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# A Chiral Synthesis of (−)-Spiro[1-azabicyclo[2.2.2]octane-3,5′-oxazolidin-2′-one]: A Conformationally Restricted Analogue of Acetylcholine That Is a Potent and Selective α7 Nicotinic Receptor Agonist

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**Abstract:** A direct, short chiral synthesis of the selective α7 nicotinic receptor agonist (−)-spiro[1-azabicyclo[2.2.2]-octane-3,5′-oxazolidin-2′-one] (AR-R17779) is presented. The key step utilized attack of the dianion of the (*R*)-HYTRA ester [(*R*)-(+)-2-hydroxy-1,2,2-triphenylethyl acetate] on quinuclidin-3-one, followed by a selective precipitation of the diasteriomeric tertiary alcohol that led to (*S*)-(−)-AR-R17779 in two additional steps.

The ubiquitous role of acetylcholine (ACh) as a key neurotransmitter has been well documented.[3] In particular, ACh is the natural agonist for neuronal nicotinic receptors, whose activation has been linked to important processes such as modulating neurotransmission and sensory gating.[4] Deficiency of ACh nicotinic activation has been associated with cognition deficits (including Alzheimer's Disease), psychosis, depression, and anxiety.[5] Not surprising, there are a multitude of ACh nicotinic receptors, and crucial to understanding the role of each of the nicotinic receptors is the discovery of agents that can selectivity mimic the action of ACh at a single nicotinic receptor subtype. To this end, we have recently disclosed the discovery of a conformationally restricted analogue of ACh (AR-R17779) which is selective for the α7 nicotinic receptor (α7 AChNR).[6,7] AR-R17779 represents an extremely useful tool for understanding α7 ACh NRs because to date it is the only potent and selective α7 AChNR agonist available.[8] AR-R17779 is a single (−)-enantiomer, and it is over 100-fold more potent as an α7 AChNR agonist than its (+)-antipode. The original racemic synthesis[6,7] that produced AR-R17779 and its (+)-enantiomer utilized the reaction of the enolate of *tert*-butyl acetate with 3-quinuclidinone (Scheme 1). The resulting *tert*-butyl *β*-hydroxyester was converted to the corresponding methyl ester [(±)-**2a**], which was then converted to the hydrazide [(±)-**3**]. The desired racemic cyclic carbamate [(±)-**4**] was obtained via a Curtius rearrangement [55% of racemate from quinuclidinone (**1**)]. Resolution of (±)-**4** with dibenzoyl-L-tartaric acid afforded AR-R17779 [(−)-**4**], but in a very poor yield (6%, 3% overall yield from **1**). Since our original synthesis of AR-R17779 required this low-yielding, classical resolution to obtain the pure, single (−)-enantiomer of **4** (AR-R17779), we desired a direct stereogenic synthesis of AR-R17779. This note details the successful outcome of that effort.

Previous reports on the use of HYTRA ester dianion enolates suggested that that reagent could attack aldehydes in a diastereogenic fashion differentiating between the faces of the aldehyde carbonyl.[9] This property of the dianion enolate of the HYTRA esters was much less precedented for prochiral ketones. However, viewing 3-quinuclinone as the appropriate precursor for the synthesis of AR-R17779, we reacted the dianion enolate of (*R*)-HYTRA ester [(*R*)-**5**][10] with quinuclidinone (Scheme 2). Not surprisingly, the reaction only provided a modest diastereoselectivity (approximately 3:2), favoring the desired (*R*,*S*)-diastereomer of **2b**. However, serendipitously, the solubility of the two diastereomers in chloroform was vastly different. This property was easily exploited with the desired (*R*,*S*)-diastereomer precipitating upon digestion in chloroform of the crude reaction solid. After recovering a second crop, the yield of the desired ester [(*R*,*S*)-**2**] was 48%. Direct conversion of the ester [(*R*,*S*)-**2**] to the hydrazide [(*S*)-**3**]was accomplished by using hydrazine in methanol with sodium cyanide as an aminolysis catalyst.[11] In this step, transesterification likely occurred first, liberating the (*R*)-HYTRA alcohol and forming the chiral methyl ester. Hydrazinolysis then followed to form (*S*)-**3**. The (*R*)-HYTRA alcohol was easily recovered in this step by simple precipitation from water. The resulting aqueous solution of the hydrazide [(*S*)-**3**] was then directly subjected to a Curtius rearrangement to afford (*S*)-(−)-**4** [AR-R17779, 37%]. The overall yield in this synthesis of stereogenically pure (−)-AR-R17779

