentially quantitative yield (95% isolated).

The synthetic product and its acetate (**2b**) were identical in all respects with to authentic samples of withaperuvin C[6,12] and its acetate.

(1) (a) J. A. Cassady and J. D.. Douros, Eds., "Anticancer Agents Based on Natural Products Models", Academic Press, New York, 1980, p 247; (b) M. Suffness and J. Douros, *J. Nat. Prod.*, **45**, 1 (1982).

(2) (a) M. J. Begley, L. Crombie, P. J. Ham, and D. A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, 296 (1976); (b) K. R. S. Ascher, N. E. Neurny, M. Eliyahu, I. Kirson, A. Abraham, and E. Glotter, *Experimentia*, **36**, 998 (1980); (c) K. R. S. Ascher, H. Schmutterer, E. Glotter, and I. Kirson, *Phytoparsitica*, **9**, 197 (1981).

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(4) (a) A. Kajikawa, M. Morisaki, and N. Ikekawa, *Tetrahedron Lett.*, 4135 (1975); (b) M. Ishiguro, M. Hirayama, H. Saito, A. Kajikawa, and N. Ikekawa, *Heterocycles*, **15**, 823 (1981); (c) M. Ishiguro, A. Kajikawa, T. Haruyama, Y. Ogura, M. Okubayashi, M. Morisaki, and N. Ikekawa, *J. Chem. Soc., Perkin Trans. 1*, 2295); (d) I. Kirson, G. Gunzberg, H. E. Gottlieb, and E. Glotter, *Ibid.*, 531 (1980); (e) M. Weissenberg, D. Lavie, and E. Glotter, *Ibid.*, 795 (1977); (f) M. Hirayama, K. Gamah, and *N.* Ikekawa, *Chem. Lett.*, 49 (1981). (g) E. Glotter, M. Zviely, and I. Kirson, *J. Chem. Res. Synop.*, 32 (1982); *J. Chem. Res., Miniprint*, 373 (1982).

(5) (a) R. Tschesche, H. Schwang, and G. Legler, *Tetrahedron*, **22**, 1121 (1966). (b) R. Tschesche, H. Schwang, H. W. Fehlhaber, and G. Snatzke, *Ibid.*, **22**, 1129 (1966).

(6) M. Sahai, P. Neogi, A.B. Ray, Y. Oshima, and H, Hikino, *Heterocycles*, **19**, 37 (1982).

(7) L. R. Row, K. S. Reddy, N. S. Sarma, T. Matsuura, and R. Nakashima, *Phytochemistry*, **19**, 1175 (1980).

(8) I. Kirson, E. Glotter, M. Sahai, and E. Keinan, unpublished results.

(9) (a) Hirayama, S. Fukatsu, and N. Ikekawa, *J. Chem. Soc. Perkin Trans 1*, 88 (1981). (b) M. Ishiguro, A. Kajikawa, T. Haruyama, M. Morisaki, and N. Ikekawa, *Tetrahedron Lett.*, 1421 (1974).

(10) M. Hirayama, K., Gamoh, and N. Ikekawa, *J. Am. Chem. Soc. 104*, 3735 (1982).

(11) I. Kirson, A. Abraham, P. D. Sethi, S. S. Subramanian, and E. Glotter, *Phytochemistry*, **15**, 340 (1976).

(12) We are grateful to Prof. A. B. Ray for providing us with an authentic samle of withaperuvin C.

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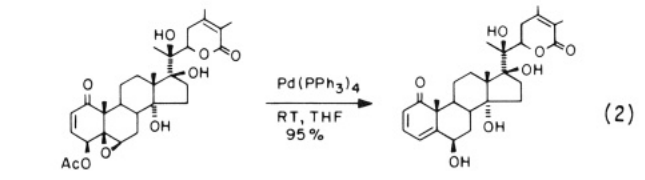


