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(7) All new compounds reported in this paper are racemic but for convenience only one stereoisomer is drawn. Thus compound **12** is (2*S*),(3*S*) and (2*R*),(3*R*); compound **13** is (2*S*),(3*R*) and (2*R*),(3*S*).
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(9) All new compounds possessed satisfactory analytical and spectral data. NMR spectral data for compounds **12–17** are collected in Table II (microfilm edition).
(10) Fractional crystallization of acids **12** and **13** substantially increased the purity of the major isomer. Care was taken, however, to assure that the isomer ratios in Table I were accurate by examination of the total crude product.
(11) Stereoselectivity is defined as (% major isomer − % minor isomer); see J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice-Hall, Englewood Cliffs, N.J., 1971, p 10.
(12) An alternative explanation involves increased proportion of reaction proceeding via boat transition state.

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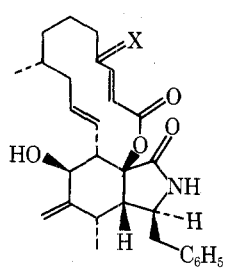
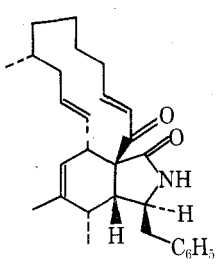
Synthesis of the Isoindolone Nucleus of the Cytochalasins

Summary: The isoindolone skeleton of the cytochalasins has been constructed stereospecifically via an intramolecular Diels–Alder reaction.

Sir: The cytochalasins are a group of microbial metabolites producing a variety of unusual biological effects upon living cells.[1] The members of this group of natural products are all characterized structurally by a saturated isoindolone skeleton fused to an 11- to 14-membered macrocyclic ring,[2-4] as shown in cytochalasins A (**1**), B (**2**), and proxiphomin



1, X = O
2, X = α-OH, β-H



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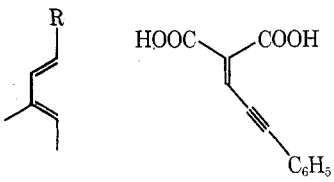
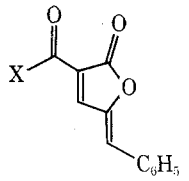
(**3**).[5] Although these compounds represent an exciting and difficult challenge for the synthetic chemist, to our knowledge no work has yet been reported in this area. We now wish to describe a stereospecific approach to the isoindolone nucleus of the cytochalasins.

Condensation of tiglic aldehyde with trimethyl phosphonoacetate (sodium hydride, benzene) produced methyl γ-methylsorbate (**4**) in 80% yield. Reduction of **4** to the alcohol **5**[6] [bp 40–45° (0.2 mm)] was effected in 87% yield with lithium aluminum hydride in ether. Diacid **6**, prepared as described[7] by condensation of malonic acid and phenyl propargaldehyde, was cyclized to the known butenolide **7**[8] by refluxing in *o*-dichlorobenzene. Compound **7** could be converted into the corresponding acid chloride **8** upon treatment with thionyl chloride in chloroform. The crude



4, R = $COOCH_3$
5, R = CH_2OH

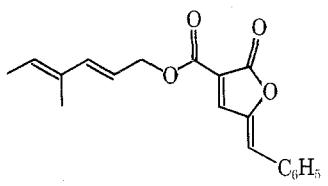
6



7, X = OH
8, X = Cl

acid chloride **8** was treated with a solution of alcohol **5** in pyridine at room temperature to produce the stable, crystalline ester **9** (80%), mp 106–108°.

Heating ester **9** in refluxing *o*-dichlorobenzene produced the crystalline tricyclic dilactone **10**: NMR ($CDCl_3$) δ 1.38



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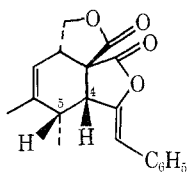
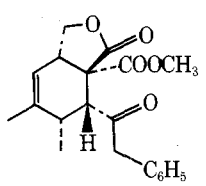
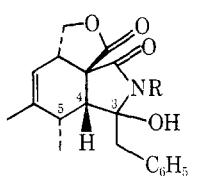


10

(3 H, d, J = 8 Hz), 1.80 (3 H, br s), 2.5 (1 H, m), 3.2 (1 H, m), 3.56 (1 H, d, J = 7 Hz), 4.65 (1 H, t, A of ABX), 5.25 (1 H, dd, B of ABX), 5.68 (1 H, s), 6.00 (1 H, m), 7.2–7.7 (5 H, m). One would expect that an endo transition state is preferred for this intramolecular Diels–Alder reaction,[9,10] thus producing the stereochemistry shown in structure **10**. The C-4–C-5 hydrogen coupling constant of 7 Hz in compound **10** supports assignment of a cis relationship to these protons.[11] Tricyclic lactone **10** was quite difficult to isolate because of its propensity for reaction with nucleophiles during chromatography. It was discovered that refluxing a methanolic solution of **10** led to formation of keto ester **11**:



11



12, R = H
13, R = $CH_2C_6H_5$

NMR ($CDCl_3$) δ 3.80 (3 H, s), 3.90 (2 H, s). The high reactivity of the butenolide ring of **10** toward nucleophiles was used in introducing nitrogen into the system.

