Scheme II

2

2a

2b

2c

2d
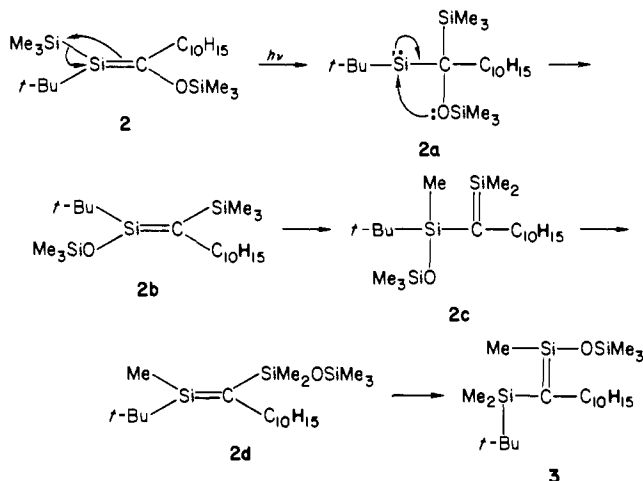
3

dimer (unlike the head-to-head dimers normally formed from silenes derived from the photolysis of acylpolysilanes[10,11]) and this was confirmed by an X-ray structure determination[12] which showed the 1,3-disilacyclobutane structure **4** (see Figure 1). INEPT[13] ^{29}Si studies and DEPT[14] ^{13}C studies confirmed that the photoisomeric silene observed in solution, i.e., **3**, had properties consistent with its being the monomeric precursor to **4** (see Scheme I). Dimer **4** did not undergo photolysis under the reaction conditions.

The pathway by which the remarkable rearrangement **2** → **3** occurs is under investigation. From the kinetics, it is clear that the disappearance of the acylsilane is a clean first-order reaction, and the silene-to-silene rearrangement is part of a consecutive series of photochemical transformations. However, the nature of the photochemical processes are not yet known, the study being complicated by the facts that more than one photochemical reaction is occurring and that silenes are known to react with ketones, dienes, and many other reagents commonly used to probe the multiplicites of photochemical intermediates.

A complex pathway involving rearrangements for which at least some precedents are known can be proposed as a working hypothesis (Scheme II). Photochemical silene-to-silylene rearrangements have been observed[15] and thus **2** could form the silylene **2a** which might reasonably be expected to collapse to the isomeric silene **2b**. Recent studies by Wiberg clearly indicate that methyl groups on the sp^2 hybridized silicon of silenes readily undergo 1,3-silicon-to-silicon migrations[16,17] so that **2b** could isomerize to **2c**. The essentially thermoneutral rearrangement of **2c** → **2d** followed by a second 1,3-methyl migration would yield the observed silene **3**. This scheme involves an uncomfortably large number of sequential migrations but we are unable to propose a simpler process at this time which involves steps for which some precedents are known. This complex chemistry is not an isolated case since photolysis of a related acylsilane, where phenyl replaces *tert*-butyl, undergoes related but different rearrangements. As part of our continuing investigations we are attempting to intercept intermediate species, such as those proposed, but obviously in such

a complex system this is a nontrivial task.

