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FACILE SYNTHESIS OF RESOLVED α-ETHYNYL-SUBSTITUTED CYCLIC AMINES

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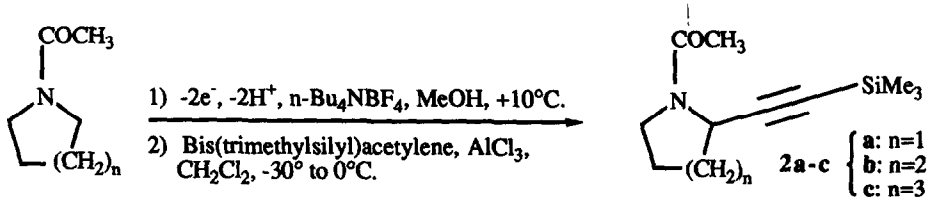
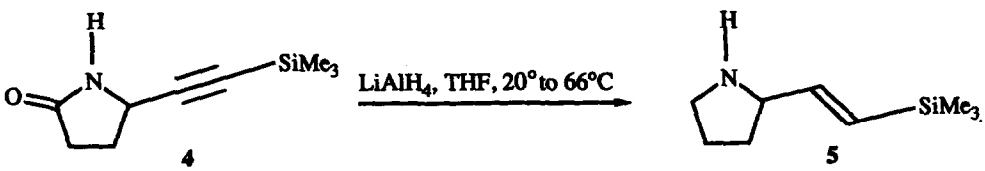
Summary: *A series of resolved α-acetylenic pyrrolidinyl, piperidinyl and perhydroazepinyl derivatives has been synthesized by a facile route including a key anodic oxidation step. Assignments of absolute configurations were based on chemical correlation and circular dichroism spectroscopy.*

As part of a current project dealing with conformationally restricted analougues of the interesting muscarinic agent N-Methyl-N-(1-methyl-4-pyrrolidino-2-butynyl)acetamide (BM 5),[1,2] we wanted access to the enantiomers of α-ethynyl pyrrolidinyl acetamide (**1a**),[3] α-ethynyl piperidinyl acetamide (**1b**), and α-ethynyl perhydroazepinyl acetamide (**1c**). The racemic precursors **2a-c** are conveniently prepared in about 70, 45 and 70% yield, respectively, from the corresponding acetamides.[4,5]

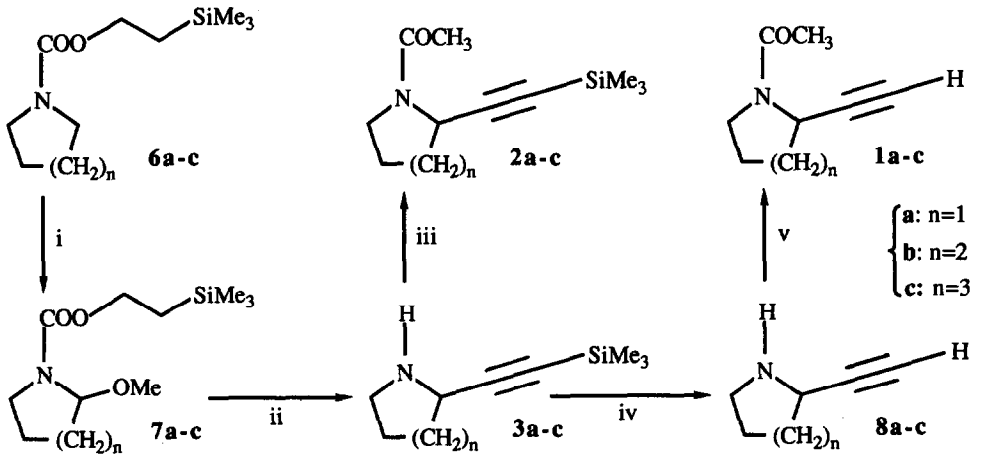


Although the enantiomers of **1a** could be separated analytically by chiral liquid chromatography on microcrystalline triacetylcellulose,[6] attempts to use this technique on a preparative scale were discouring because of a low degree of separation. Since the corresponding secondary amines (**3a-c**) might serve as synthetic precursors to **1a-c**, we chose to attempt resolution of racemic **3a-c** by fractional crystallization of the corresponding diastereomeric salts. However, preliminary attempts to prepare **3a** by reduction ($LiAlH_4$, THF, 22°C and 66°C) of the readily available lactam **4**,[3,4d] predominantly produced vinyl pyrrolidine **5**.



