performing preliminary experiments.

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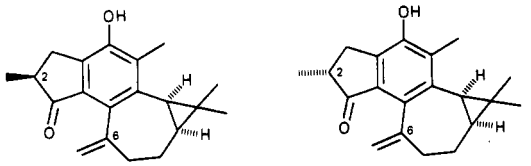
Total Synthesis of (+)-Jatropholone A and B

Summary: The first total synthesis of jatropholones A and B in homochiral form is disclosed; the absolute stereochemistry is thereby established.

Sir: High-pressure techniques (3–15 kbar) have become increasingly evident in organic synthesis. Benefits include mild reaction conditions and greatly enhanced yields for those reactions that involve a negative change in the activation volume ($\Delta V^{\ddagger}$); documented examples include the Diels–Alder reaction,[2] 1,3-dipolar cycloadditions,[3] the aldol[4] and Michael[5] reactions, introduction of protecting groups,[6] and preparation of Wittig reagents.[7] Thus the availability of the high-pressure technique permits the design of synthetic strategies not previously feasible.

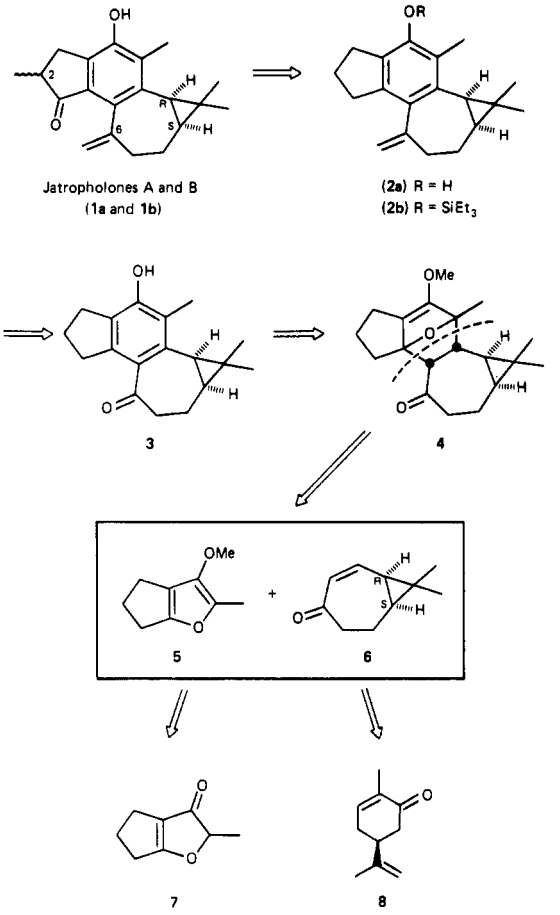
In this communication we wish to record the *first* total synthesis of jatropholone A and B (**1a** and **1b**), two novel diterpenes isolated from the roots of *Jatropha gossypiifolia L.* (Euphorbiaceae),[8] the plant that also yields jatrophone[9,10] and the hydroxyjatrophones A–C.[11] The



Jatropholones A and B

synthetic scheme, which proved viable *only* through aegis of a high-pressure Diels–Alder reaction, is short (i.e., 12 steps), reasonably efficient (ca. 6%), and establishes for the first time the absolute stereochemistry of the jatropholones.[12]

Scheme I



From the retrosynthetic perspective, assembly of the fully-substituted aromatic ring was viewed as the central synthetic challenge. Toward this end, we envisioned a Diels–Alder reaction of furan **5** with homochiral enone **6** (Scheme I). The former was anticipated to be available through O-methylation of bicyclic 3(2*H*)-furanone **7**,[14] while the latter, prepared from (*S*)-carvone (**8**), was recently exploited in our laboratory for the synthesis of (+)-hanegokedial.[15] Subsequent aromatization of the 7-oxabicyclo[2.2.1]heptene system **4**, introduction of the exo methylene, regioselective oxidation at C(3), and methylation at C(2) would then complete the synthetic venture.

