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(24) Communications concerning this paper should be directed to Professor T. Kametani.
(25) All the compounds in the synthetic sequence are racemic. To clarify the stereochemical presentation, only one enantiomer is depicted.

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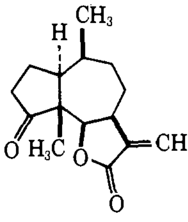
The Total Synthesis of (±)-Damsin

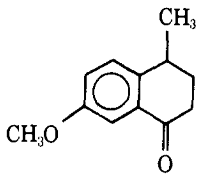
Sir:

The cytotoxic[1] compound damsin (**1**) is a representative[2] of the pseudoguaianolide family of sesquiterpenes which contains more than 50 known members.[3] Although several reports have recently appeared concerning synthetic approaches to the pseudoguaianolide sesquiterpenes,[4] no synthetic entry to this group of compounds has yet been described. We now wish to report the first total synthesis of (±)-damsin (**1**).

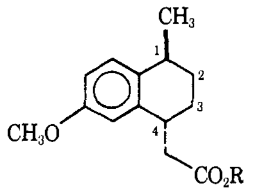


1

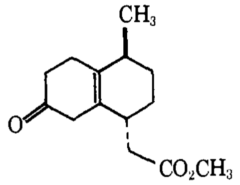
The Reformatsky reaction of 4-methyl-7-methoxytetralone (**2**)[5] with ethyl bromoacetate (zinc, 1:1 ether–benzene, reflux, 2.5 h) followed by hydrogenolysis in ethanol over 5% palladium on carbon gave an 88% yield of a single ester **3a**,[6] bp 145° (0.5 mm). The stereochemistry of **3a** follows from the observation that the lanthanide shift reagent Eu(fod)3 preferentially associates with the carboethoxy group in carbon tetrachloride solution and causes a downfield shift in the NMR which is 12.7% greater for the C-1 hydrogen signal than for that of the C-1 methyl group. Saponification of **3a** with 10% ethanolic potassium hydroxide then afforded the corresponding acid **3b**,[6] mp 81–82.5°. Reduction of **3b** with lithium and liquid ammonia in the presence of *tert*-butyl alcohol and tetrahydrofuran, followed by treatment with aqueous oxalic acid and es-



2



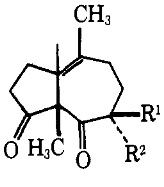
3a, $R = C_2H_5$
b, $R = H$



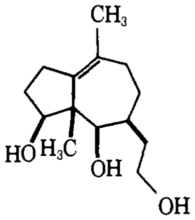
4

terification with ethereal diazomethane, afforded a quantitative yield of β,γ-unsaturated ketone **4**,[6] bp 137° (0.6 mm).

Ozonolysis of **4** at −86° in 1:1 methanol–methylene chloride followed by a reductive workup with trimethyl phosphite and a subsequent alkylation with methyl iodide (potassium carbonate, acetone, 4 hr reflux) afforded in 63% yield a 2:1 mixture of **5a**,[6] mp 87–89.5°, and **5b**,[6] mp 139–140°, which could be separated by a combination of column chromatography (silica gel) and fractional crystallization. Reduction of **5a** with sodium borohydride in methanol at 0° gave triol **6**,[6] mp 109.5–111.5°, in 62% yield. Catalytic oxidation[7] of **6** over platinum (oxygen gas, aqueous acetone, 57°, 5 h) then afforded a 96% yield of hydroxy lactone **7a** which was characterized as phenylurethane **7b**, mp 152–153°. The stereochemistry of **7a** at C-6, C-7, and C-8 follows from the fact that a nuclear Overhauser effect could not be observed in the NMR spectrum for the C-6 and C-8 hydrogens upon saturation of the C-7 methyl signal. In contrast, a NOE of 7 and 11% was observed for the C-6 and C-8 hydrogens, respectively, of the isomeric hydroxy lactone **8**,[6] mp 114–116°, which was obtained directly by reduction of **5b** with sodium borohydride in methanol at 0°. Lactone **7a** could not, however, be obtained directly by reduction of **5a** with sodium borohydride.



5a, $R^1 = CH_2CO_2CH_3$; $R^2 = H$
b, $R^1 = H$; $R^2 = CH_2CO_2CH_3$



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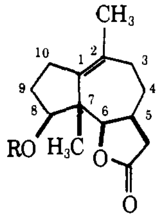
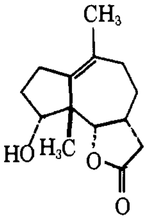
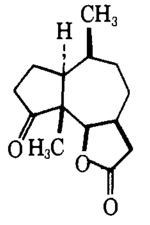


7a, R = H
b, $R = CONHC_6H_5$

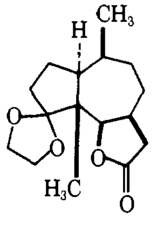


8

Catalytic hydrogenation of **7a** in ethanol over 5% palladium on carbon followed by oxidation with Jones reagent[8] gave a 46% yield of ketone **9**: mp 112–113.5°; ir (CCl_4) 1746, 1783 cm^{-1}; NMR (CCl_4) δ 1.08 (d, 3 H, $J = 6.5$ Hz), 1.18 (s, 3 H), 4.55 (d, 1 H, $J = 6.4$ Hz); mass spectrum *m/e* 236 (M^+). Ketone **9** was then converted to the corresponding ketal **10** (ethylene glycol, *p*-toluenesulfonic acid catalyst, benzene, 2.5 h reflux), mp 102.5–105.0°, in 98% yield. Treatment of **10** with ethyl formate and sodium hydride in ether solution (23 h at room temperature) followed by reduction with sodium borohydride in methanol at 0°, hydrolysis with 3 M hydrochloric acid, and reaction with *p*-toluenesulfonyl chloride in pyridine at 0° produced a 36% yield of tosylate **11**, mp 162.5–164.5°.



