type of dissymmetric system. Hence 2*R*:3*S*:4*S*:5*S*:6*S* applies to I.

(10R:11S:12R:13R) Coupled with Known (2S:3R) VIIe. N.m.r. analyses on Va and its variants[22] (*cf.* Chart I) disclosed the relative configuration ascribed to segment C-9, 10, 11, 12. Rotational properties in the V-series were consistent with a D-center at C-13, which provided the over-all D-*galacto* absolute configuration, as depicted.[23] This was confirmed *via* the alternate degradation route (Chart I), leading to known[24] (2*S*:3*R*)-2-acetamido-3-acetoxybutane (VIIe). Accordingly, specifications (10*R*:11*S*:12*R*:13*R*) are established in oleandomycin, completing the definition of all centers shown in I.[25]

(19) R. L. Lohmar, "The Carbohydrates," W. Pigman, Ed., Academic Press, Inc., New York, N.Y., 1957, pp. 241–267.

(20) N.m.r. (IIId in $CDCl_3$): C-3 H, C-5 H, complex splitting at τ 5.11; C-1, C-6 methylene, apparent doubled doublet at τ 6.08; OAc (4), τ 7.94 ± 0.01; C-6 Me, τ 9.01; C-2 Me, τ 9.06; C-4 Me, τ 9.10. The shielding relationship of the specific C-methyl groups are compatible with the configuration of P-1 but not P-2. All non-*meso* configurations at C-2,3,4 were also eliminated in these considerations (*cf.* ref. 1a).

(21) P-1 and P-2 represent known ABA types (*cf.* p. 28 and Chapters 5 and 14 in ref. 15) possessing predictable rotation and rotational shift following acetylation. The observed (+) for IIIc and (−) for IIId, and the (−) shift, are in accord with P-1; the opposite is expected for P-2.

(22) N.m.r. (Vd in $CHCl_3$): C-9 H, τ 4.58 (*J* (9a,10a) = 9 c.p.s.); C-11 H, τ 5.26 (*J* (11a, 10a/11a, 12e): 11/5 c.p.s.); C-13 H, τ 6.17 (*J* (13, 12/13, Me) = 2.5/7 c.p.s.); C-9 OAc, C-11 OAc, τ 7.87, 7.89; C-13 Me, C-10 Me, C-12 Me, τ 8.79, 9.04, 9.11 (all *J* = 7 c.p.s.); C-10 H and C-12 H, complex splitting pattern.

(23) J. A. Mills and W. Klyne, *Progr. Stereochem.*, **1**, 177 (1959).

(24) F. H. Dickey, W. Fickett, and H. J. Lucas, *J. Am. Chem. Soc.*, **74**, 944 (1952).

(25) Thanks are expressed to Dr. I. A. Solomons and to many research colleagues for their interest and stimulating discussions and to Dr. R. L. Wagner and his Physical Measurements Staff for analyses. Special gratitude is extended to Mr. M. Jefferson and Mr. C. Zervos for their technical assistance.

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Macrolide Stereochemistry. II. Configurational Assignments at Certain Centers in Various Macrolide Antibiotics[1]

Sir:

This report reveals additional support for a thesis of predictable configurational uniformity among macrolide antibiotics. Occurrence of the same absolute configuration at anomeric centers, *i.e.*, α-L:β-D (*cf.* Klyne's rule[2,3]), in various macrolide glycosides and revision of controversial specifications, *i.e.*, (β-L),[4] (2*S*:4*R*),[5] (3*R*),[6] in erythromycin are noted.

(1) (a) Part I: *J. Am. Chem. Soc.*, **87**, 1797 (1965); (b) part III: *ibid.*, **87**, 1801 (1965); (c) footnote 2c in ref. 1a.

(2) W. Klyne, *Biochem. J.*, **47**, xli (1950).

