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AN ASYMMETRIC SYNTHESIS OF 4,4- AND 6,6-DIALKYLCYCLOHEXENONES AND 4,4- AND 5,5-DIALKYLCYCLOPENTENONES. APPLICATION TO THE TOTAL SYNTHESIS OF (-)-SILPHIPERFOL-6-ENE

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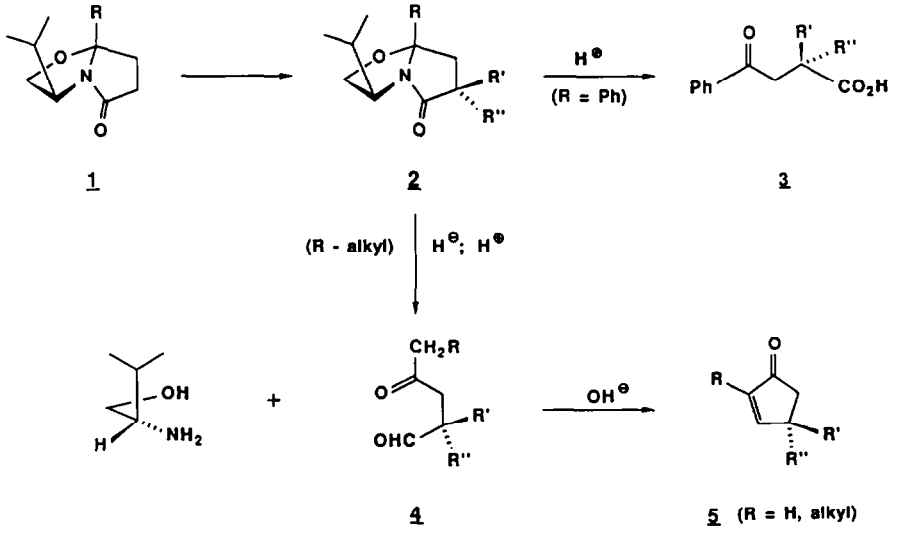
Abstract - Chiral amino alcohols have been transformed into bicyclic lactams **1** and **6** which, after metalation and alkylation, gave high diastereomeric ratios of 2,2-dialkyl quaternary products, **29** and **12**, respectively. Addition of organolithium reagents to the carbonyl of these lactams, followed by acidic cleavage, leads to enantiomerically pure cyclohex-2-enones and cyclopent-2-enones. This process was also applied to a key, chiral cyclopentenone **39**, which was used by Curran, in racemic form, to prepare the angular triquinane, silphiperfol-6-ene. The total asymmetric synthesis was carried out in 6.6% yield over nine steps.

The search for efficient asymmetric methods has matured to the point that virtually every type of functionalized molecule can be prepared in high enantiomeric purity.[1] This phenomenal achievement was unthinkable barely 15 years ago. However, the need continues to exist for more elaborately functionalized chiral molecules which can ultimately be utilized in complex synthetic programs wherein a single enantiomer is the major target. Thus chiral, non-racemic compounds with at least two functional groups or unusual architecture are still sufficiently important goals and worthy of pursuit.

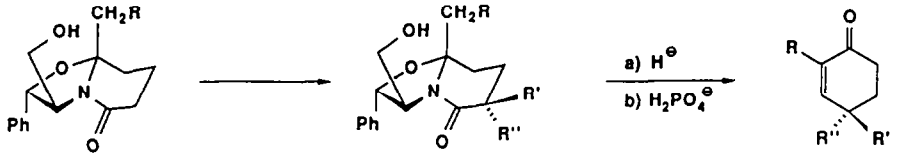
In recent years we have been engaged in a program which has successfully led to an efficient synthesis of chiral quaternary carbon compounds (Scheme 1) in high enantiomeric

SCHEME 1



purity. This work was based on the ready acquisition of bicyclic lactams of the type, **1** and their sequential alkylation in high diastereoselective excess furnishing **2**. Hydrolysis of the latter gave the chiral keto acids **3** in >95% ee.[2] Alternatively, hydride reduction of **2** followed by acidic hydrolysis gave the keto aldehydes **4** (and recoverable S-valinol) which were cyclized in good yields and high ee's to the cyclopentenones, **5**.[3] This methodology in reaching chiral quaternary carbon compounds has since resulted in asymmetric total syntheses of (-)-α-cuparenone,[4] (-)-grandisol,[5] and (+)-mesembrine[6] as a clear demonstration of its synthetic importance. Additionally, an asymmetric synthesis of 4,4-dialkylcyclohexenones **8** was reported[7] (Scheme 2)

SCHEME 2



6 7 8

which required the use of the analogous bicyclic lactams **6** and **7**. We now describe a significant extension to this asymmetric methodology which allows further elaboration to cyclohexen- and cyclopentenones with the quaternary stereocenter either at the α or γ position relative to the carbonyl.[8] Finally, we have also demonstrated the utility of this novel extension by an asymmetric total synthesis of the angular triquinane sesquiterpene, silphiperfol-6-ene (**38**).

The appropriate chiral starting material **11** was readily prepared by condensing the commercially available amino diol **9** and commercially available keto acid in refluxing benzene. Although a 14:84 mixture of lactams **10** and **11** was formed, the desired material could be readily obtained by a single recrystallization. In this manner, **11** was prepared in 60-70% yield and its structure confirmed at a later stage by X-ray crystallography (**vide infra**, **12**).

Metalation, using lithium diisopropylamide, followed by methyl iodide then metalation repeated, followed by benzyl bromide, gave a 97:3 diastereomeric mixture with **12** as the major component. As previously reported,[7] the major entry path for alkyl halides to the enolate of **11** is from the **endo**-face. Thus, benzyl bromide, as the second electrophile in the sequential alkylation, enters from the bottomside (**endo**), furnishing **12**. Confirmation of this stereochemical event was obtained from the single crystal X-ray structure of homochiral **12** (Fig. 1). It is

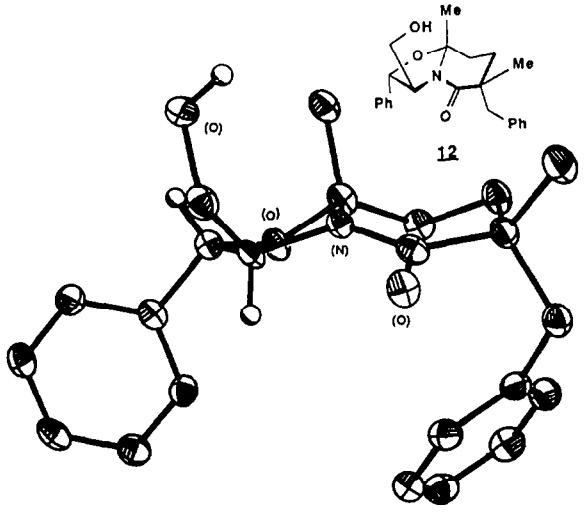
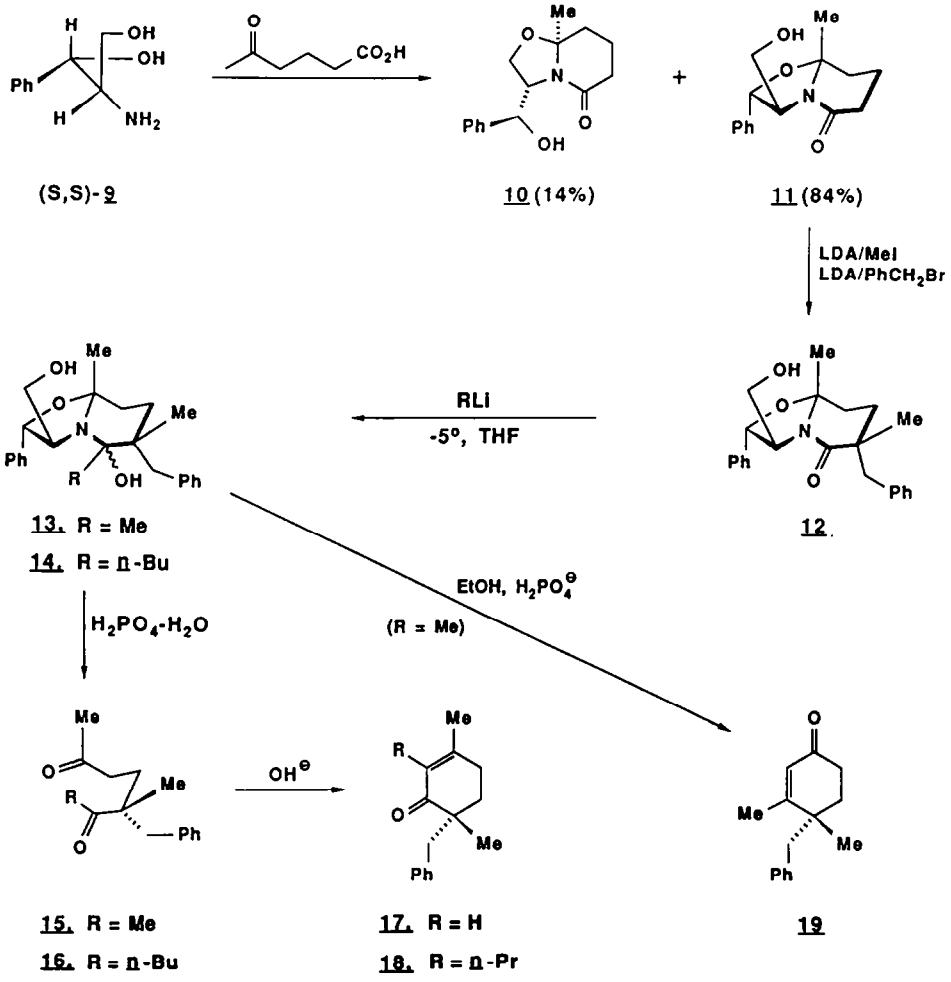


