Tetrahedron Letters Vol. 21, pp 1209 - 1212 0040-4039/80/0322-1209$02.00/0

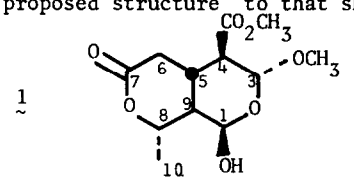
BIOMIMETIC CHEMISTRY OF XYLOMOLLIN[1]

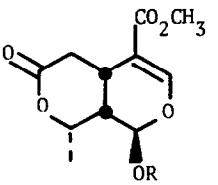
Saifunnissa B. Hassam and C. Richard Hutchinson*[2]

School of Pharmacy, University of Wisconsin,
Madison, Wisconsin 53706

Abstract: Kingiside aglucon (2b) undergoes stereoselective addition of CH_3OH to its C(3,4) enol ether double bond to give a C(1,3,9) diastereomer of xylomollin (1), a secoiridoid aglucon that has insect antifeedant properties.

Xylomollin (1) is one example of the naturally-occurring cyclopentanomonoterpenes ("iridoids") that have potentially useful biological activity.[3] Nakanishi and co-workers isolated 1 from the fruit of Xylocarpus molluscensis (Meliaceae) through use of a biological assay which revealed that 1 has antifeedant properties against the African army worm.[4] We subsequently provided chemical and spectral evidence[5] that resulted in revision of the originally proposed structure[4] to that shown as 1.





2a, R = Glu
2b, R = H

The development of a practical synthesis of xylomollin is a worthwhile objective since 1 can be isolated in only small amounts from its natural source,[4] and since it represents the first example in Nature of a trans-fused iridoid (specifically, secoiridoid).[6] We have considered a biomimetic synthetic approach to 1, based on our suggestion[5] that kingiside (2a) might be the biosynthetic precursor of 1 in vivo. To test this idea, we have investigated the chemistry of kingiside aglucon (2b) to learn if it could be transformed into 1. We report now that although 2b has been converted only to a diastereomer of 1, the reactions that 2b undergoes in vitro reveal fascinating new chemistry heretofore undescribed in the iridoid literature.[6]

Conversion of 2b to 1 requires the stereoselective addition of CH_3OH across the C-3,4 enol ether double bond, and epimerization at C-9 to the 9(R) configuration. To this end we treated (-)-tetraacetyl-2a, obtained by acetylation of 2a isolated from the red fruit of Lonicera sp. growing on the Madison campus, successively with (a) absolute methanolic $NaOCH_3$ or K_2CO_3 in CH_3OH, (b) dry Biorex 70 (H^+) resin, and (c) β-glucosidase (pH 5 citrate-phosphate buffer, 25°C 12-24 hr). Two products were obtained from these reactions: kingiside aglucon (21-42% yield) and a compound lacking significant UV absorbance (8-27% yield). The kingiside aglucon was a 1:3.3 mixture of 2b and its C-1 anomer (3, Scheme 1) as determined by the relative areas of the signals assigned to H-1 in the ^1H NMR spectrum of the aglucon mixture. Detailed analysis of this spectrum established that the $^3J_{1,9}$ values of the aglucon (Table 1) are consistent with the conformational orientation $H\text{-}1_{eq}/H\text{-}9_{ax}$ in 3. This configurational assignment is opposite

Scheme 1. Major Reactions of Kingiside Aglucon (3).

