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Application of an Organozinc Reagent Derived from (*S*)-Pyroglutamic Acid: a Formal Synthesis of Epibatidine

Willem F. J. Karstens, Marinus J. Moolenaar, Floris P. J. T. Rutjes, Urszula Grabowska, W. Nico Speckamp and Henk Hiemstra*

Laboratory of Organic Chemistry, Institute of Molecular Chemistry, University of Amsterdam Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands

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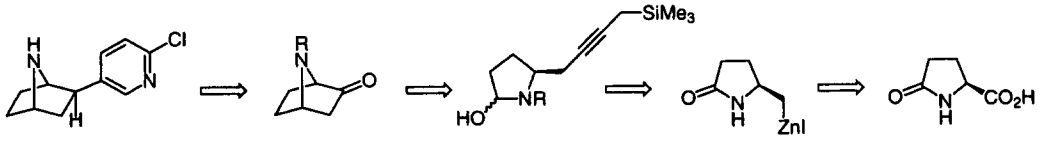
Abstract

A formal total synthesis of natural (–)-epibatidine has been developed. Key steps in the synthesis are a copper(I)-mediated coupling of an (*S*)-pyroglutamic acid-derived organozinc reagent with 1-iodo-3-trimethylsilyl-1-propyne and an *N*-acyl- or *N*-sulfonyliminium ion cyclization. Following this route, various *N*-protected hydroxylactams were converted into 7-azabicylo[2.2.1]heptane derivatives.

Keywords: epibatidine; organozinc reagent; *N*-acyliminium ions; azabicylo[2.2.1]heptanes.

The general interest in the 7-azabicylo[2.2.1]heptane skeleton has seen a strong revival[1] since the structural elucidation of (–)-epibatidine **1**,[2] isolated from the Ecuadorian neotropical frog *Epipedobates tricolor*. Among its remarkable biological properties[3] are the exceptionally strong analgesic activity and the high affinity for the nicotinic receptors.



1: (–)-epibatidine **2** **3** **4** (*S*)-pyroglutamic acid (1)

Most reported syntheses describe the preparation of racemic **1**,[4] while in some cases the incorporation of a resolution step leads to enantiomerically pure material.[5] Since the determination of the absolute stereochemistry of the natural compound,[5b] special attention has been paid to the direct preparation of enantiomerically pure **1**.[6] Our own interest in bridged azabicyclo compounds stems from the synthesis of the

* Corresponding author. Fax: +31 20 525 5670; E-mail: henkh@org.chem.uva.nl

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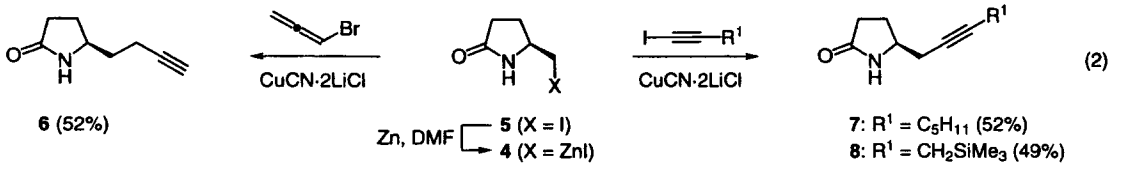
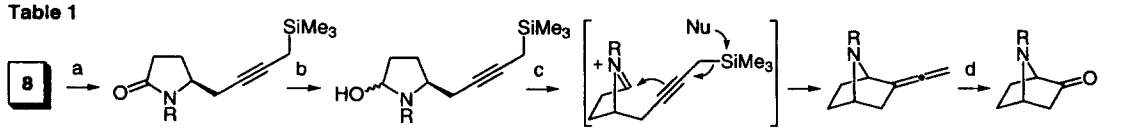
alkaloid (±)-anatoxine-a[7] and from the synthesis of enantiopure azatropane and aza-cocaine analogues.[8] In these cases, we used our *N*-acyliminium ion cyclization methodology[9] to construct the bicyclic skeleton of the target molecules. In conjunction with this work, we present a concise and straightforward synthesis of the enantiopure ketones **2a-c** (eq 1, **2a**: R = methoxycarbonyl, **2b**: R = Boc, **2c**: R = Ts), of which **2b**[5b] and **2c**[4g] have been previously converted into epibatidine. Key steps in our synthesis are the coupling reaction of the (*S*)-pyroglutamic acid-derived organozinc reagent **4** with 1-iodo-3-trimethylsilyl-1-propyne and the *N*-acyl- or *N*-sulfonyliminium ion cyclization of the *N,O*-acetals **3**. This cationic cyclization is somewhat reminiscent of the radical approach used by Clive and coworkers[6i] in the synthesis of (–)-**2b**.