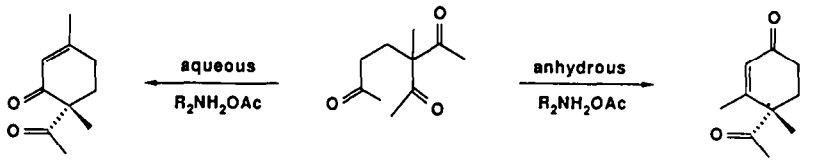
Figure 1. X-ray structure of 12.

interesting to note that the 6-membered ring in **12** (and presumably **11**) is in a boat form. Since the phenyl and hydroxymethyl groups in the 5-membered ring are each known to reside on carbons with the S-configuration, this allows ready assignment of the carbon bearing the methyl and benzyl groups (R). In a previous paper, we showed the reduction of compounds, such as **12**, which led to 4,4-disubstituted cyclohexenones (Scheme 2), and now we demonstrate further versatility by adding organolithium reagents to **12** at -5°C in THF (or 0°C in ether), which led to the carbinolamines **13** and **14** in virtually quantitative yield. Hydrolysis of the latter, using aqueous ethanol containing tetrabutylammonium dihydrogen phosphate, gave the diketones **15** and **16** which, after purification, were obtained in 67 and 60% yield respectively. Cyclization to the cyclohexenones **17** and **18** was accomplished using a catalytic amount of ethanolic potassium hydroxide in THF. Under these conditions, only a single regioisomer of the cyclohexenones was formed. In no instance could the isomeric 4,4-dialkylcyclohexenones **19** be detected by intramolecular aldol condensation of the 1,5-diketone, **15**. This mode of aldolization, wherein one carbonyl group is flanked by a quaternary carbon, has been noted before by Koga[9] and also by Frater[10] and Kreiser.[11] It is clear that the carbonyl flanked by the quaternary carbon is kinetically disfavored as the electrophilic site, thus making the more exposed carbonyl the electrophilic terminus for entry by the enolate, furnishing **17** or **18**. For purposes involving natural product syntheses, it was desirable to reach, in enantiomerically pure



form, the other cyclohexenone regioisomer, **19**. Koga[9] found that he could transform a 1,5-diketone to either regioisomer by proper choice of conditions (Scheme 3). Thus the triketone **20** (a "1,5-diketone") could be induced to cyclize in either direction if anhydrous or aqueous

SCHEME 3



21 20 22

conditions were employed. Unfortunately, no details were given concerning the mechanism of this process. However, it appeared to us that the "anhydrous" reaction (which must necessarily generate an equivalent of water) may in fact proceed through a very different pathway - perhaps involving the enamine of **20** - to give **22**. With this in mind, we studied the hydrolytic cleavage of **13** using various amounts of water and observing the ratio of diketone **15** to cyclohexenone **19**. The results are presented in Table 1. It was rather surprising to observe the ratio of

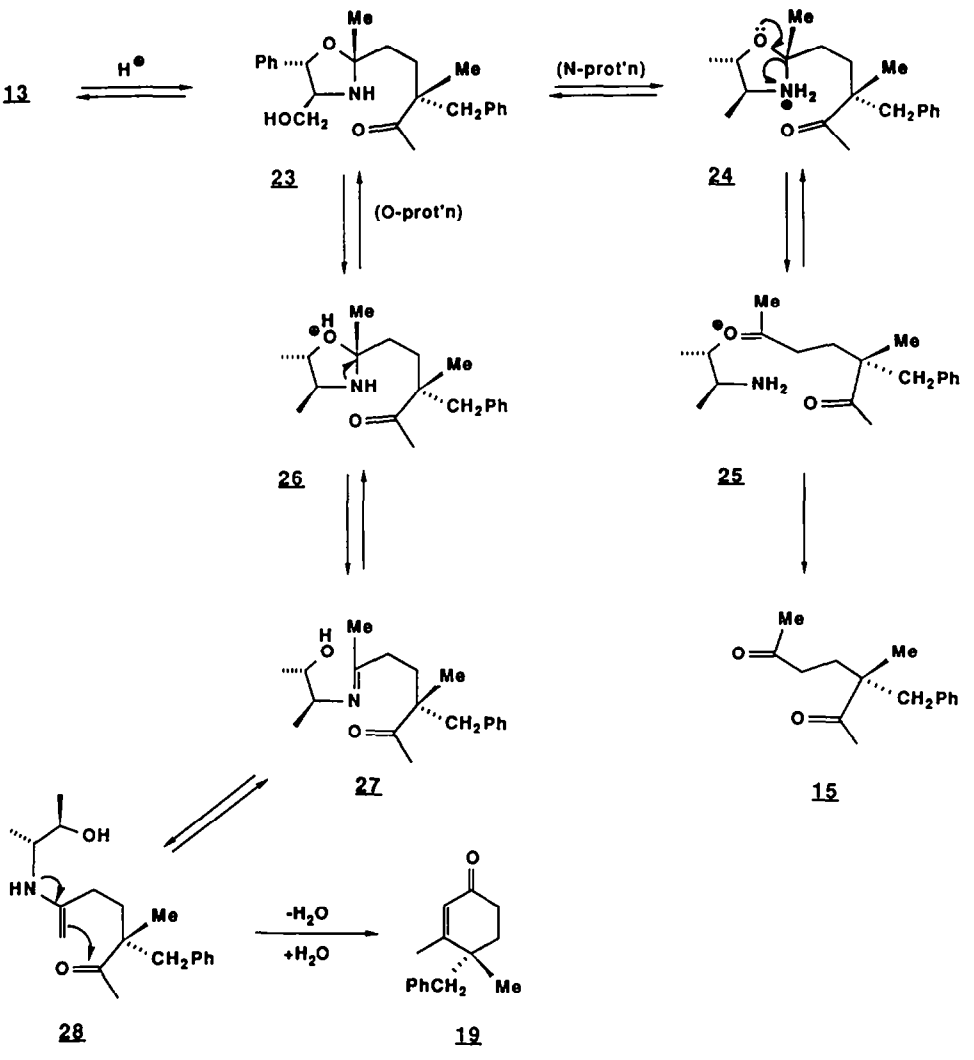
Table 1. Hydrolysis of Bicyclic Lactam **13**.

% H_2O in hydrolysis solution[a] (v/v)	% **15**	% **19**
75	100	0
50	70	30
25	15	85
0	0	100

[a]The hydrolysis solution consisted of 1-1.5 mmol carbinolamine **13** in 15 ml anhydrous ethanol, containing 0.5 g $Bu_4NH_2PO_4$. The volume of ethanol was replaced with water in each experiment to maintain 15 ml total volume. These solutions were heated to reflux for 16 h to effect complete hydrolysis.

products dramatically changing with increasing amounts of anhydrous ethanol which also produces, not the diketone **15**, but the cyclic enone **19** directly. Thus, it was easy to transform the bicyclic lactams (**13, 14**) into either product **15, 16**, or **19**. Our present rationale for this dichotomy in hydrolytic products can be summarized in Scheme 4. It is believed that the crucial process is that which involves protonation of the ring opened intermediate **23**. Thus, the carbinolamine **13**, under acidic conditions, undergoes ring-chain tautomerism with the amino ketone **23** which may then engage in a reversible N or O-protonation step. In the former (**24**), oxazolidine ring cleavage occurs to **25** as the oxonium ion which, in the presence of water, is rapidly and irreversibly cleaved to the observed 1,5-diketone **15**. However, if water is absent or in limited quantities, then formation of **24** and **25** are reversible allowing the oxazolidine **23** to undergo O-protonation to **26**. Ring cleavage to **27** can follow which, now being an imine, may exist in tautomeric equilibrium with the enamine **28**. This now represents a key differentiation in the aldol-type ring closure and can only proceed in the fashion indicated to give **19**, after **in situ** hydrolytic removal of the imine moiety. It is our belief that the amount of water present in the system dictates which of these two pathways (to **19** or **15**) will predominate. It is also consistent with the experiments performed by the earlier workers[9-11] wherein "anhydrous" conditions containing primary or secondary amines were employed. It is most probable that these reactions were initiated by imine-enamine formation on the least hindered carbonyl followed by aldolization as described for **27-28** to give the 4,4-dialkylcyclohexenone, **19**.[12]

