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THE TOTAL SYNTHESIS OF (±)-FRIEDELIN, AN UNSYMMETRICAL, PENTACYCLIC TRITERPENE

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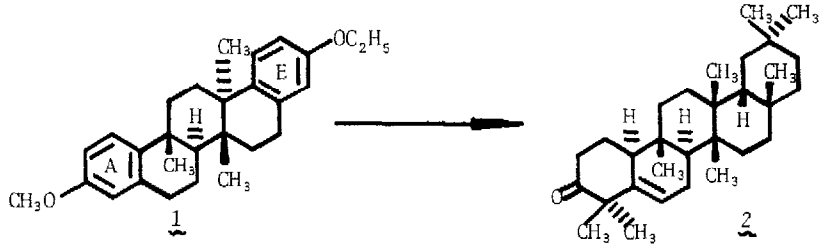
In previous reports[2] from these laboratories an efficient route to the pentacyclic diether 1 was described. A pentacyclic diaromatic compound of this type, with the trans-anti-trans BCD ring structure and the correct array of angular methyl groups, was envisaged as a useful key intermediate for the total synthesis of pentacyclic triterpenes of the friedelin (10)[3] structural group. The successful completion of the total synthesis of (±)-alnusenone (2)[2] established the

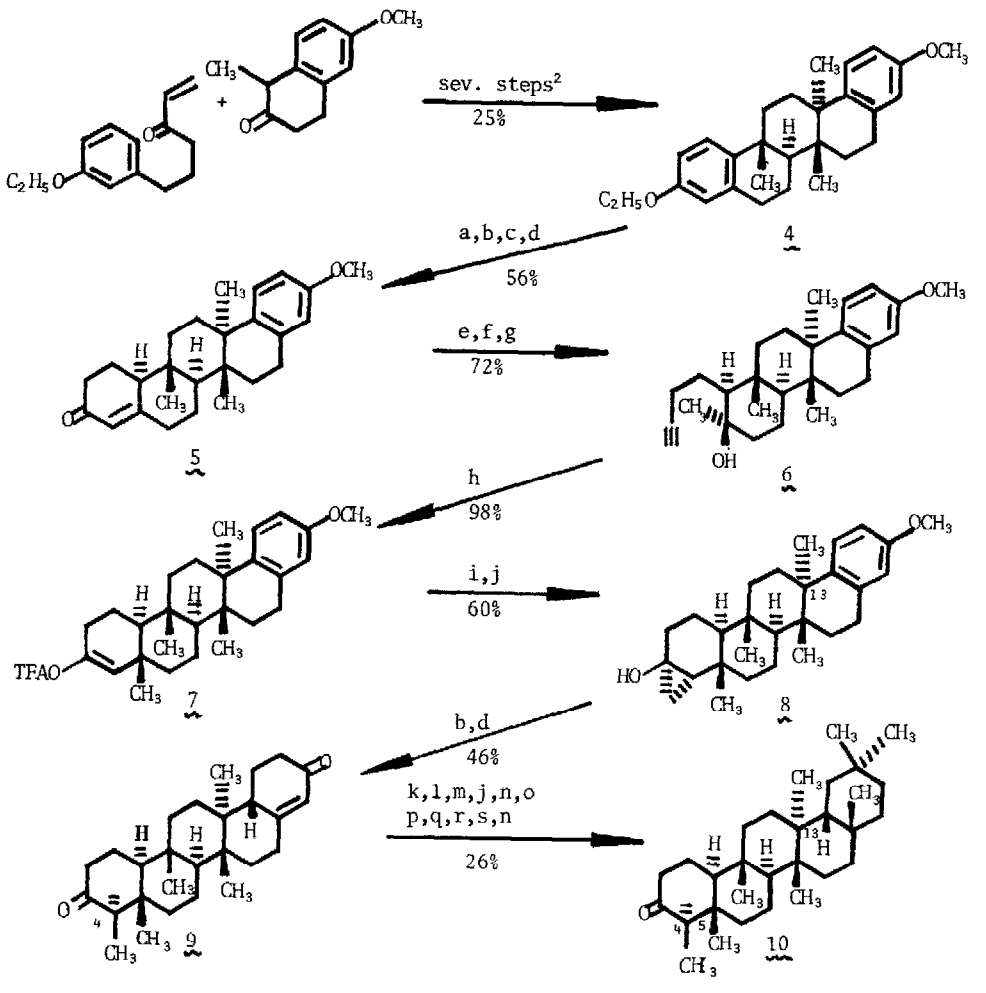


viability of this approach, and the present report describes the results of a continuation of this effort which has culminated in the first total synthesis of (±)-friedelin (10) itself.

