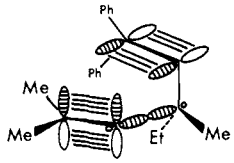
We are now able to decide which of two alternative cyclic arrays is actually preferred. The mechanisms in terms of the six orbital array are given in Chart II. For simplicity only one reactant conformation is followed through the reaction (*i.e.*, **1′**); this is one leading to the trans product *via* the C-3 inversion route but to the cis product *via* the C-3 retention mechanism. Conformer **1″** can be seen to lead to the cis product *via*



1″

alternative conformer of ethylmethyldiene **1**

the inversion route and trans product *via* the retention pathway. Further conformers are also possible. However, the C-3 inversion *vs.* retention question is independent of reactant conformation.

It is seen that the observed C-3 inversion mechanism has a six-electron Möbius array while the C-3 retention process has a six-electron Hückel cycle of basis orbitals. Only the Möbius array provides an allowed photochemical pathway.[8,9] The reaction can be alternatively analyzed as ${}_{\sigma}2_{a} + {}_{\pi}2_{a} + {}_{\pi}2_{a}$ which is more favorable than the ${}_{\sigma}2_{s} + {}_{\pi}2_{a} + {}_{\pi}2_{a}$ (*i.e.*, the retention mechanism). However, the two analyses really are identical, since a process with an odd number of a's in the Woodward–Hoffmann approach[10] will necessarily be Möbius[8] and one with an even number of a's will be Hückel.[8] In any case, the allowed mechanism is the one followed.

Acknowledgment. Appreciation is expressed to the National Science Foundation, to the National Institutes of Health (Grant GM 07487), and the U. S. Army Research Office (Durham) for support of this research. National Institutes of Health Predoctoral Fellowships to J. D. R. and L. R. S. and a Science Research Council Postdoctoral Fellowship to C. J. S. are gratefully acknowledged.

(8) (a) H. E. Zimmerman, *J. Amer. Chem. Soc.*, **88**, 1564 (1966); (b) H. E. Zimmerman, *Accounts Chem. Res.*, **4**, 272 (1971).

(9) The qualitative valence bond picture we have used previously[2-5] is in no way inconsistent with the cyclic orbital array. The former merely gives resonance contributors of varying importance along the reaction coordinate.

(10) R. B. Woodward and R. Hoffman, "The Conservation of Orbital Symmetry," Academic Press, New York, N. Y., 1970.

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Received December 26, 1973

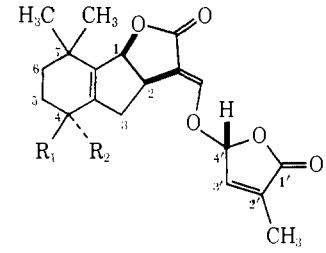
The Total Synthesis of *dl*-Strigol

Sir:

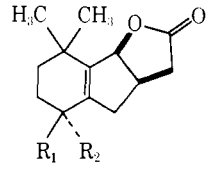
Strigol, a highly potent seed germination stimulant for the root parasite witchweed (*Striga lutea* Lour.), was isolated from the root exudates of cotton (*Gossypium hirsutum* L.) in 1966 by Cook, *et al.*[1] However, the structure and relative configuration of strigol, as depicted in **1**,[2] have only recently been derived on the basis of spectroscopic and X-ray crystallographic data.[3] The occurrence of similar stimulants in several plants suggests that strigol may be representative of a new class of plant hormones.[3] The unavailability of strigol from natural sources in quantities sufficient for biological studies aroused our interest in the chemical synthesis of this molecule. We now wish to report the first total synthesis of *dl*-strigol.

Conceptually, the most direct synthetic approach would lie in the preparation of hydroxylactone **3** followed by formylation and subsequent O-alkylation. As the stereochemistry of O-alkylation of β-dicarbonyl compounds can be profoundly influenced by solvent effects,[4] it seemed likely that the stereochemistry about the enol ether double bond would be subject to some control. To test this crucial final step in the synthetic sequence, we examined the alkylation of the model hydroxymethylene lactone **5**[5] with the bromobutenolide **9** which was prepared from 3-methyl-2-furoic acid (**6**)[6] in the following manner. Photochemical oxygenation of **6** in ethanol[7] gave (after $SnCl_2$ reduction of peroxides) the lactone acetal **7**[8] (80%). Hydrolysis to the lactol **8**[8] (H_2O, reflux, 0.5 hr, 90% yield) followed by treatment with triphenylphosphine and carbon tetrabromide in dichloromethane[9] (0°, 5 hr) afforded the required bromobutenolide **9**[10] (65–70%, bp 54° (0.4 mm)).