Total Synthesis of (±)-Retigeranic Acid

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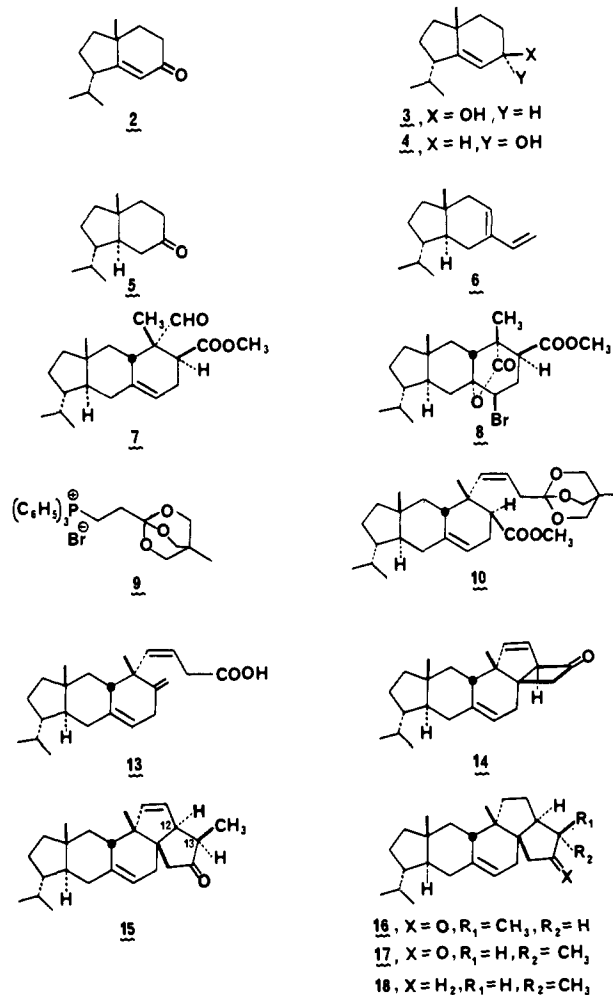*Cambridge, Massachusetts 02138*
Received February 25, 1985

Retigeranic acid is a sesterterpene monocarboxylic acid of novel structure which has been obtained from various lichens found in the Himalayas.[1,2] X-ray crystallographic analysis of the *p*-bromoanilide revealed the structure and absolute configuration shown in **1**.[2] We describe herein the first total synthesis of **1** as

1
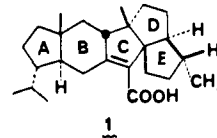
the racemate.[3] The synthesis confirms the X-ray assignment of structure and stereochemistry.

The starting point for the synthesis was the hydrindenone **2**,

2

3, X = OH, Y = H
4, X = H, Y = OH

5

6

7

8

9

10

13

14

15

16, X = O, R$_1$ = CH$_3$, R$_2$ = H
17, X = O, R$_1$ = H, R$_2$ = CH$_3$
18, X = H$_2$, R$_1$ = H, R$_2$ = CH$_3$

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(3) For purposes of the present discussion the ring designations shown in formula **1** have been adopted.

readily available in two steps from 2,6-dimethyl-5-heptenal (melonal) in 76% overall yield.[4]   Reduction of **2** by lithium aluminum hydride (ether, −20 °C for 1.5 h) led stereospecifically to the alcohol **3** (99%)[5] which was converted to the epimer **4** (89% overall yield) by the sequence: (1) Mitsunobu inversion using 1.2 equiv of triphenylphosphine, 1.4 equiv of diethyl azodicarboxylate, and 1.2 equiv of benzoic acid (ether, −25 °C for 1 h); (2) benzoate saponification (2.5% methanolic potassium hydroxide at 25 °C for 15 h).[5]   Reduction of **4** using 1.8 mol % [Rh(norbornadiene)(DIPHOS-4)]BF$_4$[6] using hydrogen (950 psi) in tetrahydrofuran at 25 °C for 6.5 h proceeded stereospecifically to form the desired trans A/B alcohol[5] which was oxidized by the Jones reagent to give ketone **5** in 93% overall yield.[7] R_f values (silica gel TLC) for **3**, **4**, and **5** were 0.15, 0.22, and 0.45 (4:1 hexane–ethyl acetate).   Reaction of **5** with 1.6 equiv of vinylmagnesium bromide in ether at 0 °C produced a 3:1 mixture of vinyl carbinols (97% total yield) which was directly dehydrated by distillation from potassium bisulfate at 150 °C and 40 mm to form diene **6** (90% purity, 82% yield).[8]   When **6** was heated under argon at 98–105 °C for 120 h neat with 5 equiv of methyl 3-formyl-*cis*-crotonate[9] a mixture was obtained from which the desired adduct **7** was isolated in 61% yield by preparative HPLC separation (DuPont Zorbax silica column using 2.5% ethyl acetate in hexane for elution; a minor impurity which remained could be removed in the next steps).   The structure of **7** was confirmed by oxidation of formyl to carboxyl and further transformation to a crystalline bromolactone determined to be **8** by X-ray crystallographic analysis.[10]

