HPLC on a Resolvex Sil 4.6 mm × 24 cm column using a mixture of 0.5 N ammonium formate (pH 4.2), methanol, and dichloromethane 2:18:80 as the mobile phase.[20] A UV detector set at 254 nm was used to monitor the column effluent.

Synthesis of 4-Amino-1-β-D-ribofuranosyl-1*H*-imidazo[4,5-*c*]pyridine (3-Deazaadenosine, 5). A solution of 333 mg (1.0 mmol) of 7-methylguanosine (2) and 42.5 mg (0.25 mmol) of 4-amino-1*H*-imidazo[4,5-*c*]pyridine hydrochloride in 10 mL of 1.0 M phosphate buffer pH 7.4 was treated with 10 mg (250 units) of purine nucleoside phosphorylase. Almost immediately a copious precipitate of 7-methylguanine began to separate from the solution. The solution was maintained at pH 7.0–7.4 for 2 days after which no further increase in product formation was observed. The solution was filtered, and the solid was washed with 2 mL of water. The combined filtrates were lyophylized, and the residue was dissolved in water–methanol (3 mL, 2:1) and loaded onto a 0.9 × 15 cm Dowex 1 (OH^-) column which had been washed with water and methanol and equilibrated in 7:3 water–methanol. The column was washed with 1:9 water–methanol prior to eluting the product with 0.07 N formic acid–methanol, 1:9. The product fractions were pooled and evaporated to give 35 mg (53 %) of 5: mp 225–230 °C [lit.[18b] 225–231 °C]; UV pH 1 λ_{max} 260 nm (ϵ 1.1 × 104), pH 13 λ_{max} 266 nm (ϵ 1.05 × 10^4) [lit.[19a] pH λ_{max} 261 nm (ϵ (1.0–1.14) × 10^4), pH 13 λ_{max} 265 nm (ϵ 1.07 × 10^4)].

Synthesis of Virazole (6). To a stirred solution of 333 mg (1.0 mmol) of 7-methylguanosine (2) and 28 mg (0.25 mmol) of 1,2,4-triazole-3-carboxamide in 10 mL of 0.25 M phosphate buffer, pH 7.8, was added 4 mg (100 units) of purine nucleoside phosphorylase. Within 5 min a copious precipitate of 7-methylguanine began to separate from the solution. The attendent drop in pH was compensated for by addition of 0.5 N NaOH. The solution was maintained at pH 7.4 for 2 days after which no further increase in product formation was observed. The insoluble materials were removed by centrifugation. The residual pellet was resuspended in 2 mL of water and centrifuged, and the supernatant liquid was combined with the original solution. The combined solutions were lyophylized, and the residue was dissolved in water (2 mL) and added to the top of a 0.9 × 15 cm Dowex 1 (OH^-) column. The column was washed with water (25 mL) and then eluted with 0.05 M ammonium phosphate buffer (pH 9). The product fractions were pooled, concentrated to a small volume, and desalted on a 1 × 15 cm Sehadex G-10 column. The product fractions were pooled and lyophylized to give 26 mg (44%) of virazole. The product was crystallized by dissolving the solid in a small amount of water and diluting the solution with absolute ethanol. The solid that separated was filtered, washed with absolute ethanol, and ether, and then dried over P_2O_5: mp 164–165 °C [lit.[17a] mp 166–168 °C]. Fast atom bombardment mass spectrometry indicated a molecular weight of 244, and the ^1H NMR spectrum agreed with the reported values.[17a]

With a proportional increase of each component, both 5 and 6 can be prepared in gram quantities.

