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ENANTIOSELECTIVE SYNTHESIS OF (+)-KJELLMANIANONE

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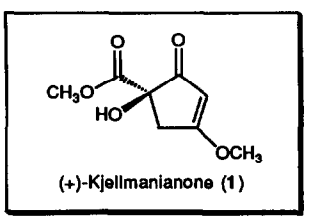
Abstract: *An asymmetric synthesis of the highly oxygenated cyclopentanoid antibiotic (+)-kjellmanianone (1) has been achieved The key step entailed enantioselective hydroxylation of the prochiral sodium enolate of β-keto ester 2 with the new, enantiomerically pure N-sulfonyloxaziridine 7b, affording 1 in 68 5% ee (60% yield) Possible transition state structures for the asymmetric oxidation are evaluated*

In 1980, Nakayama reported the isolation of the cyclopentanoid antibiotic (+)-kjellmanianone (1) from the methanol extract of the marine algae *Sargassum kjellmanianum* [1] This novel, pentaoxygenated metabolite possesses moderate activity against Gram-positive microorganisms such as *E coli* K12 and *Bacillus subtilis var niger* A combination of chemical and spectroscopic analyses established that 1 was a β-methoxy, α,β-unsaturated cyclopentenone containing geminal hydroxyl and carbomethoxy groups [1] Single-crystal X-ray analysis then elucidated the complete structure, including the *(R)*-configuration of the lone stereocenter [1]

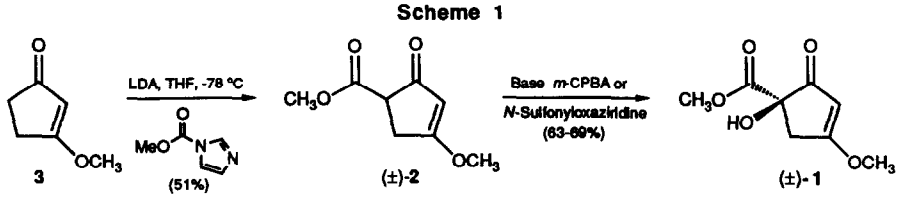


(+)-Kjellmanianone (1)

We envisioned an efficient, enantioselective construction of (+)-1, based upon hydroxylation of the prochiral enolate of β-keto ester (±)-2 with the chiral oxidizing agents recently developed by one of us (*vide infra*) The precursor 2 would in turn be readily available by acylation of vinylogous ester 3 [2]

Synthesis of Racemic Kjellmanianone Before undertaking an asymmetric synthesis of (+)-kjellmanianone, we first explored the generation of the racemate (Scheme 1) Our effort began with 3, previously prepared by House from commercially available 1,3-cyclopentanedione [3] Acylation of the vinylogous ester, via deprotonation with lithium diisopropylamide in tetrahydrofuran followed by addition of one equivalent of *N*-carbomethoxyimidazole at -78 °C, gave keto ester (±)-2 in 51% yield as a white solid Koreeda and Schlessinger have also demonstrated independently that kinetic deprotonation permits the regiospecific α-alkylation of vinylogous esters derived from 1,3-cyclopentanediones [4] *N*-Carbomethoxyimidazole proved superior to the more commonly used acylating agents such as methyl chloroformate [5]

Scheme 1



The availability of 2 in quantity set the stage for introduction of the hydroxyl group α to the two carbonyls α-Hydroxylation of a carbonyl compound can generally be effected by oxidation of the corresponding enolate with

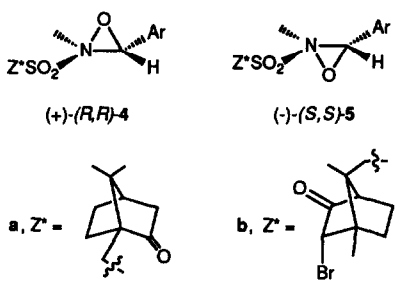
an aprotic oxidizing agent such as Vedejs' MoOPH[6] reagent, Davis' *N*-sulfonyloxaziridines,[7,8] H_2O_2,[9] or molecular oxygen.[10] Another method, known as the Rubottom reaction, involves initial enolate trapping with trimethylsilyl chloride and subsequent oxidation of the silyl enol ether with peracid[11] or osmium tetroxide,[12] followed by hydrolysis. The MoOPH reagent apparently cannot be employed for hydroxylation of stabilized enolates, including those derived from 1,3-dicarbonyl compounds. Vedejs has speculated that the latter species yield stable Mo(IV) chelates which resist oxidation.[6]

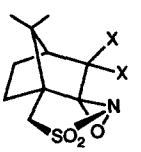
Attempted generation of the enolate of **2** with lithium diisopropylamide, followed by oxygenation with *m*-CPBA or O_2, gave only complex mixtures. The use of potassium *t*-butoxide, even at reduced temperatures, resulted in hydrolysis of the vinylogous ester. Trapping of the putative enolate with trimethylsilyl chloride also failed.

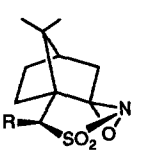
Successful deprotonation was finally achieved by treatment of **2** with excess potassium hydride at room temperature. Addition of 1.2 equivalents of *m*-chloroperbenzoic acid at room temperature then furnished racemic kjellmanianone (**1**) as a white solid in 63% yield after chromatography. This material was spectroscopically indistinguishable (IR, MS, UV, ^1H and ^{13}C NMR) from natural kjellmanianone.[1] Exposure of (±)-**1** to acetic anhydride, triethylamine, and a catalytic amount of *N*-dimethylaminopyridine also gave the expected acetate in 54% yield.