We initiated synthesis of furan **5** with commercially available 1-pyrrolidinocyclopentene.[16] Acylation with acid chloride **9**[17] followed by hydrolysis [AcOH, H_2O, THF (1:1:2)] afforded **10**[18] in 68% yield. Subsequent removal of the acetate group [H_2SO_4, H_2O, THF (1:9:5)] and cy-

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(12) On the basis of the biosynthesis of casbene,[13] Connolly suggested the absolute stereochemistry of jatropholones to be 9*S*,11*R*.[7]
(13) Evans, F. J.; Taylor, S. E. *Prog. Chem. Org. Nat. Prod.* **1983**, *44*, 1 and references cited therein.
(14) While a search of the literature revealed no examples of oxabicyclo[3.3.0]octene derivatives, the unsubstituted [4.3.0] system has been reported by Gelin and successfully utilized in a Diels–Alder-like reaction with maleic anhydride: Gelin, R.; Gelin, S.; Chantegrel, B.; Galliaud, A.; Dolmazon, R. *Bull. Soc. Chim. Fr.* **1974**, 2061.
(15) Taylor, M. D.; Smith, A. B., III. *Tetrahedron Lett.* **1983**, *24*, 1867. Also see: Taylor, M. D.; Minaskanian, G.; Winzenberg, K. N.; Santone, P.; Smith, A. B., III. *J. Org. Chem.* **1982**, *47*, 3960.
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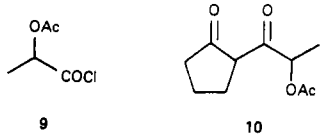
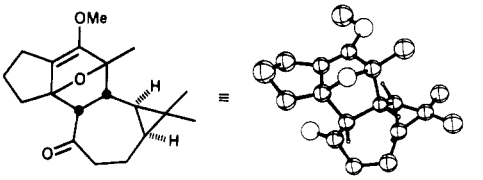


9 10

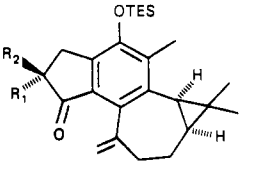
clization–dehydration (catalytic TsOH, PhH, Dean–Stark water removal) proceeded smoothly to give 3(2*H*)-furanone **7**[18] in 87% yield. Finally, O-methylation [(i) LDA (1.1 equiv, THF, HMPA; (ii) $(MeO)_2SO_2$ (1.2 equiv)] afforded furan **5**.[18] The overall yield for the five-step sequence was 57%.

Initial attempts to effect the critical Diels–Alder reaction (i.e., **5** + **6**) employing a variety of temperature, solvent, and Lewis acid protocols failed to afford even a trace of the desired cycloadduct.[19] However, when a 1:1 mixture of **5** and **6** was subjected to 5 kbar of pressure,[20] an 80% yield of a crystalline adduct (mp 48–50 °C dec) was obtained. Single-crystal X-ray analysis indicated the structure and stereochemistry (i.e., endo adduct) to be that depicted in **4**.[18,21] Aromatization was next achieved via acid treatment [2 N HCl, THF (1:5)] to afford **3**[18] in 75% yield. Subsequent methylenation [$Ph_3P{=}CH_2$ (15 equiv), PhMe, Δ],[22] albeit a slow reaction (60 h), proceeded cleanly to afford **2a**[18] in 81% yield.