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[2] Deceased: This paper is dedicated to the memory of the outstanding chemist Robert A. Mack.

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[8] Recently, a number of patents and patent applications have been published describing new α7 ACh NRs agonists (and antagonists), claiming these compounds to be potent and selective agents. However, to date, only AR-R17779 has been fully described in the peer reviewed literature.

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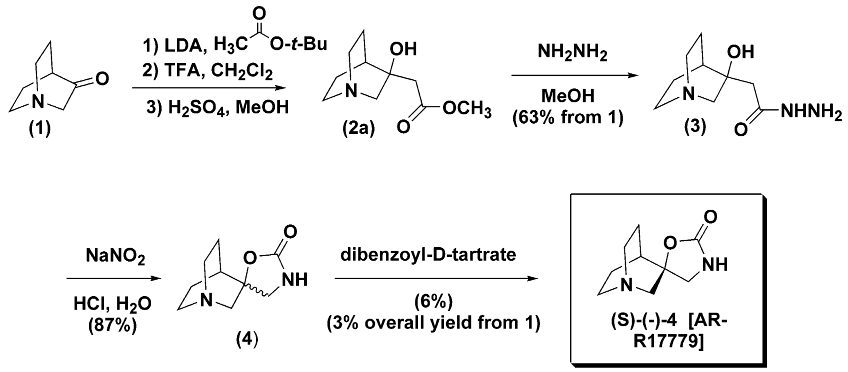
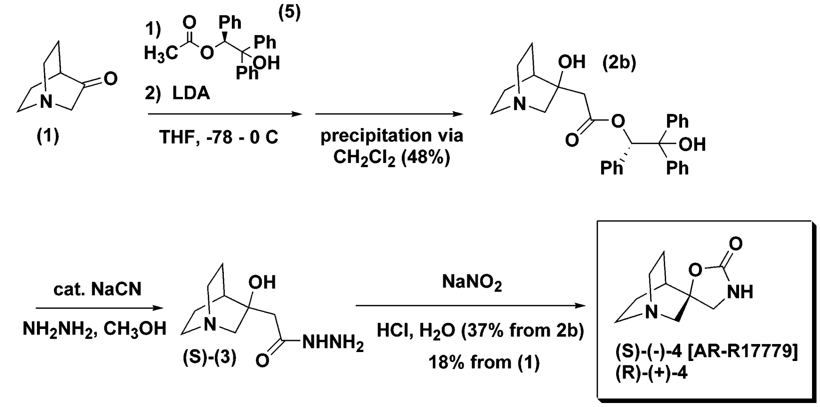
10.1021/jo049404q CCC: $27.50

**SCHEME 1**



**SCHEME 2**



was 6-fold greater than the original synthesis [18% versus 3% from quinuclidinone (**1**), respectively]. Thus, this enantioselective route provided a very direct and scaleable access to this key agonist selective for α7 ACh NRs. This synthetic route also gave easy access to the inactive (*R*)-(+)-enantiomer of **4**, using the (*S*)-HYTRA ester.

In summary, we have used the enolate of (*R*)-HYTRA ester [(*R*)-(**5**)] to provide a succinct, stereoselective, and improved route to a key pharmacological tool for studying α7 ACh NRs (AR-R17779), and this methodology provides ready access to significant quantities of this tool for further in vivo evaluations.

