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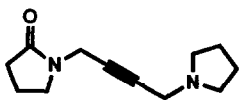
SYNTHESIS OF CHIRAL α-ACETYLENIC CYCLIC AMINES FROM α-AMINO ACIDS: APPLICATIONS TO DIFFERENTIALLY CONSTRAINED OXOTREMORINE ANALOGUES AS MUSCARINIC AGENTS

John Y.L. Chung* and James T. Wasicak
Neuroscience Research Division, Pharmaceutical Discovery, Dept. 47W,
Abbott Laboratories, Abbott Park, IL 60064

Abstract: Application of the Corey-Fuchs reaction on Boc-prolinal, Boc-4-hydroxyprolinal, Boc-piperidinal and Boc-serinal derivatives to give chiral 2-pyrrolidinyl-, 2-piperidinyl- and 4-oxazolidinyl-acetylene derivatives provided rapid access to a number of differentially constrained oxotremorine analogues as muscarinic agents.

Oxotremorine, N-(4-pyrrolidino-2-butynyl)-2-pyrrolidone (**1**), the active metabolite of tremorine, is a potent muscarinic receptor agonist capable of entering the central nervous system. However, the potential of **1** for therapy of dementia in Alzheimer's disease is limited by both peripherally and centrally associated severe side effects and by its lack of selectivity for muscarinic receptor subtypes.[1] Therefore, agonists that are more selective for muscarinic receptor subtypes are of interest. We were interested in an enantioselective synthesis of differentially constrained oxotremorine analogs **2-6** as potentially useful agents, as part of a study directed toward better understanding of the nature of the interaction of muscarinic receptors with these ligands and improving the pharmacologic profiles of oxotremorine (**1**). In this paper we describe the alkynylation of α-aminals, and subsequent manipulation leading to these targets.



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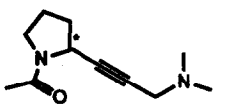
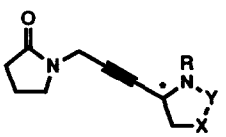


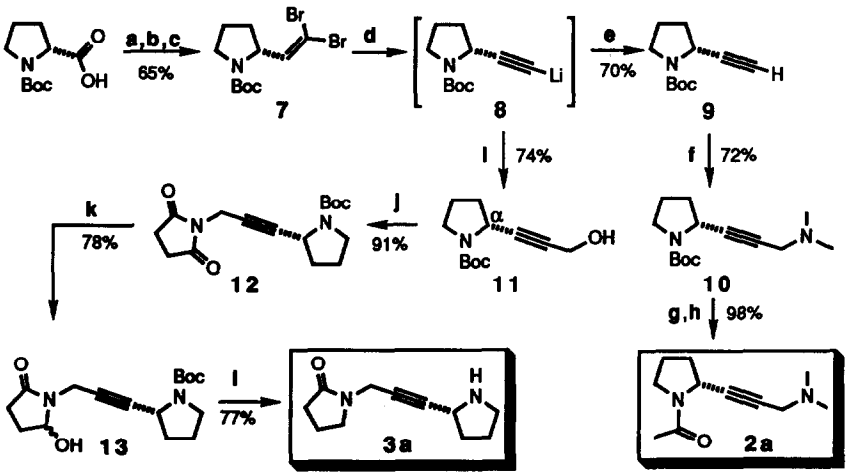
2a: (R)
2b: (S)



3: X=CH_2, Y=CH_2; **4**: X=CH_2, Y=$(CH_2)_2$;
5: X=CHOR[1], Y=CH_2; **6**: X=O, Y=CH_2;
a: R=H, (R); **b**: R=H, (S); **c**: R=Me, (R); **d**: R=Me, (S).

To prepare both enantiomers of these compounds in optically pure form, we focused our attention on the readily available cyclic α-amino acid derivatives as our chiral building blocks. Therefore, the synthetic problem was reduced to one of a chain extension of a carbonyl into an acetylene. Realizing the similarity between **2** and **3**, a common intermediate, **7**, was used as the branching point to these two types of molecules. Using the Corey-Fuchs conditions,[2] the key dibromo vinyl intermediate **7**[3] was readily synthesized from L- or D-Boc-prolinal[4] in 65% overall yield starting from the corresponding Boc-prolines. Compound **7** was then treated with 2.05 equivalent of n-butyllithium at -78°C under a nitrogen atmosphere to give the acetylide anion **8**, which could be quenched with methanol to give the terminal alkyne **9** (70%) or quenched with paraformaldehyde to give the propargyl alcohol derivative **11**[3] (45-74%).

