Tetrahedron Letters,Vol.25,No.34,pp 3739-3742,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

SYNTHESIS OF (-)-TERRECYCLIC ACID A. ABSOLUTE CONFIGURATION OF TERRECYCLIC ACID A AND QUADRONE

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Summary: (-)-Terrecyclic acid A (15) was synthesized from (+)-fenchone (1). The absolute configuration of terrecyclic acid A and quadrone was established.

In 1978 quadrone was obtained as a metabolite of the fungus Aspergillus terreus and was found to display significant in vitro activity against KB human epidermoid carcinoma of the nasopharynx and in vivo activity against P338 lymphocytic leukemia in mice.[1] Interest in the total synthesis of quadrone arises from its novel tetracyclic ring system and from its reported biological properties and a number of syntheses[2] have been reported. While in 1982 Sakai et al.[3] isolated terrecyclic acid A from the same fungus. It has the α-methylenecarbonyl arrangement reminiscent of a large number of known antitumor agents.

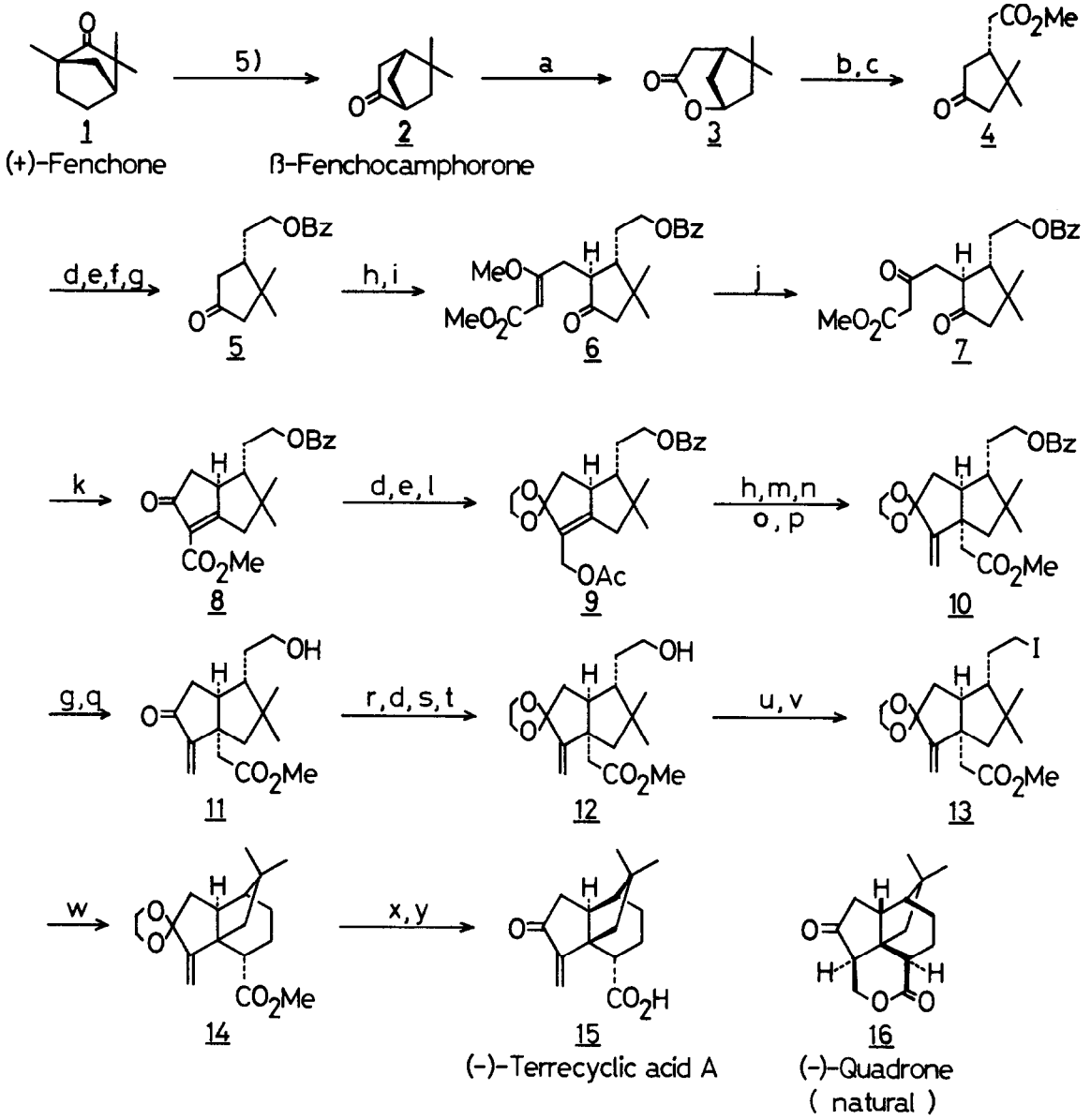
We have accomplished the synthesis of optically active terrecyclic acid A starting from (+)-fenchone (1)[4] according to the route indicated in fig.1. Baeyer-Villiger oxidation of β-fenchocamphorone (2)[5] with m-chloroperbenzoic acid in CH_2Cl_2 in the presence of disodium hydrogen phosphate at 0°C for 6 h, and then at room temperature for 18 h yielded pure δ-lactone (3) [mp 78-79°C ; $[\alpha]_D^{14}$ +24.2° (C 0.743, $CHCl_3$) ; M^+ 154], after recrystallization from ether-pentane, in 84% yield. Methanolysis of 3 with sodium methoxide in methanol at 30°C for 2 h, followed by oxidation of the resulting alcohol with chromium trioxide-pyridine complex in CH_2Cl_2 afforded keto ester (4) in 91% overall yield from 3. The keto ester (4) was converted into keto benzyl ether (5) in 98% overall yield by the following sequence: (1) acetalization with ethylene glycol (1.3 eq.) and p-toluenesulfonic acid (0.2 eq.) in refluxing benzene for 2 h, (2) reduction with lithium aluminium hydride (LAH) in ether at 0°C for 2 h, (3) O-benzylation with benzyl bromide and sodium hydride in refluxing dimethoxyethane, (4) deacetalization with p-toluenesulfonic acid in THF-H_2O (2:1). Compound 5 was deprotonated at -78°C with lithium diisopropyl amide (LDA) in THF and the resulting lithium enolates were alkylated regio and stereoselectively with methyl 4-bromo-3-methoxycrotonate[6] at 0°C for 2 h to give keto ester (6) in 40% yield (the conversion yield was 85%).[7] Treatment of 6 with hydrochloric acid in aqueous methanol at 25°C for 3 h gave diketo ester (7) in 79% yield. Cyclization of 7 was accomplished by treatment with

