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STEREOSELECTIVITY QUESTIONS IN THE SYNTHESIS OF WIKSTROMOL

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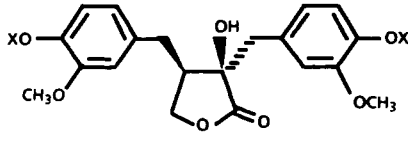
ABSTRACT.—While the Davis oxaziridine reagent generally affords oxidation products based on simple steric considerations, this concept appears to have some limitations when used to design natural product synthetic strategies. Thus, an example has been found in which the observed stereoselectivity of an enolate oxidation is "anomalous." The system in question involves an enolate oxidation performed on a lignan butyrolactone having highly oxygenated aromatic rings. Besides establishing the course of this oxidation and confirming the proposed structure of wikstromol and related lignans, a single-crystal X-ray study on a wikstromol stereoisomer provides complementary data for comparison with the "natural" isomer.

In 1988, we reported (1) the first successful total synthesis of racemic wikstromol. Wikstromol is one of those rare natural products in which the two enantiomers have acquired different names: "wikstromol" and "nortrachelogenin." Because the term "wikstromol" may be more familiar to medicinal chemists, we have chosen to use this name for the racemic material. More recently, Khamlach *et al.* (2) disclosed a preparation of (+)-wikstromol, (+)-[**1**], as well as the structurally related (−)-trachelogenin and (−)-nortrachelogenin. Wikstromol is a lignan prototype whose range of evoked biological responses includes moderate antineoplastic activity. Lee *et al.* (3) have demonstrated that MeOH extracts of the stems of "Nan-Ling-Jao-Hua" or "Po-Lun," a Chinese medicinal folklore remedy also identified by its botanical name as *Wikstroemia indica* C.A. Mey (Thymelaeaceae), exhibits inhibitory activity in vivo against Ehrlich ascites carcinoma and P-388 lymphocytic leukemia. Further work (3) identified wikstromol [(+)-nortrachelogenin] as a major antineoplastic constituent of these extracts.

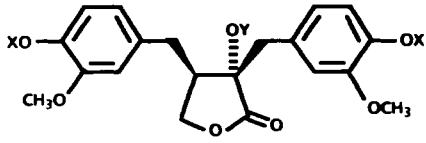
The strategy underlying our synthetic route to wikstromol involved an efficient oxidative coupling sequence in which a carboxylic acid dianion was converted into the corresponding dimeric diacid (1). This diacid, in turn, was transformed into a disubstituted butyrolactone by methodology analogous to that previously employed in successful syntheses of the naturally occurring lignans enterolactone (4) and hinokinin (5). The butyrolactone moiety, which contained two identical electron-rich aromatic rings each having a benzyl ether protecting group at the para position and a methoxyl substituent at the meta position, was then subjected to treatment with base to afford the corresponding enolate. Hydroxylation of the enolate with a variety of reagents was followed by deprotection to afford two isomeric racemic lignans, wikstromol, (±)-[**1**], and epiwikstromol, (±)-[**2**], thereby completing the synthesis.

Much attention was given in our original synthetic sequence to achieving optimal hydroxylation results. Reaction of the potassium enolate with molecular oxygen in the presence of triethyl phosphite leads in high conversion to a 1:1 mixture of the two racemic diastereoisomers (±)-**3** and (±)-**4**. Formation of the 1:1 mixture is quite reasonable considering how a small reagent, molecular oxygen, might react with the enolate intermediate. From the standpoint of our desire for a practical route to wikstromol, we were especially gratified to find that reaction of the potassium enolate with MoOPH (6,7) and with the Davis oxaziridine (8–11) gave (±)-**3** and (±)-**4** in ratios of 2.2:1 and 5.8:1, re-

spectively (1). Experimentally, compound (±)-**3** was less polar than compound (±)-**4** by both analytical tlc and preparative radial chromatography (development by 10% Et_2O/90% CH_2Cl_2). There was no question that deprotection of (±)-**3** gave a sample of synthetic racemic wikstromol identical by both ^1H and ^{13}C high field nmr spectroscopy with an authentic sample of (+)-**1**.