4β Acetoxy withanolide E — Withaperuvin C

4 — 2a

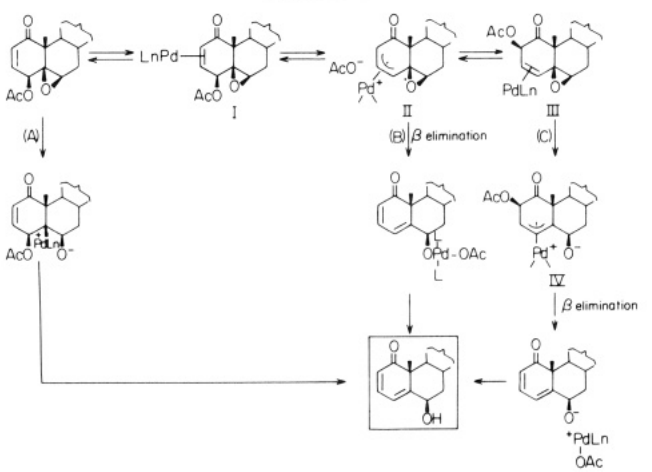
Similarly, jaborosalactone B[5] 27-acetate (**1b**) was easily obtained by the same procedure from withaferin A diacetate (**5**;[14] Table I). The synthetic product as well as its acetate derivative were identical in all respects with authentic samples of **1b** and **1c**, respectively.

Three new withanolide derivatives not yet found in nature, **7a**, **9a**, and **11a**, and their acetates, **7b**, **9b**, and **11b**, respectively, were obtained quantitatively under the same set of conditions from withanolide D 4-acetate[13] (**6**), physapubescin diacetate[15] (**8**), and ixocarpalactone A 4,16,22-triacetate[16] (**10**), respectively (Table I).

Although the best results were obtained when stoichiometric amounts of $Pd(PPh_3)_4$ were employed, it is conceivable that this reaction may also be carried out with a catalytic amount of Pd(0). From the results given in Experimental Section, it is apparent that palladim can in fact be used in catalytic quantities. However, yields are significantly lower, and turnover numbers are never greater than 2. Several reducing agents were included in the reaction mixture in order to regenerate the Pd(0) catalyst. Unfortunately, addition of hydroquinone, ferrous ammonium sulfate, cerrous sulfate, or stannous chloride did not improve the reaction significantly. For example, reaction of withaferin A diacetate (**5**) with 17% $Pd(PPh_3)_4$ and 4 equiv of one of the above reducing agents resulted in product **1b** in 50–55% yield. Reducing agents such as hydrazine or chromous chloride were incompatible with the substrate and led to complex mixtures of decomposition products.

One may envision several mechanistic pathways for the reaction (Scheme I). Path A, involving direct epoxide opening by palladium, does not seem to be a favorable process although there are some reports of the opening of nonallylic epoxides by palladium[17] and by molybdenum[18] complexes. Path B involves initial complexation of palladium to the olefin to give the η^2 complex I followed by formation of (π-allyl)palladium complex II which may undergo trans β elimination (the reverse process of trans oxypalladation[19]), leading to the final dienone system. Path C involves allylic isomerization of the 4β-acetate function leading to an isomeric allylic acetate, III, which is also an allylic epoxide. Allylic epoxides were shown to

Scheme I



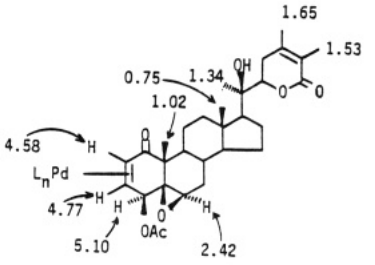


Figure 1. ^1H NMR chemical shifts of intermediate A.

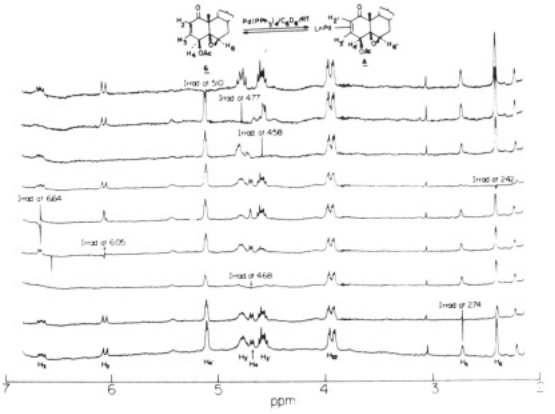


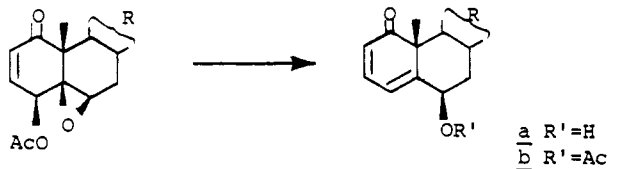
Figure 2. Spin saturation transfer between intermediate A and compound 6. Lower spectrum is a normal undecoupled ^1H NMR spectrum of **6** and intermediate A in C_6D_6 solution taken 35 min after addition of $Pd(PPh_3)_4$. The next four spectra are the results of sequential irradiation at absorptions related to protons of compound **6** (designated as H_2, H_3, H_4, and H_6). The upper four spectra are the results of sequential irradiation at absorptions related to protons of intermediate A (designated as $H_{2'}$, $H_{3'}$, $H_{4'}$, and $H_{6'}$).

