The mixture was stirred for 1.5 h at room temperature then the solvent was removed in vacuo and the residue washed with dry ether and decanted. Dry ethanol (5 mL) was added and dry NH_3 gas condensed into the vessel. After 1 h at room temperature the solvents were removed under reduced pressure, ethanol was added, and the yellow precipitate collected to give pure **17**: 497 mg (89% yield); no distinct melting point; decomposition starts at 190 °C (lit. mp 199–207 °C[14] mp 204–207 °C[15]); ^{1}H NMR (Me_2SO-d_6) δ 2.64 (t, 2 H), 3.50 (q, 2 H), 3.82, 3.85 and 3.96 (3s, 9 H), 6.96, 7.09, 7.23, 7.30, 7.66, 8.20 (6d, 1 H each), 8.0–8.8 (bs, 5 H), 10.01 and 10.40 (2s, 1 H each); FAB-MS (glycerol) 484 $(M - Cl)^+$; IR ν_{max} (Nujol) 1649, 1695, 3300 cm^{-1}.

1-Methyl-4-[1-methyl-4-(1-methyl-4-aminopyrrole-2-carboxamido)pyrrole-2-carboxamido]pyrrole-2-carboxamidopropionamidine Hydrochloride (18). A solution of 300 mg (0.58 mmol) of **17** in 10 mL of MeOH was hydrogenated over 130 mg of 10% Pd on charcoal at 40 °C. The catalyst was removed by filtration and the solvent removed in vacuo. The residue was extracted with 100 mL of cold isopropyl alcohol. The combined extracts were concentrated in vacuo to dryness, the residue was dissolved in a small volume of ethanol, and then ethyl acetate was added to precipitate the product as a white solid. The product was collected and transferred rapidly, while still moist, to a drying apparatus. Once the material is solid and dry it is less hygroscopic and represents pure **18**: 200 mg (70% yield); no distinct melting point; ^{1}H NMR (DMF-d_7) δ 3.4–3.8 (bs), 3.83, 3.90, 3.93 (3s, 9 H), 6.37, 6.55 (2d, J = 2 Hz, 1 H each), 7.10, 7.18, 7.32, 7.36 (4d, J = 2 Hz, 1 H each), 8.55 (t, J = 6 Hz, 1 H), 9.4–9.7 (bs, 4 H), 9.72 and 10.10 (2s, 1 H each); IR ν_{max} (Nujol) 1640, 1690, 3290 cm^{-1}; FAB-MS (glycerol) 454 $(M - Cl)^+$.

1-Methyl-4-[1-methyl-4-[1-methyl-4-(formylamino)-pyrrole-2-carboxamido]pyrrole-2-carboxamido]pyrrole-2-carboxamidopropionamidine Hydrochloride (Distamycin Hydrochloride) (19). A solution of 240 mg (0.46 mmol) of **17** in 30 mL of methanol was hydrogenated over 120 mg of 10% Pd on charcoal during 2.5 h. The catalyst was removed by filtration, the filtrate concentrated to 15 mL and cooled to −40 °C, and a solution of *N*-formylimidazole, prepared from 2 mmol of carbonylimidazole as described for **13**, was added. After 30 min at −40 °C the solution was concentrated to a small volume and ethyl acetate was added to precipitate the product. The latter was collected, then extracted with cold isopropyl alcohol, and filtered through charcoal. The filtrate was concentrated to a small volume and EtOAc was added to precipitate the product. The latter was collected, washed with EtOAc and hexane, and dried in vacuo. The substance is amorphous without a distinct melting point. **19**: 170 mg (71% yield); ^{1}H NMR (Me_2SO-d_6) δ 2.62 (t, J = 6 Hz, 2 H), 3.51 (q, J = 6 Hz, 2 H), 3.82 (s, 3 H), 3.85 (s, 6 H), 6.93 and 6.96 (2d, J = 1.7 Hz, 2 H), 7.06 (d, J = 1.7 Hz, 1 H), 7.19 (m, 2 H), 7.23 (d, J = 1.7 Hz, 1 H), 8.13 (s, 1 H), 8.22 (t, J = 6 Hz, 1 H), 8.73 and 8.98 (2bs, 4 H), 9.92 and 9.94 (2s, 2 H), 10.12 (s, 1 H); IR ν_{max} (Nujol) 1642, 1690, 3280 cm^{-1}; FAB-MS 482 $(M - Cl)^+$.

