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AN ASYMMETRIC SYNTHESIS OF (+)-KJELLMANIANONE

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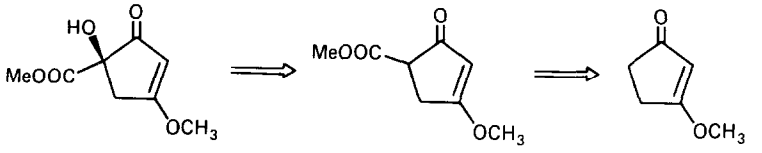
Summary: Racemic and asymmetric syntheses of kjellmanianone, a novel cyclopentenoid antibiotic, are described.

(+)-Kjellmanianone (1), member of the cyclopentanoid class of antibiotics, was isolated in 1980 by Nakayama et al.[2] from the brown algae, Sargassum kjellmanianum and shown to display moderate activity against such gram positive bacteria as E. coli K12 and Bacillus subtilis var. niger. The structure, initially derived via chemical and spectroscopic methods, was confirmed by single crystal X-ray analysis, the latter providing in addition the absolute configuration.[2] In continuing our interest in this class of antibiotics, which has recently lead to the total synthesis of (±)-methylenomycin,[3] (±)-epimethylenomycin A,[3] (±)-desepoxy-4,5-didehydromethylenomycin A,[4] (±)-sarkomycin,[5] the (±)-pentomycins (I-III),[6] their epimers,[7] dehydropentenomycin[6] and (±)-xanthocidin,[8] we wish to record here the total synthesis of kjellmanianone (1) in racemic and in both chiral forms. In addition, we have verified the absolute configuration of (+)-kjellmanianone to be R through application of the exciton chirality method developed by Nakanishi.[9]

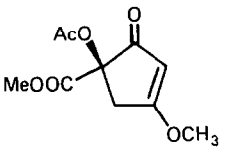
From the retrosynthetic perspective (eq 1), hydroxylation of the prochiral enol or enolate derived from 2 with a chiral hydroxylating agent was anticipated to permit asymmetric induction as the penultimate synthetic transformation. Ideal for the requisite oxidation appeared to be the oxaziridine reagents recently introduced by Davis et al.[10] and subsequently demonstrated in chiral form to be excellent asymmetric oxidation reagents.[11]



(1) (2) (3)

Kjellmanianone

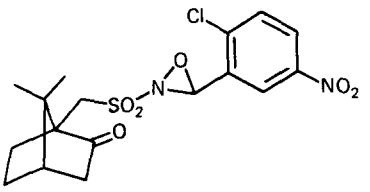
We initiated work directed at a racemic synthesis of kjellmanianone. Towards this end, acylation of 3[12] (2 eq LDA, 1 eq N-carbomethoxyimidazole, -78°C)[13] gave 2[14] in 51% yield[15] as a white crystalline solid (mp 53.5-55°C). Hydroxylation was then effected by generation of the anion of 2 with 4 eq. of KH, followed by addition of 1.2 eq of m-CPBA at room temperature to give after chromatography a 53% yield of racemic kjellmanianone (1)[14] as a crystalline solid (mp 113-115°C). That indeed kjellmanianone was in hand was demonstrated by careful comparison of the spectral data (IR, UV, ^{1}H and ^{13}C NMR, and MS) to that reported for natural (+)-kjellmanianone.[2] Furthermore, acylation of synthetic kjellmanianone ($Ac_2O/Et_3N/DMAP/CH_2Cl_2$/rt,19 h) afforded acetate 4[14] in 52% yield[15] identical in all respects to the acetate derived from natural kjellmanianone (IR, NMR).[2]



(4)

Kjellmanianone acetate

Turning next to the asymmetric introduction of the hydroxyl group, treatment of the enolate derived from 2 (4 eq KH/THF) with 1.0 equivalent of (-)-E-oxaziridine (5)[16] at -78°C for 1 min, followed by standard extractive workup (Et_2O) and careful chromatographic purification [combination of silica gel flash LC (EtOAc) and LC (Et_2O)] resulted in a 42% yield of kjellmanianone 1,[12] having a positive optical rotation, $[\alpha]_D$ + 20.4 [c=5.40, $CHCl_3$], indicating that asymmetric introduction of the hydroxyl group had indeed been accomplished. The enantiomeric excess, which proved to be 33%, was determined via chiral NMR shift reagent experiments.[17]



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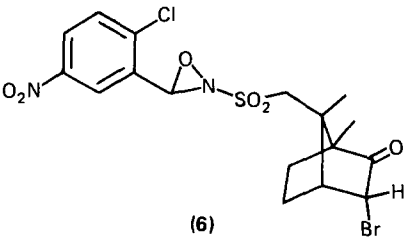


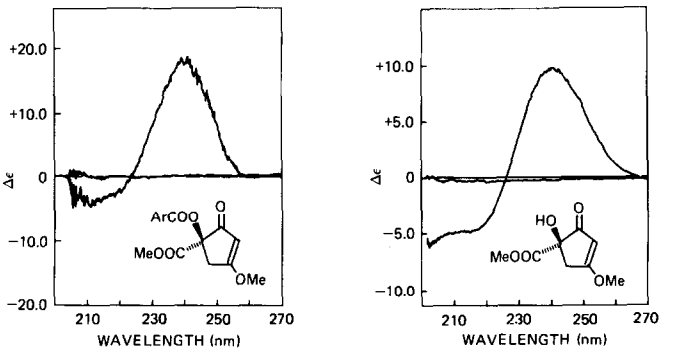
(6)