1 X=H
3 X=$CH_2C_6H_5$
6 X=Me



2 X=H, Y=H
4 X=$CH_2C_6H_5$, Y=H
5 X=$CH_2C_6H_5$, Y=$COC_{12}H_9$

Nevertheless, we were perplexed by the challenge of providing a satisfactory explanation of the observed stereoselectivity. Well-established precedent (8–11) for the bulky Davis oxaziridine suggests that attack should occur from the less hindered face of the enolate. Thus, approach of the electrophile to the enolate so as to keep the interaction of the bulky benzyl groups and the approaching oxidant to a minimum would lead to predominant formation of the diastereoisomer having both benzyl chains cis to one another. This analysis predicts that the major isomer from the hydroxylation should have been epiwikstromol and not wikstromol, just the opposite of what was observed. Thus, we were confronted with the bizarre situation of having successfully completed the synthesis of our target natural product only to realize that there still remained a serious uncertainty as to the relative stereochemistry in what had been prepared.

The simplest way to account for this anomaly would be for the accepted structure of wikstromol to be incorrect. While earlier published work (12–17) on the structure of wikstromol had been circumstantial, there were no obvious errors. Part of our concern arose from Capon and MacLeod (18). We attempted nOe experiments on several wikstromol and epiwikstromol derivatives with inconclusive results. Consequently, a single crystal X-ray study was undertaken.

Having both racemic wikstromol and racemic epiwikstromol, as well as the corresponding derivatives containing benzyl and methyl ethers in place of the free para-hydroxyl groups, provided a wide selection of crystalline materials having potential suitability for an X-ray study. Eventually, we were able to find a promising derivative in the epiwikstromol series. Thus, treatment of the benzyl-ether protected epiwikstromol derivative **4** with NaH gave the corresponding alkoxide, which in turn was reacted with 4-biphenylcarbonyl chloride to afford the racemic acylated derivative **5**. The crude colorless syrup crystallized after trituration with Et_2O. From the resulting solid mass a suitable crystal was selected and mounted on a diffractometer, and its X-ray analysis was completed. From the X-ray analysis of the epiwikstromol derivative (Figure 1), we can ascertain that the two benzyl side chains are cis to each other with reference to the butyrolactone ring. Consequently, in wikstromol, the corresponding side chains must be trans to each other. Thus, these results are in total agreement with the earlier, non-crystallographic, structural studies.

While preparing our X-ray data for publication, we noted that Khamlach *et al.* (2) report in their paper that they also have completed (19) a single crystal X-ray determination on racemic methyltrachelogenin [**6**], a molecule that has