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Short Intramolecular Diels–Alder Approach to Spirovetivanes. Total Synthesis of *dl*-Hinesol[1]

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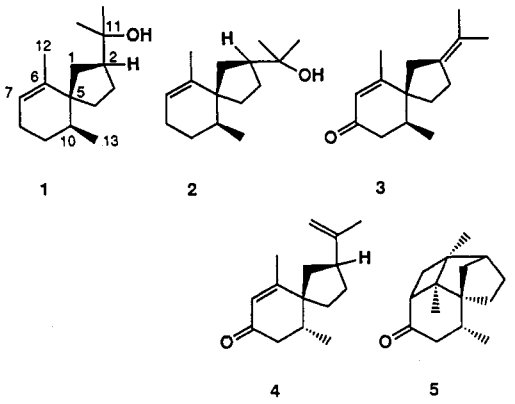
The spiro[4.5]decane skeleton[2] is present in several groups of sesquiterpenoids such as the spirovetivanes, acoranes, alaskanes, and laurenones.[3] Spirovetivanes are structurally recognized by a methyl group at C-10 and an isopropyl group at C-2. Depending on the relative stereochemistry at C-10, the spirovetivanes are divided into two groups. The more numerous group (at present), here represented by hinesol (1),[4,5] agaspirol (2),[6] and β-vetivone (3),[7] has the methyl group β (cis). The other group, here represented by solavetivone (4)[7] and solanascone (5),[7] has the methyl group α (trans).



Our synthetic plan (Scheme I) relies on the keto aldehyde 6 as a key precursor, which can be recognized as an ozonolysis product of the norbornene derivative 7, which in turn is the result of a hydrogenation of the disubstituted double bond in the norbornadiene derivative 8. Retrosynthetic disconnection a in 8 suggests an intramolecular cycloaddition transform leading to the 1-substituted cyclopentadiene 9 (R = Me) as a precursor. This strategy inherently permits control of the relative stereochemistry at C2 and C5, which we recently demonstrated in a model study in which 6 ($R_1 = R_2 = H$) was synthesized.[8] Herein we apply this intramolecular Diels–Alder-based[9] route to the specific case of *dl*-hinesol (1).[10,11]

The Diels–Alder substrate 9 (R = Me) was prepared in 48% overall yield from 3-methyl-2-cyclohexenone (Aldrich)

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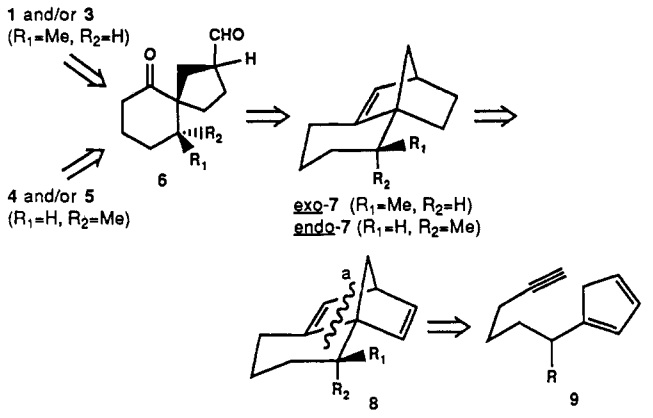
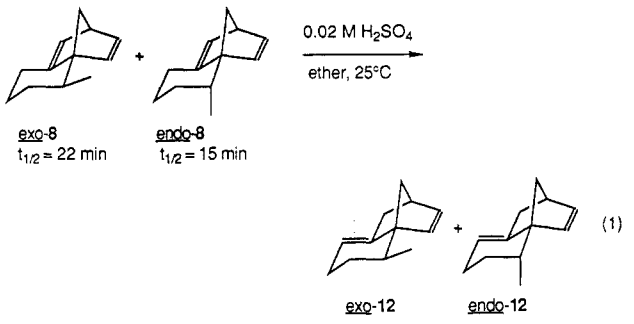
Scheme I