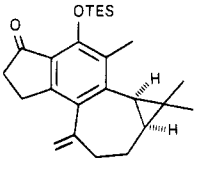


4

With ample quantities of **2a** in hand, there remained only the regioselective introduction of a carbonyl functionality at C(3) and methylation to afford the jatropholones. To discourage oxidation at C(1), the free phenolic hydroxyl group of **2a** was protected as the triethylsilyl ether **2b**[18] (TESCl, NEt_3, DMAP, CH_2Cl_2, 93%).[23] Oxidation with chromium trioxide/3,5-dimethylpyrazole[24] (15 equiv, CH_2Cl_2, −20 °C, 2.5 h) then gave the desired ketone **11**[18] (34%) along with regioisomer **12**[18] (6%) as the only isolated products; the latter were readily separated by flash chromatography (7.5% EtOAc–hexane). Final methylation [(i) LDA (1.0 equiv), −78 °C, THF; (ii) MeI → room temperature] gave **13**[18] (21%) and **14**[18] (57%) along with a minor amount [ca. 3%] of dialkylated material. Separation of the epimers (HPLC, 4% EtOAc–hexane) and careful removal of the TES group (*n*-Bu_4NF, THF)[25] gave jatropholone A (90%) and jatropholone B (88%). That in fact the jatropholones were in hand derived from careful comparison of their physical and spectral properties (i.e., mp, rotation,[26] 250-MHz ^1H NMR, and ^{13}C NMR) with those derived from authentic samples kindly provided by Professor Connolly (Glasgow University).[27]



(11) $R_1 = R_2 = H$
(13) $R_1 = H$, $R_2 = CH_3$
(14) $R_1 = CH_3$, $R_2 = H$



12

In summation, the first total synthesis of (+)-jatropholone A and B has been achieved in 12 steps and 6% overall yield from 1-pyrrolidinocyclopentene. The synthesis serves not only to demonstrate the utility of the high-pressure Diels–Alder reaction in natural product synthesis but in addition permits assignment of the absolute configuration of the jatropholones.

Acknowledgment. It is a pleasure to acknowledge the support of this investigation by the National Institutes of Health (National Cancer Institute) through Grant 22807. In addition we thank Drs. G. Furst and P. Carroll of the University of Pennsylvania Spectroscopic Facilities for aid in obtaining the high-field NMR and X-ray crystallographic data.

