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STEREOSELECTIVE SYNTHESIS OF d-PHYLLOCLADENE FROM l-ABIETIC ACID[*1]

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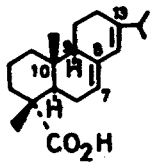
We have been studying the chemical transformation to biologically active compounds or their precursors from l-abietic acid (1), a major component of pine rosin, by using its isopropyl group at the 13-position.[1,2)]

It was reported that 13-formylmethyl-7-oxo compounds having a methyl group at the 13-position gave a D-ring via aldol condensation.[3,4)] In these cases, the steric compression of the 13-methyl group participated in a favorable direction to form the D-ring. The 13-methyl group is an extra carbon in the synthesis of phyllocladene, kaurene, grayanolides and so on. We examined if this cyclization might be extended to a compound having no methyl group at the 13-position, and it was found that the cyclization can be performed by using polyphosphoric acid (PPA)-AcOH, but not by the aldol condensations.

Now, we wish to report the stereoselective synthesis of d-phyllocladene (18) from 1 via catalytic reduction (H_2-RuO_2), PPA-AcOH cyclization and monothioketalization.

In order to obtain a compound having a 7-oxygen function (benzylic position of the C-ring of 2) and a sterically controlled functionality at the 13-position, an 7-oxo diester (2) introduced from 1[2)] was catalytically hydrogenated with H_2/RuO_2-EtOH[5)] to a 13β-methoxycarbonylmethyl ester having a hydroxyl group at the 7-position (3), which was oxidized, without purification, with CrO_3·pyridine-CH_2Cl_2 to a 13β-methoxycarbonylmethyl-7-oxo ester (4) (δ: 3.70 (s, CO_2Me × 2, 1.22, 1.10 (each s, Me); ν_{max}: 1740, 1730, 1710 cm^{-1}; ORD: a weak negative Cotton effect (trough at 313, 0° at 295, peak at 274 mμ; 2,4-dinitrophenylhydrazone: mp 176-177°)). The methoxycarbonylmethyl group at the 13-position possesses a β-configuration and the hydrogen at the 9-position possesses a α-configuration as mentioned below. The ORD curve indicates tnat the hydrogen at the 8-position possesses a β-configuration.[4)] The ester (4)

*1 New compounds indicated by mp or bp gave satisfactory analytical values. NMR spectra (δ) were measured at 60 MHz in $CDCl_3$ vs. Me_4Si as internal reference. IR data (ν_{max}), when not mentioned, were measured in CCl_4.



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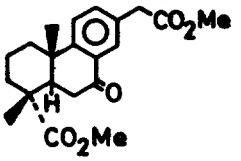

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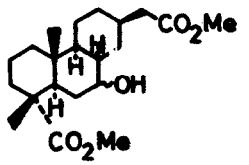

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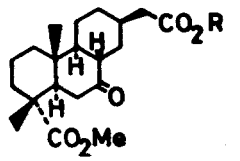
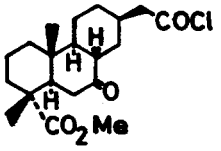


4 R=Me
5 R=H



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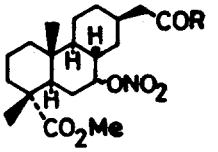
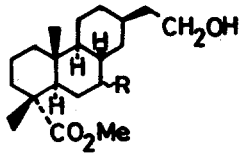
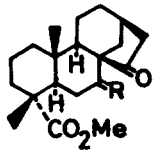


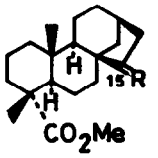
7 R=OMe, 9 R=Cl
8 R=OH

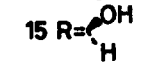


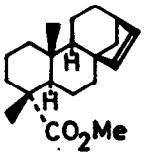
10 R=ONO2
11 R=OH



12 R=O
13 R=



14 R=O
15 R= 



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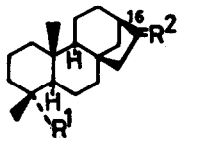
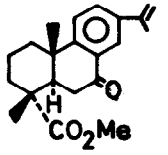


17 R^1=CO_2Me, R^2=O
18 R^1=Me, R^2=CH_2



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was partially hydrolized with KOH-H_2O-MeOH to 13β-carboxymethyl-7-oxo ester (5) (δ: 9.90 (b.s, CO_2H), 3.67 (s, CO_2Me), 1.23, 1.10 (each s, Me); ν_{max}: 3670-2250, 1730, 1700 cm^{-1}).

Ring formation was attempted as follows. The half ester (5) was treated with $SOCl_2$-pyridine to an acid chloride (6) (ν_{max}: 1800, 1725, 1710 cm^{-1}), and successively with $NaBH_4$-dioxane, but no OH-band appeared (IR). Then a dioxy ester (11) was prepared via a nitrate ester (7). The 7-oxo diester (4) was treated with $NaBH_4$-EtOH and then with HNO_3-Ac_2O to 7 (ν_{max}: 1735-1725, 1630, 1275 cm^{-1}), which was partially hydrolyzed with KOH-H_2O-MeOH to a half ester (8) (ν_{max}: 3700-2250, 1725, 1630, 1275 cm^{-1}). The half ester (8) was treated with $SOCl_2$-pyridine to an acid chloride (9) (ν_{max}: 1800, 1725, 1630, 1275 cm^{-1}), and successively with $NaBH_4$-dioxane to a hydroxy nitrate (10) (ν_{max}: 3650, 1725, 1630, 1275 cm^{-1}), which was reduced with Zn-AcOH to 11 (ν_{max}: 3650, 1725 cm^{-1}).