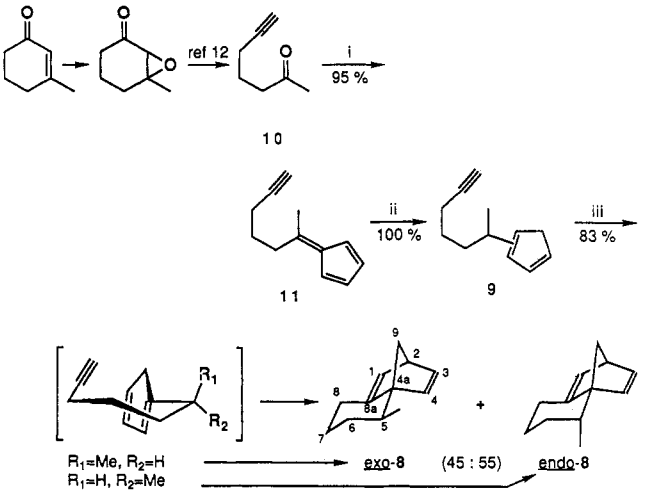


(Scheme II). The ynone **10** was synthesized by epoxidation of 3-methyl-2-cyclohexenone and fragmentation of the corresponding tosylhydrazone.[12] A pyrrolidine-catalyzed condensation with cyclopentadiene[13] afforded the fulvene **11**[14] in 95% yield, and a subsequent reduction with $LiAlH_4$[15] yielded quantitatively **9** (R = Me) as a 1:1 mixture of 1- and 2-substituted cyclopentadienes. The intramolecular Diels–Alder reaction proceeds regioselectively at 185 °C with complete conversion to the norbornadienes **8**. As expected,[8,9e] only the adduct derived from the 1-substituted cyclopentadiene double bond isomer **9** was observed. The cycloaddition products were isolated in 83% yield as a 45:55 mixture of *exo*-**8** and *endo*-**8**.[16] Attempts to affect the *exo*-**8**/*endo*-**8** ratio by prolonged heating at elevated temperature (230 °C, 3 days) or reaction at lower temperature and low conversion (160 °C, 5% conversion) were unsuccessful. In addition, heating of *endo*-**8** for 9 h at 180 °C resulted in no isomerization to *exo*-**8**. Instead a mixture of *endo*-**8** (30%) and *endo*-**12** (70%) was isolated.

The rearrangement of compounds **8** to **12** can also be achieved by acid catalysis. Thus, treatment of the mixture of *exo*-**8** and *endo*-**8** with H_2SO_4 (0.02 M) in ether at 25 °C resulted in a clean conversion (95%, 90 min, GLC) to *exo*- and *endo*-**12**, with *endo*-**8** reacting 1.4 times faster than *exo*-**8** (eq 1).

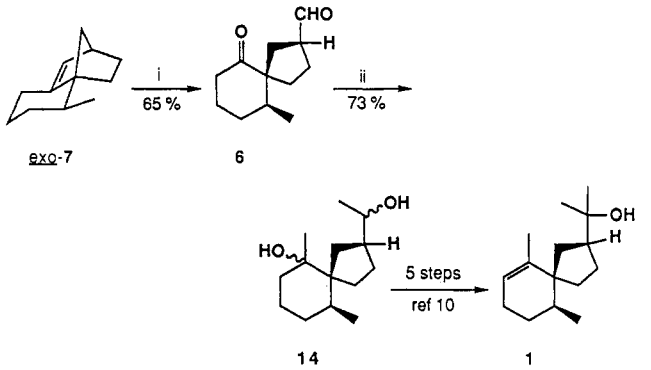


Scheme II[a]



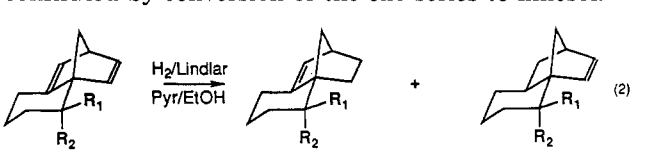
[a] (i) Cyclopentadiene (1.8 equiv), pyrrolidine (1.5 equiv), MeOH, 25 °C (2 h); (ii) $LiAlH_4$ (1 equiv), THF, 0 °C (0.5 h), 25 °C (1 h); (iii) Bu_3N, 185 °C (16 h).

Scheme III[a]



[a] (i) O_3, CH_2Cl_2, −78 °C, then Me_2S; (ii) MeLi (6 equiv), ether 0 °C, 12 h.

For initial characterization, the *exo*-**8** and *endo*-**8** isomers were separated by $AgNO_3$ impregnated silica.[17] In practice, however, the separation was achieved after a selective hydrogenation ($Pd/BaSO_4$) of *exo*-**8** in the mixture since *exo*-**8** reacted ca. 7 times faster than *endo*-**8**. The norbornene derivative *exo*-**7** was isolated in 38% yield from the mixture of *exo*-**8** and *endo*-**8**. Besides reacting faster, *exo*-**8** was also more selective toward hydrogenation of the disubstituted double bond (eq 2). The *exo*/*endo* stereochemical assignments of these compounds were ultimately confirmed by conversion of the exo series to hinesol.