(3) (a) T. Reichstein and E. Weiss, *Advan. Carbohydrate Chem.*, **17**, 65 (1962). (b) Klyne's rule (*cf.* pp. 98, 99 in ref. 3a), originally applied to steroid glycosides, is now regarded with an explicit 6-deoxypyranoside proviso to circumvent understandable exceptions involving D-glucosides (*cf.* ref. 3c,d). While the rule notably holds for oleandrose found in both macrolide and steroid glycosides (*cf.* Table I), it need not apply outside these fields. (c) R. Okazaki, T. Okazaki, J. L. Strominger, and A. M. Michelson, *J. Biol. Chem.*, **237**, 3025 (1962); S. Matsuhashi, *Federation Proc.*, **23**, 170 (1964). (d) Nucleotide-bound 4-keto-6-deoxy-α-D-glucose apparently serves as a common intermediate for both D- and L-6-deoxypyranosides in bacterial cell wall biosynthesis.[3c] It follows that while still nucleotide-bound the "completed" sugars possess the same anomeric configuration, *i.e.*, α-D- and β-L-; by invoking a *common* transferase mechanism involving *net inversion*, the resulting glycosides must occur as β-D- and α-L-, as observed and as empirically predicted by Klyne's rule.

The α-L:β-D Nature of Anomeric Centers. Table I covers cited and new assignments to anomeric centers in various macrolide[1c,7–19] and pertinent[3b] steroid[3a,20,21] glycosides involving pyranosides of known[7] 6-deoxyhexoses.

Either n.m.r.[22] or molecular rotational difference[2] (m.r.d.) or both of these methods were employed for analyses. Reference data stem from evident or predictable properties in keeping with known (hexose)[7] configuration[23] and preferred conformation[24] of the corresponding pyranoside in each case. The observed conformity suggests a biogenetic basis for Klyne's rule consistent with known ramifications of 6-deoxy sugar biosynthesis.[1c,3c,d]

Coupling of New Specifications (2R:3S:4S:9S) in Dihydroerythromycin with Established (8R:10R)[5,10] and (xylo-C-2,3,4)[6,25] in Erythromycin.[26] Confrontation in erythromycin of predictable (2*R*:3*S*:4*S*)[1b] and circumstantially derived (2*S*:3*R*:4*R*)[5,6] specifications prompted the following re-examination of established data. In recalling the isomeric pairs (A:B) of C_7 compounds (lactones, hydrazides, triols, *cf.* Chart I) derived from the nucleus of dihydroerythromycin by Gerzon, *et al.*,[10] one need only consider I and II for A as well as III and IV for B, *i.e.*, four sets of absolute configurational possibilities. However, it is now pointed out that a simple arithmetical process,[27,28]

(4) W. Hofheinz and H. Grisebach, *Ber.*, **96**, 2867 (1963).

(5) C. Djerassi, O. Halpern, D. I. Wilkinson, and E. J. Eisenbraun, *Tetrahedron*, **4**, 369 (1958).

(6) S. G. Batrakov and L. L. Bergelison, *Izv. Akad. Nauk, SSSR, Ser. Khim.*, **9**, 1640 (1964).

(7) For reviews see: (a) M. Berry, *Quart. Rev.* (London), **17**, 343 (1963); (b) H. Grisebach and W. Hofheinz, *J. Roy. Inst. Chem.*, 332 (1964).

(8) W. D. Celmer and D. C. Hobbs, Congress on Antibiotics, Prague, Czechoslovakia, June 15–19, 1964: (a) Abstract of Papers, p. 179; (b) Proceedings, Paper No. B2-262b, in press; (c) forthcoming complete manuscript.

(9) (a) P. P. Regna, F. A. Hochstein, R. L. Wagner, Jr., and R. B. Woodward, *J. Am. Chem. Soc.* **75**, 4625 (1953); (b) R. L. Wagner, F. A. Hochstein, K. Murai, N. Messina, and P. P. Regna, *ibid.*, **75**, 4684 (1953); (c) R. B. Woodward, *Angew. Chem.*, **69**, 50 (1957).