Following the completion of our synthesis, Irie and co-workers reported a very similar approach to racemic kjellmanianone.[13] They generated keto ester **2** in 20% yield from **3**, the use of methyl chloroformate as acylating agent most likely accounted for the low yield. Treatment of **2** with potassium fluoride and molecular oxygen in dimethyl sulfoxide containing 18-crown-6 and triethyl phosphite then gave (±)-**1** in 60% yield.

Asymmetric Enolate Oxidation. Synthesis of (+)-Kjellmanianone. At this juncture we embarked upon an asymmetric construction of (+)-kjellmanianone. We envisioned generation of the single stereocenter via enantioselective hydroxylation of the prochiral enolate of β-keto ester (±)-**2**. Davis et al. recently introduced the only available reagents for aprotic asymmetric oxidation, the enantiomerically pure *N*-sulfonyloxaziridines **4-7a**.[8,14] These species provide good-to-excellent chemical yields and useful enantioselectivities in asymmetric hydroxylations of ketones (63-95% ee),[14b,d,e,15,16] esters (54-85% ee),[14a] and amides (46-50% ee).[14a,c] In particular, the (camphorylsulfonyl)oxaziridine **6a**[15,17] and [(8,8-dichlorocamphoryl)sulfonyl]oxaziridine **6b**[16] afford unsurpassed asymmetric induction in oxidation of the sodium enolates of ketones (90-≥95% ee), both reagents are readily prepared and the former is commercially available.





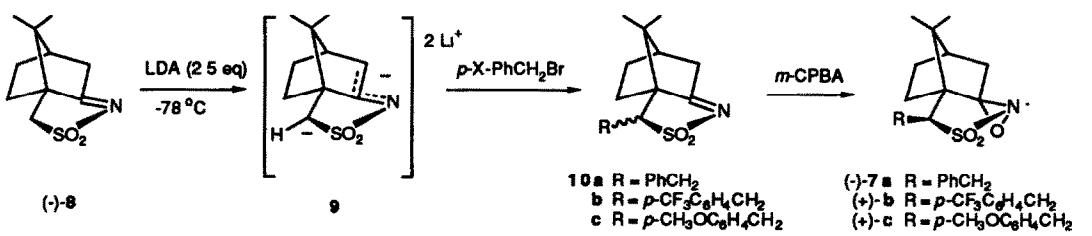


The requisite enolate anions were generated by treatment of **2** with 4.5 equivalents of potassium hydride, or with 1 1 equivalents of either lithium diisopropylamide (LDA), potassium, or preferably sodium bis(trimethylsilyl)amide, in tetrahydrofuran at room temperature. Upon addition of one equivalent of (-)-**5a** at room temperature, an exothermic reaction occurred, the mixture immediately blackened, and no identifiable products could be isolated However, the desired transformation was readily achieved simply by cooling the enolate solution to -78 °C before addition of the oxidizing agent With oxaziridines **4** and **5**, quenching after one minute led to complete consumption of starting material with modest side product formation.

Oxaziridines **6** and **7**, which react more slowly than **4** and **5**, were introduced at -78 °C followed by warming to room temperature. The hydroxylations with **6** and **7** proved to be exceptionally clean, TLC analysis indicated only the presence of **1** and a sulfonimine (RSO_2-N=CR_2) generated by oxaziridine reduction. Preparative thin layer chromatography, using ether as eluant, furnished optically active kjellmanianone. Isolated yields of **1** were 35-78%, generally higher than those obtained with **4** and **5** (33-44%). Enantiomeric purities were determined via ^{1}H NMR chiral shift reagent experiments using tris[3-(heptafluoropropylhydroxymethlene)-(-)-camphorato]-europium (III) [Eu(hfc)$_3$] [18] The results are summarized in Table I

As noted previously, the configurations of the oxaziridine rings in **4-7** strongly influence the oxidation stereochemistry [14-17] Thus, (+)-**4a,b** and (+)-**6a** gave predominantly (+)-kjellmanianone, whereas the diastereomers (-)-**5a,b** and the antipodal reagent (-)-**6a** furnished largely the (-)-enantiomer (Table 1, entries 1-11). The bromocamphor derivatives **4b** and **5b** proved less effective than **4a** and **5a**, the former affording 8-12% ee compared with 33-37% ee for the latter reagents (Table 1, entries 1-4). This suggests a possible role for the carbonyl group of **4a** and **5a** in establishing the transition state geometries (*vide infra*)

For further study of the hydroxylation reaction, we employed the more readily available (camphorylsulfonyl)oxaziridines (+)-**6a,b** and (-)-**7a**, together with the *p*-(trifluoromethyl)benzyl and *p*-methoxybenzyl derivatives (+)-**7b** and (+)-**7c** which were developed for use in this work The latter reagents were prepared by alkylation of dianion **9**, generated by metalation of (camphorylsulfonyl)imine **8** with 2.5 equivalents of LDA, affording a 1 1 mixture of the *exo*- and *endo*-sulfonimines **10** in ca 60% yield [19] Oxidation of the mixture with 0 5 equivalents of *m*-chloroperbenzoic acid in the presence of potassium carbonate gave *exo*-**7b** in 30% yield overall from (-)-**8** Under these conditions the more sterically hindered *endo*-**10** was unreactive