The observation that *exo*-**8** reacts both faster and with higher chemoselectivity for the disubstituted double bond than *endo*-**8** is consistent with a preferred endo coordination of the palladium catalyst to the norbornadiene

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system in 8 prior to reduction.[18]

Compound *exo*-7 was transformed into *dl*-hinesol (1) according to Scheme III. Ozonolysis under standard conditions afforded 6 (R_1 = Me, R_2 = H) in 65% yield, and subsequent reaction with excess MeLi gave the diol 14 (R_1 = Me, R_2 = H) as a mixture of four diastereomers. The diol 14 is an intermediate in the hinesol synthesis reported by Marshall and Brady, and applying their procedures[10] yielded a product which has ^{1}H and ^{13}C NMR spectra and also a capillary GLC retention time identical with an authentic *dl*-hinesol sample.

In conclusion, the work described in this paper provides a direct entry to the spirovetivane system as demonstrated by the synthesis of *dl*-hinesol.

Experimental Section[19]

5-(1-Methyl-5-hexynylidene)-1,3-cyclopentadiene (11).[14] To a solution of 1-heptyn-6-one[12] (8.7 g, 79 mmol) in methanol (100 mL) was added freshly distilled cyclopentadiene (11.5 mL, 139 mmol) and pyrrolidine (10.3 mL, 110 mmol). After the mixture was stirred for 2 h at 25 °C, water (100 mL) and acetic acid (20 mL) were added, and the resulting mixture was extracted with pentane/ether (3/1, 3 × 100 mL). The combined organic phases were washed with water (2 × 20 mL), dried ($MgSO_4$), and concentrated to give 11.8 g (95%) of 11 as yellow liquid, which was used without further purification in the next step.

(1-Methyl-5-hexynyl)-1,3-cyclopentadienes (9). A solution of 11 (11.8 g, 75 mmol) in THF (20 mL) was added dropwise to a vigorously stirred ice-cooled slurry of $LiAlH_4$ (2.82 g, 74 mmol) in THF (50 mL) over a 20-min period. After the addition was complete, the ice bath was removed, and the reaction mixture was stirred for 1 h at 25 °C. The reduction is accompanied by a dramatic color change from yellow to colorless. The reaction mixture was diluted with pentane/ether (3/1, 100 mL) and quenched by dropwise addition of aqueous NH_4Cl (violent reaction!). The aqueous phase was extracted with pentane (3 × 150 mL), and the combined organic phases were washed with brine (2 × 50 mL), and dried ($MgSO_4$). Concentration gave 12.7 g (theor 11.9 g) of crude 9 as a colorless liquid, which was used in the next step without further purification: ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.46–5.96 (m, 3 H, olefinic H's), 2.91 and 2.84 (2 br s, 2 H, ring CH_2 of the two isomers), 2.55 (m, 1 H, H-1′), 2.13 (dt, 2 H, J = 2.6 and 6.7 Hz, H-4′), 1.90 (t, 1 H, J = 2.6 Hz, H-6′), 1.8–2.2 (m, 4 H, H-2′ and H-3′), 1.12 (2 d, 3 H, J = 6.8 Hz, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.20, 151.72, 133.48, 132.90, 131.95, 130.13, 125.46, 124.54, 84.22 (C-5′), 68.20 (C-6′), 40.72, 40.48, 36.27, 35.30, 34.54, 33.65, 26.18, 21.08, 20.08, 18.30; MS 160 (M^+).