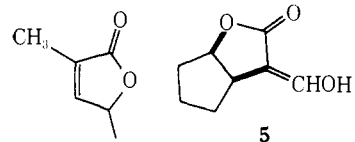
When **5** was treated with **9** (1.15 equiv) and K_2CO_3 (1.05 equiv, HMPA, 25°, 22 hr), a mixture of two diasteriomeric products was obtained (**10**, *ca.* 90%).[10]



1. R_1 = OH; R_2 = H
2. R_1 = H; R_2 = OH

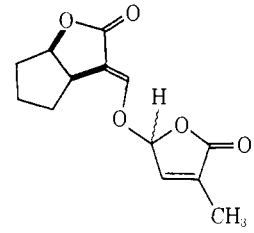


3. R_1 = OH; R_2 = H
4. R_1 = H; R_2 = OH



7. X = OC_2H_5
8. X = OH
9. X = Br

5



10

The nmr spectrum of this mixture was in close agreement with strigol for all relevant proton signals including the

(1) C. E. Cook, L. P. Whichard, B. Turner, M. E. Wall, and G. H. Egley, *Science*, **154**, 1189 (1966).

(2) The absolute stereochemistry of strigol has not been determined, and the enantiomer represented in **1** has been chosen arbitrarily. All other structures are racemic and are illustrated by one enantiomer.

(3) C. E. Cook, L. P. Whichard, M. E. Wall, G. H. Egley, P. Coggon, P. A. Luhan, and A. T. McPhail, *J. Amer. Chem. Soc.*, **94**, 6198 (1972).

(4) B. Miller, H. Marquiles, T. Drabb, Jr., and R. Wayne, *Tetrahedron Lett.*, 3081, 3085 (1970).

(5) J. D. Fissekis and B. A. Markert, *J. Org. Chem.*, **31**, 2945 (1966).

(6) D. M. Burness, *J. Org. Chem.*, **21**, 102 (1956).

(7) F. Fariña and M. V. Martín, *An. Quim.*, **67**, 315 (1971).

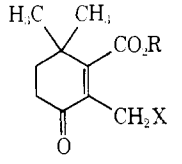
(8) J. P. van der Merwe and C. F. Garbers, *J. S. Afr. Chem. Inst.*, **17**, 149 (1964).

(9) R. G. Weiss and E. I. Snyder, *J. Org. Chem.*, **36**, 403 (1971). See also I. M. Downie, J. B. Holmes, and J. B. Lee, *Chem. Ind. (London)*, 900 (1966); J. Hooz and S. S. H. Gilani, *Can. J. Chem.*, **46**, 86 (1968).

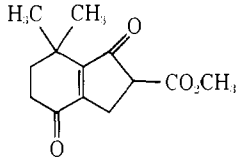
(10) Satisfactory infrared, nuclear magnetic resonance, ultraviolet, and mass spectral data were obtained.

vinyl proton of the alkoxymethylene lactone (nmr ($CDCl_3$) δ 7.37 (1, d, J = 2.4 Hz) *vs.* 7.42 (1, d, J = 2.5 Hz) for strigol) indicating that the desired *E* isomer was selectively formed.

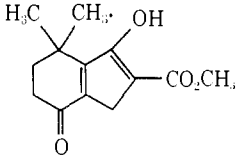
With this assurance in hand, we then proceeded with the synthesis of the hydroxylactone **3**. 2,6,6-Trimethylcyclohex-1-en-3-one-1-carboxylic acid (**11**)[11] was esterified (CH_3I, acetone, K_2CO_3, 25°, 12 hr) and then treated with *N*-bromosuccinimide in CCl_4 to give the bromide **12**[10] in nearly quantitative yield. Reaction of **12** with excess dimethyl sodiomalonate in methanol resulted in alkylation and cyclization to give a mixture of the β-keto ester **13** and its enol **14**[10] (80% overall yield from **11**). Alkylation of this mixture with methyl bromoacetate (K_2CO_3, THF, 25°, 48 hr) followed by acidic hydrolysis (acetic acid–6 *N* HCl, 1:1, reflux, 3 hr) gave diketo acid **15**: mp 136.5–137° (benzene);



11, R = X = H
12, R = CH_3; X = Br



13



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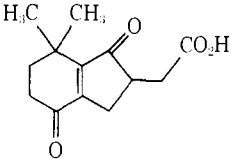


15

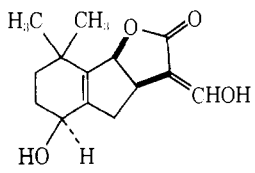
uv_{max} (95% C_2H_5OH) 260 nm (ϵ 13,300); ir (KBr) 3350–2500 (acid OH), 1710 (C=O and acid C=O), 1682 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.33 (3, s), 1.95 (2, m), 2.35–2.88 (7, complex), 10.7 (1, br); (70%).

