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SYNTHESIS OF dl-ASPTERRIC ACID,
A CAROTANE TYPE SESQUITERPENE

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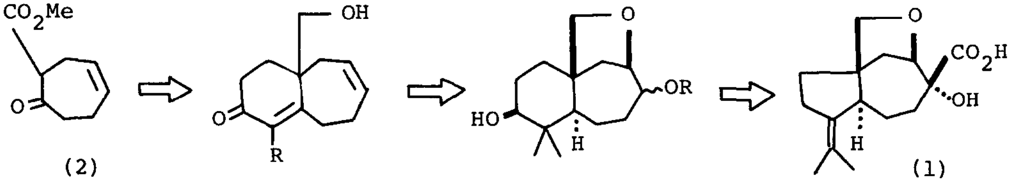
Summary: A carotane type sesquiterpene, aspterric acid (1) was stereoselectively synthesized through Robinson annulation of 2 with MVK, dimethylation of 15, introduction of cyano group to 19 and ring contraction of 25.

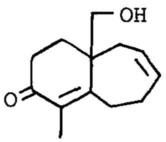
Aspterric acid is a carotane type sesquiterpenoid metabolite obtained from Aspergillus terreus IFO-6123 and its structure was established as 1 by chemical means and X-ray analysis.[1)] We wish to report here stereoselective synthesis of aspterric acid (1). Our strategy for synthesis of 1 is shown in following scheme. It should be noted that formation of isopropylidene group has to be made at the later stage of synthesis, since the isopropylidene unit in 1 is very labile to mineral acids.[1)]



The starting material (2) has been prepared from methyl 3-oxo-8-chloro-(Z)-6-octenoate by high dilution method.[2)] Since this method seems to be unadequate for preparation of large amount of 2, another route to 2 was examined. Thus, Dieckmann condensaton of dimethyl (Z)-4-octenedioate[3)] with NaH gave 2 in 57 % yield. Robinson annulation of 2 with EVK, followed by $LiAlH_4$ reduction and MnO_2 oxidation yielded the hydroxy enone (3) in 56 % yield. Treatment of 3 with Ag_2O-I_2 gave the iodo ether (4) and hydroxy ether (5) (the stereochemistry of hydroxy group will be discusssd later) in 78 % and 18 % yield, respectively; the former was converted into the latter by acetoxylation with AgOAc and hydrolysis with KOH in 78 % yield. Regiochemistry of ether linkage in 5 was determined by the fact that Jones oxidation of 5, followed by bromination resulted in the compound (6). Successive treatment of 5 with $DHP-H^+$, liq. NH_3-Li, MeI and 5% HCl afforded the hydroxy ketone A (7) and B (8) in 13 % and 11 % yield, respectively, which were independently converted into the acetates (9) and (10). The stereochemistry of 9 and 10 in hand was determined as follows. In the NOE experiments of 9 and 10, only 10 showed the 9 % increment of the integrated intensity of the Ha signal (δ 4.37, d., J=8 Hz) by irradiation at the signal of the methyl protons (δ 1.17). This observation indicates that the ring junction of 10 is trans and that of 9 is cis. Since the yield, however, was unsatisfactory, another approach to trans compound was undertaken.

Robinson annulation of 2 with MVK, followed by $LiAlH_4$ reduction, MnO_2 oxidation and Ag_2O-I_2 treatment gave the iodo ether (11) and hydroxy ether (12) (the stereochemistry of hydroxy group will be discussed later) in 74 % and 15 % yield, respectively. The iodo ether (11) was converted into 12 by acetoxylation and hydrolysis in 74 % yield. For the purpose of dimethylation, 11 was treated with t-BuOK-MeI to afford the three membered compound (13), establishing the position of ether linkage. After silylation with t-$BuMe_2SiCl$, dimethylation of 12 with t-BuOK-MeI afforded the dimethyl compound (14) in 56 % yield, which was reduced with $NaBH_4$ to give the alcohol (15) in 75 % yield. Catalytic hydrogenation of 15 on PtO_2 under medium pressure (6.5 kg/cm^2) afforded the dihydro compound (16) in 84 % yield. In order to know stereochemistry of ring junction, an attempt was made to transform 16 into hydroxy ketone A (7) or B (8). Thus, 16 was successively treated with PDC and 5% HCl to yield the hydroxy ketone, which was identical with the cis compound (7). On the other hand, desilylation of 15 with 5% HCl, followed by catalytic hydrogenation on PtO_2 under medium pressure (10 kg/cm^2) and Jones oxidation gave the diketone (17), which was identical with the oxidation product of the trans hydroxy ketone (8). Namely, 15 possessing bulky protective group gave the cis compound and the deprotected compound gave the trans compound. These results are explainable as α-oriented bulky siloxy group hindered hydrogen attack from α side to give the cis compound (16). Therefore, it seems reasonable to assume that the stereostructure of the hydroxy ether is represented by the formula 12. (The stereostructure of the hydroxy ether derived from 4 was similarly assumed to be 5.) Furthermore, from these results it is expected that catalytic hydrogenation of the compound with the free hydroxy group on the seven membered ring will afford the desired trans compound. Then, acetylation of 15, followed by deprotection with 5% HCl and catalytic hydrogenation on PtO_2 under medium pressure (9 kg/cm^2) gave 18 in 74 % yield, which was oxidized with Jones reagent and hydrolyzed with methanolic KOH to afford the desired trans compound (19)$^{4)}$ in 73 % yield. Treatment of 19 with PCl_5 in benzene yielded 20 and 21 in 47 % and 25 % yield, respectively.$^{5)}$ The former was identical with the norketone which is the degradation product of aspterric acid (1).

