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TOTAL SYNTHESIS OF (+)-GRINDELIC ACID BY STEREOCONTROLLED OXONIUM ION ACTIVATED PINACOL RING EXPANSION. CHEMICAL PROOF OF THE ABSOLUTE CONFIGURATION OF ALL GRINDELANE DITERPENES

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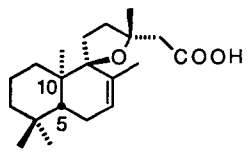
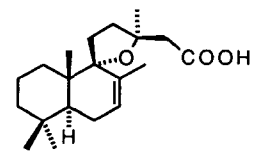
Abstract: (+)-Grindelic acid, synthesized enantioselectively from the levorotatory Wieland-Miescher ketone and (-)-linalool and necessarily formulated as **1a**, is shown to be antipodal to the major diterpenoid of *Grindelia* species.

The isolation in 1961 of grindelic acid (**1**) by Mangoni and co-workers[2] has proven to be a landmark event, since it ushered in extensive exploration of the metabolites produced by the very large genus *Grindelia*. This activitiy, which continues to the present day,[3] has defined many structurally unusual diterpenoids, the great majority of which are phytochemically related to **1**. Despite the central role attributed to grindelic acid, its absolute configuration appears not to have been deduced to the satisfaction of all. In 1986, **1** was transformed by Jakupovic, *et al* into the 6-oxo-7,8-dihydro derivative, which was found to exhibit a positive Cotton effect. On this basis, structure **1a** was advanced with the suggestion that all of its many derivatives be likewise



1a

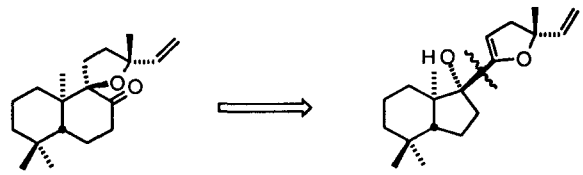


1b

formulated.[4] This conclusion was contrary to earlier spectroscopic studies by several groups on closely related compounds,[5] to the corroboration provided by chemical correlation of natural (-)-**1** with sclareol,[6] and to more recent application of the CD exciton chirality method.[7] Notwithstanding, a paper published by Shimizu, *et al* in 1991 depicts grindelic acid (and several analogs) as **1a**.[8] One consequence of this confusion is the non-definition of C-5 and C-10 configuration in reports where **1** has served as the starting point for synthetic interconversions.[9]

As part of a program to develop the use of oxonium ion-initiated ring expansions in synthesis,[10] we have turned our attention to the enantioselective elaboration of **1a**. The key step associa-

Scheme 1

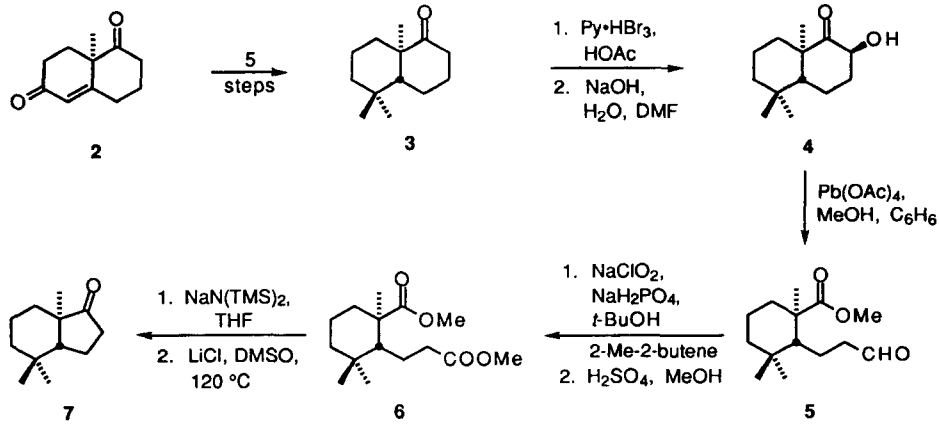


ted with this technology is that which leads to ring expansion with concurrent stereocontrolled introduction of the spirocyclic carbon atom as outlined in Scheme 1. Bond disconnection within the carbinol in the indicated manner leads to visualization of the necessary enantiopure building blocks. As will be seen, **1a** crafted in this manner is dextrorotatory and consequently constitutes the unnatural enantiomer.