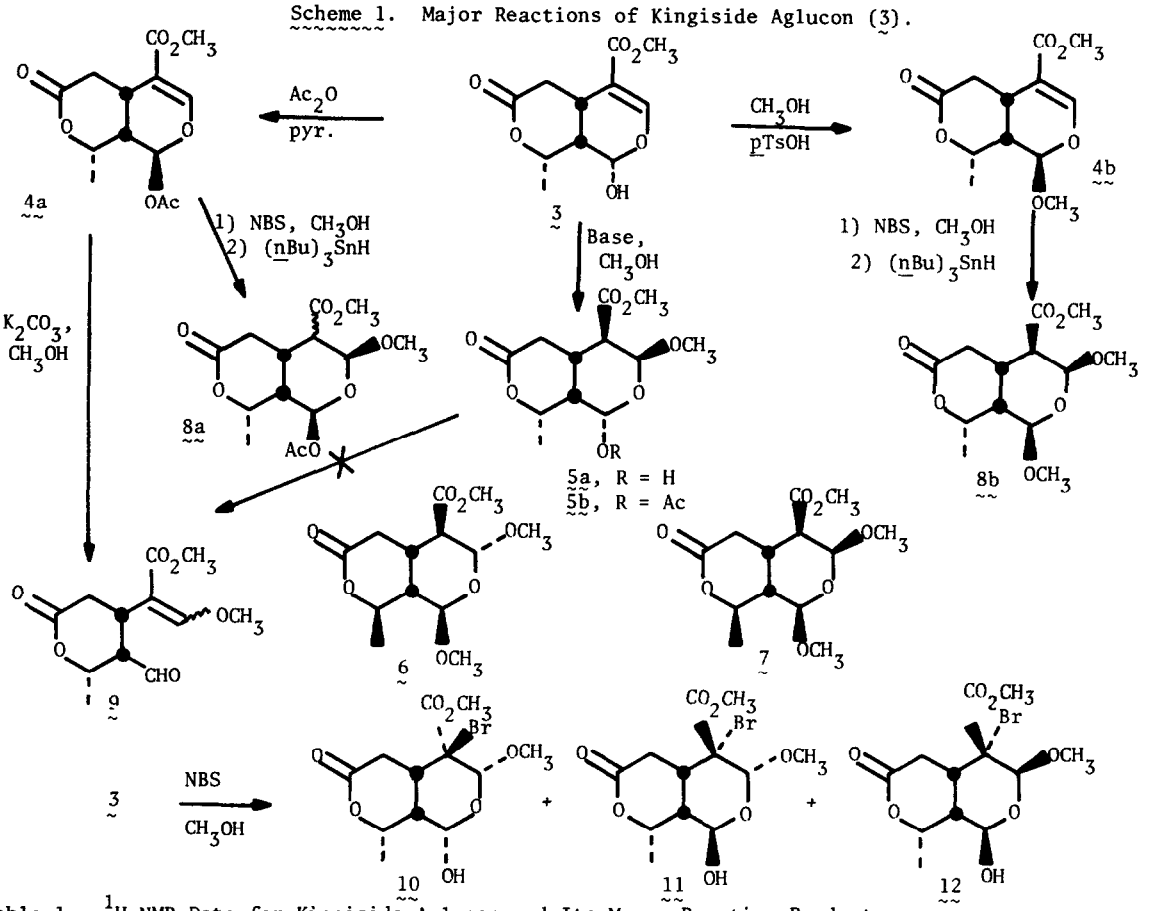


Table 1. ^{1}H NMR Data for Kingiside Aglucon and Its Major Reaction Products.

Compound	Vicinal Coupling Constants[a] (Hz)				
	$H_{1,9}$	$H_{3,4}$	$H_{4,5}$	$H_{5,9}$	$H_{8,9}$
2a	5.6	--	--	5.1	2.6
2b	8.8	--	--	6	2
3	2.4	--	--	6.5	2
4a	6.6	--	--	7	2.5
4b	8.0	--	--	5.0	2.4
5a	2.9	2.2	5	4.5	2.5
5b	2.7	1.7	6.2	5.0	2.4
6	2.4	7.7	11.4	4.8	9.6[b]
7	8.8	3.0	3.4	4.0	6.8[b]
8b	9.3	3.4	4	4	2
9	1.9	--	--	6.2	6.2

[a]Determined at 90 or 270 MHz in $CDCl_3$, $CDCl_3$ + D_2O, or C_6H_5N-d_5 by double irradiation experiments as necessary. [b]These values suggest that the solution conformation of 6 and 7 differ from that of the other secoiridoid lactones in the Table.

