Tetrahedron Letters,Vol.29,No.45,pp 5751-5754,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

SYNTHESIS OF (+)-TAXODIONE FROM (-)-ABIETIC ACID

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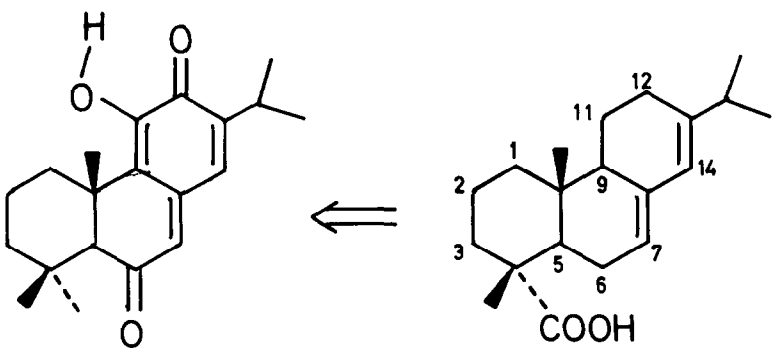
Abstract: A new stereoselective synthesis of (+)-taxodione (1) from (-)-abietic acid (2) via the iron carbonyl complex 3 is described.

(+)-Taxodione (1) a diterpenoid quinone methide was isolated from Taxodium distichum Rich (Taxodiaceae)[1]. It has significant tumor inhibitory activity against Walker Carcino sarcoma 256 in vivo[2]. Because of the unique structure of 1 as extended quinone and its interesting biological activity, it attracted considerable attention. Several syntheses have been reported[3], however, mostly with very low yields. We have recently attempted to use (-)-abietic acid (2) as starting material for the synthesis of natural products with biological activity[4,5]. As previously described, the iron carbonyl complex 3 can be easily prepared from 2 and can be used to synthesize terpenoids with an oxygen function in position[5] 12. Here we present a new synthetic approach to 1, using 3 as a key intermediate to introduce an oxygen function in ring C



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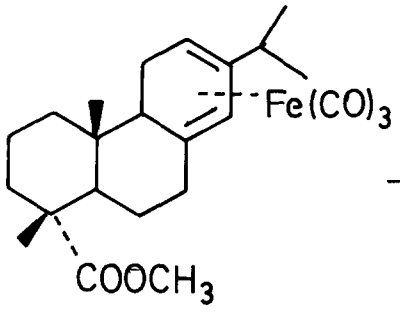

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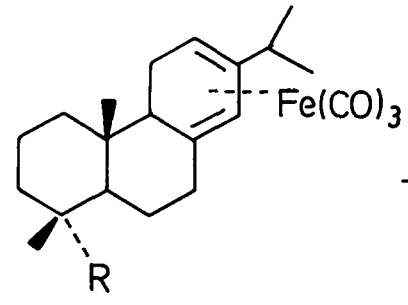
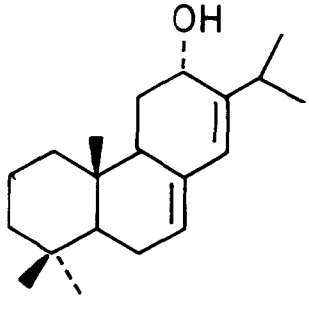


4: R = CH_2OH

5: R = CH_2OTos

6: R = CH_3



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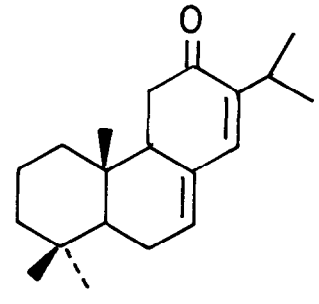

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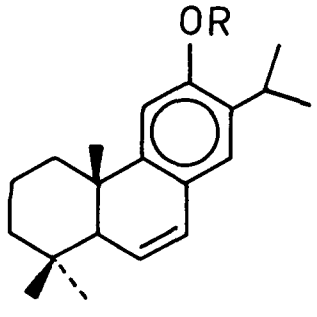
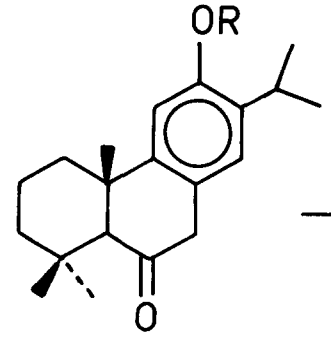


9: R = H

10: R = Ac



11: R = Ac

12: R = H

1

We found, that the conversion of the carboxyl group in 3 to a methyl group can be achieved in high overall yield leading to 6 (see scheme). After reduction of 3 with $LiAlH_4$ (THF) to 4 and tosylation in CH_2Cl_2/pyridine to 5, reduction with NaI/Zn in HMPA gave 6 (72% overall yield[6] from 3). Oxidative decomplexation of 6 with I_2 in $(Et)_2O$ in the presence of water afforded 7 as a single product (92%). The configuration of C-12 was determined by NMR experiments (COSY) and by comparison with analog compounds[5]. Oxidation of the alcohol function with benzeneseleninic anhydride in boiling benzene yielded the ketone[7] 8 as white crystals (81%). 8 could be converted to dehydroferruginol (9) (85%) by an oxidative isomerization with $Hg(OAc)_2$ in boiling acetic acid (4 hours)[8]. Acetylation of the phenolic OH (Ac_2O/pyridine) gave 80% cristalline 10. Our next goal was the introduction of a keto function in position 6. Oxidation of 10 with m-chloroperbenzoic acid[9] in CH_2Cl_2 at room temperature during a period of 3 hours afforded, after the usual workup, a complex mixture of products. The mixture was refluxed with TosOH in benzene for 1.5 hours. After isolation of the crude oil and chromatography on silica gel the ketone 11 was obtained in an overall yield of 80%. Treatment of 11 with $KHCO_3$ in MeOH removed the acetyl group[10] quantitatively. The obtained phenol 12 could be converted in 19% yield to 1 by oxidation with benzeneseleninic acid anhydride. 1 was purified by chromatography on silica and recrystallized from hexane: mp: 114°C - 116°C.

NMR: ($CDCl_3$) 2.56 s (1H), 6.16 s (1H), 6.84 s (1H), 7.55 s, br (1H), 3.15 m (1H), 2.9 m (1H), 1.24 s (6H), 1.12 d (3H), 1.10 d (3H), 1.03 s (3H).

MS: m/z 314 (M^+, 100); 299 (10); 286 (42); 271 (60); 245 (20); 231 (20); 217 (10).

UV: (MeOH) λ_{max} 320 (ε = 26300); 332 (ε = 27700); 400 (ε = 3000).

IR: (CCl_4) 3320, 2960, 2920, 2860, 1670, 1640, 1620, 1595, 1420, 1385, 1350 cm^{-1}.

This sequence presents an efficient and stereoselective synthesis of (+)-taxodione (1) and might also be valuable for the synthesis of other highly oxidized tricyclic diterpenoids (e.g. royleanones).

Acknowledgments: This work was financial supported by Deutsche Forschungsgemeinschaft (Proj.Nr. Ha-1495/1-1). We are grateful to Fa. KREMS CHEMIE (Krems/Donau, Austria) for providing us with starting material (Sacotan 90) and for financial support.

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(Received in Germany 19 August 1988)