(10) K. Gerzon, E. H. Flynn, M. V. Sigal, Jr., P. F. Wiley, R. Monohan, and U. C. Quarck, *J. Am. Chem. Soc.*, **78**, 6396 (1956).

(11) P. F. Wiley, M. V. Sigal, Jr., O. Weaver, R. Monohan, and K. Gerzon, *ibid.*, **79**, 6070 (1957).

(12) P. F. Wiley, R. Gale, C. W. Pettinga, and K. Gerzon, *ibid.*, **79**, 6074 (1957).

(13) R. L. Hamill, M. E. Haney, Jr., M. Stamper, and P. F. Wiley, *Antibiot. Chemotherapy*, **11**, 328 (1961).

(14) R. B. Morin and M. Gorman, *Tetrahedron Letters*, 2339 (1964).

(15) (a) W. Keller-Schierlein and G. Roncari, *Helv. Chim. Acta*, **45**, 138 (1962); (b) *ibid.*, **47**, 78 (1964).

(16) J. D. Dutcher, D. R. Walters, and O. Wintersteiner, *J. Org. Chem.*, **28**, 995 (1963).

(17) O. Ceder, J. M. Waisvisz, M. G. Van der Hoeven, and R. Ryhage, *Acta Chem. Scand.*, **18**, 111 (1964).

(18) P. W. K. Woo, H. W. Dion, and Q. R. Bartz, *J. Am. Chem. Soc.*, **86**, 2724 (1964).

(19) (a) K. Murai, B. A. Sobin, W. D. Celmer, and F. W. Tanner, *Antibiot. Chemotherapy*, **9**, 485 (1959); (b) W. D. Celmer, unpublished studies regarding the isolation of D-desosamine from PA-133-A,B.

(20) W. Neumann, *Ber.*, **70**, 1547 (1937).

(21) C. W. Shoppee, R. E. Lack, and A. V. Robertson, *J. Chem. Soc.*, 3610 (1962).

(22) H. Conroy, *Advan. Org. Chem.*, **2**, 308 (1960).

(23) (a) Nomenclature Committee, Division of Carbohydrate Chemistry of the American Chemical Society, *J. Org. Chem.*, **28**, 281 (1963); (b) S. Furberg and B. Pedersen, *Acta Chem. Scand.*, **17**, 1160 (1963).

(24) R. E. Reeves, *Advan. Carbohydrate Chem.*, **6**, 107 (1951).

(25) In these laboratories, the n.m.r. spectrum ($CDCl_3$) of the known O-acetylanhydride of the *meso*-1,5-diacid corresponding to lactone-A (*cf.* ref. 10 and Chart I) showed *J* 10/10 c.p.s. at τ 4.93, *i.e.*, *J* 3a,2a/3a,4a (*xylo*); *cf.* chemical proof in ref. 6.

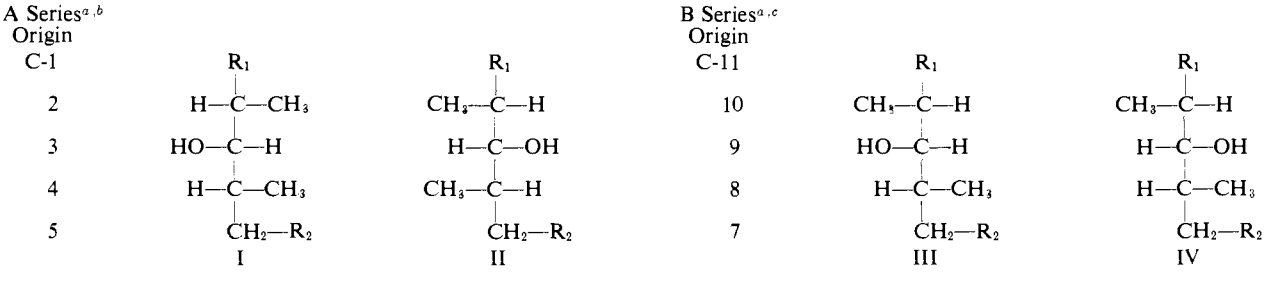
(26) *Cf.* ref. 5, 6, 10, 11, 27 for the over-all development of constitutional and configurational relationships.