The dioxy ester (11) was oxidized with CrO_3·pyridine-CH_2Cl_2, followed by Al_2O_3 or NaOMe treatment, but no desired cyclization product was obtained.[3,4] The acid chloride (6) was treated under the Rosenmund conditions, with subsequent treatment as above, but also in vain. The compound having no methyl group at the 13-position could not cause the aldol condensation as mentioned above. Then the half ester (5) was treated with BF_3·Et_2O, with or without solvent (Et_2O or AcOH), or with $(CF_3CO)_2O$ in CF_3CO_2H, which also did not give the desired product.

In the long run, 5 under PPA-AcOH conditions[6] (100°, 7 hrs., stirring) gave the desired cyclization product, a dioxo ester having a D-ring at the β-site (12) (mp 202.5°(sublim.), δ: 3.67 (s, CO_2Me), 1.24, 1.05 (each s, Me); $\nu_{max}^{CHCl_3}$: 1735, 1725, 1700 cm^{-1}) as a sole one, which was stable in silica gel chromatography, different from the compound having a D-ring at the α-site.[3] The conditions were much affected with the proportion of the reagents, moreover the PPA conditions without AcOH gave a complex mixture. Up to date, the maximum yield of 70% was obtained by a reaction mixture of the following proportions: 181 mg of 5, 9.05 g of PPA (prepared from 10 ml of 85% H_3PO_4 and 25 g of P_2O_5) and 7.3 ml of AcOH.

In order to decide the configuration of the D-ring and the hydrogen at the 9-position, 12 was converted to an 16-oxo ester (17) whose configuration had been confirmed,[2] via an 15-oxo ester (14). The selective removal of the 7-carbonyl group and exchange of the remaining carbonyl group from 15- to 16-position was carried out as follows. Fortunately, the dioxo ester (12) was converted with excess $HSCH_2CH_2SH$-BF_3·Et_2O to a desired monothioketal (13) (δ: 3.71 (s, CO_2Me), 3.20 (s, SCH_2CH_2S), 1.20, 0.90 (s, Me); $\nu_{max}^{CHCl_3}$: 1720 cm^{-1}), as the 15-carbonyl group was sterically hindered by the 10-methyl group and the 7-carbonyl group was not so hindered (The dioxo ester (12) could not give a ketal with $HOCH_2CH_2OH$-p-TsOH.). The monothioketal (13) was treated with Raney Ni (W-7) to an 15-oxo ester (14) (mp 161°(sublim.); : 3.60 (s, CO_2Me), 1.17, 0.83 (s, Me); $\nu_{max}^{CHCl_3}$: 1720 cm^{-1}; ORD: a negative Cotton effect (trough at 326.5, peak at 319, trough at 313.5, 0° at 309, peak at 286 mμ). The ORD curve suggested that the D-ring possesses a β-configuration.[7] The monoxo ester (14) was reduced with $NaBH_4$-EtOH-tetrahydrofuran to a 15-hydroxy ester (15) (mp 148-149.5°, δ: 3.62 (s, CO_2Me), 1.17, 0.83 (s, Me); ν_{max}: 3645, 1725 cm^{-1}), which was mesylated with MsCl-pyridine, and subsequently treated with γ-collidine to an unsaturated ester (16) (bp 60-70°(bath, 0.06 mmHg), δ: 5.67, 5.66 (each s, vinyl-H), 3.59 (s, CO_2Me), 1.12, 0.75 (each s, Me); ν_{max}: 1725 cm^{-1}). The ester (16) was hydroborated in the usual manner, followed by oxidation with CrO_3·pyridine-CH_2Cl_2 to give a mixture of 15- (14) and 16- (17) oxo esters in about an equal ratio.[8] The mixture was separated conveniently by the Girard reagent, which is positive for 17 and negative for 14. The physical constants (mp, mixed mp, GLC, IR, NMR, ORD) of the latter (17) were completely identical with those of the authentic

sample.[1] Then the methoxycarbonylmethyl group at the 13-position possesses a β-configuration and the hydrogen at the 9-position possesses a α-configuration. These results are reasonable on the assumption that the RuO_2 reduction of 2 occurred to the α-site because this site was much less sterically hindered than the β-site. The former (14) could be converted, by repeating the reactions, to the latter (17). Consequently, as interrelation from 17 to 18 had been published,[1] the stereoselective synthesis of d-phyllocladene (18) from l-abietic acid (1), using two carbon units of the 13-isopropyl group, has been accomplished.

The RuO_2 reduction, with maintaining the functionality at the benzylic position, may be a useful route to synthesize other natural products. The PPA-AcOH cyclization might be extended to the synthesis of 18 from 1 using three carbon units of the 13-isopropyl group by utilizing 13-isopropenyl-7-oxo ester (19), derived from 1, as a starting material and also those of other natural products having the D-ring at the same site of the 10-methyl group such as 18 with no 13-methyl group. All these works are now in progress.

References

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