butanols, and no trace of optical activity could be detected in these mixtures. However, when a single crystal of **3** weighing 313 mg was photolyzed at 8 °C to 8% conversion and the crude reaction mixture analyzed for optical activity, a specific rotation of −24.5° was observed. Cyclobutanol **4** comprises 70% of the crystal photoproduct mixture, and this material was isolated by column chromatography ($[\alpha]_D$ −21.6°) and its optical purity determined using the chiral NMR shift reagent $Eu(hfc)_3$. This indicated an enantiomeric excess of at least 80%. Following irradiation the crystal was sticky, and we attribute the less than quantitative optical yield to partial sample melting.

Mechanistically, these results indicate that the di-π-methane rearrangement of **1** and the Norrish type II reaction of **3** are stereospecific (albeit nonconcerted), topochemically controlled processes in the solid state. By determining the absolute configurations of the reactants and products and correlating them for a given crystal irradiation, the reaction stereochemistry can be mapped out in detail. This remains an important goal of future work. Unimolecular processes have at least two major advantages over bimolecular reactions for solid-state asymmetric synthesis studies. First, unimolecular reactions do not require specific crystal packing arrangements, and this increases the chances of finding a suitable chiral crystal structure. Second, each chemical event in a bimolecular solid-state reaction involves the disturbance of two lattice sites rather than one, and this may lead to a faster loss of topochemical control with a corresponding decrease in asymmetric induction.

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Total Synthesis of (+)-Methyl Homodaphniphyllate

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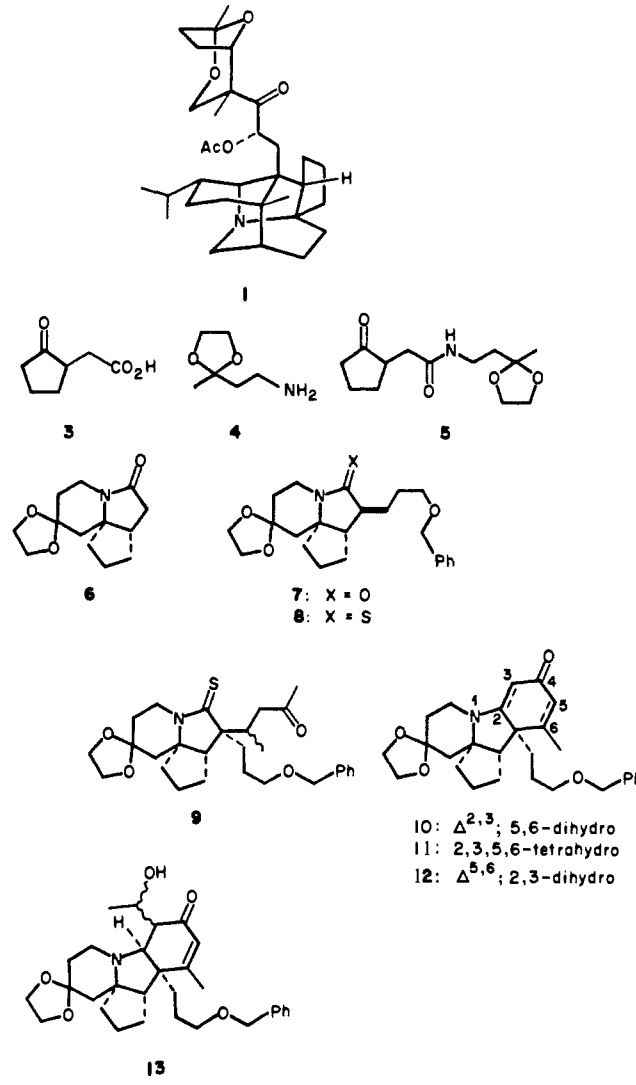
The oriental deciduous tree Yuzuriha (*Daphniphyllum macropodum* Miquel) contains a family of triterpene alkaloids, of which daphniphylline (**1**) is the prototypical member.[1] The structure of daphniphylline was elucidated by Hirata and Sakabe in 1966.[2] The *Daphniphyllum* alkaloid group now numbers some 20 compounds.[3] In this paper, we report the first total synthesis of a *Daphniphyllum* alkaloid, methyl homodaphniphyllate (**2**), a C-22 member of the group having the interesting pentacyclic nucleus of daphniphylline.