## Experimental Section

Melting points were determined in capillary tubes on an oil bath apparatus and are uncorrected. Optical rotations were measured with a digital polarimeter. NMR spectra were determined in the indicated solvent on a 200- or a 500-MHz NMR spectrometer at the ambient temperature with tetramethylsilane (TMS) as the internal standard. Chemical shifts are given in ppm and coupling constants are in hertz. Splitting patterns are designated as follows: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Infrared spectra were recorded on a FTIR spectrophotometer. Mass spectra were recorded by a quadrupole mass spectrometer for desorption chemical ionization (CI) or by a mass spectrometer for electrospray (ES). High-resolution mass spectra were obtained with a QTOF mass spectrometer. Elemental analyses were performed internally and were within 0.4% of the theoretical value when indicated by symbols of the elements, unless otherwise noted.

**(*R*)-(+)-2′,2′,1′-Triphenyl-2-hydroxyethyl-(*S*)-3-hydroxy-1-azabicyclo[2.2.2]octane-3-acetate [(*R*,*S*)-(+)-2b].** Under a nitrogen atmosphere, a 2.0 M solution of lithium diisopropylamide in THF (33 mL, 66 mmol) was added dropwise over 55 min to a suspension of (*R*)-(+)-1,1,2-triphenyl-1,2-ethanediol-2-acetate[10] (10 g, 30 mmol) in 100 mL of THF, with stirring at −78 °C. The reaction was allowed to warm gradually over 30 min to 0 °C, stirred for an additional 15 min, and then recooled to −78 °C. To this orange solution was added a solution of 1-azabicyclo[2.2.2]octan-3-one (**1,** 3.75 g, 30 mmol) in THF (60 mL) dropwise over 35 min. The reaction then was stirred for 2 h, and quenched via addition of a saturated solution of aqueous $NH_4Cl$ (55 mL) over 15 min, followed by the addition of water (100 mL). The resulting white precipitate was filtered off, rinsed with water, and dried. This solid was heated in chloroform (150 mL) and the mixture cooled to ambient temperature and filtered to give 5.7 g of ester [(*R*,*S*)-(+)-**2**]. An additional 0.9 g (total yield 48%) was obtained from the mother liquor by recrystallization: mp 225−226 °C ($CHCl_3$). HPLC (hydrocarb S 4.6 × 25 mm, 1:1 $CH_3CN$/0.5 M $NaClO_4$, 1.00 mL/min) 9.67 min (98%); $[\alpha]^{22}_{D}$ +91 (*c* 1.1, DMSO); $^{13}C$ NMR (200 MHz, DMSO-$d_6$) δ 170.0, 145.1, 144.6, 137.1, 128.7, 127.5, 126.8, 126.7, 126.5, 78.9, 78.4, 69.6, 62.6, 46.1, 45.8, 44.5, 31.4, 23.4, 21.4; $^1H$ NMR (200 MHz, DMSO-$d_6$) δ 7.61−6.98 (m, 15H), 6.57 (s, 1H), 6.30 (s, 1H), 4.25 (s, 1H), 2.74−2.28 (m, 8H), 1.81 (m, 1H), 1.58−1.20 (m, 3H), 1.20−0.97 (m, 1H); IR (KBr, $cm^{-1}$) 1715; ESMS *m*/*z* 458. Anal. Calcd for $C_{29}H_{31}NO_4$ + 1.75% $CHCl_3$: C, 74.97; H, 6.72; N, 3.01. Found: C, 75.01; H, 6.71; N, 2.96.

