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TOTAL SYNTHESIS OF PSEUDOGUAIANES—I

PREPARATION OF BICYCLO[5.3.0]DECANE SYNTHONS FOR DAMSINIC ACID AND HELENANOLIDES

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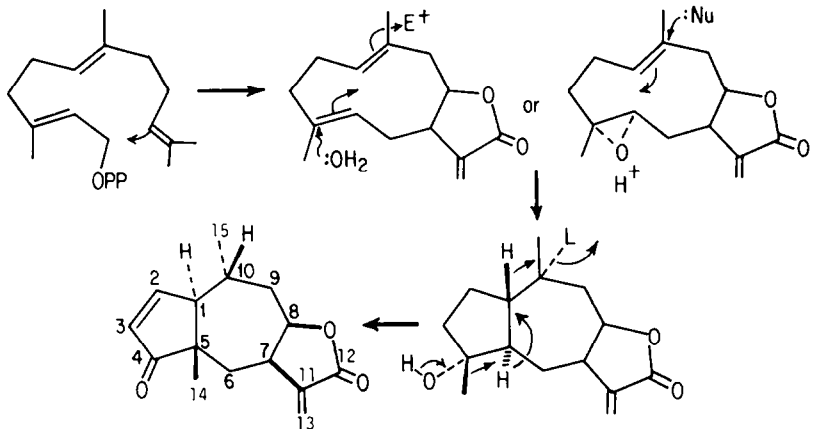
Abstract—A reaction sequence has been developed for preparing hydroazulenones suitable for total synthesis of pseudoguaiane sesquiterpenes (→1→2→4). The relative configuration of bicyclic ketone 2 at three chiral centers was established by its conversion to (±)-damsinic acid (3). Subsequently, the C-10 chiral center of 2 was inverted by employing temporary vinyl activation (2→27→4). Ketone 4 thus produced is a potential synthon for helenanolides, having the required configuration at carbons 1, 5 and 10 found in that class of sesquiterpene lactones.

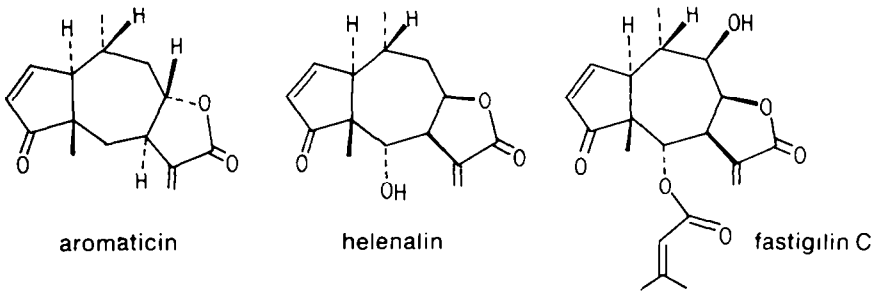
The pseudoguaianolides are a class of highly functionalized sesquiterpene α-methylene-γ-butyrolactones[1] derived from farnesyl pyrophosphate by multiple cyclizations and oxidations.[2] At some stage in their biosynthesis, a complex molecular rearrangement, including 1,2-methyl migration from C-4 to C-5,† converts the isoprenoid guaiane skeleton into the non-isoprenoid pseudoguaiane system, e.g.



These functionally- and stereochemically-complex natural products pose a fascinating challenge for the synthetic organic ehemist. In addition, a number of C_8-pseudoguaianolides have been shown to possess *in vitro* and *in vivo* anti-neoplastic activity,[3] which provides additional incentive to develop total syntheses of the natural products themselves, as well as synthetic derivatives that may have better chemotherapeutic profiles.

We have embarked on a long-range program designed to culminate in the total synthesis of fastigilin C[4] (below), a particularly active tumor inhibitor, after first preparing several less complex pseudoguaianes such as aromaticin,[5] aromatin[5] and helenalin,[6] *inter alia*. This group is progressively more highly oxygenated in the cycloheptanoid B ring and accordingly functional group manipulations will become correspondingly more numerous. As for stereochemistry, the configurations at carbons 1,5,7, and 10 shown in the above examples are typical of most C_8-pseudoguaianolides;[1] moreover, additional control of chirality will be required at carbons 6, 8, and 9. There are five or more chiral centers in our target molecules so each asymmetric carbon needs to be introduced stereoselectively in order to avoid monumental separation problems. Clearly, to reach these ultimate goals requires the development of several strategies, each with some flexiblility, to optimize the changes for achieving satisfying conclusions. Preliminary retrosynthetic analysis (Scheme 1) indicates that a C-7 "prolactone" side chain can be incorporated onto hydroazulenic synthons by 1,2-carbanion addition at a C-7 carbonyl group (A) or by 1,4-conjugate addition at the same carbon atom, when the latter serves as the β-position of an α,β-unsaturated ketone (B). Refinements in these two basic strategies will become apparent in later discussions, as various tactics are explicitly brought into focus. Diketone 1, a key starting point for our program,

†Throughout the discussion, C atoms of pseudoguaianolides are numbered in accord with established practice (*cf* Ref. 1). In the experimental section, the various compounds are also named by the IUPAC system, as found in Chemical Abstracts.

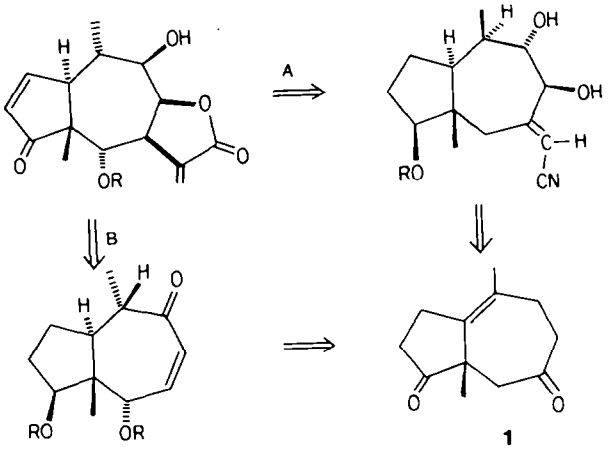


is easily prepared[7] from available compounds and also provides excellent opportunities for selective functionalization and control of regio- and stereochemistry throughout the planned sequences. Of particular relevance in the earliest stages of our work was the need to effect the net addition of hydrogen to the 1–10 double bond in **1** and its derivatives, initially by backside cis-hydrogenation and subsequently with selective C-10 epimerization as implied in Scheme 1. Workable solutions to these stereochemical problems, such as those presented in this paper, are of a magnitude comparable to the non-trivial structural considerations.