The synthetic distamycin hydrochloride shows a ΔTm of 15.5° with calf thymus DNA in 20 mM potassium sodium phosphate buffer pH 6.9 at a D/P ratio of 1.0, identical with an authentic sample from Boehringer-Mannhiem, cat. no. 10442, batch 1417211. Compound **19** also exhibited the characteristic wide spectrum antiviral activity of authentic distamycin, in tests courtesy of Prof. Erik De Clercq, Leuven, Belgium.

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The Absolute Structure of (+)-Strigol

Dee W. Brooks,*† H. S. Bevinakatti, and Douglas R. Powell

Department of Chemistry, Purdue University, West Lafayette, Indiana 47907

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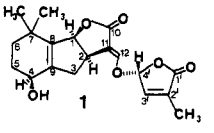
The absolute structure of the potent seed germination stimulant (+)-strigol has been established by resolution of racemic strigol via the corresponding *N*-[(*R*)-1-(1-naphthyl)ethyl]carbamate and X-ray crystallographic analysis.

Strigol (1) was isolated from root exudates of cotton (*Gossypium hirsutum* L.), and the relative structure was established by Cook and co-workers.[1] Strigol exhibited



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potent activity as a seed germination stimulant for *Striga* species and similar parasitic plants in the genus *Orobanche*.[2] It remains the most potent germination stimulant for seeds of witchweed (*Striga asiatica* (L.) Kuntze) which causes considerable damage to crops of the Gramineae family such as corn, sorghum, and sugarcane.[3] Witchweed seeds can remain dormant in the soil for several years until favorable conditions prevail including exposure to some type of chemical germination stimulant. The concept of invoking a chemical signal to break dormancy and stimulate germination of weed seeds is relevant to weed control. For parasitic weeds of the *Striga* type, inducing germination in the absence of a host plant would result in starvation of the seedling and hence offers an alternative to herbicide treatment.

Two total syntheses[4,5] of (±)-strigol were reported shortly after the structure determination. More recently, we have developed an improved synthesis of strigol,[6] and the

† Present address: Department 47K AP10, Abbott Laboratories, Abbott Park, IL 60064.

(1) (a) Cook, C. E., Whichard, L. P.; Turner, B.; Wall, M. E.; Egley, G. H. *Science (Washington, D.C.)* **1966**, *154*, 1189. (b) Cook, C. E.; Whichard, L. P.; Wall, M. E.; Egley, G. H.; Coggon, P.; Luhan, P. A.; McPhail, A. T. *J. Am. Chem. Soc.* **1972**, *94*, 6198.

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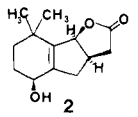
availability of synthetic intermediates enroute to strigol formed a foundation for the preparation of various analogues for evaluation of structure–activity relationships.[7] With an ample supply of synthetic racemic strigol available, we have developed a method of resolution and have determined the absolute configuration of natural (+)-strigol, which is described as follows.

Sih and co-workers[4] developed an excellent method for the resolution of the synthetic intermediate **2** into each of the two antipodes which were separately converted to (+)- and (−)-strigol. Their application of methods of Nakanishi[8] and Horeau[9] to determine the absolute configuration of (+)- and (−)-**2** resulted in contradictory predictions.[4] Our approach to solve the absolute configuration of (+)-strigol was to identify an appropriate optically pure derivatizing agent of known absolute configuration that would convert racemic strigol into a separable diastereomeric mixture. An X-ray crystallographic analysis of one pure diastereomer would provide the configuration of chiral centers in strigol relative to the known chiral center in the derivatizing agent. Finally, removal of the derivatizing agent to regenerate one enantiomer of strigol and comparison of the optical rotation with that reported for the natural product would complete the analysis.



