Synthetic Applications of Group IV Metal Imido Complex–Alkyne [2 + 2] Cycloadditions. A Concise Total Synthesis of (±)-Monomorine

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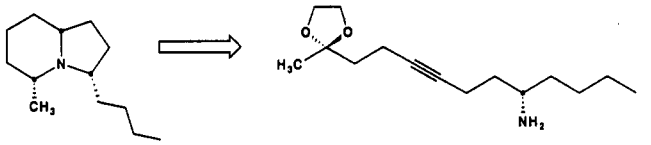
Received November 12, 1991

Summary: Monocyclopentadienyltitanium(IV) imido complexes readily undergo [2 + 2] cycloadditions with representative alkynes at ≤25 °C. The present study details the application of *a catalytic variation* of this reaction in a convergent synthesis of (±)-monomorine.

Cycloaddition reactions involving π components containing transition metal–carbon multiple bonds have become increasingly popular for the synthesis of natural products.[2] The vast majority of these cycloadditions involve metallacarbenoids and lead to unstable metallacyclic intermediates that subsequently undergo reductive elimination[3] or ligand-promoted reorganization.[4] By way of contrast, cycloadducts derived from group IV metal–carbene complexes are relatively stable and have been found useful for selective carbon–carbon bond formation.[5,6] Our interests have centered on the synthetic utilization of related classes of group IV complexes which contain reactive metal–nitrogen π bonds. In a recent publication we reported the facile generation of azametalletines via the intramolecular [2 + 2] cycloaddition of group IV metal–imido complexes with alkynes as well as several of the *selective* functionalization reactions which these species undergo.[7] This communication describes the application of the *catalytic* version of the imidotitanium–alkyne [2 + 2] cycloaddition in a convergent synthesis of the indolizidine alkaloid (±)-monomorine (1). Although 1 and related physiologically active indolizidine alkaloids[8] have been the focus of numerous synthetic studies,[9] relatively few of the total syntheses reported to date are sufficiently practical to dramatically enhance the world's supply of these intriguing compounds. Our interest in these alkaloids derives primarily from their use as initial targets to probe the synthetic utility and functional group compatibility of imidotitanium(IV)-promoted cycloadditions.



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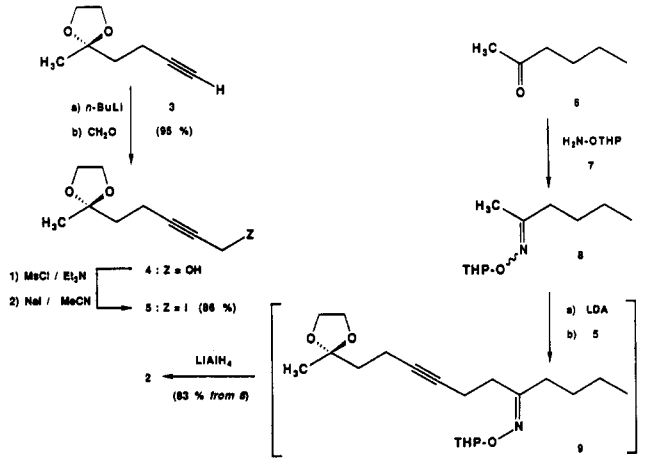
The key γ-aminoalkyne **2** required for the imidotitanium [2 + 2] cycloaddition was prepared by way of the highly convergent approach detailed below. Lithiation of 5,5-(ethylenedioxy)hex-1-yne (**3**)[10] followed by condensation of the resultant acetylide with paraformaldehyde furnished alcohol **4** in 95% yield. Sequential mesylation[11]–iodide-mediated displacement (NaI, CH_3CN) of **4** afforded iodide **5** (81% overall from **3**). Condensation of 2-hexanone (**6**) with *O*-(tetrahydropyranyl)hydroxylamine (**7**)[12] provided the corresponding oximes **8** as a mixture of syn and anti isomers. Lithiation of **8** according to the general procedure of Ensley and Lohr[13] (LDA–THF, −45 °C, 4 h) followed by alkylation with **5** secured the thermally labile oxime **9** which was immediately reduced ($LiAlH_4$, Et_2O) to deliver the γ-aminoalkyne **2** (83% overall from **8**). As is apparent from the above sequence, anions derived from *O*-(tetrahydropyranyl)-oximes (e.g., **8**) constitute extremely useful synthetic equivalents for β-aminocarbanions. To our knowledge the application of oximo ethers in this context has not been widely recognized.



Exposure of **2** to a catalytic quantity of $CpTiCl_3$ in the presence of Et_3N in THF at 25 °C[14] gave rise to the Δ^1-

(1) Fellow of the Alfred P. Sloan Foundation 1989–1991.