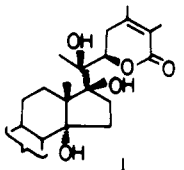
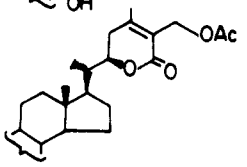
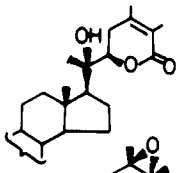
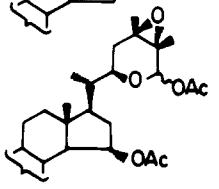
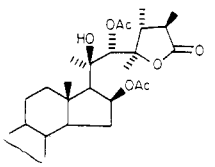
serve as useful precursors to (π-allyl)palladium complexes.[20] Therefore, the formation of an alternative (π-allyl)palladium intermediate at carbon atoms 3, 4, and 5 (IV) from III is a plausible process. This complex may undergo subsequent trans deacetoxypalladation[19d-f] to give the final dienone functionality.

For further clarification the mechanism operating in reactions of the epoxy function of withanolides with Pd(PPh)$_4$, the reaction of withanolide D 4-acetate (**6**) with

(13) D. Lavie, I. Kirson, and E. Glotter, *Isr. J. Chem.*, **6**, 671 (1968).
(14) D. Lavie, E. Glotter, and Y. Shvo, *J. Org. Chem.*, **30**, 1774 (1965); *J. Chem. Soc.*, 7517 (1965).
(15) I. Kirson, H. E. Gottlieb, and E. Glotter, *J. Chem. Res., Synop.*, 125 (1980); *J. Chem. Res. Miniprint*, 2134 (1980).
(16) I. Kirson, A. Cohen, M. Greenberg, H. E. Gottlieb, E. Glotter, P. Varenne, and A. Abraham, *J. Chem. Res., Synop.*, 1034 (1979); *J. Chem. Res., Miniprint*, 1178 (1979).
(17) M. Suzuki, A. Waranabe, and R. Noyori, *J. Am. Chem. Soc.*, **102**, 2095 (1980).
(18) H. Alper, D. Des. Roches, T. Curst, and R. Lequalt, *J. Org. Chem.*, **41**, 3611 (1976).
(19) (a) J. E. Backvall, P. Akermark and S. O. Ljunggren, *J. Am. Chem. Soc.*, **101**, 2411 (1979); (b) T Hosokawa, T. Uno, S. Inui, and S. I. Murahashi, *Ibid*, **103**, 2318 (1981); (c) J. K. Stille and R. Divakaruni, *J. Organomet. Chem.*, *169*, 239 (1979); (d) I. Arai, T. D. Lee, R. Hanna, and G. D. Daves, Jr., *Organometallics*, **1**, 742 (1982), and references cited therein; (e) P. M. Henry and G. A. Ward, *J. Am. Chem. Soc.*, **93**, 1494 (1971). (f) S. Wolfe and P. G. C. Campbell, *Ibid.*, **93**, 1497 (1971); (g) T. Majima and H. Kurosawa, *J. Chem. Soc., Chem. Commun.*, 610 (1977).
(20) (a) B. M. Trost and G. A. Molander, *J. Am. Chem. Soc.*, **103**, 5969 (1981). (b) J. Tsuji, H. Kataoka, and Y. Kobayashi, *Tetrahydron Lett.*, 2575 (1981). (c) M. Suzuki, Y. Oda, and R. Noyori, *J. Am. Chem. Soc.*, **101**, 1623 (1979).

Table I. Interconversions of Naturally Occurring Withanolides



starting material	partial structure (R)	product[a]	yield,[b] %	mp, °C (solvent)
4		2b	95	155 (MeOH)
5		1c	99	amorphous
6		7b	95	144-145 (C_6H_6)
8		9b	94	124-126 (C_6H_6-EtOAc)
10		11b	97	amorphous

[a] For practical reasons all products were acylated before isolation. [b] One equivalent of $Pd(PPh_3)_4$ was used, and the reactions were carried out at room temperature for 30 min.

the Pd(0) reagent was continuously followed by ^1H NMR (270 MHz). The resulging spectra (see the paragraph at the end of the paper about supplementary material) show the formation of two distinct intermediates, A and B, during the reaciton.