5-Methyl-5,6,7,8-tetrahydro-2*H*-2,4a-methanonaphthalene. Mixture of *exo*-8 and *endo*-8. Crude 9 (10.9 g, 63.8 mmol, 94% purity) and a few crystals of hydroquinone were dissolved in Bu_3N (300 mL) under a N_2 atmosphere. After heating at 185 °C for 16 h, the reaction mixture was allowed to cool. Ice (400 g) and HOAc (400 mL) were added, and the mixture was extracted with pentane (4 × 300 mL). The combined organic phases were washed with brine (100 mL) and dried ($MgSO_4$). Concentration and bulb-to-bulb distillation gave 8.5 g (83%) of a 45:55 mixture of *exo*-8 and *endo*-8. For analytical purposes, the two isomers were separated by gradient elution through $AgNO_3$-impregnated SiO_2.[17] *exo*-8: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.67 (dd, 1 H, $J_{3,4}$ = 5.1 and $J_{2,3}$ = 2.9 Hz, H-3), 6.61 (dd, 1 H, $J_{3,4}$ = 5.1 and $J_{2,4}$ = 1.0 Hz, H-4), 6.085 (b t, 1 H, $J_{1,2} \approx J_{1,8ax}$ = 3.3–3.4 Hz, H-2), 3.49 (m, 1 H, 8 lines obsd, $w_{0.1}$ = 10 Hz, H-2), 2.54 (b d, 1 H, $J_{8ax,8eq}$ = 16.1 Hz, H-8eq), 1.85 (d, 2 H, $J_{2,9}$ = 1.7 Hz, H-9), 2.3–1.4 (m, 6 H, including H-8ax at 1.8 ppm), 0.91 (d, 3 H, J = 7.1 Hz, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 156.10 (s, C-8a), 146.49 (d, C-4), 143.26 (d, C-3), 132.02 (d, C-1), 72.77 (t, C-9), 64.87 (s, C-4a), 48.97 (d, C-2), 30.29 (d, C-5), 30.19 (t), 25.72 (t), and 19.30 (t, C-6–8), 17.77 (q, CH_3). *endo*-8: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.74 (d, 1 H, $J_{3,4}$ = 5.2 Hz, H-4), 6.70 (dd, 1 H, $J_{3,4}$ = 5.2 and $J_{2,3}$ = 2.7 Hz, H-3), 6.094 (b t, 1 H, $J_{1,2} \approx J_{1,8ax}$ = 2.9 Hz, H-1), 3.46 (m, 1 H, 8 lines obsd, $w_{0.1}$ = 10 Hz, H-2), 2.61 (b d, 1 H, $J_{8ax,8eq}$ = 16 Hz, H-8eq), 2.15 (dd, 1 H, J_{gem} = 5.5 and $J_{2,9}$ = 1.7 Hz, one of H-9), 1.68 (dd, 1 H, J_{gem} = 5.5 and $J_{2,9}$ = 1.5 Hz, one of H-9), 2.1–1.05 (m, 6 H, including H-8ax at 1.8 ppm), 1.035 (d, 3 H, J = 6.83 Hz, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 156.85 (s, C-8a), 144.23 (d, C-4), 141.27 (d, C-3), 132.78 (d, C-1), 74.67 (t, C-9), 65.16 (s, C-4a), 48.28 (d, C-2), 34.72 (d, C-5), 33.71 (t), 27.52 (t), and 24.77 (t, C-6-8), 18.26 (q, CH_3); MS of the mixture 160.125 (M^+). Anal. Calcd for $C_{12}H_{16}$: C, 89.94; H, 10.06. Found for mixture of exo and endo isomers: C, 89.71; H, 10.30.