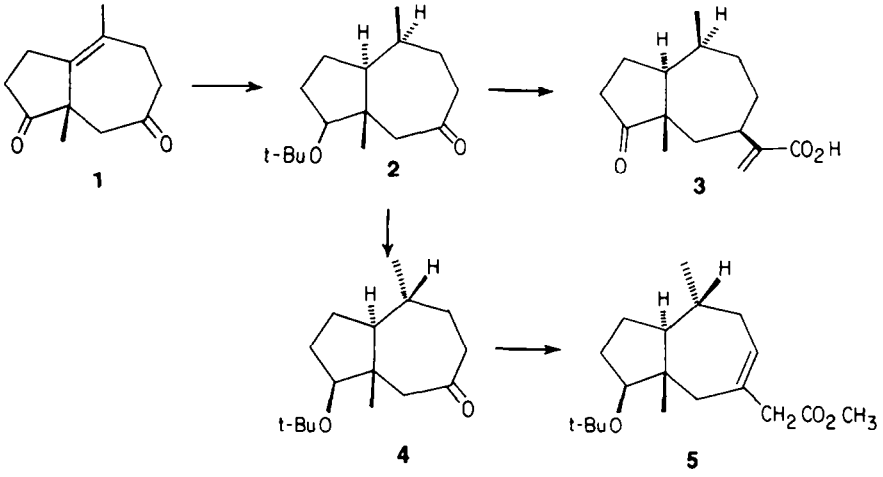
The anticipated complexity of the problems implicit in our retro-synthetic analysis is foreshadowed by the hard-won success of several groups[8–13] in synthesizing the more accessible C-10 β-methyl pseudo-guaianolides. In those instances (*cf* confertin[8–10] and damsin,[11,12,13a] below) α-side hydrogenation at C-1,10 was achieved by the combined directive effects of *several* β-oriented groups; once that task was accomplished, there was no need for subsequent C-10 epimerization. We required a synthetic pathway that would provide the opportunity, at a chosen stage after such a 1,10-hydrogenation, to epimerize a C-10 β-methyl group without interfering elsewhere in the molecule. Moreover, epimerization of C-1 to the more stable *cis*-fused ring system[1] has to be prevented, especially in the last stages when the A-ring becomes a cyclopentenone. Grieco has elegantly solved these specific problems in his recent helenanolide syntheses.[6]

In this paper, we report several inter-related approaches to diketone **1** and show its conversion[7] initially to the *cis*-dimethyl ketone **2**. The latter was first used to prepare[7] damsinic acid[14] (**3**), a natural product configurationally related to **2** at positions 1, 5 and 10. Once this sterochemical correlation had been established (see below), we undertook efforts to effect the indirect epimerization of **2** at C-10, as a means of providing access to the *trans*-dimethyl ketone **4**.[15] Since **2** has already undergone carbanionoid addition at C-7 and regiospecific deconjugation from a conjugated side chain toward C-8[7], it seemed reasonable to anticipate that **4** would similarly be convertible to **5** or equivalent synthons.[16] Such developments would set the stage for later regio- and stereocontrolled functionalizations designed to culminate in aromaticin, aromatin and more oxygenated helenanolides, once provisions are made for functionalizing C-6 and C-9 where required.

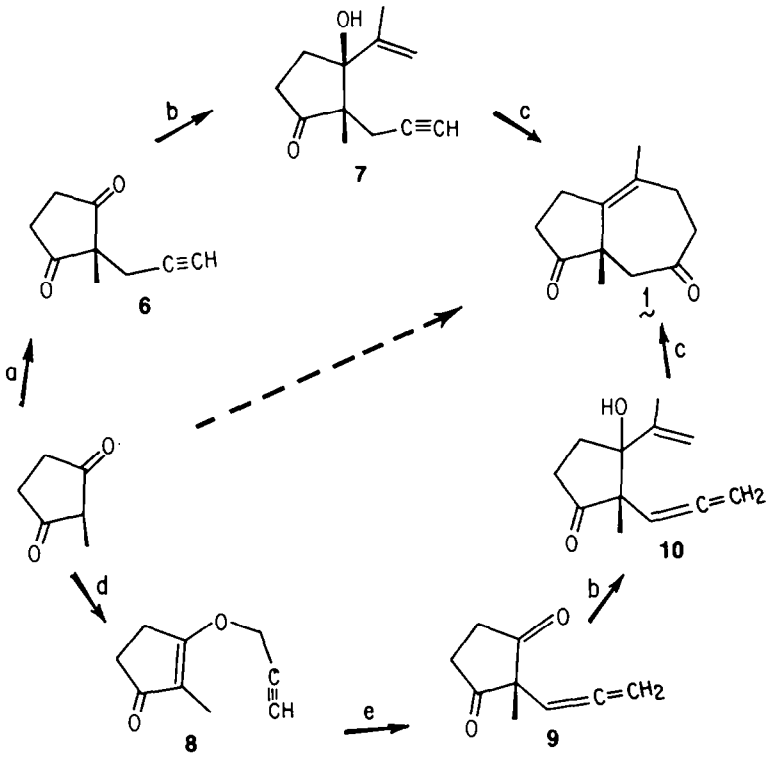
In choosing a specific hydroazulene building block, we regarded **1** as particularly appropriate, since the two CO groups at positions 4 and 7 seemed differentiable on steric grounds. It was our intention to keep the former CO group in a latent or blocked form while the latter was to be used for C_{11}-C_{13} side chain construction, e.g. **2**→**3**. We approached **1** by formolysis fo the isopropenyl-carbinols **7** and **10** derived from the diketones **6** and **9**, as shown in Scheme 3. Several exploratory attempts to induce carbinols **7** and **10** to cyclize with Lewis acids such as stannic bromide, *inter alia*, failed to yield regioisomeric bromides. However the successful CO differentiation reactions of **1** (see below) alleviated the necessity of pursuing this unyielding tack. Accord-



Scheme 1.



Scheme 2.



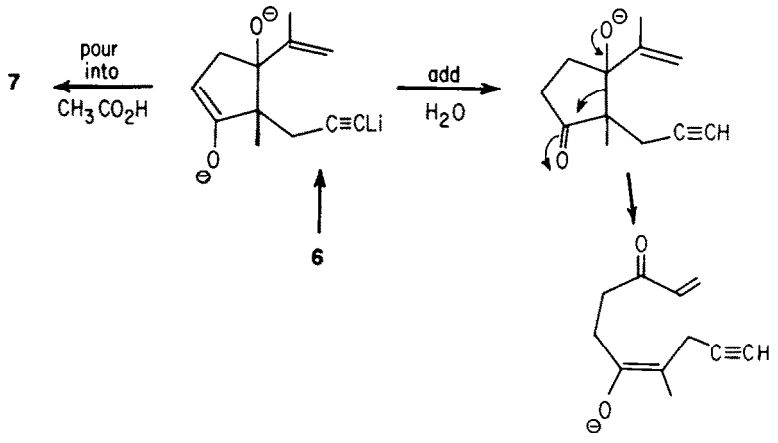
a: $NaHCO_3$, $HC{\equiv}C{-}CH_2Br$; **b**: $CH_3CLi{=}CH_2$, ether-THF, -75°C;
c: 90% HCO_2H, 80°/1 h; **d**: $HC{\equiv}CCH_2OH$, *p*-TSA, C_6H_6, Δ;
e: 315°, N_2 flow system

Scheme 3.