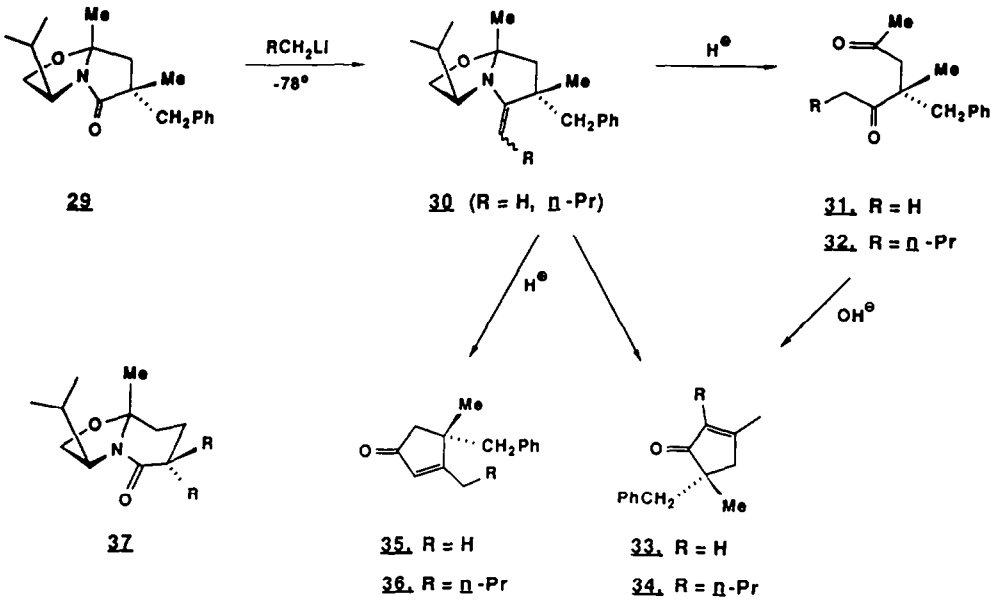
SCHEME 4



With these goals achieved, we turned to an assessment of the feasibility of reaching chiral cyclopentenones **via** an analogous route (Scheme 5). The pure diastereomer of the bicyclic lactam **29**, prepared from **1** (R = Me) was treated with methyl or **n**-butyllithium and gave **30** in quantitative yield. It is of interest to note that in the 5,5-bicyclic lactam series, the carbinol amines (e.g. **13, 14**) were not formed, but only the enamines, **30**. This may be a consequence of the ring strain in these systems wherein an exocyclic double bond in a 5-membered ring has long been known[13] to be a preferred moiety. Furthermore, in the homolog **37**, reaction with organolithium reagents, under many different conditions (solvent, T°, stoichiometry), was non-existent; only starting lactam (**37**) was recovered or decomposition resulted. This is in stark contrast to reaction of **12** and **29** with organolithiums.

Hydrolysis of the enamines **30** in aqueous ethanol containing tetrabutylammonium dihydrogen phosphate afforded high yields of the optically pure 1,4-diketones **31-32**. Base catalyzed cyclization of these diketones gave the chiral, enantiomerically pure cyclopentenones **33, 34** in near quantitative yields. Thus, the aldol was regiospecific in that only one of two possible cyclopentenones was formed. This direction of cyclization is consistent with that observed earlier (**vide supra**) for **15-16** going to **17-18**. That is, the more hindered carbonyl produces the enolate and cyclizes to the less hindered carbonyl. Once again, for purposes of a

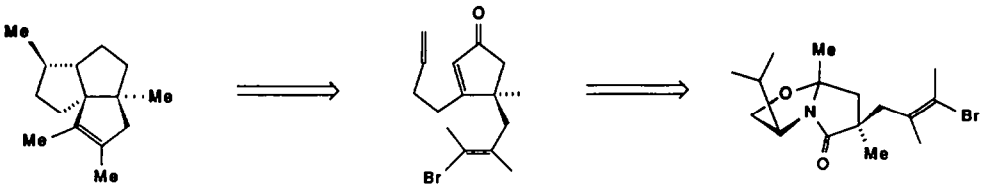
SCHEME 5



natural product target based on these studies, it was desirable to generate the isomeric cyclopentenones **35-36**. This would, in order to be successful, require a reversal in the aldolization process similar to what had been achieved for the cyclohexenones (e.g. **17 vs 19**). However, one serious difficulty surfaced quickly. The fact that **30** is an enamine would require an equivalent of water at the outset of the hydrolytic procedure to begin the cascade described in Scheme 4. Since water must, by necessity, be added and since water in excess of small traces is detrimental to the pathway leading to the desired cyclopentenones **35-36**, it would be difficult if not impossible to control this reaction as well as that described in Scheme 4. Furthermore, as might be expected, attempts to "hydrolyze" **30** under anhydrous conditions gave only starting materials. Conditions were found (n-pentanol, water, acid, reflux), after lengthy experimentation, which gave directly a 1:1 mixture of the desired cyclopentenones **35-36** and the isomeric cyclopentenones **33-34**. Thus, it was indeed possible to obtain **35,36** in 40-50% isolated yields as enantiomerically pure products, along with 40-50% yields of **33-34**. It is not certain whether it will be possible to arrive at cleavage conditions to completely transform **30** into the cyclopentenones **35-36**. Perhaps, if the reaction of **29** with organolithium reagents can be induced to provide the carbinolamine, rather than the enamine **30**, a better opportunity to control the cleavage would be in hand.

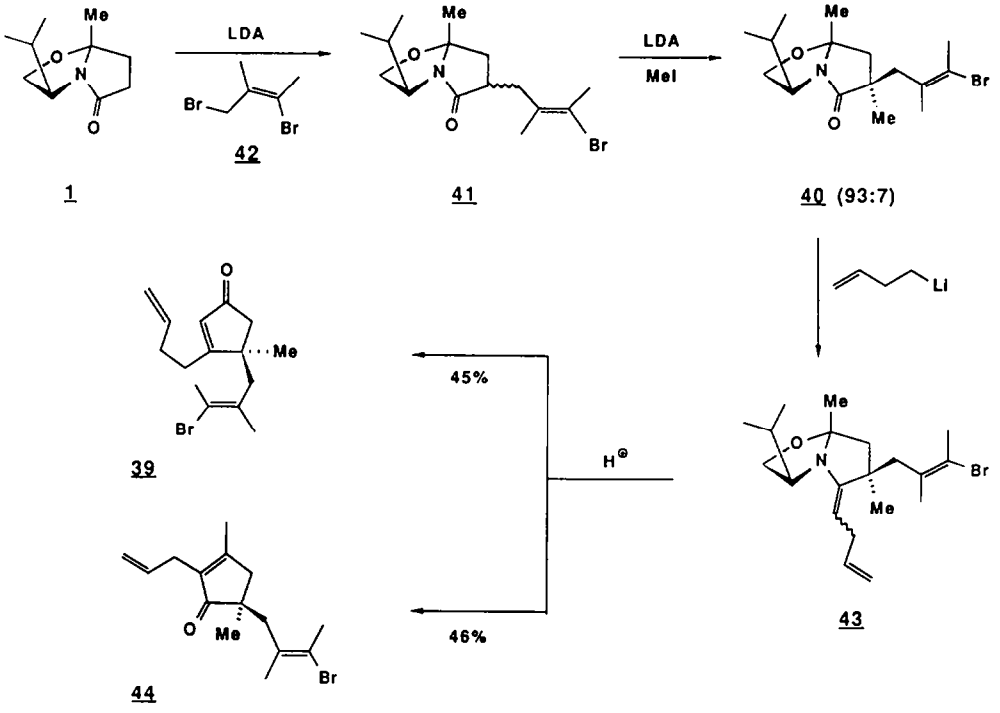
This methodology has now been applied to the total synthesis of (-)-silphiperfol-6-ene **38**, an unusual tricyclic sesquiterpene isolated from the roots of *Silphium perfoliatum* in 1980 by Bohlmann.[14] The compound has, to date, been prepared **via** total synthesis by Paquette,[15] Curran,[16] and Wender[17] and its absolute configuration established by the former. It was our intention to prepare silphiperfolene **38** using the Curran route[16] which involved the racemic precursor **39**. If the present bicyclic lactam methodology to reach enantiomerically pure quaternary carbon compounds could be adapted to prepare **39** in high enantiomeric excess from **40**, then it would constitute the first asymmetric total synthesis of the triquinane **38**.