Reaction of aldehyde **7** with the ylide prepared from **9**[11] (1.8 equiv of potassium hexamethyldisilazide in toluene) at 25 °C in toluene for 12 h resulted in selective *Z* olefination to generate the diene ortho ester **10** in 80% yield after chromatography on silica gel (9:1 hexane–ethyl acetate containing 1% triethylamine).   The ortho ester **10** was transformed into triene acid **13** by the sequence: (1) reduction of COOCH$_3$ to give the corresponding primary alcohol (**11**) (99% yield using lithium aluminum hydride in ether at 0 °C for 0.5 h); (2) dehydration of the primary alcohol to form the exocyclic terminal olefin **12** in 75% yield (2 equiv of *o*-nitrophenyl selenocyanate[12] and 2 equiv of tributylphosphine in tetrahydrofuran for 1 h at 25 °C, followed by oxidation with *m*-chloroperbenzoic acid at −78 °C in methylene chloride in warming to 25 °C in the presence of dimethyl sulfide over 15 h); (3) OBO ester cleavage[13] by exposure to 0.07 N sulfuric acid in methanol at 23 °C followed by 0.3 M aqueous sodium hydroxide. The acid **13** was converted to the corresponding acid chloride (oxalyl chloride in benzene at 23 °C for 2 h) and thence via the ketene (5 equiv of triethylamine in benzene at 23 °C for 5 min) to the cyclobutanone **14** (80% yield), infrared max 1780 cm^{-1} (CCl$_4$), TLC R_f 0.42 on silica gel using 4:1 hexane–ethyl ether. Cyclobutanone **14** contains all the correct topology and stereorelationships required for the synthesis of **1**, but it remained to modify the sizes of rings C and E.

The expansion of ring E in **14** was accomplished by the sequence: (1) reaction of **14** with 1.5 equiv of the lithio derivative

from acetaldehyde dimethylthio acetal and *n*-butyllithium in tetrahydrofuran at −78 °C to form the carbonyl adduct (73%); (2) rearrangement promoted by 3 equiv of cuprous triflate[14] in the presence of triethylamine (1.5 equiv) in benzene at 23 °C for 10 min; (3) treatment with excess sodium periodate in aqueous dioxane at 25 °C for 12 h to oxidize sulfur; (4) desulfurization using 10 equiv of aluminum amalgam in 2.5% aqueous tetrahydrofuran for 3 h at 0–23 °C. these operations provided the cyclopentanone **15**[14] in 65% overall yield. Careful hydrogenation (1 atm H$_2$, Pd–C, tetrahydrofuran containing 0.25% pyridine, 23 °C, 12–24 h) effected selective reduction of the D-ring double bond to give **16** (83%). Epimerization of **16** to the more stable **17** (89% yield) was accomplished by exposure to sodium methoxide (1 equiv) in methanol at −78 °C followed by quenching at that temperature with acetic acid.

Ketone **17** was deoxygenated to give hydrocarbon **18** in 83% yield by conversion to the tosyl hydrazone (1.2 equiv of tosyl hydrazine in ethanol at 23 °C for 12 h) followed by reaction with 3 equiv of catechol borane[15] in chloroform at 23 °C for 30 min and subsequent treatment with tetrabutylammonium acetate at 65 °C for 1 h. Olefin **18** was subjected to oxidative cleavage at the double bond by sequential hydroxylation (osmium tetroxide in pyridine at 25 °C for 1 h followed by treatment with aqueous sodium bisulfite) and glycol fission (1.1 equiv of lead tetraacetate in methylene chloride at −78 to 0 °C for 30 min) to afford the corresponding seco keto aldehyde **19** (69%). When a solution of **19** in methylene chloride was stirred with neutral alumina 4-Å molecular sieves at 23 °C for 2 h of internal aldol cyclization occurred to form (±)-retigeranic aldehyde[16] (70%) which could be oxidized cleanly by sodium chlorite[17] in 20:1 *tert*-butyl alcohol–aqueous sodium dihydrogen phosphate at 23 °C for 30 min to form **1** (85% yield).