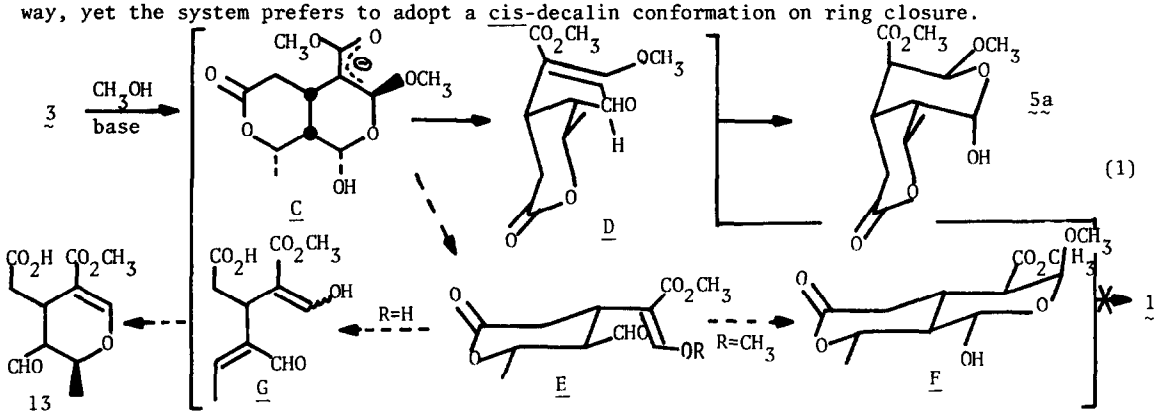
to that of the corresponding center in the 1-O-acetate (4a) and 1-O-methyl (4b) derivatives of 3, indicating that C-1 of kingiside aglucon easily undergoes anomerization. The $^3J_{5,9}$ and $^3J_{8,9}$ values of 3, 4a and 4b confirm that the relative stereochemistry of 2a was preserved on its conversion to these three aglucon compounds. This result is in contradistinction to the observation made by Inouye and co-workers[7] who documented that another secoiridoid, 8,10-dihydrosweroside, suffers C-9 racemization upon treatment with β-glucosidase and then Jones oxidation to an α-pyrone.

The structure of the second (non-UV absorbing) compound was the C-3 methanol adduct, 5a, of kingiside aglucon. Its general structural features were evident from the ^{1}H NMR spectrum (appearance of δ 3.68 resonance for OCH_3 and δ 5.16 for H-3) and UV spectrum (absence of 235 nm absorption). The high resolution electron impact mass spectrum of its 1-O-acetate (5b) showed principal ions at m/e 316(M^+), 285(M^+-OCH_3), 257(M^+-O_2CCH_3), 225(M^+-(OCH_3 + OAc + H)) and 183 (base, $C_9H_{11}O_4$). We assigned the relative stereochemistry of 5 to be as drawn based on the ^3J values listed in Table 1, from which it can be seen that the relative stereochemistry of 3 was preserved upon the trans addition of CH_3OH across its C-3,4 enol ether double bond. Subsequent experiments proved that 5 also resulted from 3 upon the latter's treatment with CH_3OH and a weak base (Et_3N, K_2CO_3 or KCN) in 56-67% yield.

The relative stereochemistry assigned to 5 was confirmed by the following data. (1) Comparison of the ^3J values for 5 with corresponding sites in 1[5] and in compounds 6[5] and 7[5] (Table 1) shows that 5 must be epimeric at C-3 to 1 and to 6, yet must have the same relative stereochemistry at H-1, H-4, H-5 and H-9 as 6 and as 7. (2) Bromomethoxylation of 4a and 4b (which results in β-addition of OCH_3 to C-3[5]) followed by reduction of the intermediate bromomethoxy adducts with $(n\text{-Bu})_3SnH$[5] gave compounds 8a and 8b. Although 8a was a ~1.5:1 mixture of C-4 epimers, 8b was a single diastereomer with $^3J_{3,4}$ = 3.4 Hz and $^3J_{1,9}$ = 9.3 Hz. The latter two pieces of data confirm the stereochemical identity at C-3 and C-4, and diastereo isomerism at C-1, of 5 and 8b.

Although the spectral data above clearly establish that 5 and 8 are cis-fused iridoids, two lines of chemical evidence indicate that these two compounds were formed via ring-opened intermediates. (1) Reaction of 3 with CH_3OD and Et_3N gave 5a whose ^{1}H NMR spectrum revealed that deuterium labeling was present at H-4 and at H-9; the area of both resonances was ca. 50% that of the area of the one proton signal for H-1. The mass spectrum of the deuterated compound corroborated that it contained ^{2}H at two sites: the M^+-31 fragment ions at m/e 243 (1.8%) had significant ions at m/e 244 (4.6%) and m/e 245 (3.1%) due to d_1 and d_2 species, respectively. (2) Bromomethoxylation of 3 gave three sets of compounds whose ^{1}H NMR spectra were consistent with their being diastereomeric at C-1, C-3 and C-4. The C-1 configuration of the major diastereomer (10, Scheme 1) was assigned the (α)OH orientation on the basis of its $^3J_{1,9}$ value, whereas C-1 in the minor products, 11 and 12, was assigned the (β)OH orientation for the same reason. The C-3 stereochemistry was determined from $^3J_{3,4}$ in the ^{1}H NMR spectra of the $(n\text{Bu})_3SnH$ derived reduction products. We conclude that the deuteration of 5a at C-9 and the formation of C-1/C-3 diastereomers during bromomethoxylation of 3, but not of 4a or of 4b, occurred through the intermediacy of a ring-opened aldehyde (D, eq 1). It thus appears that the stereoselectivity of methanol's addition to 3 is determined by influences other than

only a thermodynamic one because the possibility exists that the all trans- decalin ring system of xylomollin[5] (in which all large substituents are equatorial) could result in this way, yet the system prefers to adopt a cis-decalin conformation on ring closure.