The starting material **1** was metalated with lithium diisopropylamide and treated with the1,3-dibromopentene **42** affording a 60:40 mixture of **41** in 81% yield. Repeating the metalation on the mixture obviously leads to a single enolate and cooling to -100°C prior to addition of methyl iodide gave the requisite bicyclic lactam **40** as a 93:7 mixture of diasteromers. This ratio was assessed both by hplc and 270 MHz ^{1}H-NMR analyses which clearly depicted



(-)-38 39 40

both diastereomers. Flash chromatography on silica gel cleanly separated the mixture and the pure diasteromer **40**, presumably with the methyl in the **endo** position, was isolated in 80% yield. The stereochemical assignment of **40** is based on all the earlier work in this series wherein the second electrophile invariably enters from the **endo** face of the bicyclic lactam. Confirmatory proof, however, had to await the final natural product whose absolute configuration

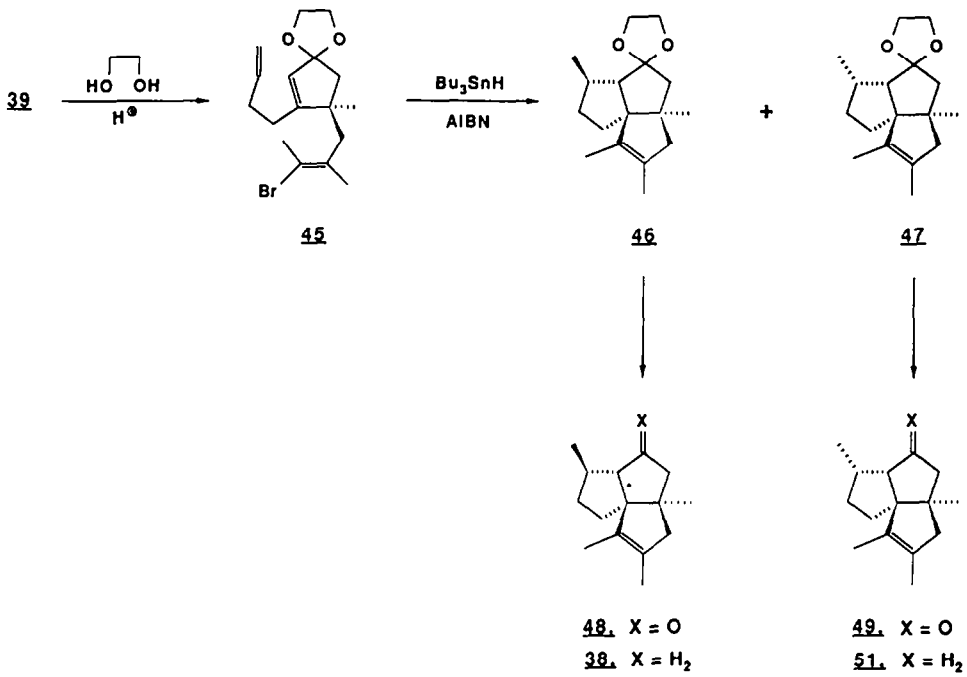


1 42 41 40 (93:7) 39 44 43

was known.[15] With **40** in hand and at least 98% de in stereochemical purity, the next step was to introduce into the lactam a butenyl moiety in the form of 3-butenyl lithium. Concern over halogen metal exchange with the bromopentenyl side chain in **40** was not minor, to say the least. If **43** could not be efficiently formed by a route involving butenyl lithium addition, it would require a different precursor than **40,** one with an alternative radical initiator than bromine and a major diversion in synthetic plan. Fortunately, our concerns were unfounded, as 3-butenyl lithium added smoothly to the lactam carbonyl at -78°. The crude enamine **43**, without isolation or purification, was directly subjected to hydrolytic conditions which involved dihydrogen phosphate in pentanol, water, and heating to reflux. These conditions, utilized earlier for the simpler cyclopentenones **33-36** gave a clean mixture containing 45% of the desired cyclopentenone **39** and 46% of the isomeric product **44**. Thus, the total yield of chiral cyclopentenones was greater than 90% based on the lactam **40**. A number of attempts were made to increase the ratio **39**:**44**, but this still eludes us. This problem has already been discussed with regard to the analogous cyclopentenones **33-36**. It should be stated here that the 45% yield of **39** represents the first reported case[11] of a 1,4-diketone furnishing a 3,4,4-trisubstituted cyclopentenone.

Pure cyclopentenone **39** was readily separated on silica using flash chromatography and was identical in every respect except optical rotation to that reported by Curran.[16] Thus, with the appropriate precursor to silphiperfol-6-ene in hand, the synthesis to enantiomeric material was completed **via** the route for racemic material, and proceeded as Curran reported.[16]

The dioxolane **45** was readily formed (90%) under the usual conditions of ethylene glycol-p-toluene sulfonic acid. Heating the dioxolane in benzene in the presence of tri-n-butyltin hydride and the radical initiator, AIBN, gave a 2.5:1 mixture of the tricyclic derivatives **46, 47**, respectively. The mixture was readily separated affording pure **46** in 53% yield and pure **47** in 12% yield. Each was then carried foward separately by initially hydrolyzing the dioxolane to the ketones **48** and **49**. The desired ketone **48** was obtained pure in 98% yield with $[\alpha]_D$ +28.65°. Wolf-Kishner reduction of **48** gave silphiperfol-6-ene **38** in 61% yield with $[\alpha]_D$ -74.06°. Similarly, 9-episilphiperfol-6-ene, **51**, was also prepared with $[\alpha]_D$ -73.15°. The natural triquinane **38** was identical in its NMR spectrum with an authentic sample of racemic material.[18] With regard to the absolute configuration of **38**, we can confirm Paquette's assignment[15] as being correct since we obtained the (-)-enantiomer. The latter is derived from **43** whose configuration is assumed to be as drawn (R). Comparison of the $[\alpha]_D$ for **38** with that reported[14] also shows some diversion. The value of -74.06° (c 1.01, $CHCl_3$) obtained in this study,



compared with that of the isolated natural material, -92.80° (c 0.8, $CHCl_3$), indicates that our synthetic sample is only 79.8% optically pure. However, we believe that **38**, prepared in this study is closer to 95% enantiomeric purity. This belief is based upon hplc analysis of valinol using chiral Pirkle Columns[19] which indicated its optical purity to be >97% ee and hplc analysis of the lactam **40**. The latter was shown to be greater than 98% de before the chiral auxiliary (valinol) was removed. Having done this, it is hard to imagine how this stereocenter could lose its integrity during any subsequent step in the synthesis. The radical-induced ring closure had no opportunity to cyclize except to the two isomers formed (**46, 47**). Furthermore, the final sesquiterpine, silphiperfol-6-ene **38** was greater than 99% purity **via** glc, ^{1}H-NMR, ^{13}C-NMR. In the original isolation by Bohlmann, a purity of 92% was reported and it is therefore possible that a strong negative rotating impurity was present. From our synthesis of epi-silphiperfol-6-ene **51**, this is probably not an impurity in Bohlmann's sample since it has a very similar $[\alpha]_D$ to silphiperfol-6-ene.

In conclusion, this paper demonstrates that the chiral bicyclic lactams are viable precursors to complex natural products with numerous stereocenters and allows their acquisition in high enantiomeric purity. The asymmetric total synthesis of silphiperfol-6-ene was completed in only nine steps from readily available materials with an overall yield of 6.6%.

EXPERIMENTAL

General

Microanalyses performed by Desert Analytics, Tucson, AZ. Preparative flash chromatography was performed on Amicon 84064, 20-45 μm silica gel. ^{1}H-NMR were recorded on an IBM/Bruker WP-270 (270 MHz) spectrometer and are reported in δ values. Melting points were obtained using a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckmann 4240 spectrophotometer and are reported as λ_{max} (cm^{-1}).

All solvents were ACS reagent grade and were redistilled and dried according to standard procedure prior to use. Tetrahydrofuran (THF) was distilled from sodium-benzophenone ketyl. Lithium diisopropylamide tetrahydrofuran complex was obtained from Aldrich (Milwaukee, WI) as a 1.5 M solution in cyclohexane. n-Butyllithium was obtained from Lithium Corp. of America (Bessemer City, NC). All other reagents were purchased from Aldrich and utilized without further purification.

Bicyclic Lactam (+)-11

A stirred solution of 13.0 g (100 mmol) of 5-oxo-hexanoic acid and 17.5 g (100 mmol) S,S-aminodiol, **9** was heated to reflux in 500 mL benzene under azeotropic removal of water for 16 h. The solution was concentrated and the residue dissolved in 600 mL ether. The ethereal solution was washed with NH_4Cl, water, Na_2CO_3, brine, dried ($MgSO_4$), and concentrated to yield 24.0 g of a colorless oil which was composed of three products in a ratio of 84.0:2.0:14.0. The crude oil was recrystallized from ethyl acetate/hexane to yield 15.7 g (60%) of pure bicyclic lactam **11** as colorless needles. mp 98-99°C; $[\alpha]^{21}_D$ 13.27° (c 1.11, EtOH). IR (KBr) 3360 br., 3000, 2950, 2860, 1625, 1500, 1395 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 7.38 (s, 5 H), 4.89 (br s, 1 H), 4.79 (d, J = 8.6 Hz, 1 H), 4.07 (dt, J = 1.9, 8.5 Hz, 1 H), 3.90 (dd, J = 1.9, 11.3 Hz, 1 H), 3.75 (dd, J = 8.5, 11.3 Hz, 1 H), 2.40-2.70 (m, 2 H), 2.25 (m, 1 H), 1.80-2.10 (m, 3 H), 1.57 (s, 3 H).
Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.03; H, 7.47; N, 5.30.