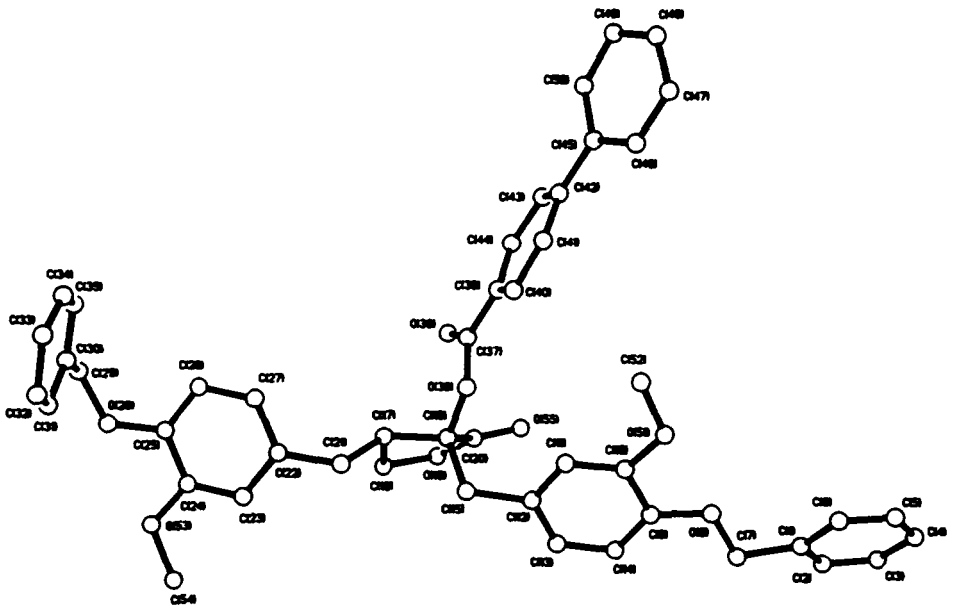


FIGURE 1. Perspective drawing of X-ray structure of (±)-**5**.

TABLE 1. Atomic Coordinates for Compound (±)-**5** (Angstroms × 10^4) and Their ESDs for $C_{47}H_{42}O_8$.

Atom	*x*	*y*	*z*	Atom	*x*	*y*	*z*
C-1	3420 (*)[a]	7413 (5)	6889 (*)	C-29	−655 (7)	547 (5)	−5730 (13)
C-2	3160 (7)	8097 (7)	7037 (15)	C-30	−52 (7)	98 (5)	−5325 (12)
C-3	3418 (9)	8479 (7)	8258 (20)	C-31	343 (8)	300 (6)	−5833 (14)
C-4	3933 (10)	8174 (9)	9317 (17)	C-32	891 (10)	−84 (12)	−5460 (21)
C-5	4173 (7)	7504 (10)	9170 (15)	C-33	1100 (12)	−696 (16)	−4543 (24)
C-6	3927 (6)	7116 (6)	7982 (12)	C-34	704 (13)	−890 (11)	−4049 (19)
C-7	3145 (7)	7063 (6)	5487 (12)	C-35	138 (8)	−509 (7)	−4407 (14)
O-8	3157 (5)	6263 (3)	5522 (10)	O-36	1524 (5)	3341 (3)	1974 (10)
C-9	2824 (6)	5872 (5)	4301 (12)	C-37	1161 (6)	2975 (4)	2455 (11)
C-10	2899 (6)	5032 (4)	4395 (11)	O-38	586 (5)	3016 (3)	1925 (10)
C-11	2558 (6)	4576 (4)	3257 (11)	C-39	1549 (6)	2506 (4)	3724 (11)
C-12	2132 (6)	4919 (5)	2030 (11)	C-40	2189 (6)	2325 (4)	4211 (11)
C-13	2072 (6)	5732 (4)	1947 (11)	C-41	2514 (6)	1895 (4)	5402 (11)
C-14	2410 (6)	6195 (5)	3064 (12)	C-42	2212 (6)	1676 (4)	6178 (11)
C-15	1751 (6)	4398 (4)	813 (11)	C-43	1576 (6)	1865 (4)	5675 (11)
C-16	1210 (6)	3912 (4)	869 (11)	C-44	1237 (6)	2256 (4)	4452 (11)
C-17	756 (6)	3510 (4)	−472 (10)	C-45	2562 (6)	1240 (5)	7483 (11)
C-18	241 (6)	4141 (4)	−1136 (11)	C-46	3205 (6)	1354 (5)	8321 (12)
O-19	226 (6)	4585 (3)	−21 (10)	C-47	3523 (7)	944 (6)	9515 (13)
C-20	765 (6)	4443 (4)	1136 (12)	C-48	3184 (8)	397 (6)	9872 (13)
C-21	1049 (6)	3260 (4)	−1392 (10)	C-49	2549 (7)	269 (6)	9071 (13)
C-22	594 (6)	2763 (4)	−2589 (11)	C-50	2240 (6)	690 (5)	7885 (12)
C-23	315 (6)	3073 (4)	−3898 (11)	O-51	3330 (5)	4733 (3)	5628 (10)
C-24	−99 (6)	2595 (5)	−4971 (11)	C-52	3366 (7)	3891 (5)	5785 (13)
C-25	−215 (6)	1807 (4)	−4763 (12)	O-53	−375 (5)	2838 (3)	−6307 (10)
C-26	56 (6)	1513 (5)	−3467 (11)	C-54	−232 (6)	3635 (5)	−6554 (11)
C-27	448 (6)	1999 (5)	−2396 (11)	O-55	853 (5)	4750 (3)	2188 (10)
O-28	−612 (5)	1383 (3)	−5897 (10)				