Oxidation of the potassium or sodium enolate with (+)-**6a** again furnished **1** in 35-40% ee, whereas the lithium enolate gave inferior results (12% ee) Neither lowering the temperature nor varying the concentration of base or of **6a** significantly increased the stereoselectivity. (+)-[(8,8-

Table 1 Asymmetric Oxidation of the Enolate of Keto Ester **2** to Kjellmanianone (**1**) Using Enantiomerically Pure *N*-Sulfonyloxaziridines **4-7** in THF

Entry	Oxaziridine	Base	Oxidation Temperature (°C)	% ee[a]	(config)	% Yield[b]
1	(+)-**4 a**	4 5 eq KH	-7 8	36 5	(*S*)-(+)	44
2	(-)-**5 a**	4 5 eq KH	-7 8	33 0	(*R*)-(+)	42
3	(+)-**4 b**	4 5 eq KH	-7 8	12 0	(*S*)-(+)	33
4	(-)-**5 b**	4 5 eq KH	-7 8	8 0	(*R*)-(+)	43
5	(+)-**6 a**	1 1 eq KHMDS	-78 to 20	36.0	(*R*)-(+)	48
7	(+)-**6 a**	1 1 eq NHMDS	-78 to 20	39 0	(*R*)-(+)	69
8	(+)-**6 a**[c]	1 1 eq NHMDS	-78 to 20	40 0	(*R*)-(+)	78
9	(+)-**6 a**[c]	1 5 eq NHMDS	-78 to 20	40 0	(*R*)-(+)	35
10	(+)-**6 a**	1.1 eq LDA	-78 to 20	12 0	(*R*)-(+)	56
11	(-)-**6 a**	1 1 eq KHMDS	-78 to 20	35 0	(*S*)-(+)	50
12	(+)-**6 b**	1 2 eq KHMDS	-78 to 0	4 0	(*R*)-(+)	49
13	(+)-**6 b**	1 1 eq KHMDS	-78 to 0	13 0	(*R*)-(+)	48
14	(-)-**7a**	1 1 eq KHMDS	-78 to 20	39 0	(*R*)-(+)	45
15	(-)-**7 a**	1 1 eq NHMDS	-78 to 20	57 0	(*R*)-(+)	64
16	(-)-**7 a**	1 1 eq LDA	-78 to 20	12 0	(*R*)-(+)	70
17	(+)-**7b**	1 1 eq NHMDS	-78 to 20	68 5	(*R*)-(+)	60
18	(+)-**7c**	1 1 eq NHMDS	-78 to 20	52 0	(*R*)-(+)	54

a) NMR determination using $Eu(hfc)_3$ b) Isolated yields c) 1 5 Equiv of (+)-**6a**

Dichlorocamphoryl)sulfonyl)]oxaziridine (**6b**), which performed impressively in the oxidation of 2-substituted 1-tetralone enolates (90-95% ee),[16] furnished (+)-**1** in only 4-13% ee (Table 1, entries 12-13) The highest enantiomeric purity, 68 5% ee, was ultimately obtained via oxidation of the sodium enolate of **2** with *exo*-(*p*-trifluoromethylbenzyl)oxaziridine (+)-**7b** (Table 1, entry 17)

Analysis of Transition Structures for Asymmetric Hydroxylation. Compelling evidence from a variety of sources indicates that the reactivity of enolates in solution is significantly influenced by aggregation [15,20] The solution structures of β-dicarbonyl enolates have been the subject of numerous studies, notably by Raban et al [21] and more recently by Arnett and co-workers [22] In nonpolar solvents such as THF, the metal counterion is chelated by the enolate oxygens Both monomeric and aggregated reactive species have been identified

Prior studies have shown that asymmetric oxidations of enolates by *N*-sulfonyloxaziridines of type **6** are affected by the geometry, substitution pattern, and solution structure of the enolate [14-16] The results generally could be interpreted in terms of "open" transition state structures dominated by nonbonded steric interactions X-Ray analysis and structure-reactivity correlations suggest that the norbornane C-C bridge in **6** and **7** is the most sterically demanding feature in proximity to the reactive oxygen [17] Based upon these considerations, we evaluated model transition state structures **A-D** (Figure 1) for the asymmetric oxidation of a monomeric enolate of **2** by (+)-**6a**