(18) All new compounds gave satisfactory 250-MHz ^1H NMR, IR, UV, and high-resolution mass spectra in accord with structures given. Representative spectral data include the following. **3**: mp 170–171 °C; ^1H NMR ($CDCl_3$) δ 5.43 (br s, 1 H, OH), 3.15 (m, 1 H), 2.55–2.90 (m, 5 H), 2.18 (s, 3 H, CH_3), 1.90–2.15 (m, 3 H), 1.62 (d, J = 9.5 Hz, 1 H, cyclopropyl CH), 1.40 (m, 1 H), 1.24 (s, 3 H, CH_3), 1.12 (m, 1 H, cyclopropyl CH), 0.91 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 210.06 (s), 152.46 (s), 142.97 (s), 134.66 (s), 130.69 (s), 128.43 (s), 123.22 (s), 43.04 (t), 32.72 (t), 28.78 (t), 28.50 (d), 28.35 (q), 27.81 (d), 24.81 (t), 20.91 (s), 19.89 (t), 15.71 (q), 12.21 (q); IR ν_{max} ($CHCl_3$) 3600 (m), 3380 (br m), 1670 (s), 1575 (s), 1340 (m), 1280 (m), 1225 (m), 1160 (s) cm^{-1}. UV (EtOH) λ_{max} 279, 225, 204 (ϵ_{max} 7000, 13 800, 20 600), [base added] 374, 261, 215 nm (ϵ_{max} 14 200, 9500, 74 800); $[\alpha]^{20}_D$ = +65.0° (*c* 1.27, $CHCl_3$). Anal. Calcd for $C_{18}H_{22}O_2$ C, 80.00; H, 8.15. Found: C, 79.82; H, 8.35. **4**: ^1H NMR ($CDCl_3$) δ 3.75 (s, 3 H, OMe), 3.40 (d, J = 11 Hz, 1 H), 2.95–1.70 (m, 11 H), 1.39 (s, 3 H, CH_3), 1.12 (s, 3 H, CH_3), 1.00 (s, 3 H, CH_3), 0.588 (m, 1 H, cyclopropyl CH), 0.248 (t, J = 9 Hz, 1 H, cyclopropyl CH); IR ν_{max} (CCl_4), 3000–2850 (m), 1700 (s), 1450 (m); mass spectrum, m/z 302.1903 (M^+ calcd for $C_{19}H_{26}O_3$, 302.1882); $[\alpha]^{20}_D$ = +73.1° (*c* 0.43, $CHCl_3$). Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.50, H, 8.61. Found: C, 75.57, H, 8.67. **5**: ^1H NMR ($CDCl_3$) δ 3.70 (s, 3 H, OMe), 2.70–2.50 (m, 4 H), 2.35 (m, 2 H), 2.14 (s, 3 H, CH_3); IR ν_{max} (CCl_4) 3000–2900 (s), 1640 (w), 1450 (m), 1340 (m), 1175 (m); mass spectrum, m/z 152.0840 (M^+ calcd for $C_9H_{12}O_2$, 152.0837). **7**: ^1H NMR ($CDCl_3$) δ 4.95 (q, J = 7.2 Hz, 1 H, α-H), 2.58 (m, 2 H), 2.39 (m, 4-H), 1.52 (d, J = 7.2 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 199.01 (s), 197.06 (s), 118.20 (s), 92.37 (d), 27.14 (t), 25.69 (t), 20.89 (t), 16.44 (q); IR ν_{max} ($CHCl_3$) 3000–2850 (m), 1700 (s), 1610 (s), 1450 (m), 1225 (m), 1030 (m); mass spectrum, m/z 138.0673 (M^+ calcd for $C_8H_{10}O_2$, 138.0681). **11**: ^1H NMR ($CDCl_3$) δ 5.23 (br s, 1 H), 4.67 (br s, 1 H), 2.95 (m, 2 H), 2.5–2.7 (m, 4 H), 2.23 (s, 3 H), 1.8 (m, 1 H), 1.58 (d, J = 8.5 Hz, 1 H), 1.23 (s, 3 H), 1.00 (t, J = 7 Hz, 9 H), 0.9–1.0 (m, 2 H), 0.85 (s superimposed upon dt, 9 H); ^{13}C NMR ($CDCl_3$) δ 205.40 (s), 150.80 (s), 145.92 (s), 143.24 (s), 137.43 (s), 136.32 (s), 135.06 (s), 133.14 (s), 144.80 (t), 37.03 (t), 33.59 (t), 28.73 (d), 28.15 (q), 26.15 (d), 22.73 (t), 21.50 (t), 19.31 (s), 15.99 (q), 14.82 (q), 6.68 (q), 5.99 (t); IR ν_{max} ($CHCl_3$) 1708 (s), 1570 (m), 1480 (m), 1460 (m), 1285 (s), 1120 (m) cm^{-1}; UV (EtOH) λ_{max} 317, 269, 225, 200 nm (ϵ_{max} 2100, 6500, 19 400), 10 600); mass spectrum, m/z 396.2456 (M^+ calcd for $C_{25}H_{36}O_2Si$, 396.2485); $[\alpha]^{20}_D$ +59.0° (*c* 0.37 $CHCl_3$). **12**: ^1H NMR ($CDCl_3$) δ 5.26 (br s, 1 H), 4.82 (br s, 1 H), 3.08 (m, 1 H), 2.75 (m, 1 H), 2.5–2.7 (m, 4 H), 2.18 (s, 3 H), 1.82 (m, 1 H), 1.64 (d, J = 8.5 Hz, 1 H), 1.24 (s, 3 H), 1.00 (t, J = 7 Hz, 9 H), 0.8–1.0 (m, 2 H), 0.85 (s superimposed upon dq, 9 H); IR ν_{max} ($CHCl_3$) 1700 (s), 1580 (m), 1455 (m), 1445 (m), 1310 (m), 1285 (m), 1110 (s) cm^{-1}; UV (EtOH) λ_{max} 321, 272, 228, 206 nm (ϵ_{max} 2700, 10 900, 20 500, 17 900); mass spectrum, m/z (CI, isobutane) 397.2574 ((M + 1)$^+$ calcd for $C_{25}H_{37}O_2Si$, 397.2563); $[\alpha]^{20}_D$ +58.0° (*c* 0.38, $CHCl_3$).