Dialkylated Bicyclic Lactam (+)-12

To a stirred solution of 3.24 g (28.6 mmol) diisopropylamine in 100 mL of THF at -78°C, 19 mL of 1.50 M (28.6 mmol) n-BuLi was added. The solution was warmed to 0°C, cooled to -78°, and 3.00 g (11.5 mmol) of lactam **11** in 10 mL THF was added slowly. The solution was warmed to 0°C, cooled to -78°C and stirred for 2 h at which time 3 equiv of methyl iodide was added., After stirring for 3 h at -78°C the reaction was quenched with 3 mL of water, concentrated, and the residue dissolved in 100 mL of ether. The solution was washed with 0.5 N HCl, $NaHSO_3$, water, brine, dried ($MgSO_4$) and purified by flash chromatography (silica gel, ethyl acetate/hexane, 1:1) to yield the methylated lactam in 71% yield. Without further purification of the ***endo-exo*** mixture it was next subjected to the second metalation-alkylation sequence. To a stirred solution of 0.40 mL (2.86 mmol) of diisopropylamine in 10 mL THF at -60°C, 1.54 mL (2.46 mmol) of 1.60 M n-butyllithium was added. The solution was warmed to 0°C, 2.19 mL HMPA was added and the solution cooled to -60°C. The above methylated lactam (0.98 mmol) in 10 mL THF was added and the solution stirred for 3 h. The solution was cooled to -78°C and 3 equiv of benzyl bromide were added. After stirring for 2 h at -78°C, 5 mL of 0.5 N HCl were added, the solution concentrated, and the residue dissolved in 50 mL ether. The solution was extracted with 0.5 N HCl, water, brine, dried ($MgSO_4$), and concentrated to yield a yellow oil. After chromatography over silica gel (1:1 ethyl acetate/hexane), pure **12** was isolated in 67% yield; $[\alpha]^{21}_D$ 134.0° (c 1.00, EtOH); mp 127-129°. IR (CCl_4) 3350 br, 2950, 1620, 1460, 1425 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 7.10-7.50 (m, 10 H), 4.68 (d, J = 8.4 Hz, 1 H), 4.20 (br s, 1 H), 4.03 (dt, J = 2.2, 8.6 Hz, 1 H), 3.88 (dd, J = 2.2, 11.3 Hz, 1 H), 3.77 (dd, J = 8.8, 11.3 Hz, 1 H), 3.38 and 2.53 (ABq, J = 13.0 Hz, 2H), 2.10 (m, 1 H), 1.75 (m, 2 H), 1.48 (s, 3 H), 1.36 (s, 3 H), 1.05 (m, 1 H).
Anal. Calcd for $C_{23}H_{27}NO_3$: C, 75.59; H, 7.45; N, 3.83. Found: C, 75.51; H, 7.41; N, 3.75.

Addition of Organolithium Reagents to Lactam 12 (R)-3-Methyl-3-benzyl-2,6-heptanedione, (-)-15

To a stirred solution of 46 mg (0.13 mmol) of **12** in 5 mL of THF at -78°C, 0.30 mL (0.50 mmol) of 1.7 M methyl lithium was added. The solution was warmed to -5°C and stirred for 3 h. The reaction was quenched with 0.25 mL of saturated ammonium chloride and concentrated **in vacuo**. The residue was taken up in 25 mL of ether, washed with water, brine, dried ($MgSO_4$), and concentrated to yield carbinolamine **13** as an oil which was carried on to the next step.

The carbinolamine **13** was heated at reflux in 5 mL ethanol, 5 mL 1.0 M $Bu_4NH_2PO_4$, and 10 mL water for 16 h. The solution was concentrated and extracted twice with 25 mL portions of ether. The combined ether layers were washed with water (2 x 25 mL), brine, dried ($MgSO_4$), and concentrated. Chromatography of the crude oil (20% ethyl acetate/hexane) yielded 20 mg (67%) of diketone, **15**; $[\alpha]^{21}_D$ = -13.53° (c 0.85, EtOH). IR (film) 2990, 2970, 1710, 1605, 1495, 1355, 1165, 750, 700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 7.15 (m, 5 H), 2.97 (d, J = 13.5 Hz, 1 H), 2.67 (d, J = 13.5 Hz, 1 H), 2.35 (m, 2 H), 2.13 (s, 3 H), 2.09 (s, 3 H), 2.00 (m, 1 H), 1.70 (m, 1 H), 1.09 (s, 3 H). This material was directly transformed into the cyclohexanone, **17** by the procedure below.

(R)-3,6-Dimethyl-6-benzylcyclohex-2-enone (-)-17

To a stirred solution of 20 mg (0.086 mmol) of diketone **15** in 15 mL of THF, 50 μL of 1 M potassium hydroxide in ethanol was added. The solution was stirred at room temperature for 1 h and concentrated. The residue was dissolved in 25 mL ether, washed with water (2 x 25 mL), brine, dried ($MgSO_4$), and concentrated. Purification by flash chromatography afforded 15 mg (83%) of pure cyclohexenone **17**; R_f = 0.56 (30% ethyl acetate/hexane); $[\alpha]^{21}_D$ = -12.6° (c 0.31, EtOH). IR (film) 2925, 1705, 1490, 1440, 1205, 745, 695 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 7.20 (m, 5 H), 5.82 (br s, 1 H), 2.97 (d, J = 13.4 Hz, 1 H), 2.70 (d, J = 13.4 Hz, 1 H), 2.30 (m, 2 H), 1.93 (s, 3 H), 1.82 (m, 1 H), 1.68 (m, 1 H), 1.05 (s, 3 H).
Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 84.33; H, 8.55.

(R)-5-Methyl-5-benzyl-2-6-decanedione (-)-16

Carbinolamine **14** was prepared as described above for **13** except **n**-butyllithium was used in place of methyllithium. Diketone **16** was prepared as described above (for **15**) in 60% yield (21.3 mg, 0.078 mmol); R_f = 0.48 (30% ethyl acetate/hexane); $[\alpha]^{21}_D$ = -23.4° (EtOH, c = 0.97). IR (film) 2940, 1710, 1610, 1500, 1465, 1370, 740, 704 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 7.18 (m, 5 H), 2.97 (d, J = 13.4 Hz, 1 H), 2.64 (d, J = 13.4 Hz, 1 H), 2.30 (m, 4 H), 2.13 (s, 3 H), 2.00 (m, 1 H), 1.69 (m, 1 H), 1.47 (m, 1 H), 1.22 (m, 1 H), 1.10 (s, 3 H), 0.88 (t, J = 7.3 Hz, 3 H). This material was transformed directly to the cyclohexenone, **18**.

(R)-2-(n-Propyl)-3,6-dimethyl-6-benzylcyclohexen-2-one, (+)-18

Prepared as described above (for **17**) in 79% yield to afford 16 mg of pure compound after chromatography (20% ethyl acetate/hexane); R_f = 0.78 (30% ethyl acetate/hexane); $[\alpha]^{21}_D$ 9.50° (c 0.4, EtOH). ^{1}H-NMR ($CDCl_3$) δ 7.18 (m, 5 H), 2.97 (d, J = 13.3 Hz, 1 H), 2.67 (d, J = 13.3 Hz, 1 H), 2.30 (m, 4 H), 1.89 (s, 3 H), 1.80 (m, 1 H), 1.60 (m, 1 H), 1.30 (m, 2 H), 1.03 (s, 3 H), 0.89 (t, J = 7.3 Hz, 3 H).
Anal. Calcd for $C_{18}H_{24}O$: C, 84.32; H, 9.43. Found: C, 84.37; H, 9.55.

(R)-3,4-Dimethyl-4-benzylcyclohexen-2-one (-)-19

The crude carbinolamine **13** (46 mg) was dissolved in 10 mL anhydrous ethanol with 0.50 g $Bu_4NH_2PO_4$. After heating at reflux for 16 h, the solution was concentrated and the residue extracted with two 20 mL portions of ether. The combined ether fractions were washed with water (2 x 25 mL), brine, dried($MgSO_4$), and concentrated. The residue was purified by flash chromatography (20% ethyl acetate/hexane) to yield 17 mg (67%) of pure cyclohexenone **19**; Rf = 0.37 (30% ethyl acetate/hexane); $[\alpha]^{21}_D$ = -51.98° (c 1.01, EtOH). IR (film) 2940, 1680, 1645, 1502, 1450 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 7.20 (m, 5 H), 5.87 (s, 1 H), 2.80 (s, 2 H), 2.40 (m, 2 H), 1.94 (s, 3 H), 1.86 (m, 1 H), 1.68 (m, 1 H), 1.12 (s, 3 H).
Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 83.79; H, 8.48.

