Supplementary Material Available: Spectroscopic data on compounds **1–18**, (±)-retigeranic acid, aldehyde, methyl ester, and also "natural isoretigeranic" acid methyl ester and a HPLC trace of naturally derived methyl retigeranate and contaminating isomer (4 pages). Ordering information is given on any currently available masthead page.

(19) We are grateful to Prof. S. Shibata, Meiji College of Pharmacy, Tokyo, for a sample of retigeranic acids and to Dr. M. Manowitz of the Givaudan Co. for a generous supply of melonal. This work was assisted financially by the National Science Foundation and the National Institutes of Health.

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

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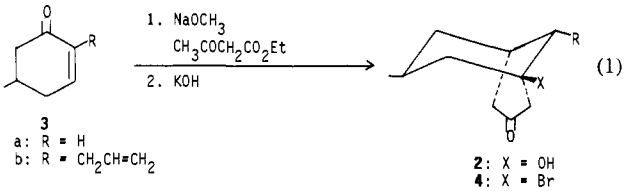
Received March 4, 1985

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



(1)

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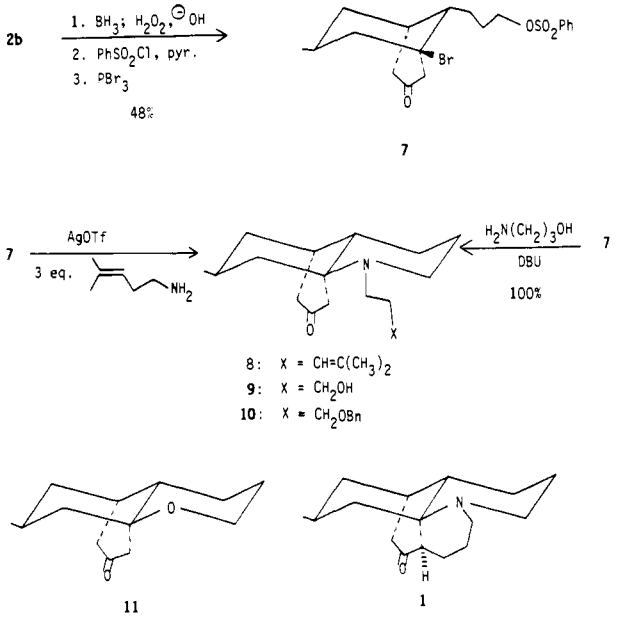
a: R = H
b: R = $CH_2CH{=}CH_2$

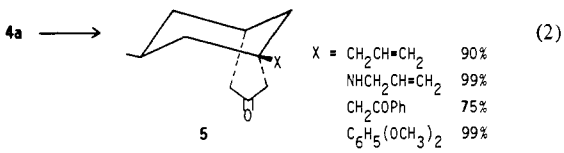
2: X = OH
4: X = Br

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 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]

Scheme I

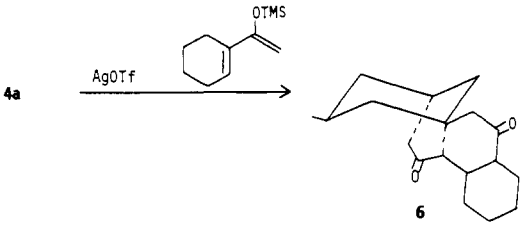


Of the several Lewis acids that might produce the bridgehead carbocation from **4a**, silver tetrafluoroborate and silver triflate afforded the best yields. In some cases the use of silver tetrafluoroborate provided largely the bridgehead fluoride. Some representative examples are depicted in eq 2. Allylsilanes,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



(2)

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



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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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0002-7863/85/1507-4341$01.50/0

proaches are strategically quite different from the existing ones and are very direct. The synthesis of (±)-lycopodine from **2b** is shown in Scheme I. Hydroxy ketone **2b** was treated with borane–THF followed by oxidative workup to provide a diol which was then monobenzenesulfonated ($PhSO_2Cl$, pyr) and brominated with phosphorus tribromide to afford **7**. Bromo ketone **7** can be transformed into lycopodine by two different pathways. In the first sequence 3-amino-1-propanol was added via the bridgehead olefin to produce amino ketone **9** in one step in quantitative yield. This compound was identical with that synthesized by Heathcock and was converted into (±)-lycopodine in two steps using Heathcock's procedures.[13] In the second route 4-methyl-3-penten-1-amine trapped the bridgehead carbocation generated by the reaction of **7** with silver triflate. The yield in this step was highly dependent on the reaction conditions. If the amine was added 2 min after the silver triflate, then product **8** was coproduced with ketone **11**. The ratio of **8** to **11** was approximately 3:1. Ketone **11**, formed by the intramolecular trapping of the bridgehead carbocation, was independently synthesized from **2b**. However, if the amine was added only 30 s after the silver triflate was added, the ratio increased to 10:1. When 3-(benzyloxy)propan-1-amine (5 equiv) was added immediately after the silver triflate, the yield of **10** was 96% with only a trace of **11** as evidenced by capillary GC. Ether **10** was cleaved to afford **9** using catalytic hydrogenation.