4 **5**

More successful experiments indicated that amines **3a-c** could be obtained by hydrolysis of amides **2a-c** in fairly good yields. Nevertheless, the following synthetic sequence turned out to be the most convenient. Acylation of pyrrolidine, piperidine and perhydroazepine with 2-(trimethylsilyl)ethyl chloroformate[7] and Et_3N in ether furnished carbamates **6a-c** in 92, 87 and 73% yield, respectively. Anodic oxidation[4a] of **6a-c** in MeOH gave methoxylated carbamates **7a-c** in 95-98% yield. These products were treated with bis(trimethylsilyl)acetylene (1.2 equiv) and anhydrous $AlCl_3$ (2.5 equiv) in CH_2Cl_2 at -30°C. Aqueous work-up with potassium sodium tartrate and potassium carbonate afforded the acetylenic amines **3a-c**, which were isolated as the oxalates in 92, 88 and 86% yield, respectively. Thus, the amidoalkylation of the carbamate protected amines **7a-c** proceeded more effectively than those of the corresponding acetyl protected cyclic amines. Racemic **3a-c** were resolved by recrystallisation of diastereomeric salts formed with appropriate optically active acids (Table I). Whereas the resolutions of **3a** and **3c** produced enantiomers of very high optical purities in acceptable yields, the resolution of the di-O-p-toluoyl-tartrates of **3b** was less satisfactory. The resolved amines were converted into the oxalates which were acetylated to give the enantiomers of **2a-c**. Desilylation (KF in refluxing MeOH) of **3a-c** produced the enantiomers of **8a-c** which were converted into the corresponding acetamides (**1a-c**). Selected physical data of the resolved compounds are shown in Table II.



Reagents: i) $-2e^-$, $-2H^+$, n-Bu_4NBF_4, MeOH, +10°C. ii) Bis(trimethylsilyl)acetylene, $AlCl_3$, CH_2Cl_2, -30°C to room temperature. iii) CH_3COCl, $NaHCO_3$ (aq), CH_2Cl_2, +4°C. iv) KF, MeOH, 64° C. v) CH_3COCl, Et_3N, Et_2O, +4°C.

Table I. Resolution of the α-Acetylenic Amines **3a-c**. Yields and Physical Data of the Diastereomeric Salts.

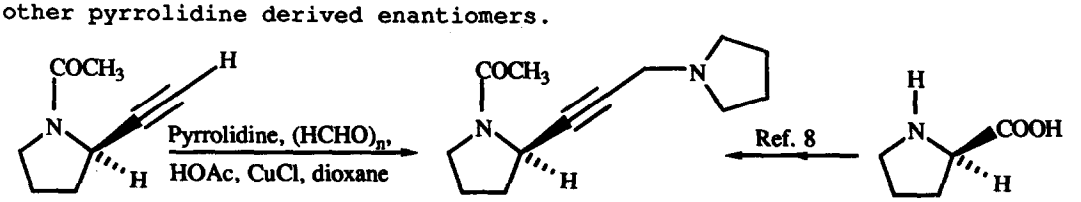
Amine	Resolving acid[a]	Recrystallisation solvent	Yield (%)	Optical purity[b] (% e.e)	$[\alpha]_D^{22}$ (c 1.4, MeOH)
(R)-3a	(+)-L-TA	95% EtOH	74	99.0	+39.2°
(S)-3a	(-)-D-TA	"	65	99.0	-38.9°
(R)-3b	(-)-4-TTA	95% EtOH/Et_2O	9	95.0	-89.7°
(S)-3b	(+)-4-TTA	"	6	94.0	+88.7°
(R)-3c	(-)-R-MA	"	52	99.8	-29.8°
(S)-3c	(+)-S-MA	"	58	99.8	+29.9°

[a] (+)-L-TA= (+)-L-tartaric acid; (-)-D-TA= (-)-D-tartaric acid; (-)-4-TTA= (-)-Di-O-4-toluoyl-L-tartaric acid; (+)-4-TTA= (+)-Di-O-4-toluoyl-D-tartaric acid; (-)-R-MA= (-)-R-mandelic acid; (+)-S-MA= (+)-S-mandelic acid.
[b] Assessed by capillary-GC analysis of diastereomeric amides of R-(-)-O-methylmandelic acid.