Previously, we successfully applied organozinc reagent **4** (derived from **5**[10] by treatment with activated Zn in DMF) for the preparation of several enantiopure allene-substituted lactams by means of an S_N2'-displacement of propargylic tosylates.[11] More recently, we set out to further explore the chemistry of this versatile reagent. For example, reaction with bromoallene[12] in the presence of CuCN·2LiCl led to the acetylenic lactam **6** in 52% yield (eq 2). The analogous propargylic lactam **7** was obtained in the same yield by subjecting 1-iodo-1-heptyne to these conditions.[13] Thus being able to generate propargyl-substituted lactams in an efficient manner, we reasoned that it should be possible to prepare the propargylsilane-substituted lactam **8** – a projected intermediate in a synthesis of epibatidine – in a similar manner. In previous experiments, we were unable to react higher order cuprates derived from propargyltrimethylsilane with pyrrolidinones **5** (or the corresponding bromide) to arrive at **8** despite the fact that this reaction works well for aliphatic and aromatic cuprates.[14] By applying the organozinc reagent **4**, however, after transmetallation with CuCN·2LiCl and reaction with 1-iodo-3-trimethylsilyl-1-propyne[15] the desired lactam **8** was formed in a respectable 49% yield. Straightforward acylation or tosylation, followed by partial reduction of the lactam carbonyl to give the *N,O*-acetals **3** now set the stage for the intramolecular *N*-acyl- or *N*-tosyliminium ion cyclization reaction (Table 1).[16]

Table 1



	9	3	10	11	2
a: R = CO_2Me	89%	95%		74%	96%
b: R = Boc	97%	97%		25%	93%
c: R = Ts	94%	95%		75%	79%
d: R = Alloc	88%	96%		27%	-

Reagents and conditions: (a) 1. **9a**: 1. LDA (1.1 equiv), –78 °C; 2. NCCOOMe –78 °C to rt; **9b**: Boc_2O, Et_3N, DMAP; **9c,d**: *n*-BuLi (1.1 equiv), THF; 2. RCl (1.2 equiv); (b) DIBAL-H (2 equiv), THF, –78 °C, 1 h; (c) HCO_2H, 0 °C to rt, 10 min; (d) 1. O_3, –78 °C, CH_2Cl_2, 10 min; 2. SMe_2, rt, 2 h.

On stirring the *N,O*-acetals **3** in formic acid a silicon-assisted cyclization *via* the cationic species **10** went to completion within a few minutes to produce the allenic bicyclic heptanes **11a** and **11c** in a clean reaction. Unfortunately, the *tert*-butyl and allyl carbamates **11b** and **11d** were only obtained in low yields, probably due to deprotection and other side reactions. The cyclizations were quenched ($NaHCO_3$) after 10 min, because prolonged exposure to formic acid led to partial solvolysis of the allene moiety. The allenes **11a–c** were then

treated with ozone in CH_2Cl_2 at –78 °C to give ketones **2a–c** in good to excellent yields, thus constituting (in the case of **2b** and **2c**) a formal synthesis of (–)-epibatidine.

In summary, we have further demonstrated the usefulness of an (*S*)-pyroglutamic acid-derived organozinc reagent *via* the synthesis of acetylene-substituted lactams. As an application, a highly efficient formal synthesis of (–)-epibatidine was developed involving as the key steps a copper(I)-mediated coupling of this zinc reagent to generate a propargylsilane-substituted lactam and an *N*-acyl- or an *N*-sulfonyliminium ion cyclization to construct the bicyclic skeleton.