(19) This failure is most probably due to instability of the furan component which was found to decompose on standing in chloroform or attempted chromatography.

(20) Our apparatus, identical with that designed by Professor P. DeShong in collaboration with Leco-Tempress Corporation (Belle Fonte, Pa), is described in: DeShong, P.; Dicken, C. M.; Perez, J. J.; Shoff, R. M. *Org. Prep. Proced. Int.* **1982**, *14*, 369. We thank Professor DeShong for allowing us to use his apparatus during our initial investigations.

(21) Compound **4** affords crystals of the monoclinic space group $P2_1$, with a = 9.364 (7) Å, b = 8.150 (3) Å, c = 11.610 (10) Å, and α = 107.04 (7)°. The structure was solved by the use of MULTAN 11/82 using 500 unique reflections with $I > 2.3\sigma$ ($2\theta < 100°$) measured on an Enraf-Nonius CAD4 diffractometer using Cu Kα radiation. Refinement with isotropic temperature factors and precalculated hydrogen positions led to R = 0.077 and R = 0.079.

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(25) Corey, E. J.; Snider, B. B. *J. Am. Chem. Soc.* **1972**, *94*, 2549.

(26) Rotations for the natural jatropholones have not previously been reported; natural material was therefore separated by HPLC and the rotations determined: jatropholone A, $[\alpha]^{20}_D$ +80.3° (*c* 0.128, $CHCl_3$); jatropholone B, $[\alpha]^{20}_D$ +107.2° (*c* 0.070, $CHCl_3$).

(27) We thank Professor Connolly (University of Glasgow) for the authentic spectra and the generous samples of jatropholones A and B.

Registry No. **1a**, 71424-66-3; **1b**, 71386-38-4; **2a**, 97315-42-9; **2b**, 97315-43-0; **3**, 97315-44-1; **4**, 97315-45-2; **5**, 97315-46-3; **6**, 82691-87-0; **7**, 97315-47-4; **9**, 55057-45-9; **10**, 97315-48-5; **11**, 97315-49-6; **12**, 97336-04-4; **13**, 97315-50-9; **14**, 97371-82-9; 1-pyrrolidinocyclopentene, 7148-07-4.

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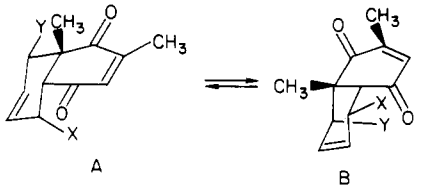
Acetylide Additions to Enediones. Regioselectivity Based on Stereoelectronic Control

Summary: Regiospecific addition of acetylide anions to enediones can be achieved without the need of protecting groups. The selectivity of these additions appears to be the result of a preference for these anions to add in an axial fashion.

Sir: We report the results of our study on acetylide additions to enediones in which the regioselectivity (and stereoselectivity) of the additions depends primarily on stereoelectronic control at the reaction site. The results of our study are listed in Tables I and II.[2] Chronologically, the first reaction studied is entry a in Table I. At the time, we believed that the remarkable regiospecificity of this reaction resulted from direct interaction between the sulfur lone pair electrons and the less-hindered, proximate carbonyl group. Such interaction would effectively preclude any nucleophilic addition to this carbonyl group and, by default, direct the acetylide to the other carbonyl group.