9



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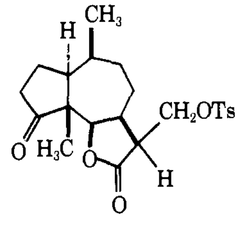

11

Tosylate **11** was heated under reflux in pyridine [9]for 5 h to give a 74% yield of (±)-damsin (**1**), mp 124–126°. The ir ($CHCl_3$) and NMR spectra as well as the TLC behavior of the synthetic material were identical with those of naturally occurring damsin (**1**).

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A Molecular Orbital Model for Bridging Regioselectivity in Di-π-methane Rearrangements

Sir:

Paquette and co-workers have recently reported several examples of regiospecificity in the di-π-methane rearrangements of benzonorbornadienes substituted by electron donor or acceptor groups.[1] While Zimmerman and co-workers have suggested a method for the rationalization of regioselectivity in hydrocarbon di-π-methane rearrangements,[2] the method is not readily extended to heteroaromatic systems. We wish to report a simple molecular orbital model, supported by CNDO/S-CI excited state calculations, which adequately accounts for the substituent effects observed in rearrangements of this type.

Paquette and co-workers found that the rearrangement of a donor-substituted benzonorbornadiene (**1**, D = MeO) gives mainly the di-π-methane product arising from meta bridging, while several acceptor substituted cases (**2**, A = CN or CO_2Et) give the di-π-methane products resulting from para bridging.

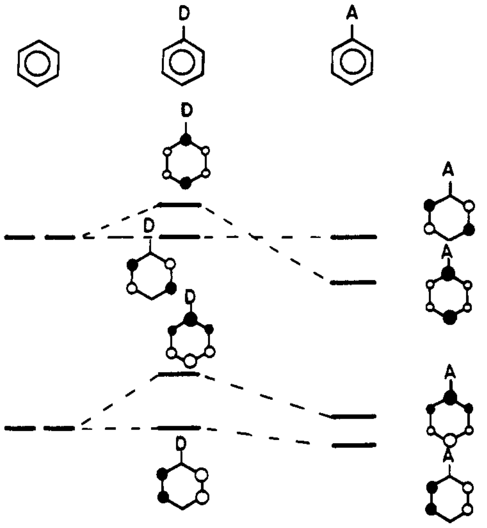
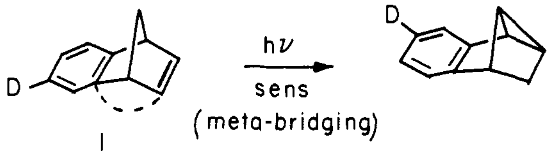
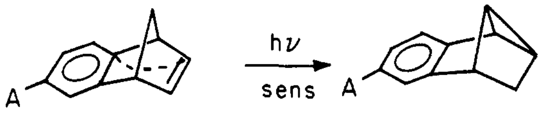


Figure 1. The degenerate HOMO's and LUMO's of benzene and energy changes upon donor (D) or acceptor (A) substitution.



1



2 (para-bridging)

A simple model to explain these phenomena can be constructed from the molecular orbitals (MO's) of substituted benzenes shown in Figure 1. Substitution of a donor (D) or acceptor (A) group on benzene splits the degeneracies of the highest occupied (HOMO) and lowest unoccupied (LUMO) molecular orbitals. Both types of groups leave the orbitals with a node at the site of substitution (a_2 in C_{2v}) essentially unchanged, but have a relatively large effect on the orbitals with the large coefficient (b_1 in C_{2v}) at the site of substitution. The major difference in the pattern of orbital energies between donor and acceptor substituted benzenes is in the vacant orbitals, the a_2 lying lowest in the former, the b_1 in the latter. A simple rationale for the pronounced regioselectivity in triplet di-π-methane rearrangements of **1** and **2** can be constructed if the triplet states of these molecules involve mainly single configurations with a half-occupied HOMO and a half-occupied LUMO. The interaction of the half-occupied LUMO of the excited aromatic moiety with the vacant LUMO of the ground-state ethylene moiety will lead to preferential meta bonding for the donor-substituted cases and para bonding for the acceptor-substituted compound. Similarly, the preferential α-naphtho-vinyl bridging in 1,2-naphthobarrelene[2a] is explicable on the basis of the larger LUMO density at the α-position of the naphthalene moiety. This explanation is similar to Zimmerman's pioneering discussions of changes in electron densities in the $\pi\pi^*$ states of substituted aromatics.[2b] However, the discussion here centers on electron densities in individual orbitals, rather than on total electron densities.

This model can also predict regioselectivity when unsymmetrical alkene substitution is present. Acceptor substituents will cause bridging at the position remote from the acceptor group, since the LUMO of the vinyl moiety has the larger coefficient at the less substituted position.[3] A case of this type