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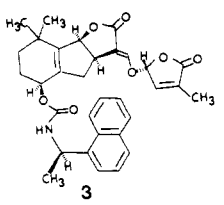
After evaluating several chiral derivatizing agents we found that (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate, which had been used effectively by Pirkle and co-workers[10] for the preparation of chromatographically separable diastereomers of racemic alcohols, proved effective in this case. Refluxing a benzene solution of racemic strigol with this isocyanate for 24 h provided equal amounts of two diastereomeric carbamates **3** and **4** in 90% yield, which were



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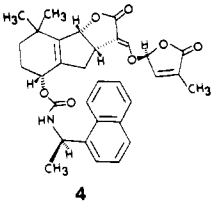

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separated by chromatography on silica gel (30–50% tetrahydrofuran in hexane). The carbamate **3** (with the larger R_f on silica gel) was readily crystallized by slow evaporation of an ethyl acetate and tetrahydrofuran mixture under a nitrogen atmosphere to provide suitable crystals for X-ray analysis. A computer-generated perspective drawing of **3** is shown in Figure 1. Carbamate **3** was then subjected to the method developed by Pirkle and Hauske[11] for the mild cleavage of carbamates, involving treatment with triethylamine and trichlorosilane to retrieve the corresponding enantiomer of strigol with observed $[\alpha]_D$ +270° (*c* 0.2, $CHCl_3$) compared to the literature value[4] for (+)-strigol $[\alpha]_D$ +293° (*c* 0.15, $CHCl_3$). Therefore, the absolute

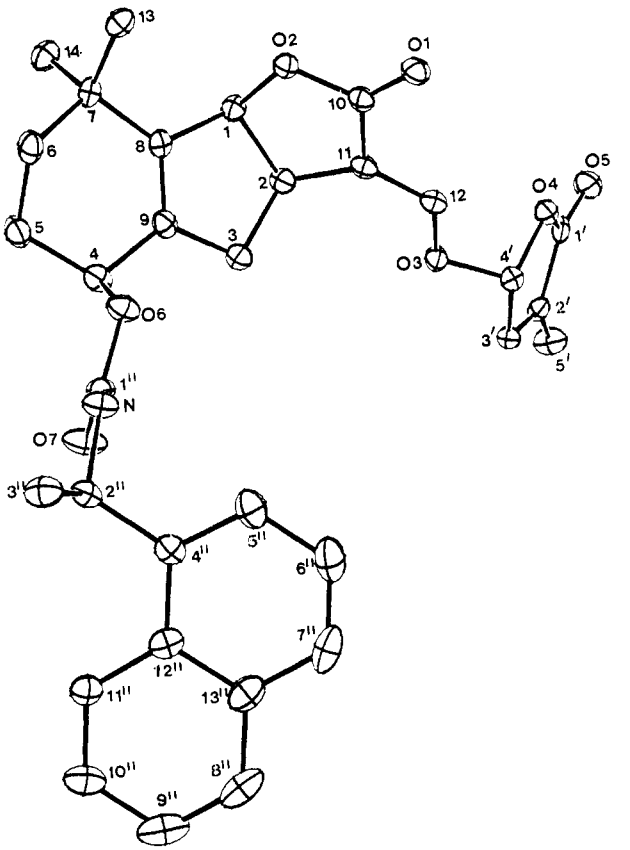

Figure 1. Computer-generated perspective drawing of (+)-strigol *N*-[(*R*)-1-(1-naphthyl)ethyl]carbamate (**3**).

configuration of (+)-strigol is established as depicted by **1**. It is noteworthy to mention that the absolute structure shown for (+)-strigol in the earlier literature which was arbitrarily chosen by Cook and co-workers[1b] and thereafter depicted by others[4,6] is the correct enantiomer.

