Bridgehead intermediates in organic synthesis: two direct syntheses of (\(+\))-lycopodine

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Bridgehead intermediates in organic synthesis: two direct syntheses of (+-)(-)lycopodine

Abstract
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.

Disciplines
Chemistry | Environmental Chemistry | Inorganic Chemistry | Organic Chemistry | Other Chemistry | Polymer Chemistry

Comments
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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.

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

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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 (±)-lycodipine (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 acetooacetate (eq 1).5 The one stereoisomer that was obtained is a result of axial addition of the ethyl acetooacetate anion.

Decarboxylation then afforded 2a in 80% yield. Keto alcohol 2b was prepared by the identical reaction sequence. The ratio of 2b to 2a of 1: 3.

(3) Johnson, W. S.; Elliott, J. D.; Hanson, G. J. J. Am. Chem. Soc. 1984, 106, 113; and references therein.

Scheme 1

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

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Many novel, biologically active peptide-based structures that incorporate N-alkylamino acid (imino acid) residues are known,1,2 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 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 of carboxylic acid esters and derivatives,5,6 anilamides,7 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 carbonyl component.9,11 A notable exception is Wenger's pivayl 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 the compound (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 BocMeLeu13 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 CH2Cl2 and overnight reaction followed by acid-base workup and silica gel chromatography, yielded 84% of 2, [α]D2 −107.3° (c 1.0, CHCl3).14 In order to examine the optical purity of this product, Boc-Me-Leu-Me-Leu-OBzl (3) was synthesized by the same method (4 h; 91%; [α]D2 +45.2° (c 1.0, CHCl3)). The dipeptides were hydrogenated (H2, Pd/C, 95% EtOH, overnight), and the

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13. Abbreviations used follow IUPAC-INIB tentative rules as described in: “J. Biol. Chem. 1972, 247, 977−983. Additional abbreviations used; Fmoc, [9-fluorenylmethyloxycarbonyl]; Aib, α-aminoisobutyric acid; BOP, benzotriazol-1-yl-oxytris(dimethylamino)phosphonium hexafluorophosphate; DPPA, diethylphosphoryl azide; DCC, dicyclohexycarbodiimide; HOBt, 1-hydroxybenzotriazole; HOSu, 1-hydroxy-7-azaspiro[4.5]decene; DMAP, 4-dimethylamino pyridine; EEDQ, N-(ethoxyethyl)carboxy-2-ethoxy-1,2-dihydroquinoline; Pfp, pentafluorophenyl.