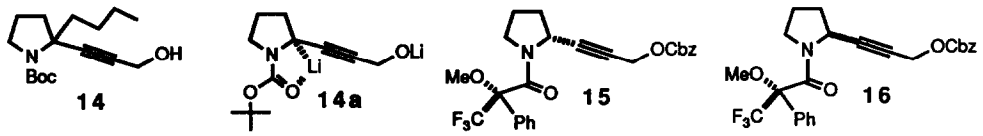
Scheme 1



Scheme 1. (a) $BH_3{\cdot}SMe_2$; (b) Pyridine·SO_3, DMSO, Et_3N; (c) Ph_3P, CBr_4; (d) 2.05 eq. n-BuLi, -78°C, 1.5 h; (e) MeOH, -78°C to r.t.; (f) $CH_2(N(Me)_2)_2$, CuCl, 80°C; (g) TFA, CH_2Cl_2; (h) Ac_2O, Et_3N; (i) excess $(CH_2O)_n$, -78°C to r.t. (j) Ph_3P, $(EtO_2CN)_2$, Succinimide; (k) $NaBH_4$, MeOH,0°C; (l) TFA, Et_3SiH.

Interestingly but not unexpectedly, in the reaction of **7** to **11** a major by-product **14**, in which the alpha carbon was n-butylated, was routinely isolated in 5-20% yield. This result suggested that deprotonation of the alpha proton of the proline derivative had occurred and that the resulting doubly stablized anion[5] **14a** reacted with the n-butylbromide generated in situ from the metal-halide exchange reaction. This observation suggested that racemization may be a problem if the anion was quenched by a proton. Subsequently, **11** and its enantiomer were converted to their Mosher amides **15** and **16**, and examined by HPLC, ^1H- and ^{19}F-NMR analysis. These studies

revealed the enantiomeric purity of **11** was ≥94% e.e.. Thus, the enantiomeric integrity of the C_α stereogenic center in **11** was almost completely conserved.

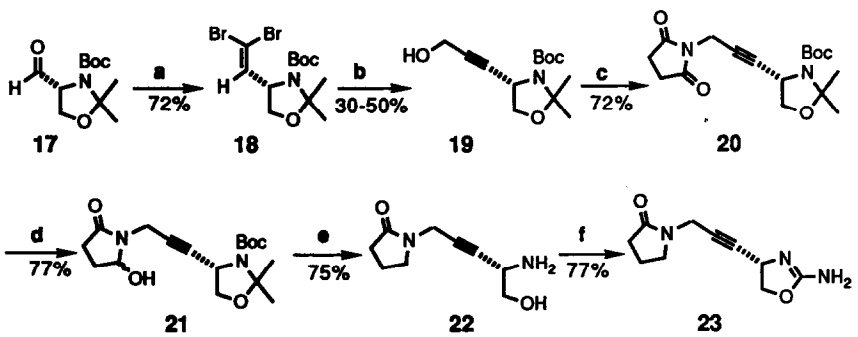


The Mannich reaction of **9** with bis(dimethylamino)methane[6] under the catalysis of CuCl in refluxing THF afforded the propargyl amine **10** in 72% yield. Removal of the Boc group followed by acetylation provided the oxotremorine analogue **2a** in 98% yield.

Compound **3a** was prepared from progargyl alcohol **11** by a three-step sequence: (1) Mitsunobu coupling with succinimide gave the imide **12**, which was then (2) subjected to $NaBH_4$/MeOH reduction to afford the hydroxy lactam **13** (71% yield from **11**), and then (3) the subsequent treatment of **13** with Et_3SiH/TFA which effected the concomitant deoxygenation and deprotection of the Boc group to give the compound **3a**[3] in 77% yield. Methylation of **3a** with paraformaldehyde in refluxing formic acid gave **3c** in 96% yield.