The total synthesis of (±)-lycopodine was effected in nine steps and in 25% yield from **3b**. This represents the first use of bridgehead olefins in natural products synthesis and only the second use of a bridgehead carbocation strategy.[14] Their use makes available new pathways by which bridged systems may be constructed.

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(13) Amino ketone **9** was identical by proton NMR, IR, UV, and mp with the Heathcock compound. Our racemic lycopodine had a ^{13}C NMR identical with the reported one (see ref 11). All compounds had proton NMR, IR, and an exact mass/analysis in accord with the assigned structure.
(14) The second Heathcock synthesis in ref 10 also makes clever use of a bridgehead carbocation intermediate.

Bis(2-oxo-3-oxazolidinyl)phosphinic Chloride (1) as a Coupling Reagent for *N*-Alkyl Amino Acids

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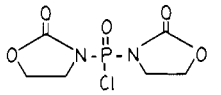
Received March 19, 1985

Many novel, biologically active peptide-based structures that incorporate *N*-alkylamino acid (imino acid) residues are known,[1-3] and the use of such residues to alter or enhance activity has become a standard modification for the peptide chemist. Nevertheless, no wholly satisfactory method for creating a peptide bond with *N*-alkylamino acids has been reported to date. In connection with ongoing work aimed at the synthesis of cyclosporin A, a novel immunosuppressive, cyclic undecapeptide that contains seven *N*-methylated residues,[4] we have sought a convenient and high-yield method for such couplings. We herein report that the title compound (**1**), previously reported as a reagent for the synthesis



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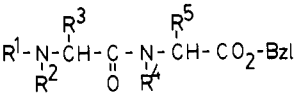
of carboxylic acid esters and derivatives,[5,6] anilamides,[5] β-lactams,[7] and, in one case, peptide cyclization,[8] provides a simple and remarkably efficient method for *N*-alkyl peptide bond formation, with a minimum of racemization.

Previous methods for couplings of *N*-alkylamino acids have, in general, suffered from low or erratic yields and high levels of racemization at the α-carbon of the carboxyl component.[9-11] A notable exception is Wenger's pivaloyl chloride–mixed carbonic anhydride method.[12] However, this technique, although chemically efficient, requires low reaction temperatures (−20 to −25 °C) and often lengthy reaction times as well as process development for each coupling to minimize racemization. Use of **1**, in contrast, allows reactions at easily obtained temperatures (0–5 °C) and in the case of dipeptides is generally complete in 4–20 h.

As a model system, the coupling of BocMeLeu[13] with Me-Leu-OBzl was carried out under several sets of conditions, varying reaction temperatures and bases. It was found that, of the bases used(*N*-methylpiperidine, *N*-methylmorpholine, triethylamine, and diisopropylethylamine), the latter two, used in the 0–5 °C range, provided the highest optical activity in the product dipeptide. Thus, the addition of triethylamine (2.2 equiv) and **1** (1.1 equiv) to a cold solution of the protected *N*-methyl amino acids (1:1) in CH_2Cl_2, and overnight reaction followed by acid-base workup and silica gel chromatography, yielded 84% of **2**, $[\alpha]_D$ −107.3° (*c* 1.0,



	R^1	R^2	R^4	R^3	R^5
2	Boc	Me	Me	*i*-Bu	*i*-Bu
3	Boc	Me	Me	*i*-Bu	*i*-Bu
4	Boc	Me	Me	*i*-Pr	*i*-Bu
5	Boc	Me	Me	*i*-Bu	*i*-Pr
6	Boc	Me	Me	*i*-Pr	*i*-Pr
7	Fmoc	Me	Me	*i*-Pr	*i*-Pr
8	Fmoc	H	Et	benzyl	Me

$CHCl_3$).[14] In order to examine the optical purity of this product, Boc-D-MeLeu-MeLeu-OBzl (**3**) was synthesized by the same method (4 h, 91%; $[\alpha]_D$ + 45.2° (c 1.0, $CHCl_3$)). The dipeptides were hydrogenated (H_2, Pd/C, 95% EtOH, overnight), and the

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(13) Abbreviations used follow IUPAC-INB tentative rules as described in: *J. Biol. Chem.* **1972**, *247*, 977-983. Additional abbreviations used: Fmoc, [(9-fluorenylmethyl)oxy]carbonyl; Aib, α-aminoisobutyric acid; BOP, benzotriazolyloxytris(dimethylamino)phosphonium hexafluorophosphate: DPPA, diphenylphosphoryl azide; DCC, dicyclohexylcarbodiimide; HOBt, 1-hydroxybenzotriazole; HOSu, *N*-hydroxysuccinimide; DMAP, 4-(dimethylamino)pyridine; EEDQ, *N*-(ethoxycarbonyl)-2-ethoxy-1,2-dihydroquinoline; Pfp, pentafluorophenyl.
(14) All products were satisfactorily characterized by ^1H NMR and TLC in two solvent systems and gave correct combustion analyses.

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