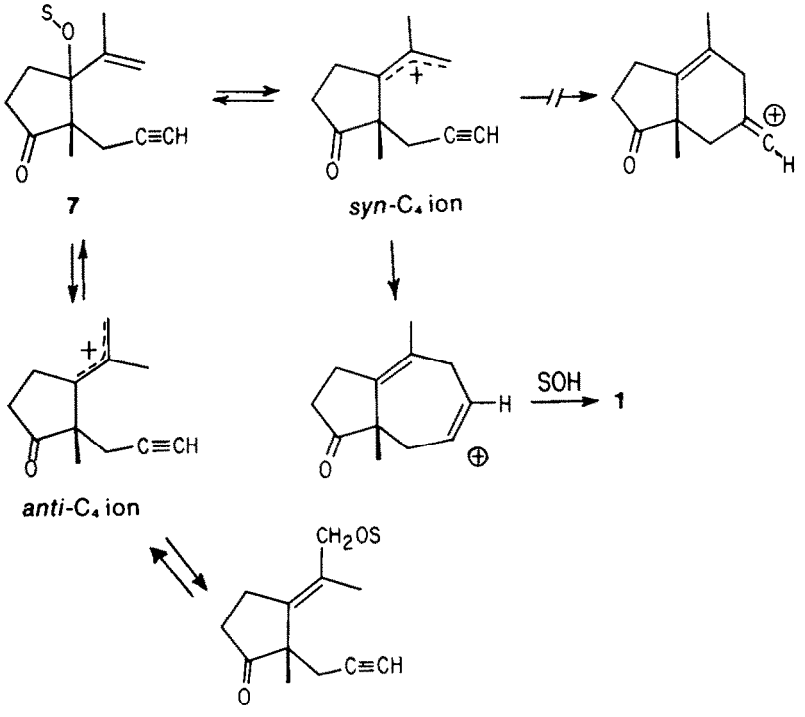
ingly, the lengthier route to **1** via the allenic ketone **9** was discarded in favor of the directly accessible propargyl ketone **6**.

The propargyl side chain was readily incorporated into 2-methyl-1,3-cyclopentanedione, by S_N2 carbon-alkylation, and the isopropenylcarbinol **7** was then formed by adding **6** to three equivalents of 2-propenyllithium. Up to two equivalents of organolithium reagent are seemingly wasted by proton abstraction from **6** but the formation of a cyclopentanone enolate[17] undoubtedly prevents retroaldolization of an otherwise "unprotected" alkoxide adduct! The correctness of this assumption is seen in the necessity for *inverse* quenching of the organolithium adduct into acetic acid in order to obtain high yields of **7**; normal addition of water generates the sensitive β-keto alkoxide *in situ* and cleavage then takes place at that stage.

Once the experimental conditions for converting **6** to **7** were well understood, this route was chosen for large-scale preparation of diketone **1**. Scheme 4 illustrates,

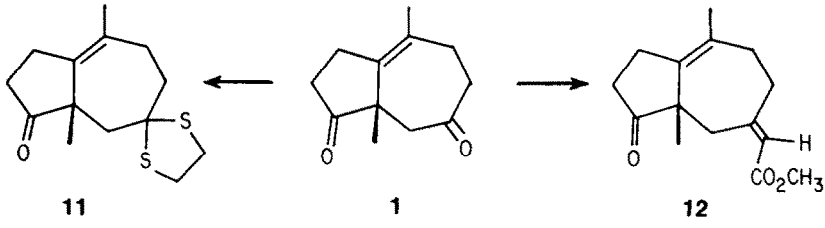


with 7, the apparent reasons for success in the electrophilic cycloheptenoid cyclizations. Firstly, the two possible isomeric allyl cations can interconvert *via* reversible solvent capture; thus generation and solvolysis of the "anti-C_4" ion does not result in a synthetic "dead end". Secondly, cyclization onto a *terminal* alkyne unit does not occur at an internal position,[18] owing to the predicted instability of *primary* vinyl cations. Had that undesired possibility occurrred, vinyl cation ring expansion rearrangement[18] would have been expected to give 1 *and* an isomer, whereas no such species were produced. Although several groups have already used this approach to form cyclohexanones,[19] the present work, to our knowledge, constitutes the first acetylenic cycloheptanone annelation.[7]



Scheme 4.

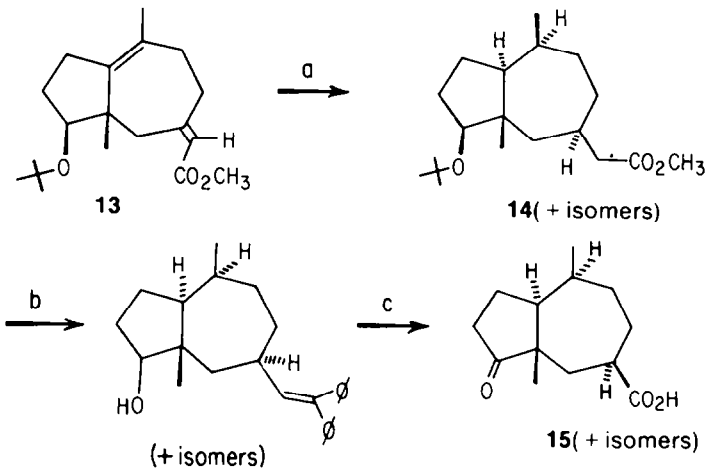
The relative reactivity of the two CO groups in 1 was shown in several nucleophilic additions; the two examples below are important both in facilitating product isolation and in further transformations relevant to γ-butyrolactone construction. In particular, selective thioketalization of crude 1, with an equivalent of ethanedithiol and BF_3-etherate results in immediate pre-



cipitation of pure **11**, thereby providing both an excellent non-chromatographic isolation procedure for **1** as well as a useful intermediate with differentiated carbonyl groups for ultimate C-1, 10 hydrogenation (see below).

