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ENANTIOSPECIFIC SYNTHESIS OF THE TRICYCLIC NUCLEUS OF ACETOXYCRENULIDE BY CLAISEN RING EXPANSION

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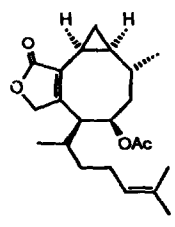
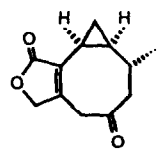
Abstract: The known *R* lactone 4 has been transformed in 9 steps into optically pure 2, a molecule possessing the ring system characteristic of the crenulide diterpenes. In the key step, chirality transfer is accomplished via a *Z*-selective Claisen ring expansion.

Detailed studies by Fenical[2] and by Sims[3] have revealed that small brown seaweeds (Phaeophyta) of the family Dictyotacea produce the unique cyclopropane-containing diterpene known as acetoxycrenulide (1).[4] From the chemical viewpoint, its bicyclo[6.1.0]-nonane framework with acetoxy and α,β-unsaturated lactone appendages is unprecedented.[5] The role of this major algal metabolite appears to be that of a chemical defense agent. At low concentrations, this substance severely debilitates herbivorous reef-dwelling fish and is often acutely toxic to them. As a consequence, the darkly colored algae are given relief from potential predation and survive in the most competitive tropical and subtropical habitats known.

To our knowledge, acetoxycrenulide has not been pharmacologically evaluated in terrestrial animal or man. Nor is its absolute configuration known. Our intent is to establish the latter while simultaneously allowing for the substance to be made available in reasonable quantity. As a first step in this direction, we have carried out synthetic studies that have culminated in the production of 2. The sequence takes noteworthy advantage of the Claisen ring expansion[6,7] to achieve concise construction of the eight-membered core.



1

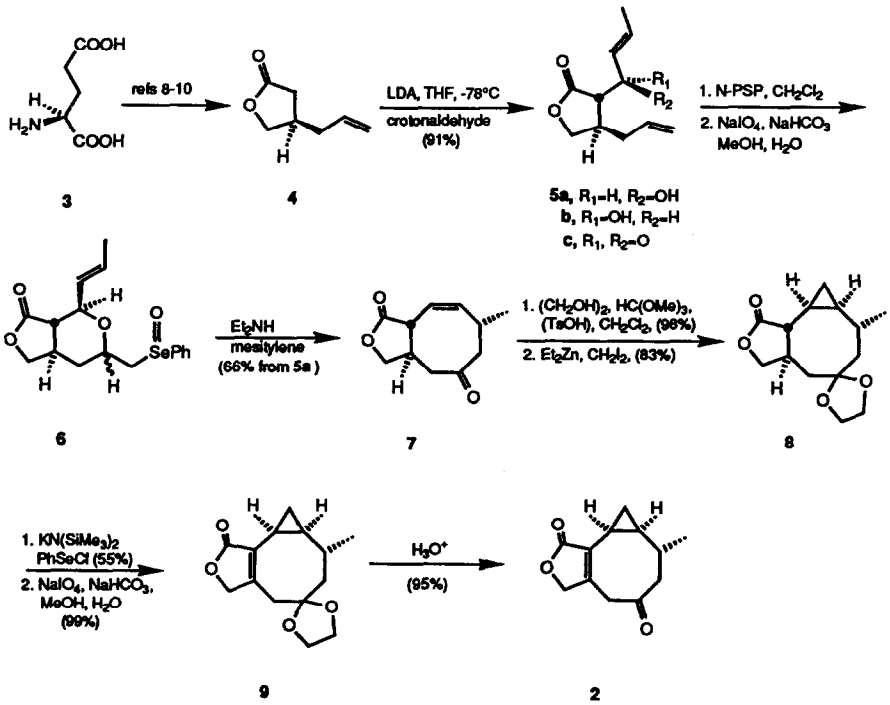


2

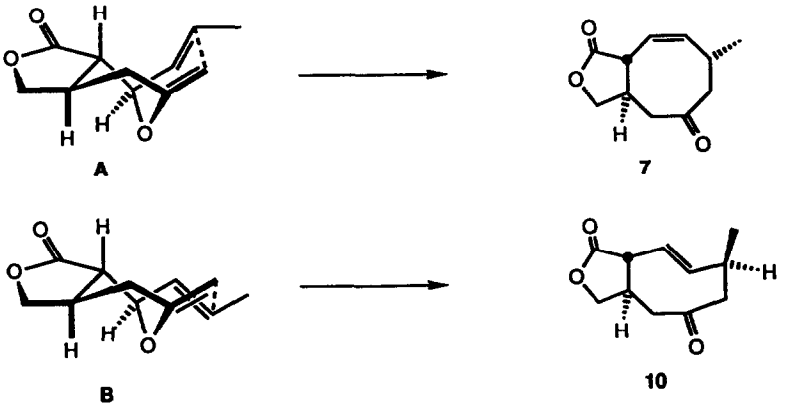
Optically pure 4, $[\alpha]_D^{20}$ +20.8° (*c* 2.4, $CHCl_3$), was prepared from *L*-glutamic acid (3)[8] via (*R*)-(-)-γ-trityloxymethyl-γ-butyrolactone[9] according to precedent.[10] Condensation of