5-Methyl-3,4,5,6,7,8-hexahydro-2*H*-2,4a-methanonaphthalene (*exo*-7). The *exo*-8/*endo*-8 mixture (1.76 g) was added to prereduced $Pd/BaSO_4$ (5%, 43 mg) in pyridine/ethanol (7/5, 120 mL) at 0 °C. The reaction mixture was stirred under 1 atm of H_2 pressure at 0 °C, and the hydrogenation was monitored by GLC analysis (SE-30 packed column). After 10 h, more catalyst (90 mg) was added. After a total of 17 h, aqueous HOAc (50%, 100 mL) was added, and the mixture was extracted with pentane (3 × 75 mL). The combined organic phases were washed with 1 M HCl (2 × 25 mL), dried ($MgSO_4$), and concentrated to give 1.70 g (96%) of a crude product, which according to ^{1}H NMR and GLC consisted of *exo*-7 (39%), *exo*-8 (4%), *endo*-8 (49%), and a byproduct *exo*-13 (8%). A fraction (1.06 g) of the crude product was eluted through $AgNO_3$-impregnated SiO_2[17] with pentane and gradually increasing concentration of ether as eluant. Three fractions were collected, the second of which was concentrated to give 360 mg of *exo*-7 (90% purity): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.50 (b t, 1 H, J = 2.6 Hz, H-1), 2.71 (b d, 1 H, H-2), 2.30 (b d, 1 H, H-8eq), 2.2–1.0 (m, 12 H), 0.93 (d, 3 H, J = 7.1 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 146.17 (s, C-8a), 126.94 (d, C-1), 55.75 (s, C-4a), 48.65 (t, C-9), 41.18 (d, C-2), 31.67 (d, C-5), 30.26 (2 t), 29.02 (t), 24.21 (t), and 19.22 (t, C-6–8 and C-3,4), 18.20 (q, CH_3). *exo*-13: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.16 (dd, 1 H, $J_{3,4}$ = 5.7 and $J_{2,3}$ = 3.1 Hz, H-3), 5.84 (d, 1 H, $J_{3,4}$ = 5.7 Hz, H-4), 2.67 (b s, 1 H, H-2), 1.91 (m, 1 H), 1.8–1.1 (m, 12 H), 0.92 (d, 3 H, J = 6.3 Hz, CH_3).

5-Methyl-1,5,6,7-tetrahydro-2*H*-2,4a-methanonaphthalene (12) via Acid-Catalyzed Isomerization of 8. To the *exo*-/*endo*-8 mixture (243 mg, 1.52 mmol) in dry ether (10 mL) at 25 °C was added concentrated H_2SO_4 (10 μL, 0.18 mmol). The reaction was monitored by capillary GLC (OV-101, 30 m, 130 °C) and found to follow first-order kinetics with $t^{1/2}_{endo}$ = 15 min and $t^{1/2}_{exo}$ = 22 min. After 90 min, saturated aqueous K_2CO_3 (0.5 mL) and anhydrous $MgSO_4$ powder were added. Filtration and concentration gave 202 mg (83%) of a 57:43 mixture of *endo*-12 and *exo*-12. *endo*-12: ^{1}H NMR ($CDCl_3$, 200 MHz, in the mixture with *exo*-12) δ 6.03 (dd, 1 H, $J_{3,4}$ = 5.8 and $J_{2,3}$ = 2.8 Hz, H-3), 5.94 (d, 1 H, $J_{3,4}$ = 5.8 Hz, H-4), 5.44 (b s, 1 H, H-8), 2.86 (b s, 1 H, H-2), 2.3–1.1 (m, 9 H), 1.03 (d, 3 H, J = 6.6 Hz, CH_3). *exo*-12: ^{1}H NMR ($CDCl_3$, 200 MHz in the mixture with *endo*-12) δ 6.03 (dd, 1 H, $J_{3,4}$ = 5.8 and $J_{2,3}$ = 2.8 Hz, H-3), 5.91 (b s, 1 H, H-4), 5.44 (b s, 1 H, H-8), 2.86 (b s, 1 H, H-2), 2.3–1.1 (m, 9 H), 0.89 (d, 3 H, J = 7.1 Hz, CH_3).

***endo*-7.** *endo*-8 (50 μL) was dissolved in pyridine/ethanol (1/1, 2 mL) and hydrogenated (1 atm of H_2) over $Pd/BaSO_4$ (5%, 18 mg) at 25 °C for 11 h. Workup (see preparation of *exo*-7) gave a product which consisted of *endo*-7 (57%), *endo*-13 (31%), and *endo*-8 (12%). *endo*-7: ^{1}H NMR ($CDCl_3$, 200 MHz distinguishable peaks in the above mixture) δ 5.52 (b t, 1 H, J = 3 Hz, H-1), 2.67 (b s, 1 H, H-2), 0.94 (d, 3 H, J = 6.8 Hz, CH_3). *endo*-13: ^{1}H NMR ($CDCl_3$, 200 MHz, distinguishable peaks in the above mixture) δ 6.19 (dd, 1 H, $J_{3,4}$ = 5.7 and $J_{2,3}$ = 3 Hz, H-3), 5.86 (b s, 1 H, H-4), 2.67 (b s, 1 H, H-2), 0.93 (d, 3 H, J = 6.8 Hz, CH_3).