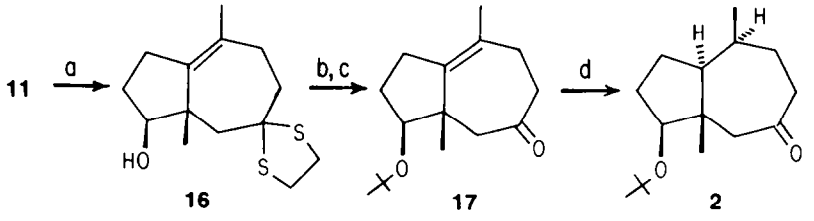
Although 1-10 hydrogenation would normally be completed before prolactone side chain construction at the C-7 CO group (i.e. **1**→**2**, **4**), we initially attempted the direct hydrogenation of dienoic ester **12**. The desired outcome (both double bonds reduced from the α-side) would allow a rapid synthesis of damsinic acid (**3**) and the much sought configuration rational assignment of **2** would then be possible. It soon became clear, however, that during hydrogenation of **12**, and the C-4 blocked hydroxyl compound **13** derived therefrom, over platinum, saturation of the 7–11 double bond was apparently occurring first and in stereorandom fashion. This, in turn, would permit[20] both possible modes of attack at 1–10, the experimental result with **13** being *four* hydrogenation products. To determine if the major isomer, at least, was **14**, we subjected the hydrogenation mixture from **13** to a Barbier–Wieland degradation sequence, which included deblocking and oxidation at C-4. The desired bisnordamsinic acid (**15**) of natural stereochemistry was available,[13] for comparison purposes by oxidative ozonolysis of **3**.

Glc of the Barbier–Wieland degradation mixture (as the methyl esters) revealed that the major component (*ca* 45%) was **15**. Because of these stereorandom results, we considered it essential in all future reaction sequences to complete C-1,10 hydrogenation *before* any additional bond-forming operations at C-7. Moreover, this satisfied the requirement, stated above, that such products could then be selectively epimerized at C-10 promptly or at a much later stage in total synthesis (e.g. *via* a transient C-9 CO group or C-8,9 double bond). The chosen path (Scheme 6) involved borohydride reduction of thioketal **11** to **16**, followed by removal of the C-7 thioketal (preferably with excess methyl iodide in aqueous acetonitrile) and then t-butylation at the C-4 OH group to provide **17**. It was now possible to hydrogenate **17** with better than 90% stereoselectivity, owing to *two* β-oriented directing groups. Partial reduction of the C_7-CO group sometimes occurs as well, necessitating "back oxidation" of crude **2** with pyridinium chlorochromate. The configuration of **2** was then established by its straight-forward conversion into (±)-damsinic acid (**3**), as shown in Scheme 7. Attachment of the arcylic ester side chain at C-7 in **2** could be accomplished by use of α-silyl ester enolates,[21] leading to **18** in high yield. Hydrogenation of **18** gave mainly the desired isomer **14**, along with *ca* 25% of epimer **19**, as indicated by the NMR signal of the major methyl ester at δ 3.61, with the



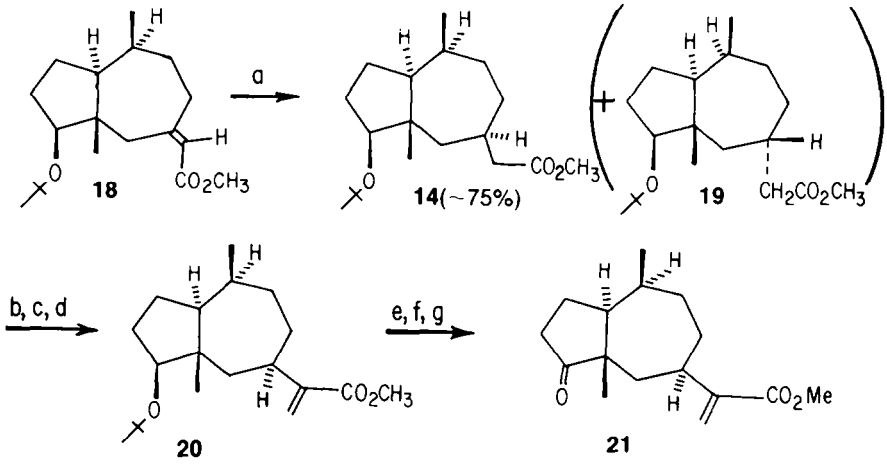
a: H_2, Pt, $CH_3CO_2C_2H_5$; **b**: excess C_6H_5Li, then H_2O^+, Δ;
c: RuO_4 acetone-H_2O.

Scheme 5.



a: $NaBH_4$; **b**: CH_3I, $CaCO_3$, CH_3CN-H_2O; **c**: isobutylene, H^+;
d: H_2, Pt, CH_3CO_2H.

Scheme 6.



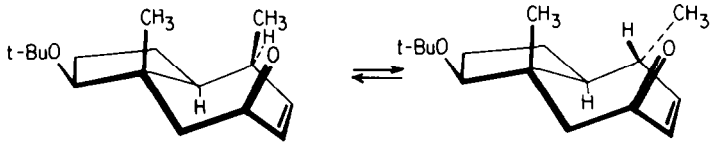
a: H_2, Pt, $CH_3CO_2C_2H_5$; **b**: LDA, CH_2O; **c**: CH_3SO_2Cl, C_5H_5N, 0°C;
d: DBU, C_6H_6; **e**: CF_3CO_2H; **f**: KOH, CH_3OH;
g: Jones reagent

Scheme 7.

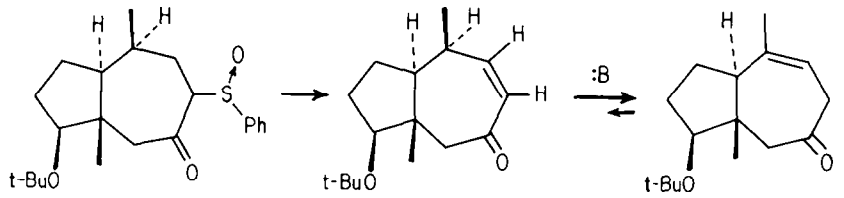
corresponding signal of epimer **19**, barely separable at 100 mHz and not integratable with accuracy, at δ 3.62. Because **14** and **19** could not be separated, this mixture was carried through the remaining steps as such. α-Methylenation was achieved by a well-known hydroxymethylation-dehydration sequence,[22] affording **20** in reasonable yield. This was followed by removal of the C-4 blocking group and Jones oxidation of the exposed OH function. Methyl damsinate (**21**) prepared by this route was compared (by glc, tlc, IR and NMR spectra) with an authentic sample generated by diazomethane esterification of (−)-damsinic acid.[14] In particular, the 100 MHz NMR spectrum of synthetic (±)-**21** showed the intense methyl ester resonance at δ 3.70, as did (−)-**21**, and the weak signal of methyl 7-epi-damsinate at δ 3.72. This synthesis of **3** served the primary, intended purpose of confirming the assigned relative configurations at carbons 1, 5 and 10 in **2**. Once this correlation had been made, we turned to the C-10 epimerization of this vital intermediated (*cf* Scheme 2). Although C-7, 11 hydrogenation in **18** had not been achieved with total stereospecificity, such additions to endocyclic C-7, 8 double bonds in C-10 epimers such as **5** are decidedly more stereoselective.[16] From examination of molecular models it can be seen that when the unfavorable C-5, 10 Me–Me interactions in **2** and **18** are relieved (*vide infra*), the conformational situation in helenanolide intermediates such as **5** is more favorable for α-attack by external reagents.