A sample of native "retigeranic acid" (3.5 mg) obtained from Prof. S. Shibata was found to have the same mobility as synthetic **1** by TLC on silica gel (R_f 0.43 in 4:1 hexane–ethyl acetate). However, this sample was shown to be a mixture of two acids by esterification with ethereal diazomethane and subsequent HPLC analysis (Du Pont analytical Zorbax silica column using 0.025% isopropyl alcohol in hexane; retention times 30 (A) and 31.2 min (B)). The components A and B were separated and compared with the methyl ester of synthetic (±)-**1**. The synthetic methyl ester and component B were completely identical by infrared, ^{1}H NMR, mass spectral, and HPLC measurements, whereas component A was clearly different. The mass spectrum of A indicated it to be isomeric with B. Analysis of the ^{1}H NMR spectra of A and B, which show a number of characteristic peaks in common, suggests that A may be a stereoisomer of B, possibly differing only at the methyl-bearing carbon of the E ring.

We surmise that native "retigeranic acid" may be a mixture of isomeric acids corresponding to esters A and B and that during preparation of the derivative for X-ray analysis crystals of the *p*-bromoanilide of **1** were obtained by fractionation of an isomeric mixture.[18]

The synthesis of (±)-retigeranic acid reported above is in principle adaptable to the chiral natural form, since resolution of an early intermediate (e.g., **2–5**) should be possible. Noteworthy features of our route to **1** include (1) the stereospecific synthesis of **5**,[5] (2) the annulations **6** → **7** and **13** → **14**, (3) the ring expansion **14** → **15**, and (4) the overall stereocontrol which was achievable. The facile nature of the internal ketene–olefin addition to form **14** argues strongly against a [π2s + π2a] mechanism for this reaction.[19]

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(7) Satisfactory proton magnetic resonance (^{1}H NMR), infrared, and mass spectral data were obtained for all major synthetic intermediates using chromatographically homogeneous samples.

(8) Analyzed by gas chromatographic (GC) and ^{1}H NMR measurements. The major impurity was the isomeric 1,3-diene with the alternative location of the vinyl-conjugated endocyclic double bond. The impurity did not interfere with the next step.

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(18) **Note Added In Proof**: Prof. Shibata's laboratory has confirmed our finding that native retigeranic acid is a mixture of components A and B (personal communication).

## Bridgehead Intermediates in Organic Synthesis: Two Direct Syntheses of (±)-Lycopodine

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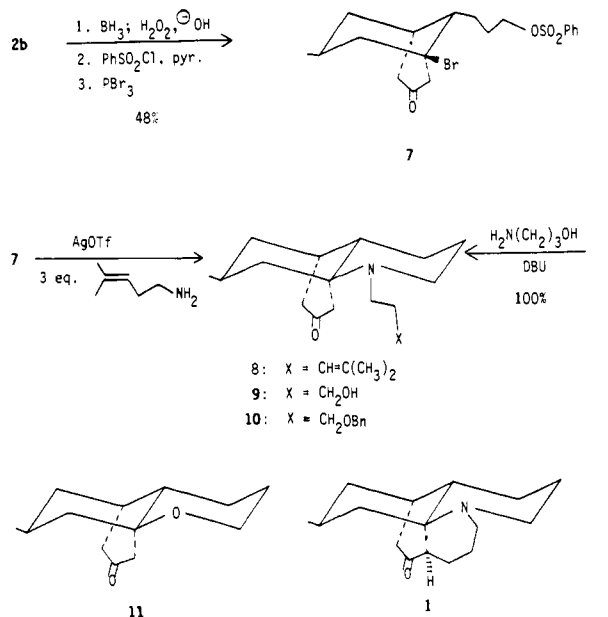Ames, Iowa 50011*