Many trials of addition of C_1-unit to carbonyl group of 20 were unfruitful. Next, after conversion of 19 to dimethylacetal, treatment with TMSCN-$SnCl_2$$^{6)}$ resulted in the methoxy cyanide A (22) and B (23) in 3 : 10 ratio and in 79 %



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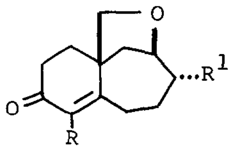
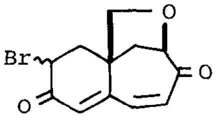


(4) R=Me, R^1=I
(5) R=Me, R^1=OH
(11) R=H, R^1=I
(12) R=H, R^1=OH



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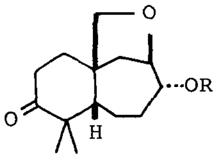
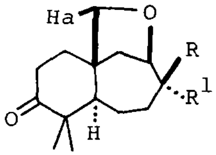
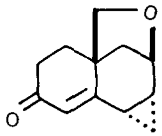


(7) R=H
(9) R=Ac



(8) R=H, R^1=OH
(10) R=H, R^1=OAc
(17) R=R^1=O



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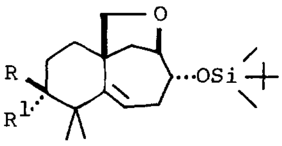
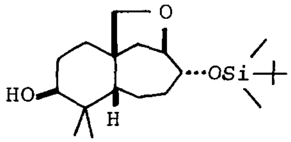


(14) R=R^1=O
(15) R=OH, R^1=H



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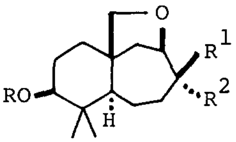
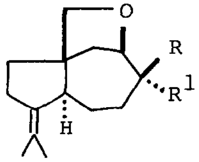
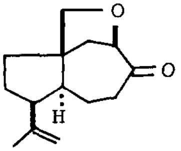


(18) R=Ac, R^1=H, R^2=OH
(19) R=H, R^1=R^2=O
(22) R=TMS, R^1=OMe, R^2=CN
(23) R=TMS, R^1=CN, R^2=OMe
(24) R=H, R^1=OAc, R^2=CO_2Me
(25) R=H, R^1=CO_2Me, R^2=OAc



(20) R=R^1=O
(26) R=OH, R^1=CO_2H



(21)

total yield from 19. The minor product (22) and major product (23) were independently transformed into the monoacetate A (24) and B (25) in 40 % and 45 % yield by the following sequence of reactions ; 1) NaOH in ethyleneglycol, CH_2N_2 2) NaI-TMSCl[7], CH_2N_2 3) Ac_2O-p-TsOH 4) 5% HCl (partial hydrolysis). Monoacetates (24) and (25) were treated with PCl_5 in benzene and finally hydrolyzed with KOH in MeOH to yield the hydroxy acid A (26) and B (1) in 34 % and 42 % yield, respectively. The hydroxy acid B (1) derived from the major product (23) was identified with an authentic sample of aspterric acid by comparison of IR and NMR (200 MHz).

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Footnotes and References

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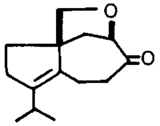
1) Y. Tsuda, M. Kaneda, A. Tada, K. Nitta, Y. Yamamoto, and Y. Iitaka, Chem. Commun., 1978, 160. Concerning the instability of isopropylidene group to acids, see reference 5).

2) R. F. Borch, and B. C. Ho, J. Org. Chem., 42, 1225 (1977).

3) A. Barco, S. Benetti, G. P. Pollini, and R. Taddia, Org. Prep. Proc. Int., 6, 217 (1974).

4) It was also confirmed by transformation of 19 to the trans diketone (17) that 18 has a trans ring junction.

5) A small amount of i was also isolated. Treatment of 20 with $BF_3 \cdot Et_2O$ afforded i.



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6) K. Utimoto, Y. Wakabayashi, Y. Shishiyama, M. Inoue, and H. Nozaki, Tetrahedron Letters, 22, 4279 (1981).

7) G. A. Olah, S. C. Narang. B. G. B. Gupta, and R. Molhotra, J. Org. Chem., 44, 1247 (1979).

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