Experimental Section

(+)-Strigol *N*-[(*R*)-1-(1-Naphthyl)ethyl]carbamate (3) and (−)-Strigol *N*-[(*R*)-1-(1-Naphthyl)ethyl]carbamate (4). A mixture of strigol (0.575 g, 1.66mmol) and (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate (0.49 g, 2.49 mmol) in benzene (25 mL) was refluxed under nitrogen for 24 h, after which the solvent was evaporated. The residue was chromatographed on silica gel with a gradient of 10–50% tetrahydrofuran in hexane to give two diastereomeric carbamates, **3** (0.32g) and **4** (0.33g) in order of elution (90% yield). **3**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.09 (s, 3), 1.17 (s, 3), 1.4–1.7 (m, 3), 1.65 (d, J = 6.5 Hz, 3), 1.94 (br s, 3), 2.0 (m, 1), 2.34 (br d, J = 15.5 Hz, 1), 2.67 (dd, J = 15.5, 9 Hz, 1), 3.57 (m, 1), 5.20 (br t, J = 6.0 Hz, 1), 5.46 (br d, J = 7.5 Hz, 1), 5.69 (m, 1), 5.88 (br s, 1), 6.54 (br s, 1), 7.34 (br s, 1), 7.4–7.6 (m, 4), 7.77 (d, J = 7.5 Hz, 1), 7.87 (dd, J = 7.5, 2.0 Hz, 1), 8.13 (br d, J = 7.5 Hz, 1). **4**: ^{1}H NMR (300 MHz, $CDCl_3$) 1.08 (s, 3), 1.16 (s, 3), 1.4–1.8 (m, 3), 1.67 (d, J = 7.0 Hz, 3), 1.95 (m, 1), 2.05 (br s, 3), 2.52 (br d, J = 15 Hz, 1), 2.79 (dd, J = 15, 9 Hz, 1), 3.65 (m, 1), 5.20 (br t, J = 6.0 Hz, 1), 5.49 (br d, J = 7 Hz, 1), 5.67 (m, 1), 6.18 (br s, 1), 6.94 (br s, 1), 7.41 (br s, 1), 7.42–7.6 (m, 4), 7.79 (br d, 7.5 Hz, 1), 7.87 (dd, J = 7.5, 2 Hz, 1), 8.13 (br d, J = 7.5Hz, 1).

X-ray Analysis of (+)-Strigol *N*-[(*R*)-1-(1-Naphthyl)-ethyl]carbamate (3). The carbamate **3** was recrystallized twice from an ethyl acetate and tetrahydrofuran mixture. A colorless plate-shaped crystal of approximate dimensions 0.15 × 0.32 × 0.38 mm was mounted on a glass fiber in a random orientation. Preliminary examination and data collection was performed with Ni-filtered Cu Kα radiation (λ = 1.54184 Å) on a Enraf-Nonius CAD4 computer-controlled diffractometer.

Cell constants and an orientation matrix for data collection were obtained from least-squares refinement, using the setting

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(9) Horeau, A. *Tetrahedron Lett.* **1961**, 506.
(10) Pirkle, W. H.; Simmons, K. A.; Boeder, C. W. *J. Org. Chem.* **1979**, *44*, 4891.
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angles of 24 reflections in the range $41° < \theta < 44°$, measured by the computer-controlled diagonal slit method of centering. The monoclinic cell parameters and calculated volume are a = 13.215 (3) Å, b = 9.548 (2) Å, c = 12.705 (4) Å, β = 118.50 (2)°, and V = 1409 (1) Å^3. For Z = 2 and FW = 543.62 the calculated density was 1.281 g/cm^3. The space group was determined to be $P2_1$.

The details of data collection, structure solution and refinement, and tables of bond distances, bond angles, tortional angles, and intensity data are provided as supplementary material. All calculations were performed on a PDP-11 computer using SDP-PLUS.[12]

(+)-Strigol (1). To a stirred solution of (+)-strigol *N*-[(*R*)-1-(1-naphthyl)ethyl]carbamate (**3**) (0.151 g, 0.349 mmol) and triethylamine (0.07 g, 0.70 mmol) in benzene (10 mL) under nitrogen was added slowly $SiHCl_3$ (1 mL of a 0.5 M solution in benzene). The mixture was stirred 16 h, after which water (10 mL) was added. The phases were separated, the organic phase was washed with saturated aqueous NaCl (10 mL), then dried over $MgSO_4$, and the solvent was evaporated to give crude material, which was purified by chromatography (silica gel, 40–50% ethyl acetate in dichloromethane) providing (+)-strigol (0.067 g, 56%); observed $[\alpha]_D$ +270° (*c* 0.2, $CHCl_3$) [lit.[4] $[\alpha]_D$ +293° (*c* 0.15, $CHCl_3$)].