The initial plan for gaining access to **4** envisioned introducing an 8,9-double bond into **2** so as to render the C-10 hydrogen vinylogously enolic, and also to reduce the conformational flexibility of the 7-membered ring.[23] When an endocyclic double bond is introduced into a 7-membered ring, conformational interconversions are rendered more difficult, in contrast to the situation in cyclohexanes. In the present case, the relevant isomers, shown in the normally preferable chair forms, should equilibrate to relieve the "diaxial" compression of Me groups at C-5 and C-10 (*cf* **22** below).

Sterically-directed kinetic enolate formation (LDA or NaH) in ketone **2** was followed by sulfinylation[24] with methyl benzenesulfinate. This direct introduction of the phenyl sulfoxide group (**2**→**23**) was faster and cleaner than the two-step sulfenylation-oxidation sequence[25] frequently employed for introducing α,β-unsaturation into carbonyl compounds. Pyrolysis of **23** afforded the enone **22** without concommitant epimerization at C-10 (as verified by observing $J_{9,10} = 7.5$ Hz, consistent with $\theta \sim 0°$). Base-induced isomerization ensued upon refluxing a xylene solution of **22**-c with 1,4-diazabicyclo[2.2.2]-octane, but unfortunately the deconjugated ketone **24** dominated the resultant equilibrium mixture (~90%), instead of the desired C-10 epimer of **22**-c. This finding was not unexpected, since medium-ring cycloalkenones tend to prefer non-planar conformations and are accordingly extensively deconjugated[26] (30% of cyclohept-3-enone and 80% cyclooct-3-enone are present at equilibrium with the corresponding 2-enones). Clearly, to achieve only the desired equilibration of **22** called for the introduction (and later removal) of an additional conjugation substituent at C-8. Without necessitation any additional steps, we subjected **23** to acid-catalyzed Pummerer rearrangement[27] (quantitative yield), reason-



22c **22t**



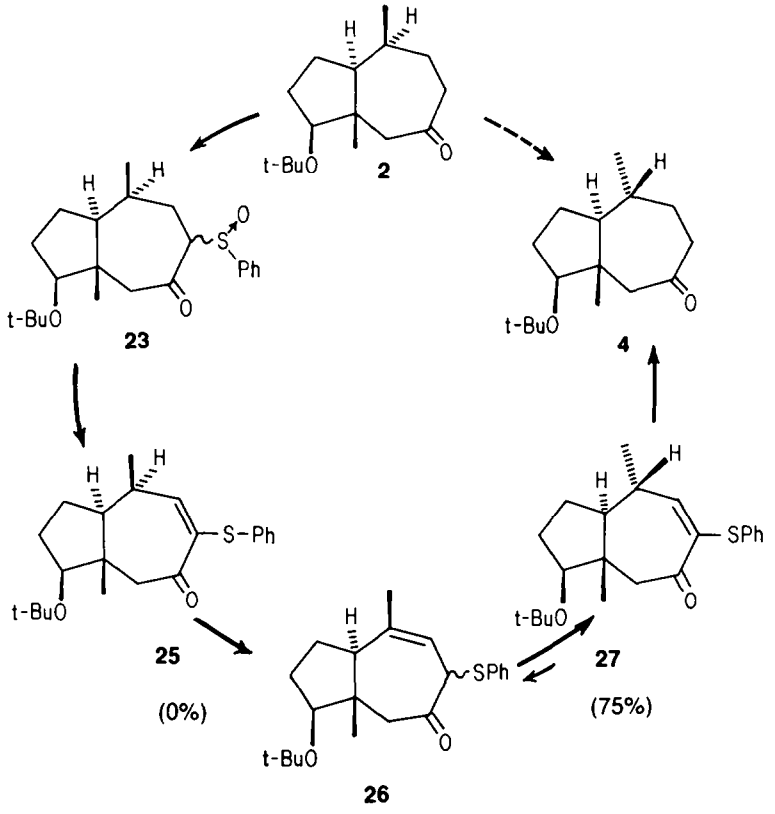
23 22c 24

ing that the α-(phenylthio) ketone **25** would have enhanced kinetic acidity at C-10. This feature, plus the expected ability of the trisubstituted α,β-double bond to favor conjugation more than the corresponding disubstituted one in **22**, led us to expect rapid equilibration of **25** without the serious loss of conjugation[28] experienced by **22**. At equilibrium (established with DBN in methylene chloride at room temperature), **25** was totally consumed and there remained at 3:1 mixture (100% recovery) of the desired **27** and **26**, which was easily separable by mplc (98:2 cyclohexane-acetone),

The rationale used during synthesis of **4** from **2** might be more widely applicable in organic synthesis. Thus in those cases where β,γ-unsaturated carbonyl compounds predominate in equilibria with *less-substituted* conjugated systems, because of alkyl substitution patterns, temporary insertion of α-arylthio (or α-alkylthio) substituents may shift such an equilibrium back toward conjugated isomers, if so desired.

EXPERIMENTAL

^{1}H NMR spectra were determined on Varian T-60 or JEOL



Scheme 8.

thus allowing recycling of the latter. Ketones **25** and **27** were readily characterizable, *inter alia*, by the angle-dependent vicinal coupling constants, $J_{9,10}$, of the respective vinyl PMR signals: in **25** ($\theta \sim 10°$), $J_{9,10}$ was 7.2 Hz for the C-9 proton (δ 6.54) whereas in **27**, ($\theta \sim 135°$), the C-9 proton signal (δ6.24) showed $J_{9,10} = 2.5$ Hz. Raney nickel hydrogenolysis[29] of **27** directly to **4** (thereby by-passing the problematic **22-t** that might otherwise isomerize out of conjugation!) completed the four-step transformation of **2** to **4** in reproducible, overall yields of 60% (approaching 100%, when recovered **23** and **26** are recycled).

MH-100 NMR spectrometers, using chloroform-d as solvent with TMS as internal standard. Mass spectra were obtained on a Perkin–Elmer Hitachi RMU-6E mass spectrometer at 70 eV ionization potential. M.ps (pyrex capillary) and b.ps were uncorrected. IR spectra were obtained with a Perkin–Elmer model 467 IR spectrometer and UV spectra recorded with a Perkin–Elmer model 202 UV-visible spectrometer. Microanalyses were performed by Atlantic microlab, Atlanta, Georgia.

"Standard workup" refers to partitioning a reaction mixture between aqueous and organic phases (usually ether, petroleum ether, methylene chloride or mixtures of these with benzene, tterahydrofuran, etc), and washing the latter with dil HCl aq, NaOH or $NaHCO_3$ as required. After the removal of acids or

bases, the organic layer was washed with sat NaCl aq, dried over $MgSO_4$ or Na_2SO_4, and then concentrated by means of a rotary evaporator at reduced pressure prior to chromatographic purification as noted.