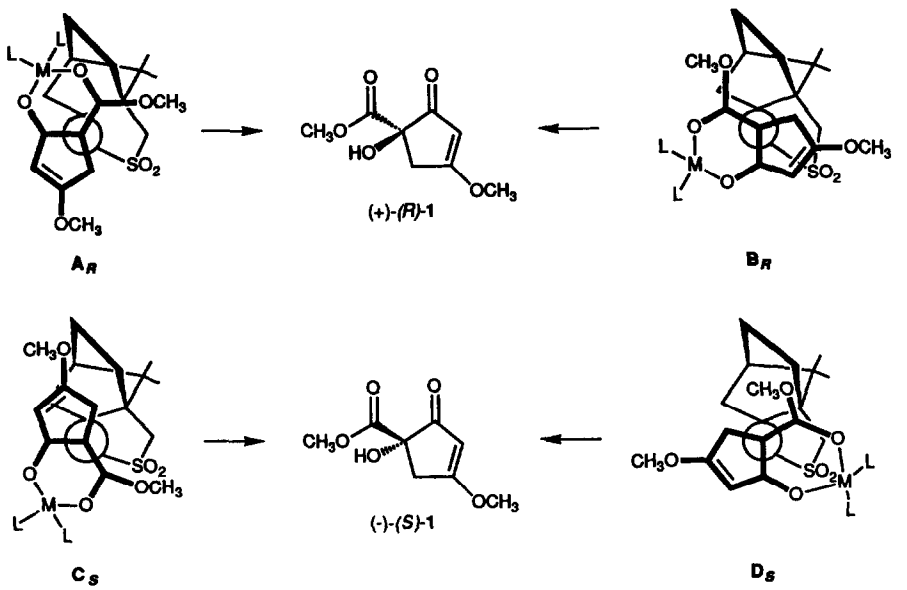
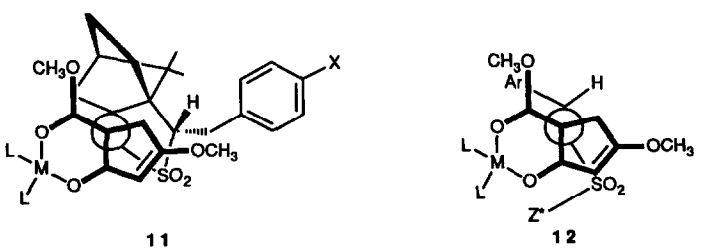


Figure 1 Proposed transition structures for asymmetric oxidation of the enolate of **2** by (+)-**6**[a]

Given the reasonable assumption that the solvated metal chelate moiety is sterically the most demanding region of the enolate, the lowest energy transition state appears to be $\mathbf{B}_R$, in accord with the observation that (+)-**6a** does furnish predominantly (*R*)-(+)-**1** Transition state $\mathbf{C}_S$, leading to (*S*)-(-)-**1**, also orients the bulky chelate in a favorable region, perhaps accounting in part for the modest enantioselectivities (35-40% ee) observed with this reagent

The benzene ring in **7a** is remote from the reactive oxygen, separated by five bonds and trans-oriented on the five-membered ring. Nonetheless, **7a** afforded markedly improved asymmetric induction vis-á-vis its desbenzyl counterpart (+)-**6a** (57 vs 39% ee, Table 1, entries 15 and 7) These results may reflect an attractive interaction (charge transfer, van der Waals, or dipole-dipole) between **7a** and the enolate, enhancing the preference for transition structure **11** (cf , $\mathbf{B}_R$, Figure 1) [23] In accord with this hypothesis, use of the more electrophilic reagent (+)-**7b** further improved the enantioselectivity (68 5% ee, Table 1, entry 17) On the other hand the electron-rich, *p*-methoxybenzyl substituted oxaziridine (+)-**7c** proved inferior to both **7a** and **7b** (Table 1, entry 18)



11 **12**

The energies of transition state structures such as **11** differ only slightly from those of diastereomeric structures, additional factors influencing these results may emerge from future experiments The behavior of **7a-c** in oxidation of simple enolates also remains to be elucidated Nevertheless, the effects of the remote *exo*-benzyl groups in **7a-c** are not readily explained in terms of our simple steric model (i e , Figure 1) [16] If stereoelectronic effects can indeed enhance the asymmetric induction, as we suggest, then optimization of these interactions may lead to further improvement in enolate oxidation stereoselectivities

The determination of the absolute configurations of oxaziridines **4** and **5** via X-ray analysis[24] lends support to the aforementioned speculation concerning the influence of the camphor auxiliary (Z*) on the asymmetric induction Oxaziridines **4a** and **5a** afforded **1** in higher ee than did **4b** and **5b** (33-37 vs 8-12%, respectively) The carbonyl group in the former reagents lies near the reactive oxygen, and thus may stabilize the transition state topology via complexation with the enolate (i e , structure **12**) For **4b** and **5b**, the disposition of the carbonyl group precludes a similar interaction

Absolute Configuration of Kjellmanianone: The Exciton Chirality Method Nakayama et al originally reported a very low specific rotation {$[\alpha]_D$ +1 6° (*c* 1.80, $CHC1_3$)} for natural kjellmanianone (**1**) [1] Our optical rotation values for (+)- and (-)-**1**, together with the corresponding enantiomeric purities, indicate that the specific rotation of enantiomerically homogeneous **1** should be ca $[\alpha]_D \pm 100°$ Furthermore, the X-ray method for determination of absolute configuration, as employed by Nakayama, can be problematic for structures lacking an atom with strong anomalous scattering. These considerations prompted us to reexamine the absolute configuration of (+)-kjellmanianone

The exciton chirality method introduced by Mason[25] and developed by Nakanishi[26] has been widely exploited for elucidation of absolute configurations Positive or negative chiralities between the electronic transition moments of two chromophores result in exciton-split CD curves with positive or negative first Cotton effects, respectively The magnitude of the split Cotton effect is greatly enhanced when the chromophores are close in space and similar in energy Kjellmanianone contains only a single chromophore, the enone moiety with a UV maximum at 242 nm Accordingly, we introduced an interacting chromophore by conversion of the tertiary alcohol to the corresponding *p*-bromobenzoate (UV max at 245 nm) The orientations of the enone and benzoate transition moments are defined in Figure 2