Bicyclic Lactam 1

Prepared as described earlier using 50 mmols levulinic acid, 50 mmols S-valinol, and 10-30 mg **p**-toluensulfonic acid in 180 mL toluene. After 30-35 h the theoretical amount of water was collected and the toluene solution was washed (bicarbonate), dried ($MgSO_4$), and concentrated to give **1** (86%) as an oil, bp 76-80° (0.05 torr); $[\alpha]^{21}_D$ 95.48° (c 2.8, EtOH).

Dialkylated Bicyclic Lactam 29

To a stirred solution of 1.30 g (7.10 mmol) of the unsubstituted lactam (**1**) in 60 mL THF at -78°C, 0.63 mL (8.52 mmol) of 1.35 M **s**-butyllithium was added dropwise. The solution was allowed to stir for 2 h at -78°C at which time 0.88 mL (14.2 mmol) of methyl iodide was added. After stirring for 2 h at -78°C the reaction was quenched with 1 mL of saturated ammonium chloride, warmed to room temperature, and concentrated. The residue was dissolved in 80 mL ether and extracted with water (2 x 80 mL), sodium bisulfite (80 mL), brine (2 x 80 mL), dried ($MgSO_4$), and concentrated to yield 1.40 g of monomethylated lactam. The crude product was dissolved in 60 mL of THF in a dry flask equipped with a magnetic stir bar under argon

atmosphere. The solution was cooled to -78°C, and 6.30 mL (8.52 mmol) of 1.35 M s-butyllithium was added dropwise. After stirring for 2 h at -78°C, 1.63 mL (14.2 mmol) of benzyl bromide was added dropwise. The reaction was stirred for an additional 2 h at -78°C, quenched with 1 mL of saturated ammonium chloride, warmed to room temperature, and concentrated. The residue was dissolved in 60 mL ether, washed with water (2 x 60 mL), brine (2 x 60 mL), dried ($MgSO_4$), and concentrated to give a 97:3 ratio of diastereomers of **29**. Chromatography of the mixture on silica gel, with 10% ethyl acetate-hexane, afforded 1.20 g (59%) of pure lactam, **29**, mp 52-53°; $[\alpha]^{21}_D$ 121.13° (c 0.97, EtOH). IR (film) 2940, 1700, 1365, 1340. ^{1}H-NMR ($CDCl_3$) δ 7.20 (m, 5 H), 3.92 (dd, J = 8.3, 7.5 Hz, 1 H), 3.69 (dd, J = 6.5, 8.3 Hz, 1 H), 3.55 (m, 1 H), 2.94 and 2.72 (ABq, J = 13.4 Hz, 2 H), 2.35 and 1.80 (ABq, J = 13.6 Hz, 2 H), 1.62 (m, 1 H), 1.44 (s, 3 H), 1.31 (s, 3 H), 1.05 (d, J = 6.7 Hz, 3 H), 0.87 (d, J = 6.6 Hz, 3 H).
Anal. Calcd for $C_{18}H_{25}NO_2$: C, 75.23; H, 8.77; N, 4.87. Found: C, 75.31; H, 8.84; N, 4.86.

Addition of Organolithium Reagents to 29 (S)-3-Methyl-3-benzyl-2,5-hexanediones(-)-31

To a stirred solution of 49 mg (0.17 mmol) of **29** in 15 mL THF at -78°C, 0.40 mL (0.68 mmol) of methyllithium (1.70 M) was added. The solution was stirred at -78°C for 1 h, quenched with 0.50 mL saturated ammonium chloride, warmed to room temperature, and concentrated. The residue was dissolved in 30 mL ether, washed with 2 x 30 mL portions of water, brine, dried ($MgSO_4$), and concentrated to yield 49 mg (100%) of enamine **30** (R = Me); R_f = 0.73 (20% ethyl acetate/hexane). ^{1}H-NMR ($CDCl_3$) δ 7.25 (m, 5 H), 4.07 (t, J = 8.0 Hz, 1 H), 3.90 (d, J = 1.0 Hz, 1 H), 3.73 (d, J = 1.0Hz, 1 H), 3.68 (dd, J = 6.6, 8.5 Hz, 1 H), 3.05 (m, 1 H), 2.76 (ABq, J = 12.6 Hz, 2 H), 2.23 (d, J = 13.4 Hz, 1 H), 1.70 (m, 1 H), 1.53 (d, J = 13.4 Hz, 1 H), 1.36 (s, 3 H), 1.21 (s, 3 H), 1.06 (d, J = 7.8 Hz, 3 H), 0.78 (d, J = 6.5 Hz, 3 H). This material was taken on to the next step without further purification.

A stirred solution of 49 mg (0.17 mmol) of the enamine **30** in 8 mL ethanol, 16 mL water, and 8 mL 1.0 M $Bu_4NH_2PO_4$ was heated to reflux for 16 h. The solution was concentrated to remove the ethanol and washed with 2 x 25 mL portions of ether. The combined ether extracts were washed with water (2 x 20 mL), brine, dried ($MgSO_4$), and concentrated. Flash chromatography (10% ethyl acetate/hexane) afforded 30 mg (80%) of pure diketone **31**; R_f = 0.58 (30% ethyl acetate/hexane); $[\alpha]^{21}_D$ = -35.55° (c 1.01, EtOH). IR (film) 2960, 2920, 1700, 1490, 1450 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 7.15 (m, 5 H), 2.95 (d, J = 18.3 Hz, 1 H), 2.84 and 278 (ABq, J = 13.0 Hz, 2 H), 2.52 (d, J = 18.3 Hz, 1 H), 2.10 (s, 3 H), 2.08 (s, 3 H), 1.23 (s, 3 H), 2.07 (s, 3 H), 1.23 (s, 3 H). The diketone was not purified further and was transformed directly to the cyclopentenone.

(S)-3,5-Dimethyl-5-benzylcyclopenten-2-one (+)-33

To a stirred solution of 30 mg (0.14 mmol) of diketone **31** in 10 mL THF at room temperature, 0.05 mL of 1 M KOH in ethanol was added. The solution was stirred at room temperature for 1 h and concentrated. The residue was dissolved in 20 mL of ether, washed with 2 x 2 mL portions of water, brine, dried ($MgSO_4$), and concentrated. Flash chromatography (20% ethyl acetate/hexane) afforded 25 mg (89%) of pure cyclopentenone **33**; $[\alpha]^{21}_D$ = 93.55° (c 0.76, EtOH). IR (film) 3060, 3020, 1708, 1690, 1630, 1496, 1455, 1430 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 7.18 (m, 5 H), 5.78 (br s, 1 H), 2.92 (d, J = 13.3 Hz, 1 H), 2.67 (d, J = 18.5 Hz, 1 H), 2.62 (d, J = 13.3 Hz, 1 H), 2.18 (d, J = 18.5 Hz, 1 H), 1.97 (br s, 3 H), 1.15 (s, 3H).
Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.84; H, 8.13.

(S)-4-Methyl-4-benzyl-2,5-nonanedione. (-)-32

Addition of n-butyllithium (0.40 mL) to **29** under conditions described above (for **31**) gave 54 mg (100%) of an isomeric mixture of enamines **30** (R = n-Pr), which was hydrolyzed as above (for **31**) to give 42 mg (91%) of (-)-**32**; $[\alpha]^{21}_D$ = -36.84° (c 0.57, EtOH). IR (film) 2940, 1705, 1455, 1360, 1070, 740, 697 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 7.15 (m, 5 H), 3.00 (d, J = 18.2 Hz, 1 H), 2.84 and 2.75 (ABq, J = 12.9 Hz, 2 H), 2.60 (m, 1 H), 2.50 (d, J = 18.2 Hz, 1 H), 2.18 (m, 1 H), 2.07 (s, 3 H), 1.50 (m, 3 H), 1.30 (m, 1 H), 1.22 (s, 3 H), 0.88 (t, J = 7.2 Hz, 3 H). This material was converted directly to the cyclopentenone.

(R)-3,5-Dimethyl-2-(n-Propyl)-5-benzylcyclopenten-2-one, (+)-34

Prepared as described above (for **33**) to yield 28 mg (84%) of pure **34**; $[\alpha]^{21}_D$ = 96.60° (c 1.00, EtOH). IR (film) 2965, 1698, 1648, 1455, 1455, 1388, 740, 700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 7.13 (m, 5 H), 2.90 (d, J = 13.2 Hz, 1 H), 2.62 (d, J = 13.2 Hz, 1 H), 2.58 (d, J = 17.5 Hz, 1 H), 2.10 (d, J = 17.5 Hz, 1 H), 2.10 (m, 2 H), 1.86 (s, 3 H), 1.25 (m, 2 H), 1.12 (s, 3 H), 0.76 (t, J = 7.3 Hz, 3 H).
Anal. Calcd for $C_{17}H_{22}O$: C, 84.25; H, 9.15. Found: C, 84.49; H, 9.34.

