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Stereospecific Total Synthesis of (-)-Kjellmanianone and a Revision of its Absolute Configuration

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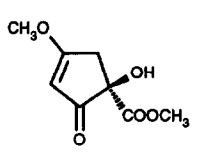
Abstract: *A fully stereocontrolled total synthesis of naturally occurring kjellmanianone 1 has been accomplished starting from tricyclo[5.2.1.0^{2,6}]decadienone 2-carboxylic ester 2. The key steps in this approach to 1 include Barton's halodecarboxylation methodology, nucleophilic epoxidation to introduce the hydroxy group and ultimately, a cycloreversion by using flash vacuum thermolysis. The R configuration of synthetic (-)-kjellmanianone was unequivocally established by an X-ray diffraction analysis of its precursor 6, implying that the previously assigned absolute configuration of (+)-kjellmanianone needs to be revised.*

Kjellmanianone 1, a highly oxygenated cyclopentenoid, was isolated by Nakayama *et al.*[1] in 1980 from the marine brown algae *sargassum kjellmanianum* and shown to possess moderate activity against gram positive bacteria, such as *E.Coli* K12 and *Bacillus subtilis var niger*. The structure of kjellmanianone was established by single crystal X-ray analysis. Using the Bijvoet method its absolute configuration was established as R. The optical rotation for the natural product was very low, *viz* $[\alpha]_D$= +1.6° (c 1.8, $CHCl_3$). Soon after its isolation, an enantioselective synthesis of (+)-kjellmanianone 1 was achieved by Smith *et al.*[2] by asymmetric hydroxylation of 3-methoxy-5-methoxycarbonyl-cyclopent-2-enone using enantiopure N-sulfonyloxaziridines in ee's up to 68.5%. Although no enantiopure (+)-kjellmanianone was obtained, its optical rotation was calculated to be $[\alpha]_D$= ~100°. By applying the exciton chirality method developed by Nakanishi[3], the absolute configuration of (+)-kjellmanianone was again established as R.



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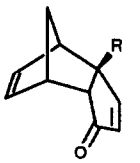
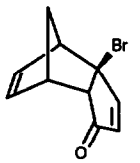


2 R= CO_2Et
3 R= CO_2H



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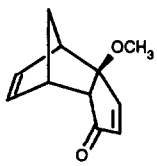

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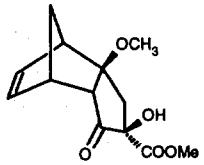

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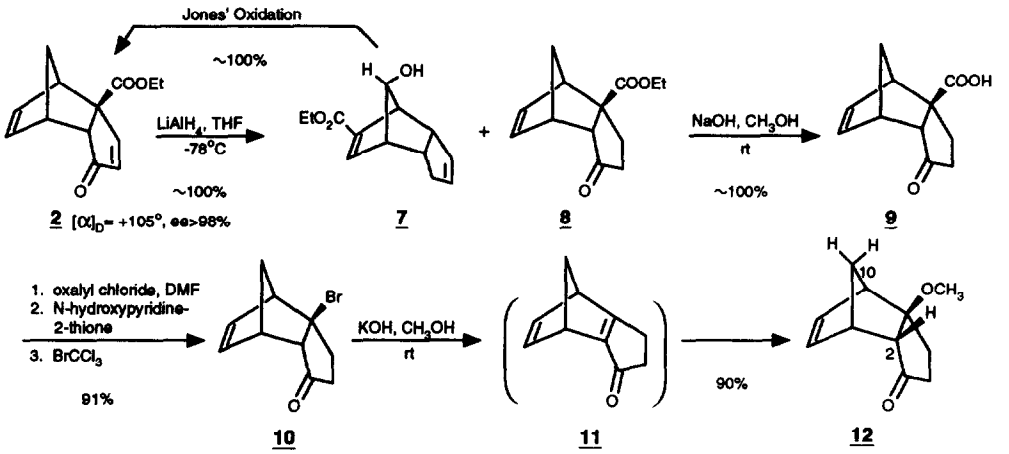
As part of our studies directed to the exploration of the tricyclo[5.2.1.0^{2,6}]decadienone system as a chiron for naturally occurring cyclopentenoids[4], we designed a stereo- and enantioselective route to enantiopure kjellmanianone 1 starting from readily available homochiral ethyl tricyclodecadienone 2-carboxylate 2[5].