One possible rationalization of this result is to postulate as follows. Methoxide must add only to the β-face of 3 → C, eq 1, which fragments stereoselectively to D, containing the 3Z enol ether double bond. Concerted addition of HO^- to D and ensuing ring closure could occur by stereospecific attack of OH^- from one of two directions. The direction leading to 5a (after stereoselective protonation of the C-4 enolate) must result in a product that does not undergo reversion to D, whereas a direction leading to the enolate of the C-1 epimer of 5a must result in a product that reverts to D (see below). Furthermore, the C-9 epimer, E, of D could undergo ring closure to F, but the resulting axial C-3 methoxyl would destabilize F and cause its reversion to D. Alternatively, E simply could undergo intramolecular trans, antiperiplanar elimination of carboxylate from C-8/9 to give products unrelated in structure to 5a or to 1.

We cite the following observations to support the above mechanistic rationalization. The fact that 5a was stable and 5b only underwent deacetylation to 5a in K_2CO_3/CH_3OH at 25°C, but that 4a rapidly underwent intramolecular ring fragmentation to give 9 as a 1·1 mixture of C-3 E/Z diastereomers is striking. These results imply that ring fragmentation of C, or the C-4 enolate of 5a, has tight stereoelectronic controls: fragmentation can occur only when the sigma bonds joining the anomeric oxygen, C-1, O-2, C-3 and C-4 (as the delocalized enolate) are mutually coplanar, i.e., all equatorially oriented (compare F and 5a, eq 1). Secondly, we did not find any products, e.g. 13, in reaction mixtures containing 5a or 9 that are known to be derived from noncyclic compounds (G) resulting from E (R=H) by β-elimination.[8] In fact, formation of 9 in CH_3OD resulted in <20% incorporation of ^2H at C-9 (by ^1H NMR analysis).

Since xylomollin fragments to E (R=CH_3) on treatment with acid[4] or base, we attempted to cause reclosure of 9 to 5a under acidic conditions (CF_3CO_2H, H_2O-THF) as model study for a possible synthesis of 1. The results of this experiment appeared to be negative (only one of the C-3 diastereomers of 9 was reisolated, but no 1, on a preparative scale).

References and Acknowledgements.[9]

(1) Supported in part by a research grant from the National Institutes of Health (CA 17127).
(2) Research Career Development Awardee of the National Cancer Institute (CA 00253), 1976-81.
(3) O. Sticher in "New Natural Products and Plant Drugs with Pharmacological, Biological and Therapeutical Activity", H. Wagner and P. Wolff, eds, Springer Verlag: Berlin, 1977. pp 145-156.
(4) Kubo, I., Miura, I. and Nakanishi, K. J. Am. Chem. Soc. 1976, 98, 6704.
(5) Nakane, M., Hutchinson, C. R., VanEngen, D. and Clardy, J. ibid. 1978, 100, 7079.
(6) cf. Plouvier, V. and Favre-Bonwin, J. Phytochemistry 1971, 10, 1697.
(7) Inouye, H., Toshida, T., Nakamura, Y. and Tobita, S. Chem. Pharm. Bull. 1970, 18, 1889.
(8) Brown, R. T., Chapple, C. L., Duckworth, D. M. and Platt, R. J. Chem. Soc. Perkin Trans. I 1976, 160; Kinast, G. and Tietze, L.-F. Chem. Ber. 1976, 109, 3640; Brown, R. T. and Chapple, C. L. Tetrahedron Lett. 1976, 787.
(9) We thank Dr. R. C. Kelly, Upjohn Company, for a gift of calcium elenolate; and Professor H. Mitsuhashi, Hokkaido University, for an authentic reference sample of (-)-kingiside. High resolution mass spectra were run by Mel Micke and Dr. H. K. Schnoes, UW Biochemistry Department; and high resolution NMR spectra by Jim Blackbourn, School of Pharmacy. We are especially indebted to Judith Lendowski for her assistance with the isolation of (-)-2a.

(Received in USA 24 December 1979)