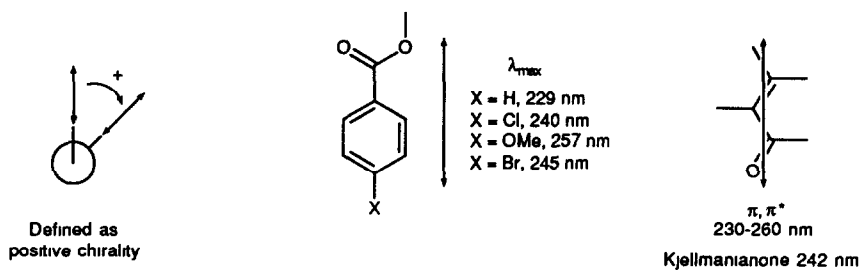


Figure 2 Definition of Positive Chirality Between Two Chromophores Orientations of the Transition Moments

CD spectra of synthetic (+)-kjellmanianone and its *p*-bromobenzoate derivative are shown in Figure 3 As expected for the positive chromophore chirality of the *R* absolute configuration, (+)-kjellmanianone

p-bromobenzoate displayed a positive first Cotton effect ($\Delta\varepsilon_{243}$ 18 4, 47% ee) The negative second Cotton effect was smaller, reflecting the unsymmetrical nature of the two chromophores. Likewise, the *p*-bromobenzoate of (-)-kjellmanianone gave a negative first Cotton effect ($\Delta\varepsilon_{243}$ -7.42; 26% ee) The exciton chirality method therefore confirms that the absolute configuration of (+)-kjellmanianone is indeed *R*, as reported by Nakayama. The CD spectra of (+)-1 and (-)-1 displayed positive ($\Delta\varepsilon_{243}$ +9 9, 47% ee) and negative ($\Delta\varepsilon_{242}$ -4 03, 26% ee) Cotton effects, respectively

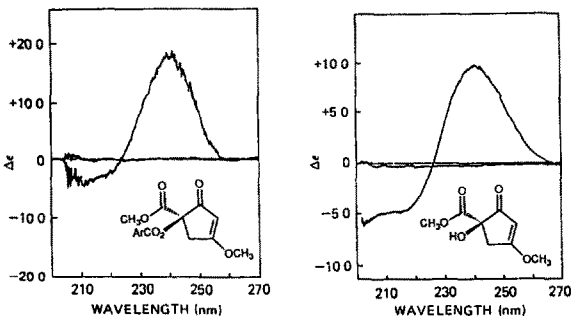


Figure 3 CD Spectra of Synthetic (+)-Kjellmanianone and the *p*-Bromobenzoate Derivative

EXPERIMENTAL SECTION

All solvents were reagent grade Tetrahydrofuran was distilled from sodium and benzophenone, triethylamine and diisopropylamine from potassium hydroxide, and methylene chloride from phosphorous pentoxide. The enantiomerically pure N-sulfonyloxaziridines **4**,[24] **5**,[24] **6a**,[17] and **6b**[16] were prepared as previously described The chiral shift reagent Eu(hfc)$_3$ was purchased from Aldrich Precoated silica gel plates with a fluorescent indicator (250 μm, E Merck) were used for analytical thin layer chromatography (TLC), with visualization via ultraviolet light or ethanolic 12-molybdophosphoric acid (7% w/v). For preparative separations, precoated silica gel GF plates (0.5 or 1 0 mm, Analtech) were employed. Silica gel 60 (particle size 0 040-0 063 mm, E. Merck) was used for flash column chromatography Melting points were determined with a Thomas-Hoover instrument and are corrected NMR spectra were measured with either a Varian T-60A (60 MHz) or Bruker WP-250 FT (250 MHz) spectrometer Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane Infrared spectra were recorded on a Perkin-Elmer Model 337 spectrophotometer for carbon tetrachloride or chloroform solutions High resolution mass spectra were obtained from the University of Pennsylvania Mass Spectroscopy Service Center on a Hitachi Perkin Elmer RMH-2 spectrometer with a Kratos DS-50-S data system. Microanalyses were performed by the Rockefeller University Microanalytical Laboratories under the direction of Mr. S. T. Bella. UV spectra were run in ethanol on a Cary 15 spectrophotometer. CD spectra were obtained with a Jasco J-414 spectropolarimeter at Merck Sharp and Dohme Research Laboratories (West Point, PA) under the guidance of Dr. William C Randall

[(3-*exo*-Benzylcamphoryl)sulfonyl]imine (10a), [(3-*exo*-(*p*-Trifluoromethyl)-benzylcamphoryl)sulfonyl]imine (10b), and [(3-*exo*-*p*-Methoxybenzylcamphoryl)-sulfonyl]imine (10c). A solution of 2 13 g (10 mmol) of (camphorsulfonyl)imine (-)-8[17] in 40 mL of dry THF was cooled to 0 °C and treated with a freshly prepared 1 M solution of LDA (25 mmol) The reaction was stirred for 1 h and cooled to -78 °C, and a solution of benzyl bromide (1 5 equivalents), *p*-(trifluorormethyl)benzyl bromide (1.5 equivalents), or *p*-methyoxybenzyl chloride (3.0 equivalents) in 5 mL of THF was then added. After stirring for 2 h at -78 °C, the mixture was warmed to room temperature, stirred overnight, quenched with 30 mL of saturated NH_4Cl solution, and extracted with ethyl acetate (3 x 30 mL) The combined extracts were washed with H_2O (2 x 30 mL) and dried over anhydrous $MgSO_4$ Concentration under vacuum afforded the crude 3-substituted imine.