2-Methyl-2-propargylcyclopentane-1,3-dione (**6**). Following Heathcock's procedure,[30] powdered $NaHCO_3$ (4.20 g, 50 mmol) was gradually added to a vigorously stirred suspension of 2-methyl-1,3-cyclopentanedione (5.60 g, 50 mmol) in 50 ml water. After the frothing had subsided, propargyl bromide (11.90 g, 100 mmol) was added and the resulting mixture heated at 80° for 16 hr under N_2. The cooled mixture was extracted with 100 ml CH_2Cl_2 and the latter washed with 5% $NaHCO_3$ aq, dried over Na_2SO_4 and evaporated to give 6.50 g of pale yellow solid. Sublimation (55°/0.2 Torr) gave 6.25 g (83%) of chunky, white prisms, m.p. 70.5–71.5°. The analytical sample had m.p. 72–73° after recrystallization (from ether-pentane): ^1H NMR δ 2.81 (4H, s), 2.48 (2H, d, J = 2.6 Hz) 2.00 (1H, t, J = 2.6 Hz), 1.12 (3H, s); IR (near) ν_{max} 3280, 1780, 1730 cm^{-1}; MS *m/e* 150 (M^+). Anal. ($C_9H_{10}O_2$), C, H.

5-Ethylene thioketal of 2,7-dimethylbicyclo[5.3.0]dec-1,2-ene-5,8,dione (**11**). In a 5 l 3-necked flask fitted with a mechanical stirrer, dropping funnel, thermometer and condenser attached to an argon inlet, was placed 638 ml of 1.39 M t-BuLi (0.887 mmol) in pentane and 670 ml ether. After cooling to −78°, a soln of 2-bromopropene (53.7 g, 0.444 mol) in 1:1 ether-THF (666 ml) was slowly added, so as to keep the reaction[31] temp below −70°. After an additional 15 m at −78°, a soln of **6** (22.2 g, 0.148 mol) in THF (439 ml) was added dropwise, so as to keep the temp below −70°. After 0.5 hr longer at −78°, the mixture was quenched by forcing it, under argon pressure, through a U-tube into vigorously stirred 20% aqueous AcOH (4 l). The aqueous layer from the two-phase mixture was extracted with ether (2 × 1400 ml) and the combined organic layers washed with water (2 × 3,900 ml), sat $NaHCO_3$ aq (2 × 2, 100 ml), sat NaCl aq (1 × 2,100 ml) and dried over Na_2SO_4. Solvent evaporation gave 30.7 g of impure **7** which was suitable for the next step. A second run starting with 22.3 g of **6** (0.149 mol) gave 31.1 g of additional impure **7**. Purified **7** (oily mixture of diastereomers) could be obtained by mplc, using 20% hexane–chloroform, as eluent, or by column chromatography over Florosil, using CH_2Cl_2 as eluent: IR (neat) ν_{max} 3500, 3300, 3090, 2125, 1735, 1640, 910 cm^{-1}; MS, *m/e* 192 (M^+); Anal. ($C_{12}H_{16}O_2$) C, H.

The combined carbinols from above were dissolved in 1,332 ml 90% formic acid and heated at 80° for 1 hr. After cooling and diluting with 2,600 ml water, the product was extracted with ether (3 × 1,400 ml) and the combined organic extracts washed with water (2 × 2,600 ml), sat $NaHCO_3$ aq and concentrated to give 43.6 g of a dark brown oil. Short-path distillation (110°/0.05 Torr) afforded 30.5 g pale yellow **1** (*ca* 70% pure by glc on 10% Apiezon L column/210°), which would be further purified by mplc using 20% hexane–chloroform. ^1H NMR δ 2.68 (2H, s), 2.65–2.4 (8H, br m), 1.82 (3H, s), 1.13 (3H, s); IR (neat) 1740, 1700 cm^{-1}; MS *m/e* 192 (M^+); Anal. ($C_{12}H_{16}O_2$) C, H.

The impure **1** (30.5 g 70% pure) was dissolved in 220 ml MeOH and treated with ethanedithiol (9.34 ml, 0.111 mol) and BF_3 etherate (20 ml). Crystallization began immediately and was allowed to proceed for 24 hr at room temp. The crystals were removed by filtration and washed with chilled MeOH. The filtrate was concentrated then cooled to −5° and seeded to give a total of 24.3 g of crystalling **11** (31% from **6**), m.p. 110–111°, ^1H NMR δ 3.20-3.03 (4H, narrow multiplet), 3.0–2.0 (10H, complex), 1.73 (3H, s), 1.10 (3H, s); IR (neat) ν_{max} 1728, 1670, 1090, 855, 845 cm^{-1}; Anal. ($C_{14}H_{20}OS_2$) C, H.

Ethylene thioketal of 2,7-dimethylbicyclo[5.3.0]dec-1,2-ene-8-ol-5-one (**16**). (2 g; of thioketal **11** 7.5 mmol) was dissolved in warm N,N-dimethylformamide (8 ml) and diluted with 16 ml of MeOH. After cooling in an ice bath, $NaBH_4$ (570 mg, 15 mmol) was added and the mixture then stirred for 2 hr while warming to room temp. The soln was then filtered diluted with 100 ml water and cooled in ice. The ppt of **16** (1.95 g, 96% yield, m.p. 125.5–126°) was recrystalized from benzene-hexane to give the analytical sample, m.p. 127–127.5°: ^1H NMR δ 3.73 (1*H, dd*), 3.5–3.1 (4*H, complex*), 2.6–1.8 (~ 11 *H, complex*), 1.57 (3*H, s*), 1.13 (3*H, s*); *IR (neat)* ν_{max} 3300 cm^{-1}, no carbonyl; MS *m/e* 252 ($M^+ - 18$); Anal. ($C_{14}H_{22}OS_2$) C, H.

2,r-7-Dimethyl-c-8-(t-butyloxy)bicyclo[5.3.0]dec-1,2-en-5-one (**17**). A heterogeneous mixture of **16** (1.85 g, 6.9 mmol), 3.5 g $CaCO_3$ and 9.5 g (69 mmol) MeI in 4 ml water and 16 ml acetonitrile was stirred for 24 hr at room temp under N_2.[32] The mixture was then filtered and partitioned between water and CH_2Cl_2. The organic layer was washed with 10% NaOH aq (2 × 50 ml), sat $NaHSO_3$ aq (2 × 50 ml) and dried over $MgSO_4$. Concentration afforded 1.33 g of dark oily hydroxyketone, which was purified by Kugelrohr distillation (120°/0.05 Torr): IR (neat) ν_{max} 3410, 1700 cm^{-1}.