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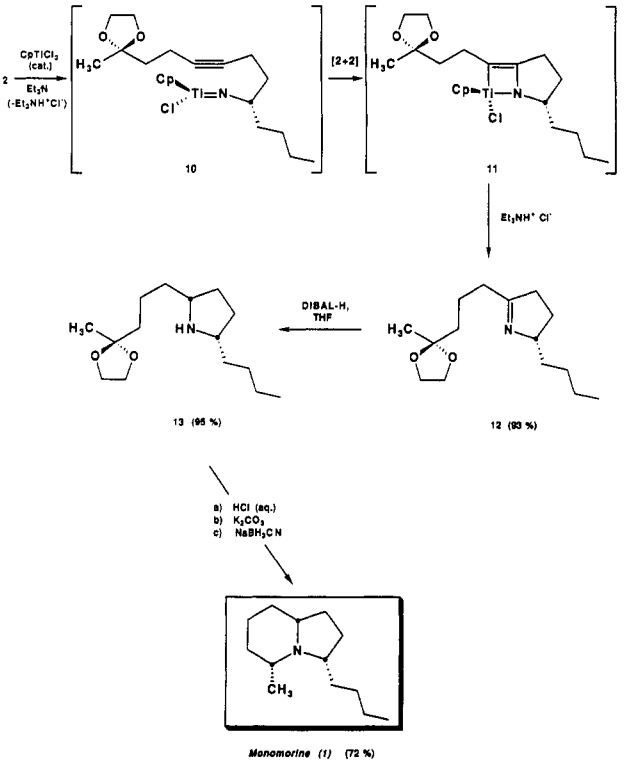
pyrroline **12** *in 93% isolated yield* by way of a [2 + 2] cycloaddition sequence involving the transient imido complex **10** and the titanetine **11**.[7] The latter transformation is most prominently characterized by its extraordinary facility and functional group compatibility. The stereoselective reduction of **12** to the *cis*-pyrrolidine **13** was efficiently accomplished by exposure to DIBALH (4 equiv, THF, $-78 \rightarrow 0$ °C) in 95% yield. The conversion of pyrrolidine **13** into (±)-monomorine (**1**) was subsequently achieved by the procedure of Stevens and Lee.[9b] Accordingly, hydrolysis of the 1,3-dioxolane moiety of **13** (aq HCl–THF) followed by treatment with K_2CO_3 and immediate reduction (THF, $NaBH_3CN/CH_3OH$, 5% aq HCl) furnished (±)-monomorine (**1**) in 72% overall yield from **13**. The spectroscopic (^1H NMR, ^{13}C NMR, IR, and mass spectral) characteristics of synthetic **1** that was prepared in the above manner were identical in all respects to those reported for synthetic[9] samples of the alkaloid.

In summary, a catalytic imidotitanium–alkyne [2 + 2] cycloaddition has been successfully exploited as the key transformation in an efficient (53% overall yield from the point of convergence) total synthesis of the indolizidine alkaloid (±)-monomorine (**1**). The utilization of this and related transition-metal-based methodologies for the synthesis of more structurally intricate ring systems will be described in future accounts from these laboratories.



(14) *Experimental procedure for the preparation of* (±)-**2-butyl-3,4-dihydro-5-[4,4-(ethylenedioxy)pentyl]-2*H*-pyrrole** (**11**). To Et_3N (260 μL, 1.9 mmol) and $CpTiCl_3$ (208 mg, 0.95 mmol) in THF (10 mL) at 25 °C was added **2** (1.20 g, 4.74 mmol) in THF (10 mL). After 1 h, 5% methanolic NaOH (4 mL) was added, and the reaction mixture was brought to dryness. The residue was triturated with hexane (3 × 10 mL) which was then filtered through powdered K_2CO_3. Concentration of the filtrate yielded **11** (1.12 g, 93%) as a slightly colored oil: ^1H NMR (300 MHz, $CDCl_3$) δ 3.88 (m, 4 H, OCH_2CH_2O), 2.55–2.2 (m, 5 H, $N{=}C(CH_2)_2$, NCH), 2.1–1.7 (m, 1 H), 1.7–1.55 (m, 5 H), 1.45–1.1 (m, 9 H), 0.86 (m, J = 7, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.70, 109.83, 72.48, 64.56, 38.71, 36.81, 36.36, 33.90, 28.82, 28.55, 23.69, 22.80, 21.14, 14.02; IR (film) 2956, 2928, 2872, 1644, 1458, 1376, 1256, 1218, 1132, 1060; high-resolution mass spectrum calcd for $C_{15}H_{27}NO_2$ (M^+) 253.2042, found 253.2034.

Acknowledgment. Support for this research by grants from the Alfred P. Sloan Foundation, the Petroleum Research Fund administered by the American Chemical Society and the National Science Foundation is gratefully acknowledged.

Supplementary Material Available: Experimental procedures complete with spectroscopic data as well as ^1H and ^{13}C NMR spectra (26 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Stereoselective Synthesis of Both Diastereomers of the α-Methyl-β-hydroxy-β-alkyl(aryl) Units by Use of Tin(II) Triflate-Mediated Aldol Reaction

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Received December 2, 1991

Summary: Both diastereomers of the α-methyl-β-hydroxy-β-alkyl(aryl) units are prepared by the tin(II) triflate-mediated aldol reaction of 1-(ethylthio)-1-(trimethylsiloxy)propene with α-keto esters in high selectivities.

Recently, a series of pyrrolizidine alkaloids has attracted much attention due to their potent hepatotoxic, carcinogenic, and mutagenic properties.[1] These alkaloids, especially 11- or 12-membered pyrrolizidine dilactones such as integerrimine, senecionine, fulvine, crispatine, etc., possess unique common structures of the α-methyl-β-hydroxy-β-alkyl units, and rather complicated multistage transformations have often been required for the stereoselective construction of these successive asymmetric centers including quaternary carbons.[2] In the course of our investigations to develop novel efficient synthetic routes to pyrrolizidine alkaloids, we were confronted with the above problem. In this paper, we would like to describe a general method for the preparation of both diastereomers of the α-methyl-β-hydroxy-β-alkyl(aryl) units by using the tin(II) triflate-mediated aldol reaction and to discuss a unique character of tin(II) triflate as a Lewis acid in order to realize the high diastereoselectivities. Enantioselective

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