(S)-3-(n-Butyl)-4-benzyl-4-methylcyclopent-2-enone (-)-36

A stirred solution of 132 mg (0.42 mmol) of enamine **30** (R = n-Pr) in 10 ml of n-pentanol, 150 mg tetrabutylammonium dihydrogen phosphate, and 60 mg sodium sulfate decahydrate was heated at reflux, under argon, for 42 h. The solution was cooled, concentrated, and the residue dissolved in 25 mL ether. The ether solution was washed 2 x 25 mL with water, brine (2 x 25 mL), dried ($MgSO_4$), and concentrated to give a yellow oil which was a 4:1 mixture of cyclopentenones **36** and **34**. Flash chromatography on silica gel (10% ethyl acetate/hexane) afforded 46 mg (45%) of (-)-**36** and 11 mg (11%) of **34**. Physical data for **36**; $[\alpha]^{21}_D$ -15.96° (c 0.99, EtOH). IR (film) 2915, 2945, 1705, 1680, 1605, 1440 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 7.16 (m, 5 H), 5.85 (br s, 1 H), 2.78 (s, 2 H), 2.57 and 2.01 (ABq, J = 18.5 Hz, 2 H), 2.40 (m, 2 H), 1.62 (m, 2 H), 1.47 (m, 2 H), 1.26 (s, 3 H), 0.99 (t, J = 7.1 Hz, 3 H).
Anal. Calcd for $C_{17}H_{22}O$: C, 84.25; H, 9.15. Found: C, 83.88; H, 9.24.

(S)-3,4-Dimethyl-4-benzylcyclopenten-2-one, (-)-35

In a manner similar to that for (-)-**36**, 40 mg of enamine **30** (R = Me) were hydrolyzed to give (-)-**35**; $[\alpha]^{21}_D$ -44.38° (c 1.06, EtOH). IR (film) 2940, 1680, 1640, 1498, 1442, 755, 698 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 7.18 (m, 5 H), 5.82 (d, J = 1.2 Hz, 1 H), 2.79 (s, 2 H), 2.55 (d, J = 18.5 Hz, 1 H), 2.15 (d, J = 1.0 Hz, 3 H), 2.01 (d, J = 18.5 Hz, 1 H), 1.27 (s, 3 H).
Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.88; H, 9.24.

***Endo* and *Exo* E-2-methyl-3-bromo-1-but-2-enyl lactam, 41**

To a stirred solution of 0.75 g (4.10 mmol) of lactam **1** in 50 mL of dry THF at -78°C under an argon atmosphere, 3.82 mL (5.73 mmol) of a 1.5 M solution of LDA in cyclohexane was added. The mixture was stirred at -78°C for 1 h at which time 1.22 g (5.35 mmol) of 1,3-dibromo-2-methylbut-2-ene[16,20] was added. The solution was stirred at -78°C for an additional 2 h and then quenched by the addition of 1 mL of saturated ammonium chloride, concentrated, and the residue dissolved in 75 mL of ether. After washing with water (2 x 75 mL), brine (2 x 75 mL), drying ($MgSO_4$), and concentration **in vacuo** a crude yellow oil was obtained. Chromatography (silica gel, 1:9 ethyl acetate/hexanes) afforded a mixture (6:4) of two monoalkylated lactams as oils, in 84% yield (1.13 g). The isomers were readily separated and characterized.

Endo isomer of **41** (0.68 g). ^{1}H-NMR ($CDCl_3$) δ 4.17 (dd, J = 8.6, 7.7 Hz, 1 H), 3.87 (dd, J = 6.3, 8.6 Hz, 1 H), 3.40 (m, 1 H), 2.97 (m, 1 H), 2.67 (dd, J = 3.8, 13.9 Hz, 1 H), 2.30 (m, 2 H), 2.31 (br s, 3 H), 1.85 (br s, 3 H), 1.80 (m, 1 H), 1.68 (m, 1 H), 1.47 (s, 3 H), 1.03 (d, J = 6.6 Hz, 3 H), 0.89 (d, J 6.6 Hz, 3 H).

Exo isomer of **41** (0.45 g). ^{1}H-NMR ($CDCl_3$) δ 4.18 (t, J = 8.3 Hz, 1 H), 3.78 (dd, J = 6.9, 8.5 Hz, 1 H), 3.60 (ddd, J = 5.5, 6.9, 8.3 Hz, 1 H), 2.79 (m, 1 H), 2.61 (dd, J = 5.3, 13.6 Hz, 1 H), 2.47 (dd, J = 9.6, 13.7 Hz, 1 H), 2.35 (m, 1 H), 2.35 (br s, 3 H), 1.87 (br s, 3 H), 1.81 (dd, J = 4.4, 14.2 Hz, 1 H), 1.66 (m, 1 H), 1.48 (s, 3 H), 1.05 (d, J = 6.6 Hz, 3 H), 0.88 (d, J = 6.6 Hz, 3 H). The two isomers of **41** were combined for the next step.

Lactam 40

To a stirred solution of 1.13 g (3.42 mmol) of the above monoalkylated lactams **41** in 50 mL dry THF at -78°C, 3.20 mL (4.80 mmol) of 1.5 M LDA in cyclohexane were added. The mixture was stirred for one hour at -78°C, and then cooled to -100°C. After stirring for an additional 15 min at -100°C, 0.275 mL (4.48 mmol) of methyl iodide was added dropwise. The solution was maintained at -100°C for 2 h and quenched with 1 mL of saturated ammonium chloride. The solvent was removed **in vacuo**, and the residue dissolved in 50 mL ether, washed with water (2 x 50 mL), brine (2 x 50 mL), dried ($MgSO_4$), and concentrated. ^{1}H-NMR and hplc (Zorbax) indicated a 93:7 ratio of diastereomers with **40** assumed to be the major product. Flash chromatography (silica gel, 1:9 ethyl acetate-hexane) afforded 0.92 g (79%) of **40** as a pale yellow oil (contaminated by less than 1 percent of the other isomer as determined by hplc); $[\alpha]^{21}_D$ -12.21° (c 0.98, EtOH). IR (film) 2950, 2865, 1720, 1645, 1460 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 4.18 (dd, J = 8.3, 9.1 Hz), 3.75 (dd, J = 7.2, 9.5 Hz, 1 H), 3.60 (m, 1 H), 2.52 and 2.40 (ABq, J = 13.7 Hz, 2 H), 2.35 (br s, 3 H), 2.14 and 2.05 (ABq, J = 14.1 Hz, 2 H), 1.86 (br s, 3 H), 1.68 (m, 1 H), 1.41 (s, 3 H), 1.19 (s, 3 H), 1.05 (d, J = 6.6 Hz, 3 H), 0.88 (d, J = 6.6 Hz, 3 H).
MS m/e calcd. for $C_{16}H_{26}BrNO_2$: 343.1148 and 345.1128. Found: 343.1121 and 345.1159

Minor Isomer 40 (exo-2-Methyl)

Isolated in 4% yield (47 mg) as an oil. ^{1}H-NMR ($CDCl_3$) δ 4.20 (dd, J = 8.6, 7.9 Hz, 1 H), 3.79 (dd, J = 8.2, 7.6 Hz, 1 H), 3.65 (m, 1 H), 2.67 and 1.97 (ABq, J = 14.0 Hz, 2 H), 2.36 and 2.21 (ABq, J = 16.0 Hz, 2 H), 2.31 (br s, 3 H), 1.77 (br s, 3 H), 1.68 (m, 1 H), 1.51 (s, 3 H), 1.28 (s, 3 H), 1.05 (d, J = 6.5 Hz, 3 H), 0.88 (d, J = 6.6 Hz, 3 H).

(R)-3-(1-But-3-enyl)-4-methyl-4-(E-2-methyl-3-bromo-1-but-2-enyl)-cyclopent-2-enone (-)-39

To a solution of 1.56 g (8.45 mmol) 1-iodobut-3-ene in 50 mL dry ether at -78°C under an argon atmosphere, 9.20 mL (15.6 mmol) of 1.7 M t-butyllithium in hexane was added dropwise over 2 min. The solution was allowed to stir at -78°C for 1 h at which time it was transferred via cannula into a stirred solution of 1.02 g (2.97 mmol) of lactam **40** in THF at -78°C. After allowing the reagents to react for 4 h at -78°C, 2 mL of saturated ammonium chloride were added to quench the reaction. The solution was concentrated and the residue dissolved in 100 mL ether, washed with water (2 x 100 mL), brine (2 x 100 mL), dried ($MgSO_4$), and concentrated to yield crude enamine **43**. Without further purification, the enamine and 600 mg of **anhydrous** tetrabutyl ammonium dihydrogen phosphate were dissolved in 25 mL of **dry** n-pentanol in a **dry** flask equipped with a reflux condenser and magnetic stir bar under argon. The mixture was heated to reflux and a solution of 165 mg (9.17 mmol) of water dissolved in 10 mL of n-pentanol was added via syringe pump over 50 h. The solution was refluxed an additional 10 h, concentrated, and the residue dissolved in 50 mL ether. After washing with water (2 x 50 mL), brine (2 x 50 mL), drying ($MgSO_4$), and concentrating, the ^{1}H-NMR of the crude oil revealed a one to one ratio of enone **39** to the undesired enone **44**. Flash chromatography (silica gel, 1:9 ethylacetate-hexane) afforded 400 mg (45%) of enone **39** and 408 mg (46%) of enone **44** as colorless oils. Enone **39**; $[\alpha]^{21}_D$ -3.13° (c 2.15, EtOH). IR (film) 2950, 2920, 1680, 1605 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 5.92 (s, 1 H), 5.82 (m, 1 H), 5.10 (m, 2 H), 2.60 and 2.22 (ABq, J = 14.0 Hz, 2 H), 2.51 and 2.14 (ABq, J = 18.3 Hz, 2 H), 2.40 (m, 4 H), 2.32 (br s, 3 H), 1.81 (br s, 3 H), 1.25 (s, 3 H).
MS, m/e calcd for $C_{15}H_{21}BrO$: 296.0776 and 298.0756. Found: 296.0786 and 298.0765.