[a](*) Indicates parameters constrained to define the origin in the monoclinic space group Cc (No. 9).

been unambiguously correlated to racemic wikstromol [**1**]. Not only is their work on racemic methyltrachelogenin confirmed by the results obtained with our racemic epiwikstromol derivative, but there is an important additional benefit. While there are only a limited number of published X-ray structure determinations on biologically active lignans (20), here is a fortuitous circumstance in which there now become available successful X-ray work and supporting high field nmr studies on two similar lignan derivatives whose major difference is in the relative configuration at two contiguous chiral centers.

With the structure of wikstromol now secure, how can we rationalize the observed behavior of the hydroxylation reagents? Considerable evidence has been published supporting the view that the chemical behavior of both MoOPH and the Davis oxaziridine is largely driven by sterics (6–11). A possible explanation for formation of the more congested *trans*-benzylic diastereoisomer characteristic of wikstromol invokes the Hammond postulate (21). A late, product-like transition state represents a situation that would be compatible with the observed stereoselectivity. This would necessitate a markedly endothermic reaction. However, the observed rapid enolate oxidation at $-78°$ is hard to reconcile with strong endothermicity. Still another potential explanation is the occurrence of some type of special initial complexation between the oxidant and the butyrolactone enolate, followed by delivery of oxygen to the alpha carbon atom of the lactone enolate. A stacking interaction between the oxaziridine (or MoOPH) and that highly oxygenated benzylic substitutent which is constrained to be out of the plane of the lactone enolate moiety might occur just prior to delivery of the oxidant. This would result in the two benzylic substituents of the favored product being trans to one another, just as observed. For several well-known reagents, binding to the substrate does take place prior to delivery of the reagent. For example, there exist publications on directed delivery of peracids to cyclohexenols (22–25) as well as the work of Evans and Morrissey (26) on stereoselective hydrogenation brought about by preliminary interaction of an organometallic reagent with suitably placed hydroxyl groups.

Natural product chemists have generally observed straightforward sterically-driven behavior with both MoOPH and the Davis oxaziridine. For example, Davis *et al.* (10) used molecular models to predict the stereochemistry of an enolate oxidation and were then able to confirm the prediction by a single crystal X-ray analysis of the major product. It is also prudent, however, to remain aware that, at least with certain types of substrates, other subtle stereoelectronic factors may play a dominant role in product determination. Exploration of the generality of this phenomenon with additional model substrates is underway.

EXPERIMENTAL

The more polar hydroxylated diastereoisomer (the precursor to epiwikstromol upon debenzylation via catalytic hydrogenolysis; 0.098 g, 0.177 mmol) was dissolved in THF (4 ml). The resulting solution was added slowly under N_2 to a precooled 0° suspension of NaH (a 60% oil dispersion that had been washed 3× with ligroin; 0.011 g, 0.26 mmol) in THF (1 ml). The mixture was stirred at 0° for 0.5 h and at room temperature for 0.5 h and then recooled to 0°. The 4-biphenylcarbonyl chloride (0.038 g, 0.177 mmol) in THF (2 ml) was added, and the resulting clear faint yellow solution was stirred at room temperature while the reaction was monitored by tlc. After 3 h, saturated NH_4Cl solution (5 ml) and Et_2O (10 ml) were added and the layers separated. The aqueous layer was re-extracted with Et_2O (10 ml), and the combined organic layers were washed with saturated brine (5 ml), dried over $MgSO_4$, and filtered, and the volatiles were removed in vacuo. The crude material was purified by radial chromatography (1 mm plate, development and elution with 1% Et_2O in $CHCl_2$) to afford the pure ester **5** as a colorless glass (0.027 g, 21%). Upon trituration of the glass with anhydrous Et_2O, there formed a mass of small crystals (mp 126–128°) from which a crystal suitable for the X-ray study was selected.