Reduction of **15** with diisobutylaluminum hydride (4 equiv) in CH_2Cl_2 (−70°, 3 hr) afforded a mixture of hydroxylactones **3** and **4** (60% yield) in a ratio of *ca.* 2:1. Separation of the two isomers was achieved by preparative thin-layer chromatography (silica gel, $CHCl_3$–acetone, 95:5, ten developments) yielding the slower moving component at the desired isomer **3**: mp 143–144° (benzene–hexane); nmr ($CDCl_3$) δ 1.08 (3, s), 1.14 (3, s), 1.4–3.0 (9, complex), 4.12 (1, t, $J \simeq$ 5 Hz), 5.48 (1, d, J = 6.8 Hz); ir ($CHCl_3$) 3600 and 3480 (OH), 1764 cm^{-1} (lactone C=O). Elution of the faster moving component yielded the diasteriomeric hydroxylactone **4** as an oil: nmr ($CDCl_3$) δ 1.09 (3, s), 1.13 (3, s), 1.4–3.0 (9, complex), 4.18 (1, t, J = 4.9 Hz), 5.49 (1, d, J = 5.4 Hz); ir ($CHCl_3$) 3600 and 3480 (OH), 1760 cm^{-1} (lactone C=O).

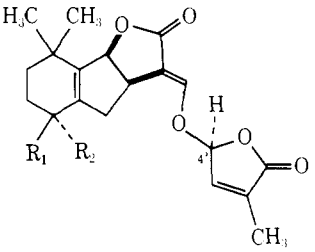
Hydroxylactone **3** was condensed with methyl formate (NaH, ether, 25°, 20 hr), and the resulting hydroxymethylene lactone **16**[10] (78% yield) was alkylated with bromobutenolide **9** (K_2CO_3, HMPA, 25°, 12 hr) to give a mixture of *dl*-strigol (**1**) and *dl*-4′-epistrigol (**17**).[12]

(11) Prepared from citral by a modification of the route of G. Wendt, *Chem. Ber.*, 74, 1242 (1941). More direct routes to **11** are currently under study.

(12) Similar transformations starting with the epimeric hydroxylactone **4** led to two other isomers of strigol (isomers C and D; **2** and **18**) possessing the unnatural configuration of the C-4 hydroxyl. These isomers were clearly distinguishable from those in the natural series by nmr spectroscopy although the ir spectra in CH_2Cl_2 were nearly identical for all four isomers.



16



17, R_1 = OH; R_2 = H
18, R_1 = H; R_2 = OH

This mixture was cleanly separated by preparative thin-layer chromatography (silica gel; $CHCl_3$–acetone, 4:1) to give isomer A (R_f = 0.32, mp 178–180° (ethyl acetate–hexane), *ca.* 25% yield) and isomer B (R_f = 0.20, mp 203–205° dec (ethyl acetate–hexane), *ca.* 25% yield). As the ir, nmr, uv, and mass spectra of both isomers A and B (**17** and **1**) are essentially identical with those of natural strigol, the relative biological potencies of these two isomers are currently being examined to ascertain the configuration at C-4′.[13]

Acknowledgment. We wish to thank Dr. C. E. Cook for helpful communications. Partial support of this work by the National Institutes of Health (AM-04874) and the Wisconsin Alumni Research Foundation is gratefully acknowledged.

(13) Note Added in Proof. Isomer B was found to be chromatographically identical with a sample of strigol kindly provided by Dr. Cook. Concentrations required for the 50% germination of striga seeds were 10^{-12} *M* for isomer A and 10^{-16} *M* for isomer B. We thank Dr. D. E. Moreland for these biological data.

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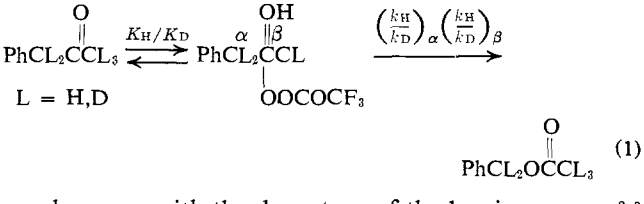
Secondary Deuterium Isotope Effects in the Baeyer–Villiger Reaction

Sir:

The application of secondary deuterium isotope studies to chemical reactions is a powerful technique for garnering mechanistic insights.[1] When the reaction mechanism can be established independently, more subtle inferences about the transition state may be made.[1] The Baeyer–Villiger reaction has been shown to follow the mechanism given below, migration being



(1)

synchronous with the departure of the leaving group.[2,3] We report observed isotope effects for the Baeyer–Villiger reaction of $PhCD_2COCH_3$ (D_2), $PhCH_2COCD_3$

(1) For reviews see S. E. Scheppele, *Chem. Rev.*, 72, 511 (1972); C. J. Collins and N. S. Bowman, Ed., "Isotope Effects in Chemical Reactions," Van Nostrand Reinhold, New York, N. Y., 1970; E. R. Thornton, *Annu. Rev. Phys., Chem.*, 17, 349 (1966); E. A. Halevi, *Prog. Phys. Org. Chem.*, 1, 109 (1966); L. Melander, "Isotope Effects on Reaction Rates," Ronald Press, New York, N. Y., 1960.

(2) (a) M. F. Hawthorn and W. D. Emmons, *J. Amer. Chem. Soc.*, 80, 6393, 6398 (1958); (b) B. W. Palmer and A. Fry, *ibid.*, 92, 2580 (1970).

(3) M. A. Winnik and V. Stoute, *Can. J. Chem.*, 51, 2788 (1973).