(−)-Strigol. In a similar manner as above (−)-strigol *N*-[(*R*)-1-(1-naphthyl)ethyl] carbamate (**4**) was treated with triethylamine and $SiHCl_3$ to provide (−)-strigol; observed $[\alpha]_D$ −272° (*c* 0.18, $CHCl_3$) [lit.[4] $[\alpha]_D$ −279° (*c* 0.11, $CHCl_3$)].

Acknowledgment. We express application to the United States Department of Agriculture and Purdue University for financial support and to Drs. S. Vail, A. Pepperman, and O. Daily for helpful discussions concerning this project. The X-ray structural facility was supported by the Monsanto Fund and the NSF Chemical Instrumentation Program (Grant 8204994).

Supplementary Material Available: A detailed description of the X-ray crystallographic experimental procedures, tables of structural solution parameters, bond distances, bond angles, tortional angles, and intensity data, and figures of the unit cell of **3** are provided (35 pages). Ordering information is given on any current masthead page.

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π-Face Stereoselection Operative during [3 + 4] Cycloaddition of Oxyallyl Cations to Isodicyclopentadiene[1]

Leo A. Paquette* and Tina M. Kravetz

Evans Chemical Laboratories, The Ohio State University, Columbus, Ohio 43210

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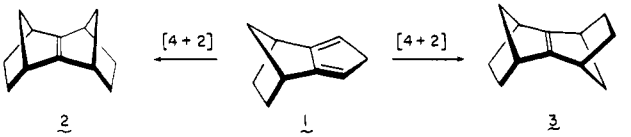
The 1,3-diphenyl-2-oxyallyl dipolar ion, generated by several different reductive methods and therefore complexed to metal ions of various type, has been added to isodicyclopentadiene. Of the six adducts possible, only five were isolated. Although the relative ratios of these ketones varied substantially with conditions, there was always encountered a strong bias for above-plane [3 + 4] cycloaddition. The structures of the adducts were elucidated by a combustion of X-ray analysis and base-catalyzed equilibration. The stereochemical course of the tetramethyl-2-oxyallyl dipolar species was also examined and shown to prefer above-plane approach. Transition-state profiles are given. The results, particularly for those processes proceeding with extended arrangements of the reaction partners, are shown to be consistent with closed-shell orbital arguments advanced earlier for anti-Alder [4 + 2] cycloadditions to isodicyclopentadiene.

Studies of the Diels–Alder chemistry of isodicyclopentadiene (**1**) have played a pivotal role in the development of our understanding of π-facial stereoselectivity during [4 + 2] cycloadditions.[2] Two detailed theories have been advanced to account for the customarily favored[3] below-plane selectivity leading to *syn*-sesquinorbornene products (e.g., **2**). In the Gleiter–Paquette view,[2b,4] the



2 **1** **3**

subjacent ψ_1 π orbital of the diene unit is characterized by disrotatory tilting of the terminal lobes toward the methano bridge as a direct consequence of strong σ/π interaction with high-lying σ levels of the neighboring norbornyl framework. As the dienophile with its filled HOMO begins to approach **1** from below in anti-Alder fashion[3] (see **4**),

4 **5**

(1) Electronic Control of Stereoselectivity. 28. For Part 27, see: Paquette, L. A.; Green, K. E.; Gleiter, R.; Schäfer, W.; Gallucci, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 8232.

(2) (a) Paquette, L. A. In "Stereochemistry and Reactivity of Pi Systems"; Watson, W. H., Ed.; Verlag Chemie International: Deerfield Beach, FL, pp 41–73. (b) Gleiter, R.; Paquette, L. A. *Acc. Chem. Res.* **1983**, *16*, 328.

(3) For key exceptions, consult: (a) Paquette, L. A.; Green, K. E.; Hsu, L.-Y. *J. Org. Chem.* **1984**, *49*, 3650. (b) Bartlett, P. D.; Wu, C. *Ibid.* **1984**, *49*, 1880. It is obviously required of a dienophile that anti-Alder approach be operative to avoid differential steric control. With highly reactive dienophiles such as the triazolinediones and tetracyanoethylene, the early timing of the transition states may depend heavily on favorable secondary orbital overlap and the Alder arrangement necessary to its realization. Under these circumstances, steric contributions from the norbornyl or norbornenyl moiety are likely to override the more subtle electronic features of the cyclopentadiene π system.

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