Flash chromatography using 20% ethyl acetate/*n*-pentane as eluant afforded 1 4 g (91%) of imine *exo*-**10a**: mp 133-4 °C; $[\alpha]_D^{20}$ -25.0° (*c*, 1.0 $CHCl_3$), IR (KBR) 1650 (m), 1335 (s), 1140 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7 35 (m, 5 H), 3 72-3.10 (m, 3 H), 2.81 (m, 1 H), 2 40-1 40 (m, 6 H), 1.18 (s, 3 H), 1.12 (s,3 H)

Anal Calcd for $C_{17}H_{21}NO_2S$ C, 67 29, H, 6 97. Found· C, 67 16, H, 7 12.

Attempted purification of 4-*exo*-**10b** or 4-*exo*-**10b** by flash chromatography proved unsuccessful Crystallization of **10c** from ethanol afforded 0 67 g (20 %) of imine *exo*-**10c**, mp 172-3 °C, $[\alpha]_D^{20}$ -14.5° (c 1 2, $CHCl_3$), IR (KBr) 1640 (w), 1320 (s), and 1170 (s) cm^{-1}, 1H NMR ($CDCl_3$, 250 MHz) δ 7 28 (m, 2 H), 6 87 (m, 2 H), 3 79 (s, 3 H), 3 62 (m, 1 H), 3 15 (m, 2 H), 2 77 (m, 1 H), 2 4-1 4 (m, 6 H), 1 19 (s, 3 H), 1 10 (s, 3 H)

Anal Calcd for $C_{18}H_{23}NO_3S$ C, 64 84, H, 6 95 Found C, 64 88, H, 7 09

(-)-[(4-*exo*-Benzylcamphoryl)sulfonyl]oxaziridine (7a) A 100-mL, three-necked Morton flask equipped with a mechanical stirrer was charged with 0 76 g (2 5 mmol) of *exo*-**10a**, 0 52 g (3 mmol) of 95% *m*-CPBA, 20 mL of methylene chloride, and 10 mL of saturated aqueous K_2CO_3 The reaction mixture was stirred for 1 5 h at 20 °C, quenched with 20 mL of saturated $Na_2S_2O_3$ solution, and extracted with ethyl acetate (3 x 30 mL) The combined extracts were washed with water (2 x 30 mL) and dried over anhydrous $MgSO_4$ Concentration on a rotatory evaporator afforded the crude oxaziridine which was purified by crystallization from ethanol, furnishing 0 76 g (95%) of *exo*-**7a** as white needles mp 166-167 °C, $[\alpha]_D^{20}$ -66 0° (*c* 2 4, $CHCl_3$), IR (KBr) 1604 (w), 1360 (s), and 1159 (s) cm^{-1}, ^1H NMR ($CDCl_3$, 250 MHz) δ 7 30 (m, 5 H), 3 62 (t, *J*=8 6 Hz, 1 H), 3 20 (d, *J* =8 6 Hz, 2 H), 2 60 (m, 1 H), 1 40-2 30 (m, 6 H), 1 34 (s, 3 H), 1 21 (s, 3 H)

Anal Calcd for $C_{17}H_{21}NO_3S$ C, 63 92, H, 6 63 Found C, 63 92, H, 6 80

(+)-[(4-*exo*-*p*-Trifluoromethylbenzylcamphoryl)sulfonyl]-oxaziridine (7b) and (+)-[(*p*-*exo*-Methyoxybenzylcamphoryl)-sulfonyl]oxaziridine (7c). A three-necked Morton flask equipped with a mechanical stirrer was charged with 3 6 g of crude **10b** or 3 4 g of crude **10c**, 50 mL of methylene chloride, and 30 mL of 10% K_2CO_3 solution The mixture was treated with 0.52 g (3 mmol) or 0 86 g (5 mmol) of 95% *m*-CPBA and then rapidly stirred for 1 5 h at room temperature The reaction was quenched with 30 mL saturated $Na_2S_2O_3$ solution, extracted with ethyl acetate (3 x 40 mL), washed with H_2O (2 x 40 mL), and dried over anhydrous $MgSO_4$. Concentration followed by flash chromatography, using 40% ethylacetate/*n*-hexane for **7b** or 25% ethyl acetate/*n*-pentane for **7c** as elutents, gave 0 5 and 1 0 g of product, respectively Further purification of **7b** by crystallization from ethanol afforded 0 41 g (36%) of *exo*-**7b** as a white solid mp 141 5-142 5 °C, IR (KBr) 1619 (w), 1363 (s), and 1159 (s) cm^{-1}, $[\alpha]_D^{20}$ +44 4° (*c* 1 46, $CHCl_3$), ^1H NMR ($CDCl_3$) δ 7 50 (AB quartet, *J* = 7 7 Hz, 4 H), 3 58 (t, *J* = 8 7 Hz, 4 H), 3 26 (d, *J* =8 7 Hz, 2 H), 2 60 (m, 1H), 2 30-1 58 (m, 4 H), 1.36 (s, 3 H), 1 24 (s, 3 H)