The essential feature of our route to kjellmanianone is based on a recent observation[6] that tricyclodecadienone carboxylic acid 3 readily undergoes bromodecarboxylation to give 4 using Barton's radical halodecarboxylation method[7]. This bridgehead bromide 4 then can be converted into the corresponding *exo*-substituted methoxy compound 5 by treatment with potassium hydroxide in methanol[6].

It was originally planned to reduce the enone olefinic bond and to perform a stereoselective methoxycarbonylation and hydroxylation to obtain kjellmanianone precursor **6**.

Unfortunately, regioselective reduction of the enone olefinic bond in methoxy enone **5** appeared to be rather problematic. Both with lithium aluminum hydride in tetrahydrofuran at -78 °C and lithium in ammonia predominant 1,2-reduction was observed and the desired 1,4-reduction product could only be obtained in 25% yield at best. Much better 1,4-regioselectivity was observed for the hydride reduction of the enone moiety in tricyclic ester **2**. When enantiopure tricyclic ester **2** ($[\alpha]_D$= +105°, ee>98%) was treated with lithium aluminum hydride in tetrahydrofuran at -78 °C, a mixture of bridge alcohol **7** and desired keto-ester **8** was obtained in almost quantitative yield in a 3:7 ratio (Scheme 1). Separation of this mixture

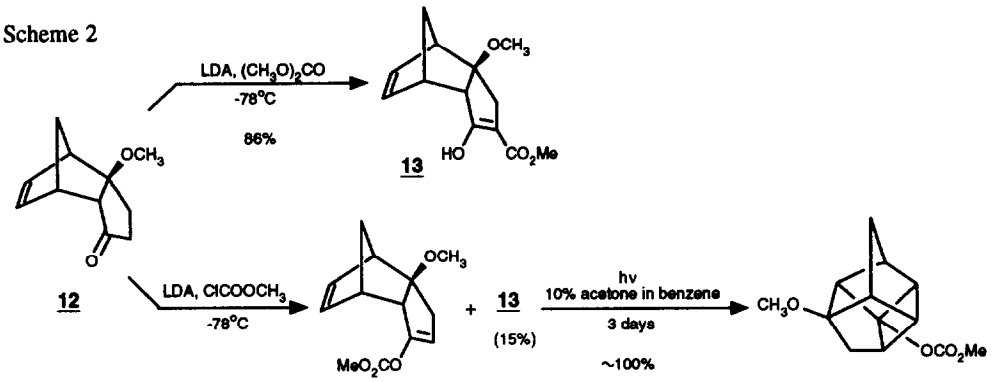
Scheme 1



by flash chromatography gave pure keto-ester **8** in 70% yield[8]. Minor product **7**, which is formed by initial stereoselective 1,2-reduction of **2** followed by Cope rearrangement[9], could be quantitatively reconverted into **2** by Jones' oxidation. Hydrolysis of ester **8** afforded carboxylic acid **9** in almost quantitative yield. Bromodecarboxylation of **9** was carried out under the same conditions as used for the transformation of carboxylic acid **3** into **4**, as described previously[6]. Conversion of **9** into the corresponding acid chloride followed by treatment with the sodium salt of N-hydroxypyridine-2-thione to give N-acyloxypyridine 2-*thiono* ester which was immediately exposed to bromotrichloromethane at reflux temperature. Bridgehead bromide **10** was thus obtained in an excellent overall yield of 91%. Treatment of this bromide **10** with potassium hydroxide in methanol (20% solution) gave tricyclic methoxy compound **12** in 90% yield. In analogy with the methoxylation of bromide **4**, it is assumed that cyclopentanone annulated norbornadiene **11** is intermediate in the conversion of **10** into **12**. In principle, the addition of methanol to the central olefinic bond in **11** can give either *endo*- or *exo*-methoxy substituted tricyclodecenone. A 2-D ^{1}HNMR analysis of **12** and especially the X-ray diffraction analysis of **6** *(vide infra)* unequivocally showed that addition of methanol to **11** proceeds exclusively *syn* to the methylene bridge to give *exo*-6-methoxy-*endo*-tricyclodecenone **12** as the sole product. A strong NOE-effect for one of methylene bridge C_{10}-protons was observed when the signal for the C_2-proton in **12** was irradiated. Such a magnetic interaction is only conceivable for *endo*-structure **12**.

