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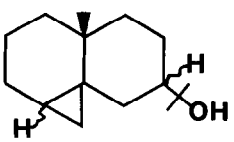
STEREOSPECIFIC TOTAL SYNTHESIS OF CYCLOEUDESMOL

Edward Y. Chen

Pharmaceutical Research and Development,
Sandoz, Inc., East Hanover, New Jersey 07936

SUMMARY: A stereospecific sequence from the allylic alcohol 3 to the new antibiotic, cycloeudesmol 2, in 9 steps (21.7% overall yield) is described. The key stereospecific construction of the bicyclo [3.1.0] hexane system was conveniently achieved by an olefin-ketocarbene cyclization reaction.

In 1974, Fenical and Sims reported the isolation of a sesquiterpene alcohol, Cycloeudesmol, from the marine algae Chondria oppositiclada Dawson[1]. Cycloeudesmol was shown to be strongly antibiotic toward Staphylococcus aureus, Salmonella cholerasins, Mycobacterium smegmatis, and Candida albicans[2]. Acid catalyzed conversion to (+)-δ-selinene, together with analytical and spectral data, led to formulation of the natural product as one of the four diastereoisomers of 1[1]. Recently, the proposed structure for cycloeudesmol, 1, was proven to be incorrect since the total syntheses of the 4 possible stereoisomers of 1 have been reported[3,4,5].



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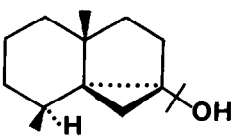

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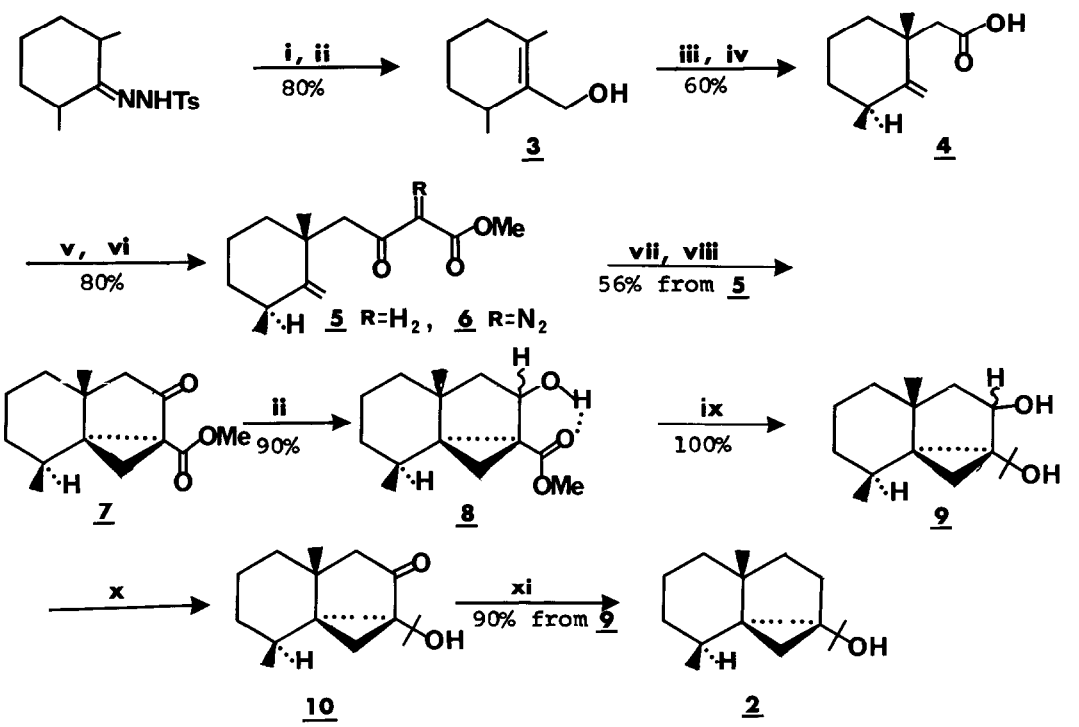
In 1980, Kurosawa, et al. isolated a sesquiterpene, Isocycloeudesmol 2 from the marine red algae Laurencia nipponia Yamada[6]. The absolute configuration of 2 was also determined by an x-ray crystallographic study[7]. Meanwhile, the careful comparison of IR and NMR spectra and the optical rotation established that isocycloeudesmol 2 was identical with cycloeudesmol.

The synthesis (Scheme I) started with the hydrazone of 2,6-dimethylcyclohexanone, which was converted to the allylic alcohol 3 in 80% yield by the

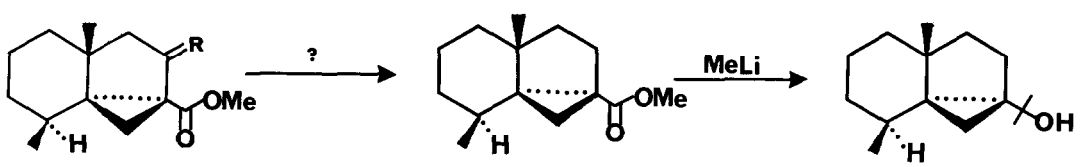
Bamford-Stevens reaction[8] (4 eq. n-BuLi, THF, TMEDA), followed by DMF trapping of the vinyl anion and $NaBH_4$ reduction. Claisen rearrangement of 3 in triethyl orthoacetate and catalytic amount of propanoic acid at 160-170°C, followed by hydrolysis (NaOH/MeOH) of the ester product gave a 60% yield of the olefinic acid 4, mp 104-105°C. The stereochemical assignment of 4 rests upon its 200MH_z NMR spectrum, which revealed the equatorial methine proton as a slightly broadened singlet (δ2.30, $^W/2$ =7Hz), reflecting only axial-equatorial and di-equatorial