While this direct substituent/carbonyl interaction may actually be operative,[3] interactions of this sort are not a necessary condition for obtaining highly regioselective addition. This is apparent from entries b and c in Table I. In both examples regiospecific acetylide additions are observed, despite the lack of any substituent interactions of the type previously discussed. Indeed, as the results in Table I indicate, *the selectivity of these additions is quite independent of the nature of X, Y, and the attacking acetylide.*[4]

On the basis of our observations, there appeared to be only a few reasonable rationales for explaining this consistent pattern of selectivity. The one that we prefer is based on the following premises: (a) the preferred reaction pathway should involve axial addition of the acetylide ion to the enedione chromophore and (b) the more-accessible conformation B is the only reactive conformation for enediones with cis-ring junctures. If the acetylide addition occurs in an axial fashion (attack at the "more-hindered" carbonyl), then the transition state will be "chair-like" and good overlap can be maintained between the double bond and the other carbonyl group during the entire addition process. Equatorial attack (attack at the "less-hindered" carbonyl) requires a "boat-like" transition state which involves poorer overlap. This should lead to an overall preference for axial attack and result in the production of **2** from **1** and **5** from **4**. The only exceptions to this rule occur when axial addition is hindered by the presence of an axial substituent at C-1 of the A ring (Table II, entries a, b, and e).



We have also considered and rejected a number of other possible rationales for our observations. The first requires that significant electronic differences (e.g., LUMO coefficients, charge densities, etc.) exist between the two carbonyl carbons.[5] These differences can be addressed from both a theoretical[6] and experimental viewpoint. If the observed selectivity has, as its origins, the fundamental electronic characteristics of the 2-methyl enedione chromophore, then epimerization of these adducts to the corresponding trans isomers **4** should represent only a minor electronic perturbation and should not dramatically alter the regioselectivity of these additions. As all of the results in Table II indicate, this is *not* the case, since acetylide additions to trans enediones **4** can produce either **5** or **6**, depending upon the nature of the substitution pattern of ring A.

(1) Recipient of a Camille and Henry Dreyfuss Teacher–Scholar Fellowship, 1981–86.

(2) The regioselectivity of these acetylide additions can be determined by using a variety of techniques, the simplest of which is proton NMR. Since the products of these additions are enones, it is quite a straightfoward matter to determine if the material in question possesses an α enone proton (δ = 5.8–6.0 ppm) or a β enone proton (δ = 6.7–7.0 ppm). Stereochemical assignments at quaternary centers were made by using combinations of ^{13}C NMR correlations, X-ray crystal structure determinations, and general literature precedents. All starting materials were prepared by either thermal or Lewis acid catalyzed Diels–Alder reactions of the appropriate diene and quinone. All products were characterized on the basis of their physical and spectral properties, including high-resolution mass spectrometry.

(3) The ultraviolet spectra of **1a** (X = H, Y = SPh) and **1b** (X = H, Y = CH_3) strongly support this sulfur/carbonyl interaction: **1a** λ_{max} (EtOH) 248, 337 nm; **1b** λ_{max} (EtOH) 238, 362 nm.

(4) Since the observed product ratios do not change when these additions are quenched prior to completion of the reaction, these reactions are most probably operating under kinetic control.

(5) Various unsaturated dicarbonyl compounds have been reported to undergo regioselective additions of nucleophiles. Some examples are the following: (a) Liotta, D.; Barnum, C.; Saindane, M. *J. Org. Chem.* **1981**, *46*, 3369. (b) Bloomfield, J. J.; Lee, S. *J. Org. Chem.* **1967**, *32*, 3919. (c) Kayser, M. M.; Morand, P. *Can. J. Chem.* **1978**, *56*, 1524. (d) Kayser, M. M.; Morand, P. *Tetrahedron Lett.* **1979**, 695. (e) Kayser, M. M.; Morand, P. *Can. J. Chem.* **1980**, *58*, 2484.

(6) We have performed a series of MNDO calculations on **12a**, **12b**, and **13**. Each of these structures has been subjected to *complete* geometric optimization, i.e., *all* bond lengths, bond angles, and dihedral angles were varied until a minimum energy structure was achieved. As can be seen from the LUMO coefficients shown with each structure, Frontier Molecular Orbital (FMO) considerations consistently predict nucleophilic attack at the *wrong* carbonyl group. Since FMO theory extrapolates to transition states on the basis of the electronic characteristics of the reactants, the complete inconsistency of these calculations with experimental results lends some additional credence to out hypothesis that the transition state is more product-like.