potassium t-butoxide in t-butanol and benzene for 15 min to give bicyclic enone ester (8) in 77% yield. Coumpound 8 was converted into allyl acetate (9) in 64% overall yield by treatment with ethylene glycol (50 eq.) and p-toluenesulfonic acid (1 eq.) in refluxing benzene for 4 h followed by reduction with LAH in ether at -20°C for 6 h and acetylation with acetic anhydride and pyridine.

Introduction of methoxycarbonylmethyl group at angular position was accomplished by Ireland-Claisen rearrangement[8] of allylacetate (9). Deprotonation of 9 with LDA in THF at -78°C, followed by trapping of the lithium enolate with t-butyldimethylsilyl chloride in THF and hexamethylphosphoramide (HMPA), and then heating at 70-80°C for 2 h gave silyl ester, which was transformed into the corresponding methyl ester (10)[9] in 86% overall yield from 9 by reaction with potassium fluoride and potassium bicarbonate in HMPA at room temperature for 1 h, followed by treatment of the produced potassium salt with methyl iodide at room temperature for 16 h.

Transformation of 10 into the corresponding keto alcohol (11) was achieved in 91% overall yield by deacetalization of 10 with 4% aqueous p-toluenesulfonic acid in THF at 25°C followed by debenzylation[10] with titanium tetrachloride (5 eq.) in CH_2Cl_2 at -20°C. Protection of the exomethylene in 11 by reaction with sodium selenophenolate[11] in absolute ethanol at 0°C for 2 h, followed by acetalization with ethylene glycol (10 eq.) and p-toluenesulfonic acid (0.5 eq.) in refluxing benzene and regeneration of the exomethylene by treatment with 30% H_2O_2-pyridine-CH_2Cl_2 (1:5:26) at 0°C for 15 min, 25°C for 1 h, and heating at 70°C for 30 min, afforded acetal alcohol (12) in 68% overall yield from 11. Reaction of 12 with p-toluenesulfonyl chloride (5 eq.) in pyridine at 0°C gave tosylate, which after heating with sodium iodide (10 eq.) in N,N-dimethylformamide containing a trace of pyridine at 40°C for 18 h, afforded acetal iodide (13) in good overall yield from 12. It was cyclized to acetal ester (14) in 62% yield by treatment with lithium bistrimethylsilylamide in THF at -78°C for 10 min, and then at 60°C for 1 h. Final transformation of 14 to terrecyclic acid A (15) was achieved in 87% yield by treatment with lithium n-propylmercaptide (16 eq.)[12] in HMPA at 60°C followed by deacetalization in THF-10% aqueous phosphoric acid (3:2) at 0°C for 1.5 h.

The synthetic terrecyclic acid A was identical with the natural product by ^{1}H-NMR, IR and mass spectroscopy. The sign of optical rotation of synthetic terrecyclic acid A, $[\alpha]_D^{25}$ -28.0° (C 0.175, $CHCl_3$), was the opposite of that of natural product, $[\alpha]_D^{21}$ +33.9° (C 0.177, $CHCl_3$). Therefore the absolute configuration of natural terrecyclic acid A is indicated as the antipode of 15 depicted in fig.1. Since natural terrecyclic acid A has already been converted into quadrone,[3] the absolute configuration of quadrone is indicated as 16.



(a) m-CPBA. (b) NaOMe. (c) CrO_3, pyridine. (d) ethylene glycol, p-TsOH. (e) $LiAlH_4$. (f) NaH, $PhCH_2Br$. (g) p-TsOH, THF/H_2O. (h) LDA. (i) methyl 4-bromo-3-methoxy-crotonate. (j) HCl, MeOH/H_2O. (k) t-BuOK. (l) Ac_2O, pyridine. (m) t-$BuMe_2SiCl$. (n) reflux, 70-80°C. (o) KF. (p) MeI. (q) $TiCl_4$. (r) $(PhSe)_2$, $NaBH_4$, (s) H_2O_2. (t) heat, 70°C. (u) TsCl, pyridine. (v) NaI. (w) $LiN(SiMe_3)_2$. (x) n-PrSLi. (y) H_3PO_4, THF/H_2O.

fig. 1

Acknowledgement. This work was supported in part by a Grant-in Aid for Special Project Research from the Ministry of Education, Japan. We gratefully acknowledge Prof. S.Danishefsky (Yale University) for supplying ^{1}H-NMR spectrum of synthetic (±)-terrecyclic acid A. We also acknowledge Prof. H.Sakai (University of Osaka Prefecture) for providing us with a sample of natural terrecyclic acid A.

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(Received in Japan 8 May 1984)