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16) A typical experimental sequence proceeded as follows (**4** → **2c**):
(S)-5-[4-(Trimethylsilyl)but-2-ynyl]pyrrolidin-2-one (**8**): To a mixture of dry LiCl (848 mg, 20 mmol) in THF (50 mL) was added CuCN (896 mg, 10 mmol). The resulting solution was cooled to –40 °C and treated dropwise with a solution of organozinc reagent **4**[11] (prepared from (*S*)-5-iodomethylpyrrolidin-2-one **5** (10 mmol)) in DMF (10 mL). The mixture was stirred at 0 °C for 10 min, recooled to –30 °C and 1-iodo-3-trimethylsilyl-1-propyne (2.38 g, 10 mmol) was slowly added by syringe. The mixture was stirred at –30 °C for 4 h and then allowed to reach ambient temperature overnight. After the addition of saturated aqueous NH_4Cl (100 mL), the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), concentrated and purified by flash column chromatography (5% MeOH in EtOAc) to give pure **8** as a white solid (1.03 g, 4.92 mmol, 49%): mp 68-69 °C; $[\alpha]_D$ –48 (*c* 0.7, MeOH); IR ($CHCl_3$) ν 3430, 3000, 2960, 2900, 2215, 1685, 1250, 840; ^1H NMR (400 MHz,) δ 6.02 (br s, 1H), 3.78-3.72 (m, 1H), 2.43-2.19 (m, 5H), 1.88-1.79 (m, 1H), 1.42, (t, *J* = 2.6 Hz, 2H), 0.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.6, 80.2, 73.9, 53.7, 29.9, 26.8, 26.2, 6.9, –2.2; HRMS (EI) calcd for $C_{11}H_{19}NOSi$ 209.1236, found 209.1226.
(S)-N-(p-Toluenesulfonyl)-5-[4-(trimethylsilyl)but-2-ynyl]-pyrrolidin-2-one (**9c**): To a solution of **8** (302 mg, 1.44 mmol) in THF (2.5 mL) at –78 °C was slowly added *n*-BuLi (1.0 mL, 1.6 M in hexanes). After stirring for 30 min at –78 °C, TsCl (303 mg, 1.59 mmol) was added and the reaction mixture was allowed to attain room temperature. Quenching with saturated aqueous NH_4Cl (10 mL), dilution with Et_2O (25 mL), washing with brine (15 mL), drying (Na_2SO_4) and purification by flash chromatography (EtOAc/hexanes 1:4) yielded **9c** as a colorless oil (491 mg, 1.39 mmol, 94%): $[\alpha]_D$ –111 (*c* 0.9, $CHCl_3$); IR (neat) ν 2956, 2221, 1733, 1360, 1169; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.3 Hz, 2H), 4.45-4.40 (m, 1H), 2.75-2.59 (m, 3H), 2.39 (s, 3H), 2.34-2.16 (m, 2H), 2.08-2.02 (m, 1H), 1.28 (t, *J* = 2.6 Hz, 2H), –0.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 144.7, 135.7, 129.3, 128.3, 81.1, 72.8, 58.6, 30.7, 25.5, 23.5, 21.5, 6.8, –2.2. HRMS (FAB) calcd for $C_{18}H_{26}NO_3SSi$ (M + 1): 364.1403, found 364.1413.
(1R,4S)-N-(p-Toluenesulfonyl)-2-vinylidene-7-azabicyclo-[2.2.1]-heptane (**11c**): To a solution of **9c** (432 mg, 1.22 mmol) in THF (5.0 mL) at –78 °C was slowly added DIBAL-H (1.22 mL, 1.5 M in toluene) and the reaction was allowed to reach completion (1 h, –78 °C). A few drops of saturated aqueous Na_2SO_4 and EtOAc (20 mL) were added to the reaction and the resulting mixture was stirred at rt for 1 h. The mixture was filtered over Celite and concentrated *in vacuo*. The crude compound **3c** (413 mg, 1.16 mmol, 95%) was dissolved in ice-cold formic acid (2 mL) and stirred for 10 min, reaching room temperature. The mixture was poured into saturated $NaHCO_3$ (30 mL), extracted with Et_2O (3 × 10 mL), washed with brine (10 mL), dried (Na_2SO_4) and purified by flash chromatography to give **11c** as a white crystalline solid (238 mg, 0.86 mmol, 75%): mp 135-136 °C; $[\alpha]_D$ –147 (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) ν 3030, 2957, 1972, 1340, 1151; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J* = 8.2 Hz, 2H), 4.69-4.64 (m, 2H), 4.57 (br d, *J* = 4.3 Hz, 1H), 4.25 (br t, *J* = 4.5 Hz, 1H), 2.41 (s, 3H), 2.25-2.18 (m, 1H), 2.06-1.89 (m, 3H), 1.68 (m, 1H), 1.49-1.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 143.6, 136.7, 129.2, 128.0, 100.7, 78.2, 62.9, 59.7, 36.5, 30.8, 29.8, 21.5; Anal.: Calcd for $C_{15}H_{17}NO_2S$: C, 65.43; H, 6.22; N, 5.09. Found: C, 65.37; H, 6.15; N, 5.03.
(1R,4S)-N-(p-Toluenesulfonyl)-7-azabicyclo-[2.2.1]-heptan-2-one (**2c**): Standard ozonolysis of **11c** (200 mg, 0.73 mmol) in CH_2Cl_2 (10 mL) at –78 °C (10 min), followed by stirring with dimethyl sulfide (5 mL) at room temperature for 2 h gave ketone **2c** as a white crystalline solid (152 mg, 0.57 mmol, 79%): mp 127.5-128.0 °C; $[\alpha]_D$ –66 (*c* 1.0, $CHCl_3$); Anal. Calcd for $C_{13}H_{15}NO_3S$: C, 58.85; H, 5.70; N, 5.28. Found: C, 58.79; H, 5.65; N, 5.23. All other spectroscopic data were identical to those described in the literature.[4g]