**(*S*)-(−)-2′,2′,1′-Triphenyl-2-hydroxyethyl-(*R*)-3-hydroxy-1-azabicyclo[2.2.2]octane-3-acetate [(*S*,*R*)-(−)-2b].** Using the identical conditions described above, reaction of 2.75 g (8.27 mmol) of (*S*)-(−)-1,1,2-triphenyl-1,2-ethanediol-2-acetate, 940 mg (7.51 mmol) of 1-azabicyclo[2.2.2]octan-3-one (**1**), and 10.3 mL (20.6 mmol) of a 2.0 M solution of lithium diisopropylamide in THF provided 1.74 g (51%) of the *S*,*R*-ester [(*S*,*R*)-(−)-**2b**]: mp, 223−224 °C ($CHCl_3$); $[\alpha]^{22}_{D}$ −88 (*c* 1.0, DMSO); chiral HPLC (96.5%); $^{13}C$ NMR (200 MHz, DMSO-$d_6$) δ 170.0, 145.1, 144.6, 137.1, 128.7, 127.5, 126.8, 126.7, 126.5, 78.9, 78.4, 69.6, 62.5, 46.1, 45.8, 44.4, 31.4, 23.4, 21.4; $^1H$ NMR (200 MHz, DMSO-$d_6$)

*δ* 7.48 (m, 2H), 7.38−7.00 (m, 13H), 6.58 (s, 1H), 6.03 (s, 1H), 4.28 (s, 1H), 2.70−2.31 (m, 8H), 1.93−1.71 (m, 1H), 1.57−1.00 (m, 4H). Anal. Calcd for $C_{29}H_{31}NO_4$ + 1.74% $CHCl_3$: C, 74.97; H, 6.72; N, 3.01. Found: C, 74.43; H, 6.78; N, 3.03.

**(*S*)-(−)-Spiro[1-azabicyclo[2.2.2]octane-3,5′-oxazolidin-2′-one] [(*S*)-(−)-4, AR-R17779].** Hydrazine (2 mL, 64 mmol) and KCN (40 mg, 0.61 mmol) were added to a suspension of (*R*,*S*)-(+)-**2b** (5.66 g, 12.4 mmol) in MeOH (225 mL). The suspension was then heated to reflux under a nitrogen atmosphere for 24 h, cooled to ambient temperature, and concentrated to a semisolid in vacuo. The semisolid was heated to reflux in water, then cooled and filtered. The resulting white solid was recrystallized from methanol to give returned (*R*)-(+)-1,1,2-triphenyl-1,2-ethanediol-2-acetate [**5**, 2.88 g (80%), $[\alpha]^{22}_D$ +219 (*c* 1.0, MeOH) (lit. value, +220)].

The aqueous filtrate, containing the hydrazide [(*S*)-**3**], was concentrated to 30 mL, cooled in an ice bath, and acidified to pH 1 with concentrated HCl. A solution of sodium nitrite (880 mg, 12.8 mmol) in water (5 mL) was added dropwise over 15 min (gas evolution), and the resulting solution was heated to 80 °C and stirred for 3 h. The solution was then cooled in an ice bath, basicified to pH 11 with concentrated $NH_4OH$, saturated with NaCl, and extracted with $CHCl_3$ (4 × 50 mL). The organic extract was cooled in an ice bath and treated with HCl gas to afford the hydrochloride salt of (*S*)-(−)-**4** [(−)-AR-R17779] as a white solid (1.0 g, 37%): $[\alpha]^{22}_D$ −63.9 (*c* 1.0, MeOH) identical in all physical aspects as has been previously reported.[6]

**(*R*)-(+)-Spiro[1-azabicyclo[2.2.2]octane-3,5′-oxazolidin-2′-one] [*R*-(+)-4].** Reaction of 1.0 g (2.18 mmol) of ester (*S*,*R*)-(−)-**2b** with 0.34 mL of hydrazine and 7 mg (5 mol %) of KCN under the above conditions gave hydrazide [(*R*)-**3**] along with returned (*S*)-1,1,2-triphenyl-ethane-1,2,-diol (500 mg), $[\alpha]^{22}_D$ −206 (*c* 1.0, EtOH) (lit. value, −214). Following treatment with $NaNO_2$ (155 mg, 2.25 mmol), the intermediate hydrazide (*R*)-**3** was converted to [*R*-(+)-**4**] and isolated as its HCl salt (150 mg, 31%): $[\alpha]^{22}_D$ +63 (*c* 1.0, MeOH). The other physical properties were identical to its antipode.

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