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# THE SYNTHESIS OF dl-CORIOLIN

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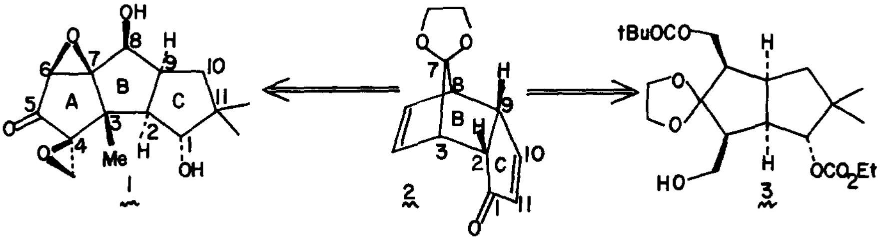
Abstract: The formal synthesis of coriolin (1) from methanoindene 2 is described.

Coriolin (1) is a member of the cis, anti, cis-tricyclo$[6.3.0.0^{2,6}]$undecanoid (hirsutane) class of sesquiterpenes.[1] The compact, highly functionalized nature and biological activity of coriolin (1) and its congeners has led to the completion of several total syntheses to date.[2]

In our initial publication,[3] we showed how a methanoindene such as 2 could be used to provide easy access to two of the three rings of coriolin (1) via conversion into intermediate 3.

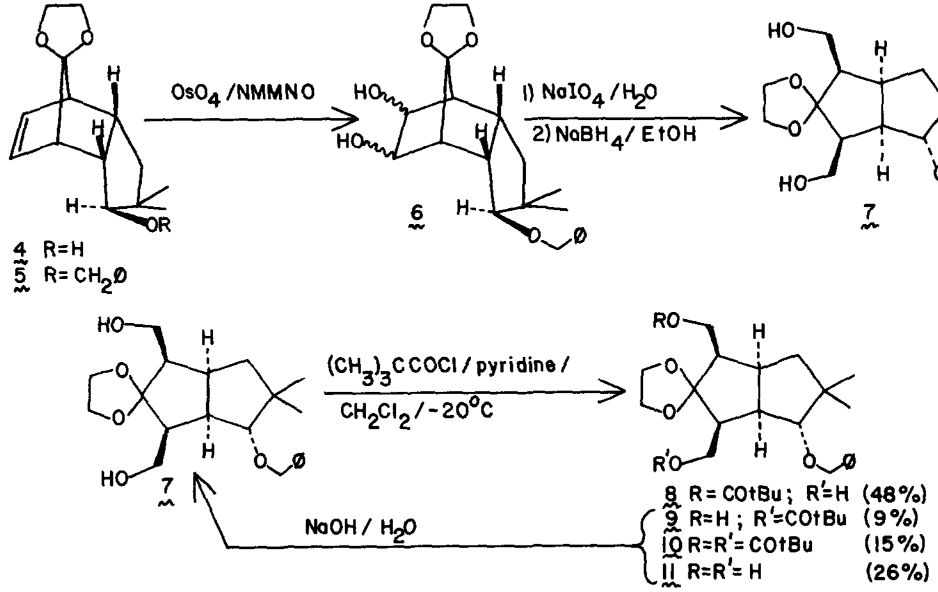


However, the problem of selective hydrolysis of either the ester or the carbonate in 3 caused us to modify this reported route. This modification has led to the total synthesis of coriolin (1).

The exo-alcohol 4[3] was transformed into benzyl ether 5 (Scheme I) (KH;$nBu_4NI$;THF;benzyl bromide; 96%). Hydroxylation of 5 ($OsO_4$;$H_2O$;acetone;N-methylmorpholine-N-oxide)[4] gave diol 6, which was treated with $NaIO_4$ in aqueous DME, immediately followed by $NaBH_4$ in ethanol, to give diol 7 (80% from 5).

Treatment of diol 7 with pivaloyl chloride (pyridine;$CH_2Cl_2$;-20°C) produced four compounds (8-11) in the indicated yields. The desired monoester 8 was separated chromatographically (48% yield) and the crude mixture of 9,10, and 11 saponified ($CH_3OH$;$H_2O$;NaOH) to afford starting diol 7 (98%), which was resubmitted to the acylation conditions. In this way, after two recycles of 9,10, and 11, an 86% yield of intermediate 8 was obtained. Although the acylation regioselectivity was not as great in this series as in the previous ones studied,[3] this route

*Scheme I*



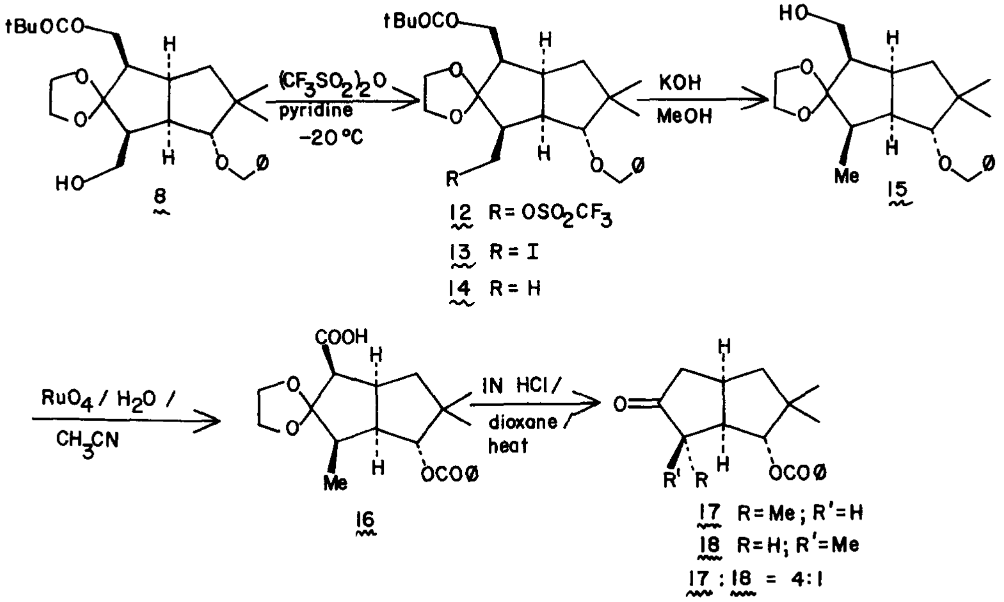
offers a significant improvement in that one need not worry about the lability of the C-1 carbonate alluded to earlier. Therefore, all of the undesired products are easily and quickly recycled.