The known keto acid **3**[4] is treated sequentially with triethylamine, ethyl chloroformate, and amine **4**[5] to obtain keto amide **5** (89%). When this substance is heated in anhydrous toluene with *p*-toluenesulfonic acid, tricyclic lactam ketal **6** is formed in 83% yield. Alkylation of the derived lithium enolate, formed by treatment of **6** with lithium diisopropylamide (LDA) in THF, with the benzyl ether of 3-bromopropanol provides lactam **7** in 73% yield. Thiolactam **8** is formed from **7** in 76% yield by reaction with Lawesson's reagent[6] in THF with ultrasonication,[7] followed by sequential treatment of the initial product with aqueous base, aqueous acid, and finally, ethylene glycol and *p*-toluenesulfonic acid in refluxing benzene.[8] The preformed lithium enolate of thiolactam **8** (LDA, THF) is allowed to react with pent-3-en-2-one (0 °C) to obtain the Michael adduct **9** in 84% yield. Although this reaction shows reasonably high stereoselectivity at the new side-chain stereocenter (4.8:1), we have not determined the stereochemistry at this point.



The fourth ring is closed by reaction of thiolactam **9** with triethyloxonium fluoborate in $CHCl_3$, followed by triethylamine. The tetracyclic vinylogous amide **10** is formed in 74% yield. Reaction of 10 sequentially with trimethyloxonium fluoborate in CH_2Cl_2 at 0 °C, $NaBH_4$ in methanol, and HCl in aqueous ether provides the saturated amino ketone **11** (87%). This material is treated with lithium 2,2,6,6-tetramethylpiperidide in THF at −78 °C and the resulting enolate selenylated with phenylselenyl chloride.[9] The resulting α-phenylseleno ketone is oxidized by *m*-chloroperoxybenzoic acid in methanol–CH_2Cl_2 at −20 °C to obtain enone **12** (59%).

The lithium enolate of enone **12** (LDA, THF, −78 °C) is treated with acetaldehyde in THF at −78 °C to obtain a mixture of diastereomeric aldols **13**, which is dissolved in acetone and treated with concentrated sulfuric acid. A complex series of transfor-

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(8) In the thiation reaction, surprisingly, one of the oxygens of the dioxolane ring is partially replaced by sulfur. Thus, the crude thiolactam, a mixture of a dioxolane (ca. 25%) and an oxothiolane (ca. 75%), is hydrolyzed and reconverted to dioxolane before continuing the synthesis. We have not investigated the mechanism of the intriguing transformation.
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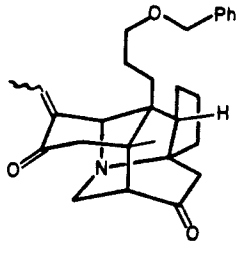
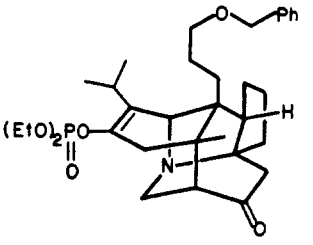
mations ensues, including dehydration, deketalization, and intramolecular Michael addition. The product, pentacyclic diketone **14** (mixture of *E* and *Z* double-bond isomers), is obtained in 69% overall yield, based on enone **12**.

The final methyl group of methyl homodaphniphyllate is added by reaction of **14** with lithium dimethylcopper; the resulting enolate is trapped with diethyl phosphochloridate in THF at 25 °C in the presence of triethylamine to obtain enol phosphate **15** (88%). Treatment of **15** with LDA in a mixture of THF and hexamethylphosphoric triamide, followed by addition of diethyl phosphochloridate, gives bis(enol phosphate) **16** (73%). Reduction of **16** with lithium and *tert*-butyl alcohol in ethylamine gives unsaturated alcohol **17**. Oxidation of the primary alcohol (Jones reagent, 100%) and Fischer esterification (6 N HCl, refluxing methanol, 16 h, 75%) afford methyl dehydrohomodaphniphyllate (**18**).