Intermediate A was formed very rapidly upon addition of $Pd(PPh_3)_4$ to the starting material in C_6D_6 solution. We assign this intemediate as the η^2 palladium complex I (Scheme I) on the basis of its NMR spectrum as shown in Figure 1.

The above assignment was further supported by the observation of spin saturation transfer[21] between the starting material and intermediate A. This interesting phenomenon clearly indicates that a rapid exchange (of the order of a few seconds) occurs between these two species. Moreover, it allowed us to assign unambiguously the four downfield signals related to the protons at positions 2–4 and 6 on the basis of several double resonance experments, in which irradiation of these protons in intermediate A was shown to affect the corresponding protons in the starting material via the mechanism of spin saturation transfer (Figure 2). Conversely, irradiation of these protons in the starting material was found to affect the corresponding H's in intermediate A (Figure 2). Very similar behavior was observed by treating a simpler model compound, benzalacetone (12), with $Pd(PPh_3)_4$ (see the paragraph at the end of the paper about supplementary material).

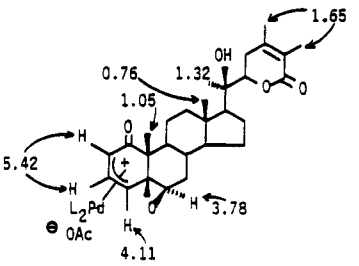


Figure 3. ^1H NMR chemical shifts of intermediate B.

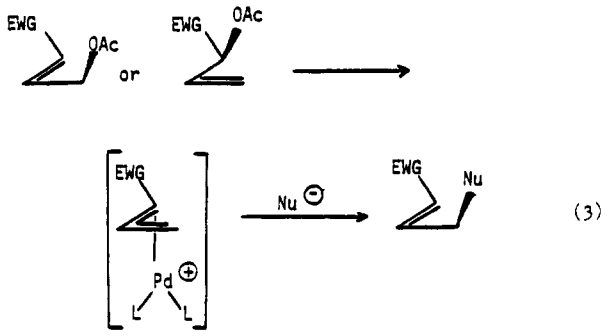
The formation of intermediate B from intermediate A is a relatively slow process, as can be seen from the ^1H NMR spectrum. We assign this intermediate to be the η^3 palladium complex II (Scheme I) as shown in Figure 3.

Intermediate B is quite stable, with a lifetime on the order of 10 h in neutral benzene solution. However, one would expect that conversion of intermediate B to the final dienone via epoxide opening should be facilitated by catalytic amounts of acid. Indeed, addition of traces of

(21) (a) S. Forsen and R. A. Hoffman, *Acta Chem. Scand.*, 17, 1787 (1963); *J. Chem. Phys.*, 39, 2892 (1963); (b) D. Cheshnovsky and G. Navon, *Biochemistry*, 19, 1866 (1980), and references cited therein.

acetic acid-d_4 to the reaction mixute in C_6D_6 pushed the reaction to completion within 1 h, and intermediate B was no longer observed in the NMR trace of the reaction (see the paragraph at the end of the paper about supplementary material).

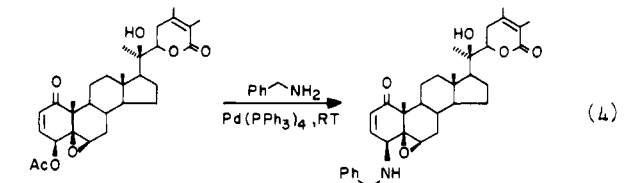
The formation of the (π-allyl)palladium intermediate B was also supported by chemical evidence. Nucleophilic attack by "soft" nucleophiles and amines on such electrophilic (π-allyl)palladium complexes would be expected to occur from the face opposite the palladium atom, at either end of the allylic unit.[22] However, when the allylic system is conjugated to an electron-withdrawing group (EWG), the nucleophilic attack occurs regioselectivity at the allylic position remote from that group[23] (eq 3).



(3)

Therefore, trapping of the (π-allyl)palladium intermediate II by a primary amine[24] is expected to result in the 4β-amino derivative.

Indeed, treatment of withanolid D 4-acetate (**6**) with benzyl amine and $Pd(PPh_3)_4$ in THF at room temperature resulted in the expected amino derivative **13** as the sole product (eq 4).