Anal Calcd for $C_{18}H_{20}F_3NO_3S$ C, 55 80, H, 5 20 Found C, 55 71, H, 5 19

Further purification of **7c** by crystallization from ethanol afforded 0 80 g (46 %) of *exo*-**7c** as a white solid mp 163-4 °C, $[\alpha]_D^{20}$ 60 0° (c 1 0, $CHCl_3$), IR (KBr) 1350 (s), and 1150 (s) cm^{-1}, 1H NMR ($CDCl_3$, 250 MHz) δ 7 05 (AB quartet, J = 8 5 Hz, 4 H), 3 79 (s, 3 H), 3 57 (t, J = 7 8 Hz, 1 H), 3 14 (d, J = 7 8 Hz, 2 H), 2 60 (m, 1 H), 2 30-1 50 (m, 6 H), 1 35 (s, 3 H), 1 22 (s, 3 H)

Anal Calcd for $C_{18}H_{23}NO_4S$ C, 61 87, H, 6 63 Found C, 61 87, H, 6 63

(±)-5-Carbomethoxy-3-methoxy-2-cyclopenten-1-one (2). To a solution of 5 64 mmol of LDA (generated from 8 0 mL of diisopropylamine and 2 4 mL of 2 4 M *n*-butyllithium) in 10 mL of tetrahydrofuran at -78 °C was slowly added a solution of 0 529 g (4 72 mmol) of 3-methoxy-2-cyclopenten-1-one (3) in 4 mL of tetrahydrofuran After the addition was complete, stirring was continued for 15 min The bath was then removed for 5 min, the system was again cooled to -78 °C, and a solution of 0 714 g (5 66 mmol) of *N*-carbomethoxyimidiazole in 4 mL of tetrahydrofuran was added After stirring for 15 min, an additional 5 64 mmol of LDA was added via a cooled syringe After stirring at -78 °C for 10 min, the reaction mixture was poured into 10% HCl Addition of solid sodium chloride was followed by extraction with ether and then methylene chloride The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo Flash chromatography with ethyl acetate as eluant gave 0 466 g (58%) of **2** as a pale yellow solid An analytical sample was obtained via a second flash chromatography mp 53 5-55 0 °C, IR 3010 (w), 2950 (w), 1735 (s), 1700 (s), 1600 (s), 1435 (w), 1360 (s), 1158 (s) and 994 (s) cm^{-1}, ^1H NMR ($CDCl_3$, 250 MHz) δ 2 80 (dd, *J* = 18, 8 Hz, 1 H), 3 08 (dd, *J* = 18, 3 Hz, 1 H), 3 56 (dd, *J* = 8, 3 Hz, 1 H), 3 78 (s, 3 H), 3 91 (s, 3 H), 5 30 (s, 1 H), high resolution mass spectrum (EI) *m/z* 170 0573 (M^+, calcd for $C_8H_{10}O_4$ 170 0579)

Anal Calcd for $C_8H_{10}O_4$ C, 56 47, H, 5 92 Found C, 56 42, H, 5 92

(±)-Kjellmanianone (1) A solution of 108 mg (0.635 mmol) of (±)-**2** in 3 mL of tetrahydrofuran was added to 330 mg (2 88 mmol) of a 35% mineral oil suspension of potassium hydride at room temperature under nitrogen The mixture was stirred for 1 h and 550 mg (3 20 mmol) of *m*-chloroperbenzoic acid was added After 5 h the reaction was quenched with isopropanol, extracted with methylene chloride, and washed with 10% aqueous Na_2CO_3 Purification by flash chromatography using ethyl acetate as eluant gave 74 2 mg (63%)

of racemic kjellmanianone as a white solid. An analytical sample was prepared by flash chromatography with ethyl acetate as eluant. This material was spectroscopically indistinguishable (IR, UV, ^1H and ^{13}C NMR, MS) from natural (+)-kjellmanianone: mp 126 0-128 0 °C (dec), IR 3545 (br), 3010 (w), 2950 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 2.75 (dd, J = 18, 1 Hz, 1 H), 3.19 (dd, J = 18, 1 Hz, 1 H), 3.79 (s, 3 H), 3.95 (s, 3 H), 5 36 (t, J = 1 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 40 7, 53 4, 59.3, 79.1, 101 1, 178.6, 190 1, 199 6; high resolution mass spectrum (EI) m/z 185 0530 (M^+; calcd for $C_8H_{10}O_5$: 186.0528).