Table I. Anomeric Configurational Analyses

6-Deoxy sugars: Hexose[7]	Glyoside	N.m.r.[a]: Chem. shift, τ	N.m.r.[a]: $J_{1,2}$, c.p.s.	M.r.d.,[b] ΔM_D	Conclusion
L-Oleandrose	Oleandomycin[8]	(4.99)[8]	(3.5/1.0)[8]	(−263°)[8]	(lit. α-L-)[8]
	Oleandrin[20]	...	...	(−263°)[20]	α-L-
L-Cladinose	Erythromycin-A[11]	5.05	4.0/1.0	(−297°)[11]	α-L-
	Erythromycin-B[12]	5.08	4.0/1.0	(−270°)[12]	α-L-
L-Mycarose	Magnamycin-A[9]	...	...	(−389°)[9a,b]	α-L-
	Tylosin[13,14]	4.90	2.5/<1	(−269°)[13]	α-L-
	Spiramycins[7]	4.90	2.0/<1	...	α-L-
	Leucomycins[7]	4.90	2.0/<1	...	α-L-
L-Arcanose	Lankamycin[15]	...	...	(−524°)[15]	α-L-
D-Desosamine	Oleandomycin[8]	(5.74)[8]	(7.0)[8]	(− 80°)[8]	(lit. β-D-)[8]
	Erythromycin-A[11]	(5.42)[4]	(7.1)[4]	(− 34°)[11]	(lit. β-D-)[4]
	Erythromycin-B[12]	5.56	7.0	(− 52°)[12]	β-D-
	Narbomycin[7]	5.67	7.0	...	β-D-
	PA 133-A,B[19]	5.63	7.7	...	β-D-
D-Mycaminose	Magnamycin-A[9]	(5.52)[4]	(7.1)[4]	...	(lit. β-D-)[4]
	Tylosin[13,14]	5.40	7.0	...	β-D-
	Spiramycins[7]	5.50	7.0	...	β-D-
	Leucomycins[7]	5.48	6.5	...	β-D-
D-Mycosamine	Pimaricin[16,17]	...	...	(−308°)[17]	β-D-
D-Mycinose	Chalcomycin[18]	...	(7.1)[18]	...	(lit. β-D-)[18]
	Tylosin[13,14,18]	5.73	7.0	(− 98°)[14]	β-D-
D-Chalcose	Chalcomycin[18]	...	(7.1)[18]	...	(lit. β-D-)[18]
	Lankamycin[15]	...	...	(− 75°)[15]	β-D-
D-Oleandrose	Lanafolein[21]	...	...	(− 60°)[21]	β-D-

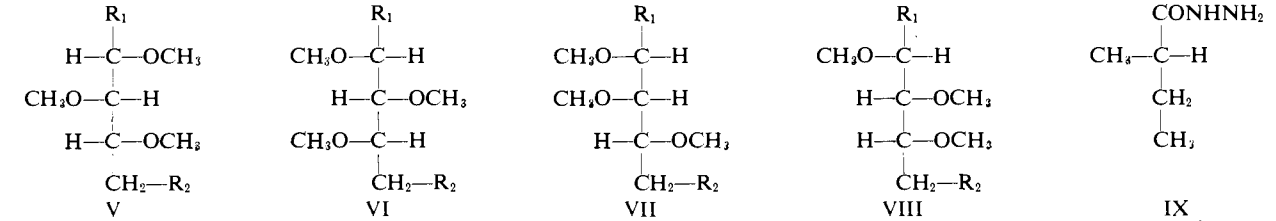
[a] All 6-deoxypyranosides in these cases evidently follow a preferred conformation correlated with series, *i.e.*, L(1C) and D(C1). Since all L-examples are also 2-deoxy sugars, their expected $J_{1,2}$ values follow accordingly, *i.e.*, α-L(1C): $J_{1e,2a}$ = 2.5–4.0, $J_{1e,2e}$ = <1–2.5 c.p.s.; β-L(1C): $J_{1a,2a}$ = 9.0–9.5, $J_{1a,2e}$ = 2.0–4.0 c.p.s. Only D-sugars possessing an axial proton at C-2 were examined, *i.e.*, β-D(C1): $J_{1a,2a}$ = 6.5–7.5 c.p.s.; α-D(C1): $J_{1e,2a}$ = 2.0–4.0 c.p.s. [b] Calculated from available [α]D data (*cf.* citations) where M_D = [α]D × mol. wt./100 and ΔM_D = M_D of glycoside (or appropriate derivative) minus M_D of the corresponding aglycone (*cf.* ref. 2). All given ΔM_D values possess correct sign and reasonable magnitudes compared to M_D values known or predictable for the α-L(1C) or β-D(C1) pyranoside in question.