(4)

6 13

Further applications of organopalladium chemistry for other useful transformation in the withanolide series such as specific reductions[25] and highly controlled amination reactions are now under investigation.

Experimental Section

General Remarks. Melting points (uncorrected) were determined on a Fisher-Johns apparatus. Elemental analyses were performed in the microanalytical laboratory of the Weizmann Institute of Science. ^1H NMR spectra were recorded at 270 MHz on a Bruker WH-270 NMR spectrometer. ^{13}C NMR spectra were recorded at 22.63 MHz on a Bruker WH-90 NMR spectrometer, with the aid of Fourier transform analysis, and were proton-noise decoupled. Chemical shifts in both ^1H and ^{13}C NMR spectra were measured relative to tetramethylsilane (δ 0.00). Splitting paterns are designated as follows: s, singlet: d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Ultraviolet spectra were recorded of

Table II. ^1H NMR Data[a]

	compd											
proton	1b[b]	1c[b]	2a	2b[b]	7a	7b[b]	9a[b]	9b[b]	11a[b]	11b[b]	13[b]
2H	6.02 (d; 9.7)	6.00 (dd; 9.7, 1.2)	6.02 (dd; 9.7, 0.9)	6.03 (dd; 9.7, 0.6)	6.04 (d; 9.7)	6.09 (dd; 9.7, 1.2)	6.00 (d; 9.7)	6.05 (dd; 9.7, 1.2)	6.00 (d; 9.7)	6.05 (d; 9.7)	6.17 (d; 9.7)
3H	6.91 (dd; 9.7, 6.1)	6.90 (dd; 9.7, 6.1)	6.90 (dd; 9.7, 5.9)	6.93 (dd; 9.7, 5.9)	6.92 (dd; 9.7, 6.2)	6.95 (dd; 9.7, 5.9)	6.98 (dd; 9.7, 5.9)	6.95 (dd; 9.7, 5.9)	6.88 (dd; 9.7, 5.9)	6.95 (dd; 9.7, 5.9)	6.89 (dd; 9.7, 6.2)
4H	6.11 (d; 6.1)	6.26 (d; 6.1)	6.13 (d; 5.9)	6.30 (d; 5.9)	6.15 (d; 6.1)	6.31 (d; 5.9)	6.07 (d; 5.9)	6.32 (d; 5.9)	6.06 (d; 5.9)	6.32 (d; 5.9)	2.87 (d; 6.2)
6H	4.57 (t; 2.1)	5.46 (t; 3.0)	4.65 (t; 2.6)	5.56 (t; 3.2)	4.59 (t; 2.7)	5.51 (t; 2.3)	4.54 (t; 2.8)	5.50 (t; 3.2)	4.54 (t; 2.7)	5.51 (t; 2.9)	3.02 (t)
22H	4.42 (dt; 12.9, 3.1)	4.38 (dt; 12.9, 3.1)	4.88 (dd; 11.5, 6.2)	4.87 (dd; 11.2, 6.2)	4.21 (dd; 13.0, 4.0)	4.25 (dd; 12.0, 4.0)	3.65 (dt; 8.0, 5.0)	3.83 (dt; 10.2, 4.1)	5.09 (s)	5.09 (s)	4.20 (dd; 13.0, 4.0)
18H	0.79 (s)	0.76 (s)	1.19 (s)	1.21 (s)	0.97 (s)	0.97 (s)	0.79 (s)	0.84 (s)	1.21 (s)	1.24 (s)	0.83 (s)
19H	1.47 (s)	1.31 (s)	1.50 (s)	1.37 (s)	1.48 (s)	1.36 (s)	1.46 (s)	1.39 (s)	1.47 (s)	1.41 (s)	1.25 (s)
21H	1.03 (d; 7)	0.96 (d; 7)	1.41 (s)	1.42 (s)	1.28 (s)	1.28 (s)	0.91 (d; 6.8)	0.87 (d; 6.8)	1.40 (s)	1.26 (s)	1.26 (s)
27H	4.89 (q; 14.4, 12.0)	4.83 (q; 14.0, 2.0)	1.87 (s)	1.88 (s)	1.88 (s)	1.88 (s)	1.40 (s)	1.33 (s)	1.16 (d; 7)	1.17 (d; 7)	1.88 (s)
28H	2.07 (s)	2.02 (s)	1.94 (s)	1.94 (s)	1.95 (s)	1.95 (s)	1.25 (s)	1.34 (s)	1.15 (d; 7)	1.16 (d; 7)	1.94 (s)

