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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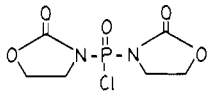
Received March 19, 1985

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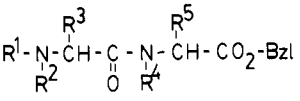
of carboxylic acid esters and derivatives,[5,6] anilamides,[5] β-lactams,[7] and, in one case, peptide cyclization,[8] provides a simple and remarkably efficient method for *N*-alkyl peptide bond formation, with a minimum of racemization.

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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(14) All products were satisfactorily characterized by ^1H NMR and TLC in two solvent systems and gave correct combustion analyses.

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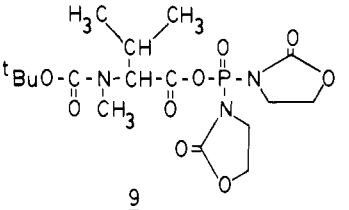
crude products were compared by HPLC. Under conditions that allowed complete resolution of the diastereomers,[15] essentially no racemization (<0.2%) was observed in either case.

Synthesis of a series of bis-*N*-methylated dipeptides by the above method indicated that steric hindrance in the carboxyl component plays a larger role than that in the nucleophile in determining yields. Compound **4**, in which branching of both the imino acid side chain and of the N-protecting group hinder access of the nucleophile to the initially formed anhydride **9**, is formed only



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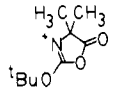
with difficulty (4 days, 36%). Reversal of the imino acids side chains, however, allowed facile synthesis of **5** (4 h, 80%). The effect of the N-protecting group is demonstrated by compounds **6** and **7**, where replacing the *tert*-butyl carbamate of **6** with the flatter and less hindered Fmoc[13,16] group resulted in a shorter reaction time and a higher yield (16 h, 66%, vs. 5 days, 32%). The main byproduct of the reactions leading to **4** and **6** has been identified as the symmetrical anhydride (Boc-MeVal)$_2$O resulting from disproportionation of **9**.[17-19] We have found that, in these highly hindered systems, the symmetrical anhydride is unreactive toward the amine and represents a dead-end product.[20]

The utility of **1** as a coupling reagent appears to be quite general and not limited to *N*-methyl amino acids. Thus, condensation of *N*-Et-Ala-OBzl with Fmoc-Phe proceeded smoothly to yield **8** (overnight, 81%). Preliminary work in this laboratory has indicated that **1** may also be advantageously applied to the synthesis of larger N-alkylated peptides, as well as solution and solid-phase synthesis of non-N-alkylated peptides.[21] The only limitation we have encountered to date was in an attempted coupling of Boc-Aib[13] with Aib-OBzl, where only a small amount of product was formed. Presumably, the low yield was due to the "gem-dimethyl" effect[22] promoting intramolecular cyclization to the 5-oxo-Δ^2-oxazolinium cation **10** and subsequent decomposition,[9,23] since the starting acid was quantitatively consumed. In spite of this apparent[24] limitation, when compared with a wide range of other reagents, including several phosphorus-based compounds (BOP,[13,25] DPPA,[26] diphenylphosphoryl chloride[27]) which have been previously used for amide bond formation, compound **1** has proven to be the most useful in terms of yield, racemization levels, and convenience.[28] Further studies extending the applications of **1** toward solution and solid-phase syntheses of cyclosporin A and other hindered peptide systems are under way.



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Acknowledgment. This work was supported in part by a grant from the National Institutes of Health (AM 32007).

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Mechanism of Oxygen Atom Transfer from High Valent Iron Porphyrins to Olefins: Implications to the Biological Epoxidation of Olefins by Cytochrome P-450

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Received January 28, 1985

The mechanisms by which the cytochrome P-450 monooxygenase enzymes effect hydrocarbon oxygenation has inspired many studies of model metallaporphyrin catalysts.[1-3] The rate-limiting step for most of these oxygenations occurs prior to oxygen atom transfer from the active oxidant, a high-valent iron-oxo-heme complex, to the substrate so that kinetic studies of this most interesting but mysterious reaction have not been feasible. Only in the case of the manganese porphyrin catalyzed olefin epoxidation by hypochlorite (OCl^-) under phase-transfer conditions[4] has it been possible to obtain kinetic data for oxygen atom transfer from the metal to the olefin. Those kinetic studies revealed the presence of a reversibly formed intermediate which is in equilibrium with free substrate and a highly oxidized form of the catalyst.[5] By observing the kinetic behavior of different manganese porphyrin catalysts with a range of olefins, both individually and in direct competition, we obtained kinetic data which revealed that the equilibrium binding of the olefin to the oxidized porphyrin is sensitive to steric effects on both the porphyrin and the olefin but is little influenced by the electronic properties of the substrate.[6] Furthermore, the stereochemistry of the olefin and the epoxide are retained throughout most of these reactions. These results led us to speculate that the intermediate is a metallaoxetane rather than a charge-transfer complex. We now extend these studies to the more biologically relevant *iron* porphyrin catalyzed epoxidation reactions using a different oxygen atom transfer reagent.

Our present work was inspired by a report that pentafluoroiodosylbenzene (F_5PhIO) epoxidizes norbornene in the presence of iron(III) tetrakis(2,6-dichlorophenyl)porphrin chloride (Fe-

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