Table II. Yields and Physical Data of Some Resolved α-Acetylenic Cyclic Amines and Related Derivatives.

Compound	Yield (%)	Mp/Bp (mmHg) (°C)	$[\alpha]_D^{22}$ (c 1.4, MeOH)	Compound	Yield (%)	Mp. (°C)	$[\alpha]_D^{22}$ (c 1.4, MeOH)
(R)-3a·oxalate	-	160-161	+33.8°	**(R)-8a**·oxalate	74	139-140	+27.7°
(S)-3a·oxalate	-	160-161	-34.4°	**(S)-8a**·oxalate	84	139-140	-28.6°
(R)-3b·oxalate	-	137-138	+20.4°	**(R)-8b**·oxalate	88	116-117	+16.0°
(S)-3b·oxalate	-	135-137	-18.7°	**(S)-8b**·oxalate	86	118-119	-16.5°
(R)-3c·oxalate	-	145-146	+18.3°	**(R)-8c**·oxalate	92	157-158	+12.8°
(S)-3c·oxalate	-	145-146	-18.7°	**(S)-8c**·oxalate	88	157-158	-12.7°
(R)-2a	96	70-71 (0.04)	+159°	**(R)-1a**	76	43-47	+146°
(S)-2a	98	72-73 (0.05)	-161°	**(S)-1a**	70	43-47	-143°
(R)-2b	87	oil	+188°	**(R)-1b**	75	51-52	+180°
(S)-2b	87	oil	-180°	**(S)-1b**	87	51-53	-177°
(R)-2c	99	72-74 (0.02)	+190°	**(R)-1c**	89	101-102	+197°
(S)-2c	98	70-72 (0.01)	-190°	**(S)-1c**	79	101-102	-194°

The absolute configuration of the acetamide **(+)-1a** was determined by chemical correlation; **(+)-1a** was converted into **(+)-9** by a Mannich reaction. The absolute configuration of **(+)-9** has recently been unambiguously established by total synthesis from (+)-D-proline.[8] This establishes the absolute configuration **(+)-(R)-1a** as well as that of the other pyrrolidine derived enantiomers.



(+)-(R)-1 **(+)-(R)-9** (+)-D-Proline

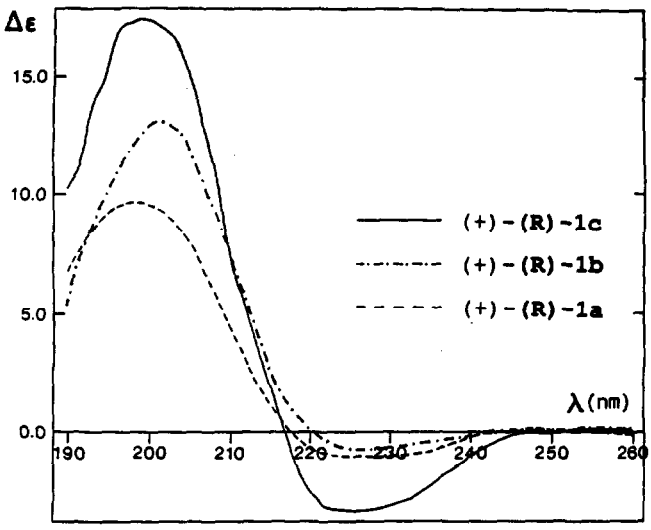


Fig 1. CD-spectra of (+)-(R)-1a-c

The absolute configurations of the enantiomers of **1b** and **1c** were deduced from their circular dichroism (CD) spectra (Figure 1). Compounds **1a-c** produced UV spectra with a single maximum at 200±2 nm, corresponding to an allowed π/π^* transition of the amide group, having a molar absorptivity of about 10000. CD spectra of acetonitrile solutions of the dextrorotatory enantiomers of **1a-c** were very similar; they consisted of two bands - a strong positive band at about 200 nm and a weak negative band at about 230 nm. The latter corresponds to a forbidden n/π^* transition. In addition, the bands produced by the homologues had similar molar ellipticities. The consistency of the CD spectra of the homologuous enantiomers strongly indicates that (+)-**1b** and (+)-**1c** have the same absolute configuration as (+)-(R)-**1a**. This allowed assignment of the configuration of all stereoisomers in Table II.

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