[a] Recorded at 270 MHz; solvent $CDCl_3$; δ values with multiplicity and coupling constants (in hertz) in parentheses. [b] Additional NMR data [δ (multiplicity; coupling constants in hertz)]. **1b**: C_{27} OAc, 2.05 (s). **1c**: C_6 and C_{27} OAc, 2.00 (s). **2b**: C_6 OAc, 2.05 (s). **7b**: C_6 OAc, 2.06 (s). **9a**: 15 H, 4.82 (dt, 9.5, 3.0); 26 H, 6.13 (s). C_{15} and C_{26} OAc: 1.99 (s). **9b**: 15 H, 4.86 (dt; 9.5, 3.0); 26 H, 6.12 and 6.02 (s). C_6, C_{15}, and C_{26} OAc: 2.02 (s), 2.05 (s), and 2.16 (s). **11a**: 16 H, 5.33 (m), 23 H, 4.54 (d, 8.2). C_{16} and C_{22} OAc: 2.11 (s), 2.21 (s). **11b**: 16 H, 5.33 (m), 23 H, 4.54 (d; 8.0). C_6, C_{16}, and C_{22} OAc: 2.04 (s), 2.10 (s), and 2.21 (s). **13**: $C_6H_5CH_2$: 3.84 (q; 17.6, 13.5); $C_6H_5CH_2$, ~6.20 (m).

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Table III. ^{13}C NMR Data[a]

carbon	1c ($CDCl_3$)	2a (CD_3OD)	7b (CD_3OD)	7b ($CDCl_3$)	9b ($CDCl_3$)	11b ($CDCl_3$)	13
1	204.39	208.21	206.54	204.39	204.39	204.17	[b]
2	120.02	118.40	121.42	120.02	120.45	120.66	122.14
3	139.60	142.89	142.08	139.60	139.82	138.14	139.66
4	126.83	126.76	127.41	126.83	127.03	127.19	55.05
5	152.85	160.58	154.71	152.85	152.65	152.48	59.61
6	75.63	75.03	74.66	75.63	74.49	75.68	64.46
7	38.08	37.49	[b]	38.19	37.44	30.37	31.00
8	31.34	35.76	32.20	30.80	30.85	35.50	29.45
9	49.30	44.23	43.85	49.46	49.19	37.81	42.77
10	53.78	55.67	55.45	53.94	53.56	53.61	51.62
11	21.36	22.66	22.87	21.41	21.41	22.54	20.97
12	39.34	35.76	39.27	39.80	39.54	39.90	39.49
13	42.88	55.78	40.67	41.10	43.32	43.69	42.94
14	55.72	84.74	57.23	56.32	58.85	54.10	56.85
15	24.38	31.61	24.92	24.00	77.24	35.06	23.84
16	27.35	37.65	22.01	21.95	37.44	75.40	22.06
17	51.84	88.51	55.24	54.59	50.33	57.44	54.75
18	12.03	18.71	14.40	13.86	12.84	14.83	13.49
19	18.12	21.25	18.34	18.07	18.39	18.23	15.86
20	38.84	79.83	76.00	75.09	38.51	78.27	75.08
21	13.27	19.47	20.77	20.82	13.21	22.78	20.65
22	78.22	82.90	82.64	80.90	68.34	77.29	80.90
23	30.10	33.50	31.93	31.56	29.88	73.25	31.50
24	156.97	153.36	152.49	148.55	61.39	41.64	148.93
25	121.96	122.02	122.02	121.86	60.68	39.91	121.90
26	165.28	169.11	168.68	165.85	91.75	180.05	166.03
27	57.99	12.35	12.35	12.46	16.56	12.82	12.46
28	20.55	20.61	20.44	20.55	18.39	14.12	20.55
acetate	170.24, 169.91 (C=O)		171.75 (C=O), 21.25 (CH_3)	170.15 (C=O), 20.98 (CH_3)	170.24, 170.89 × 2 (C=O)	170.10, 169.26, 170.80 (C=O)	135.22, 128.86, 127.14[c]
	21.04 and 20.88 (CH_3)				21.04, 21.41 × 2 (CH_3)	21.52, 21.40 × 2 (CH_3)	39.59[d]

[a] Chemical shifts are in δ units relative to Me_4Si (δ 0.00). [b] Not detected. [c] All for $C_6H_5CH_2NH$. [d] For $ArCH_2NH$.