The C-3 hydroxymethyl group in 8 did not readily succumb to reduction to the corresponding methyl group by standard reduction techniques. However, a three-step sequence (see Scheme II) commencing with preparation of the trifluoromethanesulfonate 12 ($[CF_3SO_2]_2O$;$CH_2Cl_2$;pyridine;-20°C), followed by displacement with iodide ($nBu_4NI$;ØH;reflux) to give 13, and immediate zinc reduction (DME;$CH_3OH$;reflux), produced the necessary alkyl derivative 14 in 81% overall yield (3 steps from 8). Saponification of 14 (KOH;$CH_3OH$;reflux) gave the alcohol 15 (100%). Attempts to use the C-8 β-hydroxymethyl to introduce the C-8 β-hydroxyl failed. Therefore, it was removed at this time. Treatment of 15 with ruthenium dioxide ($NaIO_4$;$H_2O$; $CH_3CN$)[6] gave the acid 16 in 90% yield.[7] Hydrolytic decarboxylation of 16 (Scheme II) (1N HCL;$H_2O$;dioxane;reflux) gave an 87% yield of a 4:1 mixture of ketones 17 ($J_{1,2}$ = 5.6Hz) and 18 ($J_{1,2}$ = 8.6Hz). Ketone 18 has been converted into coriolin (1) by Matsumato and coworkers.[2e] Those identities for these compounds were secured by comparison with spectra of authentic samples.[8]

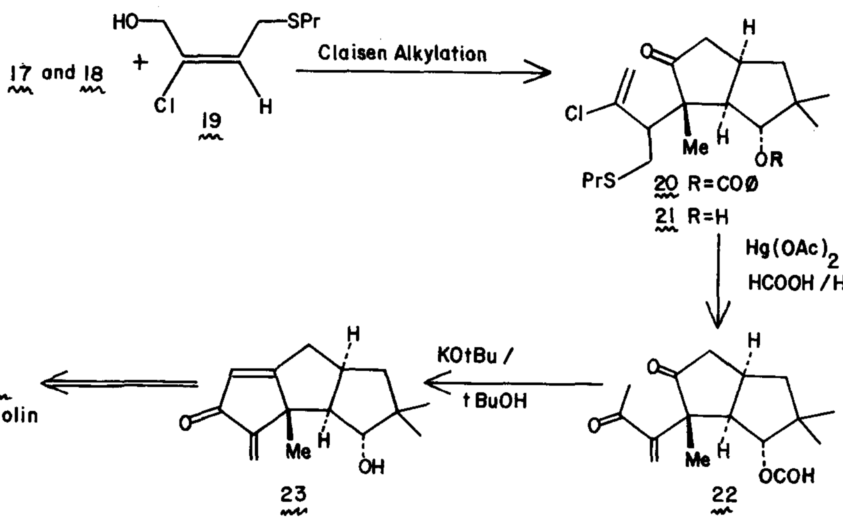
The annulation of the A-ring was carried out according to the precedents of Lansbury,[9] which would allow us to usefully employ both isomers 17 and 18. Claisen alkylation (Scheme III) of a mixture of 17 and 18 using modified conditions:[10] (1) $CH(OMe)_3$ (1 equiv); MeOH (10 equiv); p-TsOH; benzene; room temperature → 60°C then 2) 19 (1.1 equiv)[11]; p-TsOH; mesitylene; 60-165°C) gave an 85% yield of the C3 isomer 20.[12]

Saponification of the benzoate ($nBu_4NOH$;$H_2O$;$CH_3OH$; 96%) gave alcohol 21. Hydrolysis of

*Scheme II*



*Scheme III*



the vinyl chloride and elimination of the thiopropyl group occurred in one step upon treatment of 21 with 4 equiv of $Hg(OAc)_2$ in 88% HCOOH (room temperature; ammonium formate; 48h)[13] to afford enone formate 22 in 84% yield. Aldol dehydration of 22 was accomplished by treatment with KOtBu in tBuOH followed by p-TsOH/ØH/reflux. These conditions also served to hydrolyze the formate ester, and gave the known 23 (81%). The spectroscopic data of this compound exactly matched those reported by Ikegami.[2c] Since this material (23) has been converted into coriolin (1) by Ikegami and co-workers our formal total synthesis of dl-coriolin (1) is complete.

Experimental details of the reactions described as well as our efforts to utilize this technology for the synthesis of other cyclopentanoid natural products will be presented in due course.

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12. Precedent (see ref. 10) indicates that the C3 β-methyl isomer (20) is exclusively formed. We have observed the formation of only one major product 20 as well as what we believe is a very small amount (<5%) of the C8 alkylated material. Details will be disclosed in the full paper.
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