Anal Calcd for $C_8H_{10}O_5$ C, 51 61; H, 5 41. Found C, 51.83; H, 5 46

Kjellmanianone Acetate. To a solution of 39 8 mg (0.21 mmol) of (±)-kjellmanianone in 2 mL of methylene chloride at room temperature were added 44 μL of acetic anhydride and 3 5 mg of 4-dimethylaminopyridine The resultant solution was stirred for 19 h Work-up consisted of extraction with ether, washing with 10% HCl and saturated Na_2CO_3, drying over $MgSO_4$, and concentration in vacuo Preparative thin layer chromatography, using ether as eluant, gave 25 3 mg (52%) of the desired acetate as a very pale yellow solid mp 113 0-115 0 °C, IR 3010 (s), 1710 (s), 1740 (s), 1590 (s), 1310 (s), 1230 (b), 1075 (w), 1040 (w), 990 (w), 905 (w) and 815 (w) cm^{-1}, ^1H NMR ($CDCl_3$, 250 MHz) δ 2.18 (s, 3 H), 2 74 (dd, J = 18, 1 Hz, 1 H), 3.69 (dd, J = 18, 1 Hz, 1 H), 3 78 (s, 3 H), 3.93 (s, 3 H), 5 36 (t, J = 1 Hz, 1 H), high resolution mass spectrum (EI) m/z 228 0643 (M^+, calcd for $C_{10}H_{12}O_6$ 228 0633)

Enantioselective Generation of Kjellmanianone. A. Via Oxaziridines 4 and 5. To a 35% mineral oil suspension of potassium hydride (154 0 mg, 1 34 mmol) under nitrogen were added 6 mL of tetrahydrofuran and a solution of 32 8 mg (0 19 mmol) of (±)-2 in 2 mL of tetrahydrofuran. After stirring at room temperature for 1 h, the reaction mixture was cooled to -78 °C and stirring was continued for 1 h Then 91 5 mg (0 22 mmol) of 2-[(-)-camphor-10-ylsulfonyl]-3-(2-chloro-5-nitrophenyl)oxaziridine (5) was added After 1 min the reaction was quenched at -78 °C by the addition of 0 5 mL of 2-propanol followed by water The reaction mixture was extracted with methylene chloride, the organic layer was washed with brine, and the saline solution was reextracted with ethyl acetate The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo Preparative thin layer chromatography, using ether as eluant (0 5 mm plate, two developments), gave 28 5 mg (42%) of (+)-kjellmanianone (33% ee)

Enantioselective Generation of Kjellmanianone. B. Via Oxaziridines 6 and 7 A solution of 86 0 mg (0 5 mmol) of (±)-2 in 10 mL of tetrahydrofuran was cooled to 0 °C and 0 6 mmol of the appropriate base (Table 1) was added via syringe. The mixture was stirred for 0 5 h, cooled to -78 °C, and treated with a solution of 137 mg (0 6 mmol) of oxaziridine 6 in 5 mL of THF When the addition was complete, the cold bath was removed The reaction then was stirred for 2 h and quenched with 5 mL of 0 2 N HCl The mixture was next diluted with 5 mL of water and extracted with two 15-mL portions of methylene chloride The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo Preparative TLC, using 20% ether in methylene chloride as eluant, gave pure 1. Yields are summarized in Table 1

Optical rotations measured for (+)-kjellmanianone 39% ee, $[\alpha]_D$ +40 0° (c 0 5, $CHCl_3$), 39% ee, $[\alpha]_D$ +37 9° (c 1 4, $CHCl_3$); 40% ee, $[\alpha]_D$ +38.4° (c 1 7, $CHCl_3$); 57% ee, $[\alpha]_D$ +57 0° (c 8 5, $CHCl_3$), 68 5% ee, $[\alpha]_D$ + 67 9° (c 3 4, $CHCl_3$) Mean optical rotation for 48 7% average ee. $[\alpha]_D$ +48 2° Calculated specific rotation for enantiomerically pure (+)-kjellmanianone $[\alpha]_D$ +99 1°

Determination of Enantiomeric Purity of Kjellmanianone. In an NMR tube, ca 10 mg of kjellmanianone was dissolved in 0 5 mL of $CDCl_3$ containing TMS A series of 250-MHz ^1H NMR spectra were acquired after successive additions of tris[3-(heptafluoropropylhydroxy-methlene)-(+)-camphorato]europium (III) [Eu(hfc)$_3$] in 5-mg portions In the presence of ca 0.4 equiv of Eu(hfc)$_3$, the enantiotopic methyl groups of the vinylogous methyl ester were separated by 0 2-0 25 ppm The shift reagent experiment was first performed on a sample of racemic 1 to determine absorption positions

Kjellmanianone *p*-Bromobenzoate. A solution of 34 0 mg (0 18 mmol) of (±)-kjellmanianone in 3 mL of methylene chloride was treated with 141 μL (1.02 mmol) of triethylamine, 13 mg of 4-dimethylaminopyridine, and 107 8 mg (0.49 mmol) of *p*-bromobenzoyl chloride This mixture was heated at 30 °C for 25 5 h The mixture then was poured into ether and washed with 10% Na_2CO_3, 10% HCl, and brine The organic layer was dried over $MgSO_4$ and the ether was removed in vacuo Purification by thin layer chromatography, using ether as eluant, gave 55 5 mg (82%) of kjellmanianone *p*-bromobenzoate as a pale yellow semisolid NMR ($CDCl_3$, 250 MHz) δ 2 85 (dd, J = 18, 1 Hz, 1 H), 3.73 (dd, J = 18, 1 Hz, 1 H), 3 75 (s, 3 H), 5 38 (dd, J_1 = J_2 = 1 Hz, 1 H), 7.57 (d, J = 8 Hz, 2 H), 7 92 (d, J = 8 Hz, 2 H), high resolution mass spectrum (EI) m/z 369 9894 (M^+, calcd for $C_{15}H_{13}O_6Br$ 370 0712)

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