Certain modifications of the previous (±)-alnusenone (2) synthesis were deemed wise at the outset of the present work. In the alnusenone scheme[2] the aromatic E ring of the diether 1 was reduced and methylated before reduction and methylation of the aromatic A ring. The known[2,4] ease of the latter transformation dictated this strategy. For the friedelin (10) work such a sequence has disadvantages. First, the overall yield observed[2] for the alteration of the aromatic E ring was only 14%, principally as a result of the initial Birch reduction. It was felt that this could be improved in the friedelin scheme by reversing the aromatic ring modification sequence--i.e., A before E rather than E before A.

Secondly, the process envisaged for the alteration of the aromatic A ring entailed a cationic cyclization as one step (eq. 6→7). Had this reaction been performed on the acetylenic alcohol precursor 3 in which the severe steric strain in the CDE ring system had already been introduced by prior modification of the aromatic E ring, there was a distinct possibility that backbone rearrangement[3] would compete effectively with cyclization. Thus, it seemed wise to undertake modification of the aromatic A ring first; completion might then lead to a higher yield in the

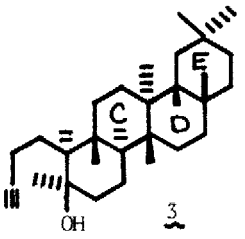
SCHEME I: TOTAL SYNTHESIS OF (±)-FRIEDELIN (10)[a]



(31 steps, 0.3% overall yield)

[a] a, $(C_6H_5)_2PLi$, THF[5]; b, Li, NH_3, DME, EtOH; c, CH_3I, DMF; d, 5% HCl, EtOH, C_6H_6; e, H_2O_2, aq. NaOH, CH_3OH; f, $pTsNHNH_2$, HOAc, CH_2Cl_2[6]; g, CH_3Li, Et_2O; h, CF_3CO_2H, $(CF_3CO)_2O$; i, LDA, THF; j, Zn-Ag, CH_2I_2, THF[7]; k, $Li(OtBu)_3AlH$, THF, C_6H_6, 0^0; l, DHP, $POCl_3$, CH_2Cl_2; m, $Li(OtBu)_3AlH$, THF, C_6H_6, reflux; n, $CrO_3 \cdot 2Py$, CH_2Cl_2; o, KOtBu, CH_3I, THF; p, Li, NH_3, THF, tBuOH; q, $ClPO(NMe_2)_2$, DME, HMPA, nBuLi[8]; r, Li, $EtNH_2$, tBuOH; s, pTsOH, CH_3OH, THF.

Birch reduction but, more important, would relegate the introduction of the principal source of steric strain--the cis-D/E ring fusion--to the later, less sensitive stages.



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To implement this scheme, it was necessary to prepare the pentacyclic diether 4 in which the location of the ethoxy and methoxy groups were interchanged from their locations in the (±)-alnusenone precursor 1 (SCHEME I). This was accomplished in 25% overall yield from the appropriate precursors shown by the same procedures previously reported.[2]

Selective reduction of the aromatic A ring did occur in superior yield in this case, and modification of this ring along the same lines as reported[9] previously in the total synthesis of (±)-shionone led through the acetylenic alcohol 6 to the enol trifluoroacetate 7. Methylenation of the enolate derived from this material 7 by treatment with lithium diisopropylamide provided the cyclopropyl alcohol 8.

In contrast to the experience in the (±)-shionone synthesis,[9] cleavage of the cyclopropyl alcohol 8 was not particularly efficient at this state. While both base (KOtBu, Et_2O) and acid (5%HCl, EtOH, C_6H_6) afforded predominately the desired 4-methylketone, in neither case was the yield better than 75%, and when coupled with the subsequent Birch reduction of the aromatic E ring, the enedione 9 was available only in 35% overall yield. Since the complication in the more favorable acid catalyzed cleavage appeared to entail backbone rearrangement[3] of the pentacyclic system not seen in the (±)-shionone work, an adequate solution to the problem was found when the aromatic E ring was reduced first and then the resulting dihydrocyclopropyl alcohol cleaved by acid treatment.

Completion of the synthesis from the enedione 9 by the introduction of the requisite E ring methyl groups followed the pattern used in the previous (±)-alnusenone synthesis[2] after provision was made to protect the C3 oxygen function. (±)-friedelin (10), mp 246.5-248°, so formed gave tlc and glpc behavior and infrared, pmr and mass spectra identical to those of an authentic sample of the natural product isolated from cork.[3]

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