Bicyclic intermediate **3**, conveniently available in five steps[11-13] from the (-)-Wieland-Miescher ketone (**2**),[14] was brominated with pyridinium bromide perbromide in acetic acid[15] and exposed to sodium hydroxide in aqueous DMF at room temperature[16] to produce the α-hydroxy ketone **4** in 84% overall yield (Scheme 2). This functionalization efficiently sets the stage for oxidative cleavage of ring B with lead tetraacetate.[17] Direct oxidation of the resulting aldehydo ester **5** to **6** with iodine and potassium hydroxide in methanol[18] proved less effective (52% over the two steps) than sequential treatment with sodium chlorite[19] and acidic methanol[20] (87% for three steps). Cyclization with net ring contraction was subsequently accomplished smoothly by sodium hexamethyldisilazide-promoted Dieckmann reaction[21] (99%) and heating of the β-keto ester so formed with lithium chloride in DMSO at 120 °C[22] (91%). Colorless, oily **7** exhibited $[\alpha]_D^{25}$ -116.7 (*c* 0.68, $CHCl_3$).

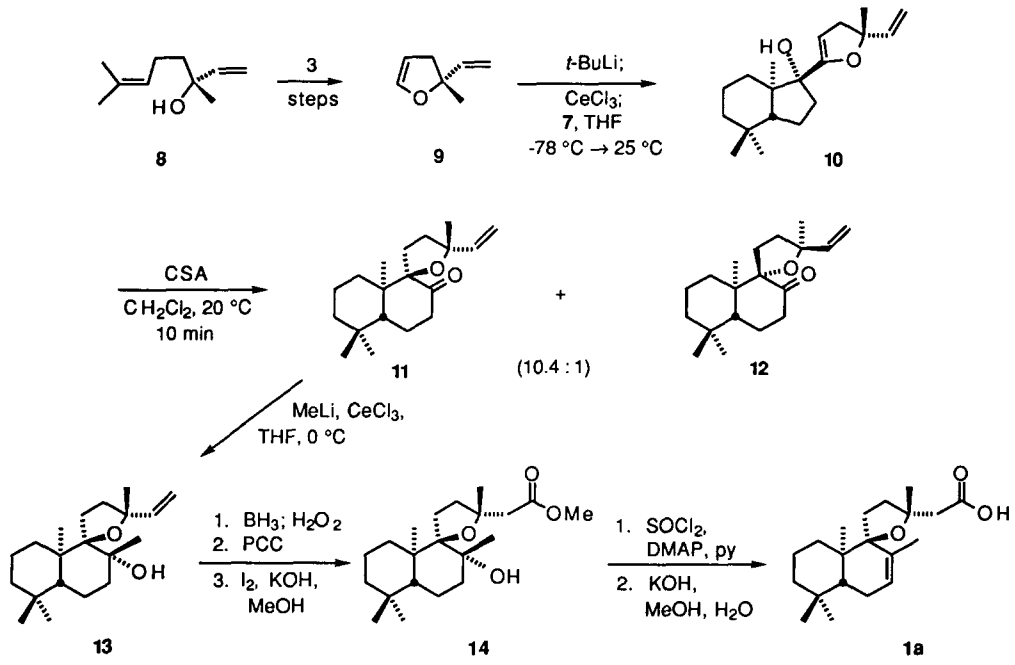
The conversion of (*R*)-(-)-linalool (**8**) into **9** has previously been detailed.[10c] In contemplating the condensation of **9** with **7** (Scheme 3), it is of importance to recognize that the carbonyl group in the ketone is not only very sterically hindered, but positioned as well within a five-

Scheme 2



membered ring. Consequently, **7** is particularly amenable to enolization and recourse must therefore be made to the cerate of **9**[10c] in order to profit from its reduced basicity.[23] Because of the anticipated sensitivity of **10**, this alcohol was subjected directly to acid-promoted ring expansion. Use of a catalytic quantity of camphorsulfonic acid in CH_2Cl_2 resulted in complete conversion to **11** and **12** within 10 min (76% overall). The ratio of these products (10.4:1), which were difficult to separate by chromatography, was ascertained by GC analysis. If the final requisite carbon is now introduced by reaction of the spiro ketone mixture with methyllithium in the presence of anhydrous cerium trichloride, carbinol **13** (87%) could be readily separated from its diastereomer (10%). The structural assignments to **11** and **13** were firmly established on the basis of ^1H-^1H COSY and NOE studies performed at 300 MHz.

Scheme 3



Finally, the vinyl substituent in **13** was transformed efficiently into an acetic ester residue as in **14**. Exposure of this advanced intermediate to thionyl chloride in pyridine containing DMAP[24] was met with conversion to a mixture of exocyclic and endocyclic olefins (*ca* 2:1). Saponification of the latter isomer delivered the targeted **1a** which proved to be spectroscopically identical to natural grindelic acid except for the optical rotation. Whereas natural **1** exhibits $[\alpha]_D^{24}$ -132.3 (*c* 0.034, $CHCl_3$),[25] our colorless, crystalline synthetic sample is characterized by $[\alpha]_D^{24}$ +134.3 (*c* 0.035, $CHCl_3$).

The successful enantioselective construction of **1a** presented here and its demonstrated levorotatory optical character require that natural grindelic acid be formulated as **1b**. The question of the absolute configuration of all grindelane diterpenoids will hopefully now be put to rest.

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