The piperidine series (**4a-d**) and 4-(*tert*-butyl-dimethyl)siloxy pyrrolidine series (**5a-d**, R^1=TBDMS) were similarly obtained from the corresponding N-Boc aminals in comparable yields as outlined in Scheme 1 . To further demonstrate the generality of the methodology, we also subjected serinal derivative **17**[7] to the same reaction sequence (Scheme 2). As before, aldehyde **17** was smoothly converted to hydroxylactam **21**. Treatment of **21** with TFA/Et_3SiH effected the expected reduction and also the total deprotection of the Boc and acetonide groups to provide amino alcohol **22**. Compound **22** was used as a branching point to the various heterocyclic

Scheme 2



Scheme 2. (a) Ph_3P, CBr_4; (b) 2.05 eq. n-BuLi, -78°C,1.5 h; excess $(CH_2O)_n$, -78°C to r.t.; (c) Ph_3P, $(EtO_2CN)_2$, Succinimide; (d) $NaBH_4$, MeOH, 0°C; (e) TFA, Et_3SiH; (f) BrCN, MeOH, K_2CO_3.

derivatives for further SAR studies. For example, reaction of **22** with cyanogen bromide provided the amino oxazoline **23** in good yield. The cyclic guanidine analogue of **23** is currently being prepared.

The interesting biological activities of these conformationally semi-rigid oxotremorine analogs will be published elsewhere.[8]

References and Notes

* Current address: Merck Sharp & Dohme Res. Labs, P.O. Box 2000, Rahway, NJ 07065.

1. Davidson, M.; Hollander, E.; Zemishlany, Z.; Cohen, L.J.; Mohs, R. C.; Davis, K.L. in *Current Research in Alzheimer Therapy*, 1988, Giacobini, E. and Becker, R., eds., Taylor & Francis, New York, p 333.

2. Corey, E.J.; Fuchs, R.L. *Tetrahedron Lett.*, **1972**, *36*, 3769.

3. All new compounds gave satisfactory elemental analyses and spectroscopic data supporting their structures. (**7**): mp 65-66°C; $[\alpha]^{26}_D$=-17.4° (c 1.15,MeOH). (**9**): $[\alpha]^{26}_D$=+117.6° (c 1.15, MeOH). (**11**): $[\alpha]^{26}_D$=+137.1° (c 0.62, MeOH). (**3a**·oxalate salt): mp 85-87°C; $[\alpha]^{26}_D$=+19.6° (c 0.28, MeOH). (**2a**·2 oxalate salt): mp 102-103°C; $[\alpha]^{26}_D$=+83.8° (c 0.6, MeOH). (**4a**·1.3 oxalate salt): mp 77-81°C; $[\alpha]^{23}_D$=+10.9° (c 0.96, MeOH). (**22**): mp 59-60°C; $[\alpha]^{23}_D$=+6.7° (c 0.33, MeOH).

4. For a review of N-protected α-amino aldehydes, see Jurczak, J.; Golebiowski, A., *Chem. Rev.* **1989**, *30*, 1197.

5. The *tert*-Boc group as an activator for α'-lithiation of carbamates of pyrrolidines and piperidines is well documented. Beak, P.; Lee, W.K., *Tetrahedron Lett.*, **1989**, *30*, 1197, and references therein.

6. Amstutz, R.; Close, A.; Gmelin, G., *Helv. Chim. Acta*, **1987**, *70*, 2232.

7. Garner, P.; Park, J.M., *J. Org. Chem.*, **1987**, *52*, 2361.

8. (a) After this work had been completed, publication of compound **2a** became known. However, the compound was prepared by a different method: Lundkvist, J.R.M.; Ringdahl, B.; Hacksell, B., *J. Med. Chem.*, **1989**, *32*, 863. Lundkvist, J.R. M.; Wistrand, L.-G.; Hacksell, U., *Tetrahedron Lett.*, **1990**, *31*, 719. (b) Compounds of **2a** type prepared by a strategy similar to ours have been disclosed recently: Trybulski, E.J.; Kramss, R.H.; Mangano, R.M.; Rusinko III, A., 199th ACS National Meeting, Boston, Massachusetts, April, 1990; Abst. Med. Chem. 106.

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