COMPOUND (±)-**5**.—^{1}H nmr ($CDCl_3$, 300 MHz) δ 7.976 (d, J = 8.1 Hz, 2H), 7.628 (d, J = 8.4 Hz, 2H), 7.591 (d, 1H), 7.50–7.25 (m, 14H), 6.914 (s, 1H), 6.835 (s, 2H), 6.739 (d, J = 7.8 Hz, 1H), 6.625–6.575 (m, 2H), 5.121 (s, 2H), 5.054 (s, 2H), 4.326 (ca. t, J = 8.4 Hz, 1H), 3.845 (s, 3H), 3.722 (s, 3H), 4.00–3.60 (m, obscured by other peaks, 1H), 3.671 (dd, J = 10.2, 9.2 Hz, 1H), 3.459 (d, J = 14.4 Hz, 1H), 3.213 (d, J = 14.4 Hz, 1H), 3.076 (dd, J = 13.8, 6.3 Hz, 1H), 2.835 (dd, J = 13.8, 9.6 Hz, 1H); ^{13}C nmr ($CDCl_3$, 75 MHz) δ 173.09, 164.71, 156.20, 149.92, 149.28, 147.69, 147.12, 146.35, 139.71, 137.03, 130.45, 130.31, 128.98, 128.51, 128.34, 127.99, 127.82, 127.28, 127.20, 127.03, 125.78, 123.02, 120.45, 114.35, 113.62, 112.01, 81.82, 71.08, 70.97, 69.23, 55.99, 42.87, 37.13, 32.06; ir ($CHCl_3$) 3015, 2945, 1785, 1715, 1605, 1505, 1455 cm^{-1}.

X-RAY[1].—A colorless needle of (±)-**5**, dimensions 0.18 × 0.22 × 0.28 mm, was selected. All measurements were collected on a Nicolet R3m diffractometer system using MoKα radiation (λ = 0.71073 Å). Two quadrants of data were collected from 3–45° in 2θ. Unit cell parameters were determined by least squares fit of 25 reflections, which yielded a = 23.523 (4), b = 16.739 (2), c = 11.137 (2) Å, β = 117.68 (1)° and V = 3883.3 (9) Å^3. For Z = 4 the computed denisty was 1.26 g/cc. Examination of systematic extinctions indicated that the monoclinic crystal belonged to space group *C2/c* or *Cc*. Data collection and reduction gave 3022 reflections with F>4σ (F).

The structure was successfully solved by direct methods (XS:TREF) in the monoclinc space group *Cc* and refined by full-matrix least squares. The non-hydrogen atoms were refined with anisotropic temperature parameters, hydrogen atoms were allowed to ride on their respective carbons (C-H = 0.96 Å) with fixed hydrogen isotropic temperature parameters U(H) = 0.08, an extinction correction was made, and a weighting scheme based on σ(F) was employed. The final residuals were R(F) = 0.0527 and wR(F) = 0.0525 with a value of 1.12 for the goodness-of-fit. The largest and mean |shift/esd| in the final cycle were 0.001 and 0.000, and the minimum and maximum excursions in the final difference map were −0.28 and 0.29 e−/Å^3, respectively.

[1]Atomic coordinates for this structure have been deposited with the Cambridge Crystallographic Data Centre and can be obtained on request from Dr. Olga Kennard, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K.

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