In a similar fashion treatment of the enolate derived from 2 with (+)-E-oxaziridine (5)[16] (1 eq) lead to a 44% yield of kjellmanianone (1) in this case having a negative optical rotation: $[\alpha]_D$-23.0 (c=0.46, $CHCl_3$); the enantiomeric excess was 36.5%.[17]

To explore in some detail the asymmetric induction process, in particularly the necessity for the proximate relationship of the camphor carbonyl and the oxaziridine ring, we examined (-)-and (+)-E-oxaziridines 6. Interestingly, these reagents proved to be considerably less efficient than 5; in particular (-)-E-oxaziridine 6[16] gave (+)-kjellmanianone in 8% enantiomeric excess while (+)-E-oxaziridine 6[15] gave (-)-kjellmanianone in 12% enantiomeric excess. These results suggest that the proximity of the carbonyl group to the active site in 5 and 6 is in fact of considerable importance in establishing the transition state geometry for hydroxyl delivery.

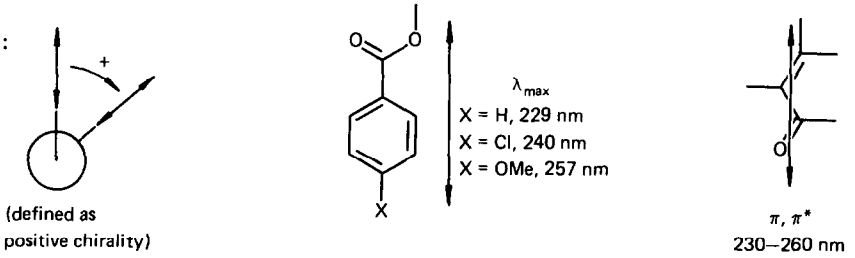
Finally, in view of the quite low specific rotation, $[\alpha]_D$ + 1.5°[c = 1.80 $CHCl_3$], observed in natural (+)-kjellmanianone (ca. 1.2% enantiomeric excess), in conjunction with the uncertainty often associated with the determination of absolute configuration via the anomalous dispersion of oxygen atoms (i.e. Bijvoet method), and the availability of synthetic material in both enantiomeric forms, we have reexamined the question of absolute configuration of (+)-kjellmanianone (1). The exciton chirality method developed by Nakanishi et al. appeared to be the procedure of choice. Towards this end, the p-bromobenzoates of both enantiomers of 1 were prepared from synthetic material. The CD spectra of (+)-kjellmanianone p-bromobenzoate along with that of (+)-kjellmanianone (1) are illustrated in Figure I.

Figure I:



In the exciton chirality method the relative twist or handedness between the electric transition moment of any two chromophores (cf. enone and benzoate) gives rise to a split Cotton effect assuming that the chromophores are both close in space and of similar energy. Positive chirality as well as the direction of the enone and benzoate transition moments are defined in Figure II. Consistent

Figure II:



with the depicted R absolute configuration, (+)-kjellmanianone p-bromobenzoate displays a positive Cotton effect. Of interest is the fact that (+)-kjellmanianone (1) also displays a similar, albeit less intense, positive Cotton effect. Conversely, (-)-kjellmanianone p-bromobenzoate and (-)-kjellmanianone (1) display negative Cotton effects.

In summary, the racemic and asymmetric synthesis of kjellmanianone (1) has been achieved. Chirality was induced via application of asymmetric oxaziridine oxidation reagents. Finally, the absolute configuration of 1, as defined by Nakayama et al., has been confirmed.

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14. a) The structure assigned to each new compound was in accord with its infrared (CCl_4 or $CHCl_3$) and 250 MHz NMR spectra ($CDCl_3$); b) Analytical samples of all new compounds, obtained by chromatography (LC or TLC), gave satisfactory C and H combustion analysis within 0.4% and appropriate parent ion identification by high resolution mass spectroscopy.

15. All yields recorded here were based on isolated material after-purification via chromatography (TLC or LC on silica gel).

16. The optical purity of oxaziridines 5 and 6 in these experiments was greater than 93%.

17. The optical purity of kjellmanianone obtained from 2 and (-) 5 was determined by a series of 250 MHz ^1H nmr spectra obtained at increasing concentrations of the chiral shift reagent, tris[3-heptafluoropropylhydroxymethylene)-d-camphorato]-europium (III) derivative-[$Eu(hfc)_3$]. At a concentration of .06 eq of $Eu(hfc)_3$ the enantiotopic CH_2 doublet of the ring protons of 1 separate by .02 ppm. Likewise at a concentration of 0.4 eq of $Eu(hfc)_3$ the enantiotopic CH_3 singlets of the exomethyl ester separate by 0.23 ppm. Integration of expanded plots gave an isomeric ratio of 2:1; the enantiomeric excess ratio therefore was 33%. In a similar fashion the optical purity of the product derived from 2 and (+)-5- was determined. More specifically, at a concentration of .09 eq. of $Eu(hfc)_3$ the enantiotopic CH_2 doublets separate by .03 ppm, while at a concentration of .30 eq of $Eu(hfc)_3$ the enantiotopic CH_3 singlets separate by .20 ppm. Integration of expanded plots gave an isomer ratio of 2.15:1; therefore the enantiomeric excess was 36.5%.

18. After completion of this manuscript, Irie et al. reported the synthesis of racemic kjellmanianone along similar lines; see H. Irie, J. Katakawa, M. Tomita and Y. Mizuno, Chem. Letters, 537 (1981).

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