(S)-2-Allyl-3-methyl-5-(E-2-methyl-3-bromo-1-but-2-enyl)-5-methylcyclopent-2-enone (-)-44[20]

$[\alpha]^{21}_D$ -59.13° (c 2.50, EtOH). IR (film) 2930, 2895, 1680, 1630, 1415, 1365. ^{1}H-NMR ($CDCl_3$) δ 5.78 (m, 1 H), 4.95 (m, 2 H), 2.94 (m, 2 H), 2.56 and 2.22 (ABq, J = 19.0 Hz, 2 H), 2.53 and 2.27 (ABq, J = 13.7 Hz, 2 H), 2.32 (br s, 3 H), 2.04 (br s, 3 H), 1.71 (br s, 3 H), 1.08 (s, 3 H).
Anal. Calcd for $C_{15}H_{21}BrO$: C, 60.61; H, 7.12; Br, 26.88. Found: C, 60.57; H, 7.18; Br, 27.08.

(R)-3-(1-But-3-enyl)-4-methyl-4-(E-2-methyl-3-bromo-1-but-2-enyl)- cyclopent-2-enone 1,3-dioxolane Ketal, 45

A stirred solution of 152 mg (0.51 mmol) of **39**, ethylene glycol (0.20 mL) and pyridinium p-toluenesulfonate (PPTS) (20 mg) in 50 mL of benzene was refluxed under azeotropic removal of water for 89 h. The reaction was concentrated and the residue dissolved in 50 mL ether, washed with water (2 x 50 mL), brine (2 x 50 mL), dried ($MgSO_4$), and concentrated. Silica gel chromatography (1:9 ethyl acetate-hexanes, 0.1% Et_3N) afforded 158 mg (90%) of dioxolane **45** as a colorless oil. The dioxolane was immediately subjected to radical cyclization, since it would completely revert back to enone **39** in 24 h at room temperature in CH_2Cl_2. ^{1}H-NMR ($CDCl_3$) 5.88 (m, 1 H), 5.38 (s, 1 H), 5.03 (m, 2 H), 3.91 (m, 4 H), 2.47 and 1.80 (ABq, J = 14.0 Hz, 2 H), 2.34 (br s, 3 H), 2.30 (m, 2 H), 2.10 (m, 4 H), 1.82 (br s, 3 H), 1.12 (s, 3 H).

2-Oxo-silphiperfol-6-ene-1,3-dioxolane Ketal, 46

A solution of tri-n-butyltin hydride (0.25 mL, 0.93 mmol) and azoisobutyronitrile (AIBN, 20 mg) in dry benzene (3 mL) was added over 2 h via a syringe pump to 158 mg (0.46 mmol) of **45** in 10 mL of refluxing benzene. The solution was heated at reflux for an additional 4 h, concentrated, and purified by silica gel chromatography (3% ether in hexanes), to yield 64 mg (53%) of **46** and 14 mg (12%) of the epi-derivative **47** as colorless oils. The two epimers were hydrolyzed to the ketones immediately after purification.

46: ^{1}H-NMR ($CDCl_3$) δ 3.83 (m, 4 H), 2.50 (br d, J = 15.9 Hz, 1 H), 2.02-1.20 (m, 15 H), 1.03 (s, 3 H), 1.02 (d, J = 6.5 Hz, 3 H).

47: ^{1}H-NMR ($CDCl_3$) δ 4.00 (m, 1 H), 3.80 (m, 3 H), 2.27 (d, J = 8.3 Hz, 1 H), 2.08 (br s, 2 H), 1.92 (m, 1 H), 1.70-1.20 (m, 15 H), 1.14 (d, J = 6.9 Hz, 3 H), 1.13 (s, 3 H).

2-Oxo-silphiperfol-6-ene (+)-48

A solution of 64 mg (0.24 mmol) of **46** and five drops of concentrated H_2SO_4 in 10 mL of acetone was refluxed for 20 min. After evaporation of the solvent, the residue was dissolved in 20 mL of ether, washed with water (2 x 20 mL), brine (2 x 20 mL), dried ($MgSO_4$), and concentrated to yield 52 mg (98%) fo **48** as a colorless oil. No further purification was attempted prior to the next step; $[\alpha]^{21}_D$ +28.65° (c 1.04, $CHCl_3$). IR (film) 2950, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 2.40 (dd, J = 0.9, 16.7 Hz, 1 H), 2.27 (d, J = 16.7 Hz, 1 H), 2.18 (br s, 2 H), 2.05 (m, 2 H), 1.85-1.60 (m, 3 H), 1.58 (br s, 6 H), 1.35 (m, 1 H), 1.12 (d, J = 6.4 Hz, 3 H), 1.09 (s, 3 H).

The epimer **47** was similarly hydrolyzed to the ketone **49**. IR (film) 2900, 1720 cm^{-1} ^1H-NMR ($CDCl_3$) δ 2.38 (dd, J = 1.6, 16.9 Hz, 1 H), 2.27 (m, 2 H), 2.18 (br s, 2 H), 2.08 (d, J = 16.9 Hz, 1 H), 1.87 (m, 2 H), 1.66 (m, 1 H), 1.56 (br s, 3 H), 1.52 (br s, 3 H), 1.22 (m, 1 H), 1.12 (s, 3 H), 1.00 (d, J = 6.6 Hz, 3 H). No further purification or characterization was attempted prior to the next step.

(-)-Silphiperfol-6-ene 38

A solution of 89 mg (0.41 mmol) of **48**, 2 mL of hydrazine monohydrate and 380 mg of potassium carbonate in 2 mL of 2-hydroxyethylether was heated at 150°C for 4 h after which time the temperature was raised to 210°C. The reflux condenser was replaced by a short path distillation head and part of the reaction mixture was distilled. The reflux condenser was returned to the flask and the mixture was heated at 210°C for an additional 12 h. After cooling, the residue and the distillate (1 mL) were diluted with water, combined, and extracted (2 x 20 mL) with pentanes. The pentane extracts were washed with water (2 x 40 mL), brine (2 x 40 mL), dried ($MgSO_4$), and carefully concentrated on a rotary evaporator in an ice bath to give a volatile colorless oil. The crude product was purified by silica gel chromatography (pentanes) to give 51 mg (61%) of (-)-silphiperfol-6-ene **38** as a colorless oil; $[\alpha]^{21}_D$ -74.06° (c 1.01, $CHCl_3$). Lit.[13] $[\alpha]^{25}_D$ -92.8° (c 0.80, $CHCl_3$). IR (film) 2940, 2860, 1450 cm^{-1}. ^1H-NMR ($CDCl_3$) δ 2.20 and 1.94 (ABq, J = 16.0 Hz, 2 H), 1.70 (m, 1 H), 1.62-1.10 (m, 11 H), 1.54 (br s, 3 H), 1.51 (br s, 3 H), 0.99 (s, 3 H), 0.95 (d, J = 6.6 Hz, 3 H). ^{13}C-NMR δ 136.0, 127.4, 72.1, 59.1, 52.5, 49.7, 41.5, 40.4, 36.7, 30.1, 29.2, 24.7, 19.7, 14.1, 10.8.

9-Epi-silphiperfol-6-ene 51

Prepared as described for **38**; $[\alpha]^{21}_D$ -73.15° (c 0.95, $CHCl_3$). IR (film) 2920, 2860, 1480 cm^{-1}. ^1H-NMR ($CDCl_3$) δ 2.07 (br s, 2 H), 2.02-1.00 (m, 16 H), 0.98 (s, 3 H), 0.93 (d, J = 6.5 Hz, 3 H). ^{13}C-NMR ($CDCl_3$) δ 136.4, 126.4, 77.2, 71.8, 53.3, 52.2, 42.4, 37.7, 34.8, 30.4, 25.9, 22.5, 15.1, 14.2, 10.0.

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