Using the procedure of Hajos *et al.*[33] 2.33 g of the above hydroxyketone was reacted with excess isobutylene in CH_2Cl_2, in the presence of 1:1 phosphoric acid–boron trifluoride as catalyst. Workup provided 2.16 g (76% yield) of **17**, purified by Kugelrohr distillation (90–100° at 0.3 Torr) or sublimation (50° at 0.025 Torr), melting at 48–50°. The analytical sample (from pentane, 0 to −5°) had m.p. 51.5–52°: ^1H NMR δ 3.57 (1H, dd, J ≃ 10, 7 Hz), 2.8–1.5 (complex), 1.66 (3H, s), 1.18 (9H, s), 0.98 (3H, s); IR (neat) 1710 cm^{-1}; MS *m/e* 250 (M^+). Anal. ($C_{16}H_{26}O_2$) C, H.

t-2, t-7-Dimethyl-t-8-(t-butyloxy)-r-1H-bicyclo-[5.3.0]decan-5-one (**2**). In a Parr hydrogenator **17** (1.5 g) dissolved in 75 ml AcOH containing 0.4 g PtO_2 was shaken for 2 hr an initial pressure of 48 psig. After filtration of the catalyst and solvent evaporation, the crude oil product was dissolved in 50 ml CH_2Cl_2 and treated with 1.7 g (excess) pyridinium chlorochromate[34] at room temp for 2 hr (to "back-oxidize" carbinol to ketone). The mixture was then filtered through a short Florosil column (*ca* 4 g), which was washed with EtOAc. Solvent evaporation left a colorless oil containing 90% of **2** and 10% of the C-1, 10 epimer (by glc on 3% OV-1 column at 155°); recrystallization from pentane (or from MeOH) gave pure **2** (1.09 g, 73%) as fine, white needles, m.p. 64–64.5°: ^1H NMR δ 3.40 (1H, dd, J = 8, 7.5 Hz), 2.9–1.3 (complex), 1.50 (9H, s), 1.01 (3H, d, J = 7 Hz), 0.85 (3H, s); IR (neat) 1690 cm^{-1}; MS *m/e* 252(M^+). Anal. ($C_{16}H_{28}O_2$)C,H.

Similar results were obtained with EtOAc as solvent but the reaction was much slower, requiring 2–3 days.

Methyl [t-2,t-7-dimethyl-t-8-(butyloxy)r-1H-bicyclo[5.3.0]dec-5-ylidene]acetate (**18**). A pentane-THF soln of lithium diisopropylamide was prepared from n-BuLi (1.9 M, 1.52 ml in pentane) and diisopropylamine (364 mg, 3.6 mmol). After cooling to −70°, methyl trimethylsilylacetate (456 mg, 3.1 mmol) was added and, after 20 m, a soln of **2** (604 mg, 2.4 mmol) in 10 ml THF. After warming during 15 m, the reaction was quenched into 10% aqueous AcOH and subjected to a standard workup. Glc analysis (3% OV-1 column, 150°) revealed *ca* 20% recovered **2** and 80% of **18** (as a 5:1 mixture of *E* and *Z* isomers). Using mplc, 530 mg (72%) of **18** was eluted with 2% hexane $CHCl_3$ and 171 mg of recovered **2** was eluted with 50% hexane–$CHCl_3$. Kugelrohr distillation (140°/0.1 Torr) afforded pure **18** as an oil, in 97% yield based on recovered **2**. ^1H NMR δ 5.57 and 5.67 (1H, br s), 3.67 (3H, s), 3.37 (1H, t, J = 7 Hz), 2.93 (2H, br), 2.27 (2H, s), 2.1–1.3 (complex). 1.16 (9H, s), 0.94 (3H, d, J = 6.5 Hz), 0.83 (3H, s); IR (neat) ν_{max} 1720, 1630, 1200, 1150 cm^{-1}; MS *m/e* 308 (M^+). Anal. ($C_{19}H_{32}O_3$)C, H.

Methyl [t-2,t-7-dimethyl-t-8-(t-butyloxy)r-1H-bicyclo-[5.3.0]dec-5-yl]acetate (**14**). A soln of unsaturated **18** (635 mg, 2.06 mmol) in EtOAc (20 ml) was hydrogenated over PtO_2 (70 mg) at ambient temp and pressure. When the reaction was complete, the catalyst was filtered off, the soln evaporated and the product purified by Kugelrohr distillation (120°/0.05 Torr), yielding 596 mg (93%) of **14**, showing a single peak by glc analysis (3% OV-1/180° or 10% Apiezon, 250°). Nevertheless, NMR analysis (see Discussion) revealed the presence of *ca* 25% of the C-7 epimer. ^1H NMR δ 3.616 and 3.605 (resolvable at 100 MHz (3H, s), 3.34 (t, 1H, J = 7 Hz), 2.20 (2H, br s), 2.0–1.2 (complex), 1.11 (9H, s), 0.92 and 0.89 (3H, overlapping d's, J ≃ 6 Hz), 0.85 (3H, s); IR (neat) ν_{max} 1740, 1200, 1160, 1095 cm^{-1}; MS *m/e* 310 (M^+). Anal. ($C_{19}H_{34}O_3$)C,H.

Methyl damsinate (**21**). Lithium diisopropylamide in 3 ml THF was prepared from n-BuLi (1.90 M, 1.32 ml of pentane soln, 2.5 mmol) and then at −70° hexamethylphosphoramide (358 mg, 2.0 mmol) in 1.5 ml THF was added. After stirring for 20 m at −75°, ester **14** (571 mg, 1.84 mmol) in 3 ml THF was added. After 0.5 hr longer, the temp was raised to −20° and gaseous for-

maldehyde (from heating 800 mg of paraformaldehyde at 180°) swept into the flask, with a N_2 stream. Whem this process was completed, the reaction was quenched into 10% aqueous AcOH and subjected to a standard workup. Glc analysis (3% OV-1, 197°) revealed *ca* 37% of hydroxymethylation product and *ca* 63% recovered **14**. Preparative tlc (7% ether-CH_2Cl_2) provided 170 mg pure product for the next operation; in 5 ml CH_2Cl_2, this material was treated with Et_3N (100 mg, 1.00 mmol) and methanesulfonyl chloride (80 mg, 0.70 mmol). After 15 m, the soln was partitioned between ether (20 ml) and water (20 ml), then worked up in the standard way to give the hydroxyl methanesulfonate derivative (200 mg, 96%).

The above mesylate (200 mg, 0.48 mmol) in 5 ml benzene containing 1,8-diazabicyclo[5.4.0]-7-undecene (DBU, 137 mg, 0.9 mmol), was stirred for 14 hr, then briefly heated, treated with 0.5 ml AcOH and partitioned between 10:1 ether-pentane (20 ml) and water (20 ml). Standard workup gave **20** in quantitative yield, with glc (3% OV-1, 165°) showing partial resolution of the peaks due to C-7 epimers. ^{1}H NMR δ 6.03 (1H, br s), 5.43 (1H, br s), 3.73 (3H, s), 3.4 (1H, t, J = 7 Hz), 2.2-0.7 (complex), 1.11 (9H, s) (9H, s) 0.99 (3H, d, J = 7 Hz), 0.88 (3H, s); IR (neat) ν_{max} 1720, 1625, 1270, 1200, 1100 cm^{-1}.