Table IV. Ultraviolet, Circular Dichroism, and Infrared Spectral Data

compd	UV (MeOH) λ_{max}, nm	CD, $[\theta]_{nm}$	IR ($CHCl_3$) ν_{max}, cm^{-1}
1b	218	$[\theta]_{400}$ 0, $[\theta]_{380}$ 0, $[\theta]_{345}$ −19 560, $[\theta]_{275}$ 0, $[\theta]_{248}$ +24 100	1718, 1703, 1690, 1660, 1388, 1365, 1218, 1203, 1173, 1015
2a	222, 314	$[\theta]_{430}$ 0, $[\theta]_{380}$ +7230, $[\theta]_{354}$ 0, $[\theta]_{313}$ −45 180, $[\theta]_{268}$ 0, $[\theta]_{245}$ +20 280	3576, 3464, 3412, 1708, 1682, 1645, 1357, 1241, 1210, 1119
7b	219	$[\theta]_{290}$ 0, $[\theta]_{250}$ +18 460	3590, 1745, 1714, 1674, 1392, 1253, 1142, 1010
9b	216	$[\theta]_{265}$ 0, $[\theta]_{215}$ +19 190	1732, 1697, 1645, 1369, 1257, 1139, 1058, 1030, 967, 934, 875
11b		$[\theta]_{310}$ 0, $[\theta]_{287}$ −60 000, $[\theta]_{211}$ −27 700	3560, 1782, 1758, 1752, 1745, 1655, 1255, 1235, 1212, 1166, 1115, 1040
13	219, 254	$[\theta]_{290}$ 0, $[\theta]_{253}$ +14 200	3560, 3100, 3029, 1763, 1693, 1642, 1358, 1318, 1235, 1212, 1072, 1012

methanol solutions by using a Cary-18 spectrophotometer. CD spectra were measured in methanol with a Cary 60 recording spectropolarimeter. Infrared spectra were taken of chloroform solutions, in a NaCl cell on a Nicolet instrument. High-resolution mass spectra were determined on a Varian MAT-731 spectrometer.

The progress of all reactions was monitored by thin-layer chromatography (TLC) which was performed on aluminum sheets precoated with silica gel (Merck, Kieselgel 60, F-254, Art. 5549). Flash chromatography was carried out on silica gel (Merck, Kieselgel 60, 230–400 mesh, Art. 9385). Preparative TLC was performed on glass plates precoated with silica gel (Merck, Kieselgel 60 F_{254}, Art. 5717).

Given below is representative experimental procedure illustrating the reactions carried out with stoichiometric quantities of palladium complex.

Conversion of 4β-Acetoxywithanolide E (4) into Withaperuvin C 6-Acetate (2b). To a solution of 4 (27.6 mg, 0.05 mmol) in 1.2 mL of benzene was added $Pd(PPh_3)_4$ (60.7 mg, 0.051 mmol) under an argon atmosphere, and the mixture was stirred at room temperature for 30 min (complete disappearance of starting material was evident from TLC analysis). Pyridine (0.5 mL) and acetic anhydride (1 mL) were added, and the mixture was stirred at room temperature for additional 8 h. The solvent was removed with an argon stream, and the residue was washed through a short bed of silica gel with ethyl acetate. The solvent was removed under reduced pressure, and the solid residue was further purified by flash chromatography with ethyl acetate/hexane (1:1) to furnish 27.3 mg (yield 95%) of withaperuvin C 6-acetate (**2b**), mp 155 °C (recrystallized from methanol).

Table I includes the results of all experiments carried out with stoichiometric amounts of Pd(0). Physical data and spectral characteristic are given in Tables II–IV.

The following is a representative experimental procedure for the reactions carried out with catalytic amounts of palladium.

Conversion of Withaferin A Diacetate (5) into Jaborosalactone B Diacetate (1c). To a solution of withaferin A diacetate (**5**; 77 mg, 0.138 mmol) in THF was added $Pd(PPh_3)_4$ (37 mg, 0.032 mmol, 24%) under an argon atmosphere, and the mixture was stirred at room temperature for 24 h and then worked up with pyridine and acetic anhydride as above. Final purification by flash chromatography yielded 44.2 mg (58%) of jaborosalactone B diacetate (**1c**) as an amorphous solid.

Similarly, compounds **4**, **6**, **8**, and **10**, when treated with 0.25 equiv of $Pd(PPh_3)_4$ at room temperature for 24 h followed by acetylation, gave rise to **2b** (63%), **7b** (65%), **9b** (39%), and **11b** (62%), respectively. Yields were calculated on the basis of recovered starting material.