Methoxycarbonylation of methoxy ketone **12** was conveniently accomplished with lithium diisopropyl amide and dimethyl carbonate (Scheme 2). The corresponding β-keto ester **13**, which appeared to be

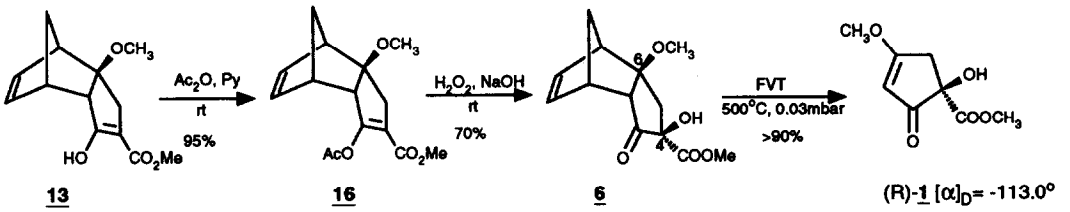
Scheme 2



completely enolized, was obtained in 86% yield (based on consumed **12**). When methyl chloroformate was used instead of dimethyl carbonate enol carbonate **14** was isolated in 60% yield along with only 15% of **13**. This enol carbonate could be quantitatively converted into 1,3-bishomocubane ester **15** by photolysis in benzene containing 10% of acetone, which provides additional evidence for the *endo*-configuration of the 6-methoxytricyclodecadecenone **12**.

A general method to hydroxylate β-ketoesters involves epoxidation of its enolate with *meta*-chloroperbenzoic acid followed by hydrolysis[10]. However, since the strained norbornene double bond in **13** may effectively compete in this epoxidation reaction, nucleophilic epoxidation of enol acetate **16** was applied (Scheme 3). Acetate **16** was obtained in nearly quantitative yield by acylation of enolate **13** with

Scheme 3



acetic anhydride and pyridine. Treatment of **16** with alkaline hydrogen peroxide proceeded smoothly to give the desired α-hydroxy-β-keto ester **6** as a single compound in 70% yield. This result indicates that alkaline hydroxylation of enolates derived from β-keto-esters may be a good alternative in those cases for which *m*-CPBA cannot be used.

Although epoxidation of enol acetate **16** is expected to occur exclusively from the sterically less hindered *exo*-face of the molecule to produce *exo*-hydroxy-ester **6**, any ambiguity about the resulting structure was excluded by an X-ray diffraction analysis of the product obtained. Indeed the anticipated structure **6** was fully confirmed[11].

In the final step, kjellmanianone **1** was produced in almost quantitative yield by thermal cycloreversion

of **6** applying the technique of flash vacuum thermolysis at 500 °C and 0.03 mbar. Crystallization from diisopropyl ether gave enantiopure (-)-kjellmanianone as a crystalline compound, $[\alpha]_D$= -113.0° (c 1.15, $CHCl_3$), m.p. 157-158 °C. The spectral data of **1** are in full agreement with its structure and identical to those reported[1,2]. The optical rotation observed for our enantiopure kjellmanianone is considerably higher than that calculated by Smith *et al.*[2] based on their asymmetric synthesis of (+)-kjellmanianone (ee 68.5%, $[\alpha]_D$= +67.9°).

Based on the known absolute configuration of starting tricyclic ester (+)-**2**[5], the absolute configuration of **6** is R at C_4 as shown in Scheme 3. As no configurational change is conceivable during the cycloreversion reaction, the absolute structure of (-)-kjellmanianone synthesized above also has the R-configuration. Consequently, the R-configuration of (+)-kjellmanianone as established by Nakayama and Smith using X-ray diffraction and the exciton chirality method, respectively, must be revised to S. Although there is no doubt about the correctness of the X-ray structure analysis of natural kjellmanianone, a reliable determination of its absolute configuration was in fact impossible as it is almost a racemic mixture (ee ≤ 1.5%). At that time the racemic nature of natural kjellmanianone was probably not realized. Our result also shows that the exciton chirality method as used by Smith *et al.*[2] should be considered with great care, especially for those compounds for which no precedents are available. In this case, the direction of chirality, positive or negative, which is crucial for the structure determination, is not unambiguous.

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