The crude **20** (156 mg) from the above experiment was converted to methyl damsinate as follows. After setting in 3 ml trifluroroacetic acid for 1 hr at 0°, the solvent was evaporated off under reduced pressure and a soln of NaOMe (108 mg, 2 mmol) in 5 ml MeOH added. After 0.5 hr at room temp, excess trifluoroacetic acid was added (to neutrality) and solvents removed *in vacuo*. The residue was partitioned between CH_2Cl_2 (20 ml) and water (20 ml) and the organic layer subjected to a standard workup. Treatment of the deblocked alcohol with pyridinium chlorochromate[34] (215 mg, 1.0 mmol) in 8 ml CH_2Cl_2 for 2 hr, followed by dilution with 50 ml ether and filtration, followed by Florosil chromatography (1 g), gave on concentration 113 mg (89% yield, based on **20**) of (±)-**21**, purified further by tlc (20% ether-pentane). This material was shown to be identical on glc by co-injection (3% OV-1, 160°) with authentic **21**, prepared from (−)-**3** with ethereal diazomethane, and gave IR and NMR spectra which corresponded well (except for weak peaks due to the C-7 epimer) with (−)-**21**. ^{1}H NMR δ 6.09 (1H, br s), 5.5 (1H, br s), δ 3.72, 3.70 ("weak" and "strong"), FT-100 in Hz spectra, 3H, s), 2.5–1.5 (complex), 1.05 (3H, d, J = 7 Hz), 1.04 (3H, s); IR (neat) ν_{max} 1735, 1720, 1625, 1150 cm^{-1}.

t-2,*t*-7-*Dimethyl*-4-(*phenylsulfinyl*)-*t*-8-(*t-butyloxy*)-*r*-1 H-*bicyclo*-[5.3.0]*decan*-5-*one* (**23**). To a refluxing soln containing NaH (378 mg, 8.98 mmol) and methyl benzenesulfinate (747 mg, 4.79 mmol) in 10 ml 1,2-dimethoxyethane (DME) was slowly added ketone **2** (1.005 g, 3.99 mmol) dissolved in 10 ml DME. After 4.5 hr reflux, the mixture was cooled and partitioned between 2:1 pentane–$CHCl_3$ and sat NH_4Cl aq. A standard workup afforded 1.592 g (> 100%) of yellow oil, which was purified by preparative tlc (96% CH_2Cl_2 4% EtOAc providing 1.42 g (95%) yield) of oily **23** (diastereomeric mixture) along with *ca* 5% recovered of **2**. ^{1}H NMR δ 7.68–7.24 (5H, m), 3.9–3.1 (2H, m), 2.90–0.7 (complex); IR (neat) ν_{max} 3040, 1690, 1255, 1210, 1061 cm^{-1}. Anal. $C_{22}H_{32}O_3S$)C, H.

t-2,*t*-7-*Dimethyl*-4-(*phenylthio*)-*t*-8-(*t-butyloxy*)-*r*-1H-*bicyclo*-5.3.0]*dec*-3,4-*en*-5-*one* (**25**). A soln of CH_2Cl_2 (13 ml) containing **23** (1.64 g, 4.36 mmol), Ac_2O (0.45 ml, 4.8 mmol) and 20 μl of methanesulfonic acid was stirred under argon for 4 hr at 25°. The soln was then partitioned between 175 ml of 2:1 pentane-CH_2Cl_2 and 200 ml water and worked up in the standard manner. Solvent evaporation afforded 1.55 g of solid material, from which pure **25** could be obtained in 80% yield by slow recrystallization from pentane (25° to −20°), or by silica gel chrotography (96% CH_2Cl_2–4% EtOAc): m.p. 127–127.5°. ^{1}H NMR δ 7.38–7.20 (5H, m), 6.54 (1H, d, J = 7.2 Hz), δ 3.42 (1H, t, J = 8 Hz), δ 2.85–0.86 (complex); IR (nujol mull) ν_{max} 1678, 1205, 1580 cm^{-1}; UV $\lambda_{max}^{95\%}$ C_2H_5OH 258 nm (6700). Anal. ($C_{22}H_{30}O_2S$)C, H.

c-2,*t*-7-*Dimethyl*-4-(*phenylthio*)-*t*-8-(*t-butyloxy*)-*r*-1 H-*bicyclo*-[5.3.0]*dec*-3,4-*en*-5-*one* (**27**). A soln of **25** (38.5 mg, 0.1 mmol) in 1 ml CH_2Cl_2 was treated with 1.3 μl diazabicyclononene (DBN) at 25° for 2 days, then partitioned between 50 ml portions of 2:1 pentane–CH_2Cl_2 and 10% aqueous AcOH. Standard workup afforded 41.4 mg of oily **27** (75%) plus **26** (25%), which was cleanly separated by mplc (225 psig pressure, with cyclohexane, then 1.6% acetone–98.4% cyclohexane). This separation could also be efficiently performed on a 1–2 g scale. Recrystallization of **27** from pentane gave the analytical sample, m.p. 110–111°. ^{1}H NMR δ 7.36–7.10 (5H, m), δ 6.24 (1H, d, J = 2.5 Hz), δ 3.40 (1H, t, J = 8 Hz), δ 2.85–0.80 (complex); IR (nujol mull) ν_{max} 1668, 1580, 1198 cm^{-1}; UV $\lambda_{max}^{C_2H_5OH}$ 257 nm (7400); Anal. ($C_{22}H_{30}O_2S$)C, H.

c-2,*t*-7-*Dimethyl*-*t*-8-(*t-butyloxy*)-*r*-1 H-*bicyclo*[5.3.0]-*decan*-5-*one* (**4**). Raney Ni prepared from 5.68 g of 50/50 Ni–Al alloy[29] was suspended in 18 ml of 95% EtOH and crystalline **27** (0.966 g) added. The mixture was refluxed for 2.4 hr, then filtered through Celite, which was rinsed with 300 ml of hot 95% EtOH. Solvent evaporation yielded 0.651 g (> 100%) of **4**, accompanied by carbinol from "over-reduction" of the ketone group. This material was dissolved in 5 ml CH_2Cl_2, along with 1.11 g pyridinium chlorochromate.[34] After 2 hr at 25°, additional CH_2Cl_2 was added and the mixture filtered through Florosil. Solvent evaporation afforded 0.619 g (96% yield) of **4**, recrystallized from pentane at −78°, m.p. 35.5–36.5°. ^{1}H NMR δ 3.42 (1H, t, J = 8 Hz), δ 2.80–0.76 (27H, complex); IR (neat) ν_{max} 1690, 1200 cm^{-1}; Anal. ($C_{16}H_{28}O_2$)C, H.

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