Thus, on heating a dilute *o*-dichlorobenzene solution of ester **9** for 2.5 hr, followed by cooling in ice, and saturating with ammonia, crystalline tricyclic lactam **12** could be readily isolated (32% yield from **9**): mp 174–175°[12]; ir (film) 3400, 3300, 1750, 1710 cm^{-1}; NMR ($CDCl_3$) δ 3.1 (2 H, AB q, J = 14 Hz).

Similarly, treatment of the crude Diels–Alder product **10** with benzylamine produced lactam **13**[11,12] (36% frm **9**): ir ($CDCl_3$) 3350, 1740, 1700 cm^{-1}; m/e found 417.19520. Work is now in progress to utilize systems such as **12** and **13** in a total synthesis of the cytochalasins.

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(13) Fellow of the Alfred P. Sloan Foundation, 1975–1977; National Institutes of Health Research Career Development Awardee, 1975–1980.

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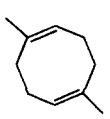
Transannular Cyclizations. A Stereoselective Synthesis of the Cyclopentanoid Monoterpenes

Summary: A highly stereoselective method of cyclopentanoid ring formation by transannular cyclization of cyclooctane systems is described. Its utility is illustrated by a total synthesis of the monoterpene iridomyrmecin.

Sir: We wish to report an approach to the synthesis of the cyclopentanoid class of monoterpenes which commences with the novel head-to-tail isoprene dimer 1,5-dimethyl-1,5-cyclooctadiene[1] (1) and which makes use of a transannular cyclization[2] to construct the carbon framework of a key intermediate in a stereoselective manner. The route, illustrated by the total synthesis of the naturally occurring insecticide iridomyrmecin, isolated from the Argentine and *Iridomyrmex humilis*, could potentially be diverted at suitable points to synthesize many of the cyclopentanoid monoterpenes.[3]

The diene **1**[4] was converted into alcohol **2a**[5] (75% yield)



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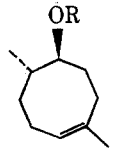
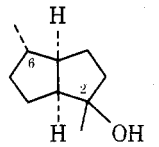


2a, R = H
b, R = SO_2CH_3

by a selective monohydroboration–oxidation sequence employing 9-borabicyclo[3.3.1]nonane,[6] and thence to the sulfonate ester **2b** with methanesulfonyl chloride and triethylamine in methylene chloride.[7] Without purification, this ester was subjected to solvolysis for 12 hr at 60° in aqueous dioxane in the presence of an excess of sodium carbonate. The alcohol **3** (60% yield overall from **2a**) thereby produced has the indicated orientation of the C-6 methyl group (exo- to the cis-fused bicyclo[3.3.0]octane system) that both follows from and is required for a successful synthesis of iridomyrmecin. The stereochemical control observed in this cyclization is the result of π-electron participation in the solvolytic removal of the sulfonyloxy group and thus the exo orientation at C-6 can be attributed directly to the trans relationship of the methyl group and the sulfonate moiety in **2b**. Though the reaction could have alternatively occurred without assistance while still generating the product of transannular cyclization, consideration of molecular models indicates that the C-6 epimer would be expected to be the predominent product of such a process.[8] Alcohol **3** was transformed into olefin **4** (70% yield) by a *p*-



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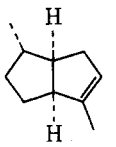

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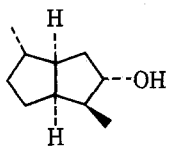
toluenesulfonic acid catalyzed dehydration in pentane at reflux to effect azeotropic removal of water. A second hydroboration–oxidation sequence using diborane served to convert olefin **4** into alcohol **5** (60% yield) containing a small amount of a second alcohol, possibly that resulting from attack by diborane on the endo face of olefin **4**. Alcohol **5** was converted into the corresponding ketone (**6**, 90%



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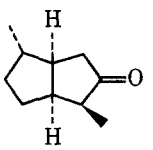
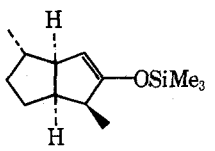


6

yield) by Jones oxidation.[9] The kinetic enolate of this ketone was generated with lithium diisopropylamide in tetrahydrofuran solution and then trapped by trimethylsilyl chloride to form the unstable enolsilyl ether **7**. Without isolation of intermediates, the enol ether **7** was cleaved with



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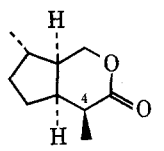

iridomyrmecin

ozone in methanol–methylene chloride solution,[10] the resulting acid–aldehyde was reduced with sodium borohydride, and the hydroxy acid was subjected to aqueous hydrochloric acid to effect lactonization. The crude material thus formed (40% overall yield from ketone **6**) crystallized spontaneously and could be recrystallized from pentane to afford needles with mp 57–58° (lit. 59° for racemic iridomyrmecin).[11,12] Further confirmation of the structure was provided by the conversion of iridomyrmecin into the more stable C-4 epimer, isoiridomyrmecin, by the known procedure.[11,12]

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