Chart I. Dihydroerythronolide Degradation Products[a]: Absolute Configurational Considerations



	R_1	R_2	*cf.*	M_D	*cf.*	M_D
Lactones	CO————	—O	A:	−7.2°	B:	+81°
Hydrazides	$CONHNH_2$	OH	A:	−74°	B:	+12°
Triols	CH_2OH	OH	A:	0° (I = II)	B:	−21° (III = IV)

Model Systems (R_1:R_2 = CO—O)[d]:



	V	VI	VII	VIII	IX
M_D	−7.6°	+7.6°	+68°	−276°	+44°[e]

[a] *Cf.* ref. 10. [b] *Cf.* ref. 6, 25. [c] *Cf.* ref. 5. [d] *Cf.* ref. 30. [e] *Cf.* footnote 21 in ref. 10.

involving consideration of hydrazides A:B and model compounds, leads to I:III as the sole set for A:B.[29]

(27) P. A. Levene, *J. Biol. Chem.*, **23**, 145 (1915).

(28) H. Margenan and G. M. Murphy, "The Mathematics of Physics and Chemistry," D. V. Nostrand Co., Inc., Princeton, N. J., 1956, *cf.* pp. 313 and 545.

(29) The sign and expected magnitude of molecular rotational contribution from α and γ centers in the hydrazides I, II, III, IV are derived as follows: (α) From (+)(*S*) IX, [M]D +44°; (γ) from (−)(*R*:*R*) triol, *i.e.* III, = IV, [M]D −10.5°. It follows that the arithmetical sum of rotational contribution (RC) from α, β, and γ centers must equal the observed [M]D in each hydrazide case, *i.e.* (A = −74°) and (B = +12°). Knowing the sign and reasonable magnitude of RC at α and γ, their *net* sign and value (N) can be approximated in all possibilities. Thus, in I (N = −55°), II (N = +55°), III and IV (N = +33.5°). Each *pair* of possibilities is then tested with consistent signs for the RC of the unknown β center, *i.e.*, for I:III (a) if −55° + β = −74° then +33.5° + β = +12° or (b) if −55° − β = −74 then +33.5° − β = +12. Expression (a) is untenable while (b) leads to reasonable sign and values for the RC of the β center, *i.e.*, −19° in I and −21.5° in II. It turns out that all other sets of possibilities receiving like inspec-

This conclusion is substantiated by MD correlations involving lactones A:B and models[30] (*cf.* V with I and VII with III in Chart I). The above specifications then follow.[26]

tion become disqualified due to their untenable arithmetic. Now, knowing only the *sign* of RC at all centers, it is possible to check the magnitude of apparent RC from the α center, *e.g.*, since $-\alpha - \beta - \gamma = -74$ then $+\alpha - \beta - \gamma = +12$, *i.e.*, $\alpha = 43°$ (*cf.* 44° for IX).

(30) (a) A. K. Bose and B. G. Chatterjee, *J. Org. Chem.*, **23**, 1425 (1958); (b) G. G. Maher, *Advan. Carbohydrate Chem.*, 257 (1955).