Scheme I[9]



Reagents: i, 4 eq. n-BuLi/THF,-30°C—>0°C,DMF; ii, $NaBH_4$, MeOH, iii, excess $CH_3C(OEt)_3$,EtCOOH, 100°—>160°C; IV, NaOH, MeOH, 60°C, 2 hrs; V, 2.5 eq. MeLi, Et_2O; VI, NaH, $CO(OMe)_2$, diglyme, Δ; VII, TsN_3. Et_3N, MeCN, RT; VIII, $CuSO_4$, cyclohexane, reflux, 8 hrs; IX, 4 eq. MeLi, Et_2O; X, Jones reagent; XI, NH_2NH_2, KOH, ethylene glycol, reflux, 10 hrs.

couplings to the adjacent methylene protons. The α-methylene protons appeared as 2 doublets at δ 2.33 and δ 2.60 J=12.6Hz. The ^{13}C-NMR spectrum did not show the presence of the corresponding epimer which could have been produced in a minor amount and removed during recrystallization.[10] With correct stereochemistry in the A ring now assured, the principal remaining problem was to stereospecifically construct the bicyclo[3.1.0]hexane moiety. The acid 4 was converted in 67% yield to the α-ketoester 5 by a 2-step sequence. Thus, reaction of acid 4 with 2.5 eq. of methyllithium in ether gave a colorless, oily methyl ketone which was directly converted to 5 by selective methoxycarboxylation [NaH, $CO(OCH_3)_2$, diglyme][11]. It should be noted that an initial attempted reaction of the acid chloride of 4 with Meldrum's acid[12] followed by methanolysis to give 5 did not produce any detectable amount of 5. Diazoester 6 [IR: 2133, 1723, 1652 cm^{-1}] was prepared under standard conditions (TsN_3, Et_3N, RT) followed by washing with aq. NaOH solution. The stage was now set for closure of the bicyclic system, a key step of this synthetic strategy to cycloeudesmol. The crude 6 was subjected to thermolysis in refluxing cyclohexane or benzene using anhydrous cupric sulfate as catalyst to afford the tricyclic ketoester 7 mp 93-94°C, in 54% yield from 5 after recrystalization from Et_2O/hexane. The stereochemical assignment of 7 was mainly based on a previous work[3a] where a similar ketocarbene cyclization[13] catalized by Cu(II) stereospecifically gave a bicyclo[4.1.0]heptane system. Dreiding models indicate that the carbenic carbon generated from 6 can only attack the double bond function from the α-face, leading to a β-cyclopropane product. With the correct stereochemistry of the 3 chiral centers in hand, the remaining problems of removing the keto function and converting the ester group to a dimethyl carbinol were relatively simple. $NaBH_4$ reduction of 7 gave only one isomer 8 as evident by a sharp doublet (δ 4.37, J=7Hz, 1H) in its NMR spectrum. The IR spectrum shows an intramolecular hydrogen bonding (3498, 1691 cm^{-1}). However, no attempt was made in assigning the stereochemistry of the hydroxy group. Several attempts at reducing the keto function of 7 directly to the corresponding methylene unit did not produce any useful results. Reduction of the toluene-sulfonyl hydrazone 7a (mp 164-167°) with catecholborane according to Kabalka's procedure[14] gave less than 7% of the desired 11 which could be easily



7. R = O
7a. R = N-NH-Ts

11

2

converted to the final product by simple treatment with excess methyllithium reagent. Wolff-Kishner reduction of 7 also gave a complex mixture. The ester group of 8 was converted in quantitative yield with an excess of MeLi in ether to the dimethyl carbinol 9, mp 83-85°C, [δ 0.35 (d, J=5Hz, 1H), δ 0.43 (d, J=5Hz, 1H), δ 4.36 (d, J=4Hz, 1H)]. The diol 9 was then oxidized with 1.1 eq. of Jones reagent to the keto-alcohol 10, which was, without any purification, converted under Wolff-Kishner reduction conditions (6 eq. NH_2NH_2, KOH, reflux, 12 hrs) to the desired crystalline cycloeudesmol 2 in 90% yield from 9. Synthetic 2, which has a considerably higher melting point,[15] had IR, ^{1}H-NMR, ^{13}C-NMR and MS identical to those of the natural product.

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References and Notes

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9. The structure assigned to each new compound was in accord with its IR, ^{1}H-NMR (90 and/or 200 MHz), ^{13}C-NMR spectra as well as MS and acceptable elemental analysis. All yields recorded here are based upon purified material. Melting points and boiling points are uncorrected.
10. It is easier for the vinyl ether group to approach the double bond from the less hinder side leading to 4 as the major product. However, the product ratio was not determined.
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15. Natural cycloeudesmol had mp 99.5-100.5°C (hexane-isopropyl ether)[4] and mp 93-94°C (hexane)[1]. Synthetic cycloeudesmol had mp 108-109°C (hexane-ether).

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