14



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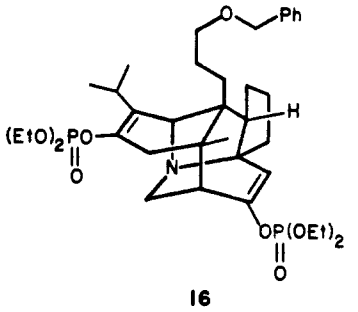
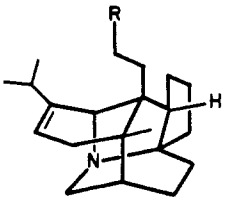
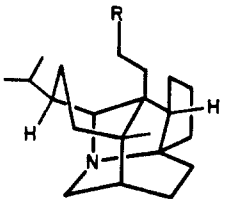


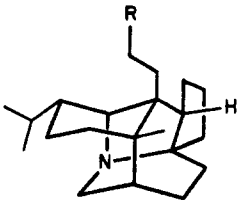
16



17: R = CH_2OH
18: R = CO_2Me



19: R = CH_2OH
20: R = CO_2Me



21: R = CH_2OH
2: R = CO_2Me

Reduction of the double bond with proper introduction of the final stereocenter has been a demanding task. The double bond is exceedingly unreactive to normal conditions for hydrogenation. Eventually, we were able to accomplish complete reduction using 1800 psi of H_2 over rhodium on alumina in methylcyclohexane solvent[10] at 130 °C for 24 h. The product formed under these conditions has the correct constitution and is similar spectrally with methyl homodaphniphyllate. However, it is clearly different, and has been assigned the diastereomeric structure **20**, even though molecular models indicate that the "bottom" face of the double bond in **18** is much more hindered than the top. We assume that double-bond rearrangement is the problem, and that isomerization occurs to the less hindered exocyclic position. In the exocyclic isomer of **18**, hydrogenation from the bottom face of the double bond is not unexpected.

At this point it was clear that intramolecular assistance by the functionalized side chain was desirable. With unsaturated alcohol **17** we evaluated the possible use of a cationic rhodium complex that had shown promise for intramolecular hydrogenation of relatively hindered double bonds.[11] However, the drastic conditions required to achieve any hydrogenation in our system caused general degradation of both the substrate and the catalyst, giving none of the desired reduction product. Success was finally realized with Pearlman's catalyst (palladium hydroxide on carbon);[12] reduction of alcohol **17** over this catalyst (1600 psi of H_2, 120 °C, 24 h, ethanol) gives alcohols **19** and **21** in a ratio of 1:1 (100%). Oxidation of the mixture (Jones reagent) and Fischer esterification (6 N HCl, refluxing methanol) give an easily separable 1:1 mixture of amino ester **20** and methyl homodaphniphyllate (**2**), identical by TLC mobility and 500-MHz ^1H NMR spectroscopy with an authentic sample.

Acknowledgment. This work was supported by a grant from the National Science Foundation (CHE-84-18437). We are especially indebted to Professor Y. Hirata for assisting us in obtaining a sample of codaphniphylline and to Professor S. Yamamura for supplying us with an authentic specimen of methyl homodaphniphyllate.

(10) The unsaturated amino ester is not soluble in methylcyclohexane. Thus, toluene is actually employed as solvent. The entire solvent is rapidly hydrogenated, giving methylcyclohexane. After the initial loss of pressure in this reduction, the hydrogenation bomb is repressurized to 1800 psi to complete the reduction.

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Incorporation of 3′-Methyltyrosine and 5′-Methyl-DOPA into Naphthyridinomycin

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Our studies[2] and those of Zmijewski[3,4] on the biosynthesis of naphthyridinomycin (**1**), an anticancer antibiotic produced by *Streptomyces lusitanus*,[5,6] have identified the primary precursors to the entire skeleton except for C-9 and C-9′. With five such precursors (tyrosine, ornithine, serine, methionine, and the piece yet to be identified) and numerous peripheral modifications, the number of chemically—and biochemically—rational pathways that could be envisioned for the formation of **1** is extraordinarily large. Nonetheless, we report here a few simple experiments that define the first steps of the biosynthetic pathway.

Since tyrosine is a precursor while dihydroxyphenylalanine (DOPA) is not,[3] we reasoned that ring methylation might procede hydroxylation. To test this, 3′-methyl-[2-^{13}C]tyrosine (**2**) was synthesized in two steps from 3-methyl-4-methoxybenzyl chloride (**3**)[7] and diethyl acetamido[2-^{13}C]malonate[8] in 73% yield (based on labeled malonate) (Scheme I).

Three 200-mL production broths were inoculated in standard fashion with a seed culture of *S. lusitanus*.[2] The labeled **2** (50

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