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Macrolide Stereochemistry. III. A Configurational Model for Macrolide Antibiotics[1]

Sir:

A model (*cf.* **1** and **2**) is proposed as a vehicle of configurational thought in macrolide antibiotic problems[2] dealing with molecular structures, biogenesis, and mode of action. The model's nucleus can be specified as: 2-D, 3-L, 4-D, 5-L, 6-L, 8-L, 10-D, 11-L, 12-L, 13-D, or D-*threo*-L-*gulo*-L-*ido*-, or (2*R*:3*S*:4*R*:5*S*:6*S*:8*R*:10*R*:11*S*:12*R*:13*R*)-2,4,6,8,10,12-hexamethyl-3,5,11,13-tetrahydroxy-9-ketotridecanoic acid 1,13-lactone. A carbohydrate corollary states that any L- or D-6-deoxypyranoside substituent bears an α-L- or β-D-specification at the anomeric center (*cf.* **2**). There are no provisions for predicting the configuration at other carbohydrate or at *exo*-macrocyclic asymmetric centers or the precise position of sugar substitution. The model operates on the premise that the absolute configuration ascribed to a given center is general and is not altered by "extra" oxygen substitution involving replacement of hydrogen at an asymmetric center in certain macrolide antibotics. This

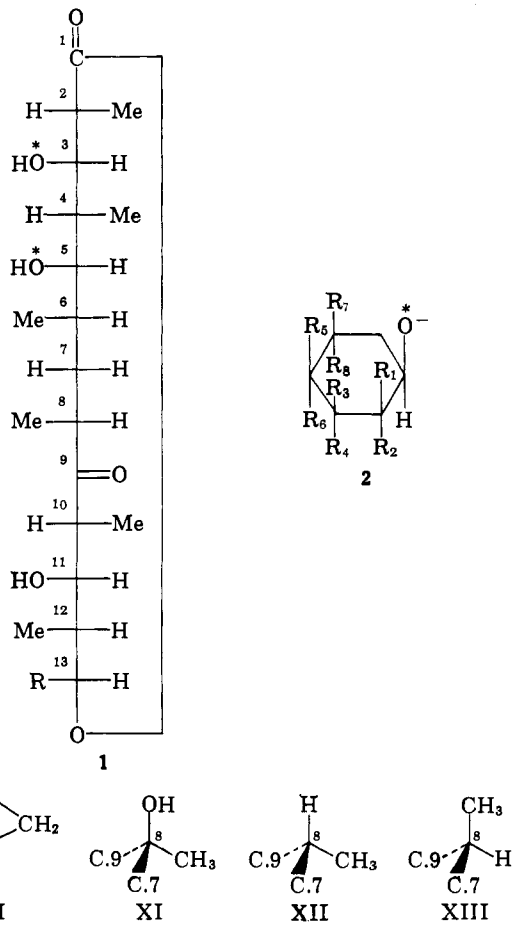

Figure 1

of earlier[1c,3] evidence for and concepts of a principle of configurational standardization among macrolide antibiotics. The model is tied with Gerzon's propionate rule,[4] Klyne's glycoside rule,[1b,5] and the total absolute