Received March 4, 1985

The use of carbocation-based methodologies in natural products synthesis is often complicated by undesired rearrangements and by mixtures of stereoisomers produced from the planar carbocation. Notable exceptions are the elegant carbocationic cyclizations of both Johnson and Van Tamelen.[1] Recently, the allylic silane moiety has been employed by Fleming and others to control the partitioning of the carbocation to form a single alkene.[2] Johnson has discovered that optically active acetals can be used to effect enantioselective carbocation cyclizations.[3] Despite these advances in select systems, the aforementioned drawbacks remain unsolved. However, bridgehead carbocations offer attractive advantages. In small ring bicyclic systems such as bicyclo-[2.2.2]octanes and bicyclo[3.3.1]nonanes the bridgehead carbocation does not suffer hydride shifts. Indeed, there are examples in which Friedel–Crafts reactions have been conducted on bridgehead halides.[4] Additionally, the large energy difference between the bridgehead carbocation and the analogous acyclic carbocation provides a strong driving force for carbon–carbon bond formation. Moreover, there is no stereochemical ambiguity as to the newly created quaternary carbon, since attack from only one face is enforced by the structure of the bicyclic system. We have studied the intermolecular reactions of both the carbocations derived from 1-bromobicyclo[3.3.1]nonanes and the related bridgehead enones and herein report our results along with an extremely direct synthesis of (±)-lycopodine (1).

The initial studies were done with bicyclononane 2a and then extended to 2b. Bicyclononane 2a had been synthesized by Okamoto and co-workers from cyclohexenone 3a and ethyl acetoacetate (eq 1).[5] The one stereoisomer that was obtained is a result

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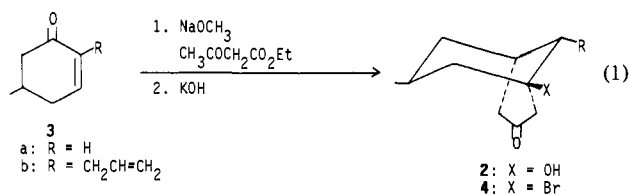
of axial addition of the ethyl acetoacetate anion. Decarboalkoxylation then afforded 2a in 80% yield. Keto alcohol 2b was prepared by the identical reaction sequence. The ratio of 2b to

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Scheme I

its C-9 epimer was determined by capillary GC to be 20:1. Alcohol 2a was then converted into bromide 4a with phosphorus tribromide. An analogous sequence was used to convert 2b into 4b in 87% yield. Compound 3b was synthesized from 3a by the method of Baraldi.[6]

Of the several Lewis acids that might produce the bridgehead carbocation from 4a, silver tetrafluoroborate and silver triflate afforded the best yields. In some cases the use of silver tetrafluoroborate provided largely the bridgehead fluoride. Some representative examples are depicted in eq 2. Allylsilanes, enol

(2)

X =	
$CH_2CH=CH_2$	90%
$NHCH_2CH=CH_2$	99%
CH_2COPh	75%
$C_6H_5(OCH_3)_2$	99%
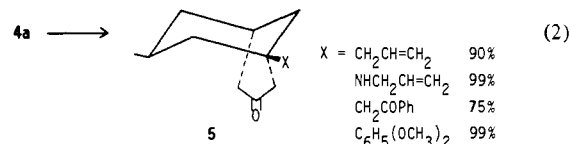
silyl ethers, substituted benzenes, and amines all afford excellent yields of product 5. In the case of allylamine, the triflate was first generated and then the amine was added. In the remaining cases the silver triflate was added to a mixture of 4a and the nucleophile. The reaction of 4a with the enol silyl ether of acetyl cyclohexene provided the tetracyclic diketone 6. Presumably this results from
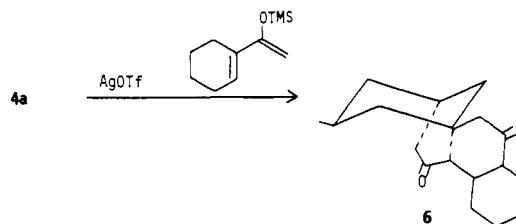
the reaction of the enol silyl ether with the bridgehead carbocation followed by an intramolecular Michael addition catalyzed by the trimethylsilyl triflate formed in the initial step. However, a Diels–Alder reaction with the bridgehead enone (derived by initial loss of triflic acid) cannot presently be ruled out.[7]

The synthesis of lycopodine has already been achieved by Stork,[8] Ayer,[9] Heathcock,[10] Wenkert,[11] and Schumann.[12] Our ap-

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