Preparation of 4β-(Benzylamino)withanolide D (13). To a solution of withanolide D 4-acetate (**6**; (76 mg, 0.148 mmol) and benzylamine (43.6 mg, 0.297 mmol; 2 equiv) in THF was added $Pd(PPh_3)_4$ (43.6 mg, 0.037 mmol). The mixture was stirred for 45 min under an N_2 atmosphere (until no starting material could be detected by TLC). The solvent was removed by an argon stream, and the residue so obtained was washed with ethyl acetate through a short bed of silica gel. Further purification by preparative TLC (eluted with hexane/ethyl acetate, 3:7) afforded **13** [R_f 0.75; yield 56.2 mg (58%)] as an amorphous powder. Physical data and spectral characteristics are given in Tables II–IV.

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Registry No. **1b**, 6128-32-1; **1c**, 20045-65-2; **2a**, 81644-34-0; **2b**, 81644-36-2; **4**, 79396-43-3; **5**, 22848-79-9; **6**, 22848-70-0; **7a**, 85151-00-4; **7b**, 85151-01-5; **8**, 74747-53-8; **9a**, 85151-02-6; **9b**, 85151-03-7; **10**, 71801-59-7; **11a**, 85151-04-8; **11b**, 85151-05-9; **12**, 122-57-6; **13**, 85151-06-0; benzylamine, 100-46-9; $Pd(PPh_3)_4$, 14221-01-3.

Supplementary Material Available: ^1H NMR traces for the reaction between $Pd(PPh)_3$ and compound **6** in C_6D_6 and in acidic C_6D_6; spin-saturation-transfer experiment between benzalacetone and its Pd complex (3 pages). Ordering information is given on any current masthead page.

Total Synthesis of (±)-Justicidin P. A New Lignan Lactone from *Justicia extensa*[1]

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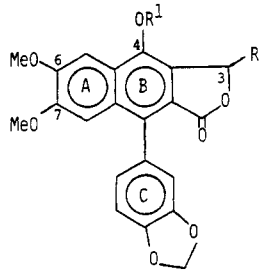
The total synthesis of (±)-justicidin P, a new lignan lactone from *Justicia extensa* (Acanthaceae), is described. Justicidin P exists at 25 °C as two rotamers, evidenced by proton NMR studies and confirmed by a theoretical calculation of the rotational barrier. Two other natural products, diphyllin and justicidin A, have also been synthesized.

In a continuing search for biologically active compounds from plant sources, Dr. N. G. Patel of our Department has studied the plant *Justicia extensa* (Acanthaceae), an African herbaceous plant obtained from Longwood Gardens, Kennett Square, PA. Extracts of its leaves show insecticidal and antiviral properties; the active principle, named justicidin P, was isolated and its structure determined as shown below on the basis of spectral data.[2] Justicidin P



1, R=OMe; R^1=Me (justicidin P)
2, R=H; R^1=Me (justicidin A)
3, R=R^1=H (diphyllin)

comprises about 1% of the dry leaves. Among hundreds of known natural lignans,[3] justicidin P is the first one which has a methoxy group on the lactone ring. Herein we describe a total synthesis of (±)-justicidin P, unambiguously confirming its structure.

Justicidin P is a C(3)-methoxylated derivative of justicidin A (**2**)[4] which can therefore be viewed as a synthetic precursor. Justicidin A, in turn, can be prepared from another natural lignan, diphyllin (**3**).[4a,5] Several syntheses of diphyllin and justicidin A have appeared in the literature.[6] A potentially convenient way to construct these arylnaphthalene lactones would involve conjugate addition of aryldithiane anion to 2-butenolide followed by alkylation with aryl aldehyde. In fact, several groups have successfully employed this methodology in the synthesis of various lignans.[7] We have thus synthesized diphyllin and justicidin A by this highly efficient route.[8]

With justicidin A in hand, the only remaining step would be introduction of the C(3) methoxy group. This was

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(2) The isolation and structure determination of justicidin P will be published elsewhere.

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(8) Justicidin A was prepared from 2-(3,4-dimethoxyphenyl)-1,3-dithiane in ca. 30% overall yield by the following transformations: (1) (a) *n*-BuLi, (b) 2-butenolide, (c) piperonal; (2) CF_3CO_2H; (3) HgO/BF_3–Et_2O; (4) $PyH^+Br_3^-/AcOH$;[9] (5) MeI/K_2CO_3.

(9) For aromatization of the B ring that gives diphyllin.

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