Table I. Macrolide Specifications

Macrolide[o]	Aglycone centers: Evident	Aglycone centers: Predicted	Anomeric centers[c]: Evident	Anomeric centers[c]: Predicted
Oleandomycin (I)	(2*R*:3*S*:4*S*:5*S*:6*S*:8*R*:10*R*:11*S*:12*R*:13*R*)[a]	Same	(β-D:α-L)[b]	Same
Erythromycin-A (II)	(2*R*:3*S*:4*S*)[c] (8*R*:10*R*)[d] (13*R*)[e]	Same and (5*R*:6*R*:11*R*:12*S*)	(β-D)[c,f] (α-L)[c]	Same
Erythromycin-B (III)	(*xylo*-C-2,3,4)[e,g]	(2*R*:3*S*:4*S*:5*R*:6*R*:8*R*:10*R*:11*S*:12*R*:13*R*) (*xylo*-C-2,3,4)[h]	(β-D:α-L)[c]	Same
Erythromycin-C (IV)	*Cf.* II	*Cf.* II		(β-D, α-L)
Lankamycin (V)	(*galacto*-C-10,11,12,13)[i]	(2*R*:3*S*:4*R*:5*S*:6*S*:8*S*:10*R*:11*S*:12*R*:13*R*) (*galacto*-C-10,11,12,13)[h]	(β-D, α-L)[c]	Same
Narbomycin (VI)	(6*S*:8*R*)[j]	Same and (2*R*:4*R*:5*S*:12*R*:13*R*)	(β-D)[c]	Same
Methymycin (VII)	(4*S*:6*R*)[k]	Same and (2*R*:3*S*:10*S*:11*R*)		(β-D)
Neomethymycin (VIII)	(4*S*:6*R*)[l]	Same and (2*R*:3*S*:10*R*:11*S*)		(β-D)
Chalcomycin (IX)	(4*S*:6*S*)[m]	Same and (5*S*:8*S*)	(β-D, β-D)[m]	Same
Picromycin (Xa)	"(4*S*:6*R*)[n]"	(2*R*:3*S*:4*S*:6*R*:10*S*:11*R*)		(β-D)
Picromycin (Xb)	"(2*R*:4*S*)[n]"	(2*R*:4*S*:5*S*: *R*:10*S*:11*R*)		(β-D)

[a] *Cf.* ref. 1a. [b] *Cf.* footnote 8 in ref. 1b. [c] Ref. 1b. [d] *Cf.* ref. 3e. [e] Ref. 4. [f] *Cf.* footnote 4 in ref. 1b. [g] *Cf.* footnotes 6, 11, and 27 in ref. 1b. [h] *Cf.* relative configuration. [i] W. Keller-Schierlein (private communication); *cf. Helv. Chim. Acta*, **47**, 78 (1964). [j] *Cf.* ref. 3f. [k] *Cf.* ref. 3c. [l] *Cf.* ref. 3b. [m] *Cf.* footnote 18 in ref. 1b. [n] This follows from ref. 3a,b according to the assigned structures in each case (Xa, ref. 6 and Xb, ref. 7). [o] *Cf.* ref. 2.

extends the applicability range of the model in its otherwise self-evident constitution-configuration matching workings.

Derivation. The current model represents fruition

(1) (a) Part I: *J. Am. Chem. Soc.*, **87**, 1797 (1965); (b) part II: *ibid.*, **87**, 1799 (1965); (c) footnote 1c in ref. 1a.

(2) For reviews see: (a) M. Berry, *Quart. Rev.* (London), **17**, 343 (1963); (b) H. Grisebach and W. Hofheinz, *J. Roy. Inst. Chem.*, 332 (1964)

(3) (a) R. Anliker, D. Dvornik, K. Gubler, H. Keusser, and V. Prelog, *Helv. Chim. Acta*, **39**, 1758 (1956); (b) C. Djerassi and O. Halpern, *J. Am. Chem. Soc.* **79**, 2022 (1957); *Tetrahedron*, **3**, 255 (1958); (c) C. Djerassi and J. A. Zderic, *J. Am. Chem. Soc.*, **78**, 6390 (1956); (d) C. Djerassi and O. Halpern, *ibid.*, **79**, 3626 (1957); (e) C. Djerassi, O. Halpern, D. I. Wilkinson, and E. J. Eisenbraun, *Tetrahedron*, **4**, 369 (1958); (f) V. Prelog, A. M. Gold, G. Talbot, and Z. Zomojski, *Helv. Chim. Acta*, **45**, 4 (1962).

(4) K. Gerzon, E. H. Flynn, M. V. Sigal, Jr., P. F. Wiley, R. Monohan, and U. C. Quarck, *J. Am. Chem. Soc.*, **78**, 6396 (1956).