the lithium enolate of 4 with crotonaldehyde in cold tetrahydrofuran proceeded to give in a 1:1 ratio the diastereomeric alcohols 5a and 5b, which were readily separated by chromatograpy (see Scheme I). Their independent conversion to keto lactone 5c established the trans exclusivety of the aldol process while making available a pathway for conversion of 5b into the utilitarian less polar epimer 5a. The configurational assignments shown were corroborated by X-ray crystallographic studies on later intermediates.[12]

Scheme I



The cyclization of 5a to 6 could be effected by initial reaction with N-(phenylseleno)phthalimide[13] in dichloromethane. Following transient formation of the phenylselenonium ion, intramolecular attack by the neighboring hydroxyl generated the tetrahydropyran ring[14] wile retaining stereochemistry at the three original chiral centers. Simultaneously, the stage was set for introduction of the exocyclic vinyl ether double bond by selenoxide elimination. The relatively stable 6 was heated in mesitylene containing diethylamine to effect sequential loss of PhSeOH and Claisen rearrangement.[15] Since the latter sigmatropic process is usually *Z*-selective in its ring expansion mode,[7] a kinetic bias for vinyl ether conformer A was anticipated because this transition state pathway is uniquely capable of leading to the cis double bond isomer 7. The stereoselectivity for α orientation of the secondary methyl also follows from adoption of the chairlike topography given by A. Although 7, $[\alpha]_D^{20}$ +7.1° (*c* 0.85, $CHCl_3$), was produced efficiently (66% overall from



5a), care had to be exercised to avoid migration of the double bond into conjugation with the lactone carbonyl.[16]

Protection of the ketone carbonyl in 7 proceeded in virtual quantitative yield. Exposure of the ketal to diethylzinc and diiodomethane according to Sawada and Inoue[17] resulted in smooth cyclopropanation from the less hindered π surface to give 8, $[\alpha]_D^{20}$ -50.5° (c 0.39, $CHCl_3$). With all of the carbon atoms necessary for the northern sector properly set, the time had arrived to remove the two centers originally utilized for stereoinduction and to introduce the intra-ring double bond. To this end, the potassium enolate of 8 was allowed to react with phenylselenenyl chloride at -78 °C in 1,2-dimethoxyethane and the resulting cis α-phenylseleno lactone (55%) was quantitatively converted into 9, $[\alpha]_D^{20}$ +105.7° (c 0.35, $CHCl_3$), by periodate oxidation.

Significantly for our purposes, 9 underwent efficient acid hydrolysis to give 2, $[\alpha]_D^{20}$ +165.3° (c 0.95, $CHCl_3$), without any evidence of double bond isomerization. To demonstrate beyond doubt that the Simmons-Smith cyclopropanation had indeed proceeded under strict steric control, we completed a single-crystal X-ray analysis (see Figure).[12] The study proved not only confirmatory of the stereochemical assignments, but signaled as well that neither of the potentially enolizable *allylic* α-carbonyl protons is properly stereoaligned for ab-

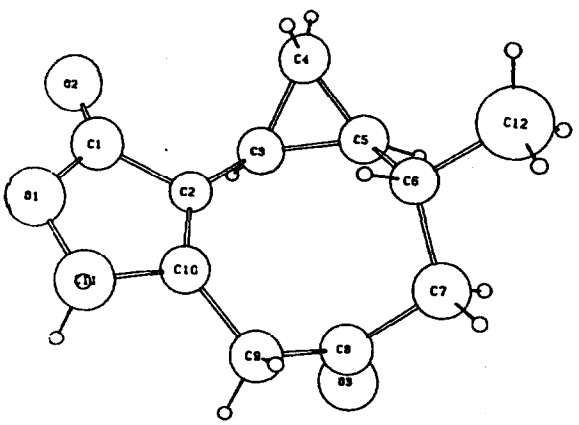


Figure. Computer-generated perspective drawing of the final X-ray model of 2.

straction by a base. It is likely that the solution structure of 2 parallels that seen in the solid state, with rigic constraints on its dynamic behavior, since attempts to achieve clean enolization of this keto lactone have not been fruitful.

These anticipated findings necessitate that the C_8 sidechain in 1 be present from the outset of this 9-step synthesis. Our intention is to report on such an approach in the near future.

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