10-Methyl-6-oxospiro[4.5]decane-2-carboxaldehyde (*exo*-6). *exo*-7 (160 mg, 75% purity, 0.74 mmol) was dissolved in CH_2Cl_2 (20 mL) and cooled to −78 °C. A flow (8 mL/s) of O_3 was passed over the vigorously stirred reaction mixture until a purple color persisted. After the excess ozone was removed by passing a stream of N_2 through the mixture for 5 min, Me_2S (800 μL) was added,

(18) (a) Although η^4-*endo* coordination of norbornadiene (nbd) is favored,[18b] it has been reported[18c] that nbd was hydrogenated from the exo face and that the exo/endo selectivity is sensitive to substituents in nbd. (b) Maitlis, P. M.; Espinet, P.; Russel, M. J. H. In *Comprehensive Organometallic Chemistry*; Wilkinson, G.; Stone, F. G. A., Abel, E. W., Eds.; Pergamon: Oxford, 1982; Vol. 6, pp 363–365. (c) Baird, W. C., Jr.; Surridge, J. H. *J. Org. Chem.* **1972**, *37*, 304. Baird, W. C., Jr.; Franzus, B.; Surridge, J. H. *J. Org. Chem.* **1969**, *34*, 2944.

(19) All compounds, or their indicated stereoisomeric mixtures, for which characterizing data are provided were purified by the indicated methods to a level of purity of at least 94% as shown by GC analyses.

and the cooling bath was removed. After the mixture was stirred for 18 h at 25 °C, water (5 mL) was added, and the resulting mixture was extracted with pentane/ether (9/1, 50 mL). The organic phase was washed with brine (5 mL) and 10% aqueous $NaHCO_3$ (2 mL) and dried ($MgSO_4$). Concentration gave a crude product (140 mg), which was purified by HPLC to give 93 mg (65%) of *exo*-**6**: ^1H NMR ($CDCl_3$, 300 MHz) δ 9.58 (d, 1 H, J = 2.1 Hz, C*H*O), 2.75–1.7 (m, 14 H), 0.90 (d, 3 H, J = 6.89 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 214.30 (C-6), 203.80 (C-11), 61.45 (C-5), 50.24 (C-2), 41.67, 37.99, 35.23, 31.76, 29.85, 25.43, 23.07, 16.07 (CH_3); M/S 194 (M^+); IR (NaCl, $CDCl_3$) 2970 (s), 2880, 2260, 1720 (s), 1700 (s), 1460, 890 (s), 705 cm^{-1}.

2-(1-Hydroxyethyl)-6,10-dimethylspiro[4.5]decan-6-ol (*exo*-14). To **6** (66 mg, 0.34 mmol) in anhydrous ether (5 mL) was added 1.55 M MeLi (1.1 mL, 1.7 mmol) in ether. The reaction mixture was stirred overnight at 25 °C and was then quenched with brine (0.8 mL). The ether layer was separated, and the water phase was extracted with ether (2 × 8 mL). The combined organic phases were dried ($MgSO_4$) and concentrated to give 56 mg (73%) of **14** as a mixture of four diastereomers.

***dl*-Hinesol (1).** Compound **14** (56 mg) was transformed into *dl*-hinesol by utilizing the procedure described by Marshall and Brady.[10] Isolation by HPLC gave 7 mg of pure *dl*-hinesol (**1**). The ^1H NMR (lit.[10]), ^{13}C NMR, and capillary GLC data were identical with those of a sample of *dl*-hinesol provided by Professor Ibuka:[11f] ^{13}C NMR (100 MHz, $CDCl_3$)[20] δ 140.1 (s, C-6), 121.63 (d, C-7), 71.95 (s, C-11), 51.38 (d, C-2), 48.78 (s, C-5), 36.67 (d, C-10), 35.57 (t), 33.22 (t), 28.39 (q), 27.93 (2 C, t and q), 27.65 (t), 24.16 (t), 19.86 (q, C-12), 16.15 (q, C-13).

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(20) Our ^{13}C NMR spectrum is identical with that of the authentic sample, but it differs somewhat from the ^{13}C NMR spectrum reported by Deslongchamps et al.[11e] The largest differences in these authors' data compared to our data reported above are the following chemical shift values: 31.78 vs 48.78 (C-5), 32.82 vs 36.67 (C-10), and 23.98 vs 19.86 (C-12). However, these authors' data were obtained with CCl_4 instead of $CDCl_3$ as the solvent. For several related spiro[4.5]decane derivatives, the quaternary, spirofused carbon atom (C-5) has a chemical shift in the range of 43.5–54.6 ppm. See: (a) Wenkert, E.; Buckwalter, B. L.; Craveiro, A. A.; Sanchez, E. L.; Sathe, S. S. *J. Am. Chem. Soc.* **1978**, *100*, 1267. (b) Suzuki, M.; Kowata, N.; Kurosawa, E. *Tetrahedron* **1980**, *36*, 1551. (c) Oppolzer, W.; Gorrichon, L.; Bird, T. G. C. *Helv. Chim. Acta* **1981**, *64*, 186. See also ref 3.

Improved Preparation of γ-Ketocyclobutanones

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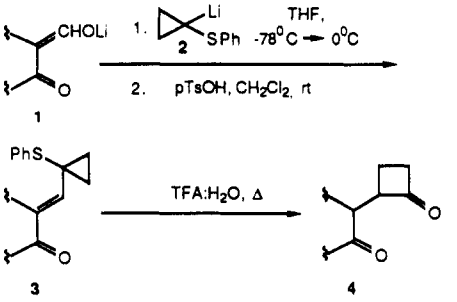
We have previously described[1] the preparation of γ-ketocyclobutanones by reaction of the lithium salts of 2-hydroxymethylene ketones **1** with lithiocyclopropyl phenyl sulfide (**2**) to afford β-(1-phenylthio)cyclopropyl enones **3**, followed by treatment with refluxing aqueous trifluoroacetic acid to effect rearrangement and hydrolysis to form the diones **4**. While this synthesis of enones **3** worked reasonably well on a small scale, difficulties were encountered, for reasons still not apparent, when the reactions of **1** with **2** were conducted on the larger scales necessary to prepare adequate quantities of γ-ketocyclobutanones (**4**) for exploration of their chemistry. Accordingly, a modification of the procedure for preparing **3** was sought that would work well on multigram quantities.

Table I. Synthesis of γ-Ketocyclobutanones from 2-Pyrrolidinomethylene Ketones

reactant	product (% yield)[a]	product (% yield)[a]
5	**6** (76)	**11** (75)[b]
7	**9** (69)	**12** (67)[c]
8	**10** (65)	**13** (85)

[a] Yield refers to directly crystallized or chromatographically purified material that was homogeneous by TLC. [b] A 3:2 mixture of unidentified diastereomers. [c] A 5:4 mixture of unidentified diastereomers.



2-Pyrrolidinomethylene ketones seemed promising as an alternate to **1** as reactant, because such enamino ketones are very readily prepared from α-hydroxymethylene ketones[2-4] and are known usually to undergo predominantly 1,4-addition with nucleophiles[2,3,5] (as opposed to 2-(alkylthio)methylene,[6] 2-(silyloxy)methylene,[7] or 2-alkoxymethylene ketones,[2,8] all of which give significant and usually predominant amounts of products of 1,2-addition). Accordingly, 2-(pyrrolidinomethylene)cyclohexanone (**5**)[9] was prepared by standard procedures[2,10] and treated with **2**. The result was encouraging because 58% of (phenylthio)cyclopropyl enone **6** was obtained directly, β elimination of pyrrolidine from the initial 1,4 adduct having occurred spontaneously. In the reaction of **1** with **2** a separate acid-catalyzed β elimination of water from the initial adduct was required. An improvement in yield was readily achieved once the avidity of **5** for water was appreciated. The tendency of such enamino ketones to absorb and cling tenaciously to water has been documented,[11] and we were unable to prepare neat samples of **5** that did

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