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Synthesis of 3-Azidopiperidine Skeleton Employing Ceric Ammonium Nitrate (CAN)-Mediated Regioselective Azidoalkoxylation of Enol Ether: Total Synthesis of D_2 Receptor Agonist (±)-Quinagolide

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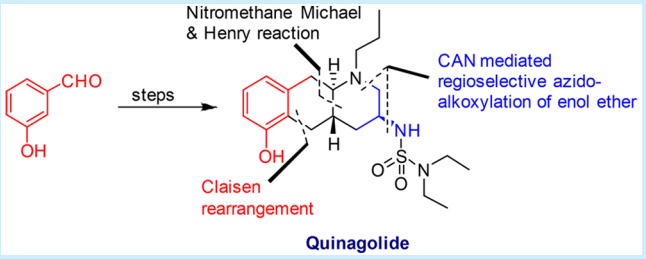
Supporting Information

ABSTRACT: The total synthesis of (±)-quinagolide, which is a D_2 receptor agonist, was accomplished via a ceric ammonium nitrate (CAN)-mediated regioselective azidoalkoxylation of enol ether route. Key features of the synthesis include Claisen rearrangement, PPTS (pyridinium *p*-toluenesulfonate)-catalyzed one-pot acetal deprotection, followed by a diastereoselective Henry reaction, which enables construction of the required *trans* ring junction and CAN-mediated regioselective azidoalkoxylation of enol ether. The PPTS-catalyzed intramolecular diastereoselective Henry reaction to fix three contiguous stereocenters on tetrahydronaphthalene and the first-of-its-kind synthesis of the 3-azidopiperidine skeleton, using a CAN-mediated regioselective azidoalkoxylation of enol ether, are important findings of the present work.



Ergot alkaloids and their synthetic derivatives are well-known for their biological activities.[1] Ergolines CQ 32-084 (**1**), pergolide (**2**), and apomorphine (**3**) are well-known dopamine agonists. Quinagolide (**4**), which is a selective D_2 receptor agonist that is used for the treatment of elevated levels of prolactin has the combined structural features of both ergolines and apomorphine (see Figure 1).[2,3] Quinagolide hydrochloride is marketed by Ferring Pharmaceuticals (Lausanne, Switzerland) under the trade name Narprolac. The synthesis and biological activity of quinagolide was first reported by Nordmann et al. in racemic form, using *β*-tetralone[2] as the starting material and, subsequently, in the year 2000, Banziger et al. reported the large-scale synthesis of a quinagolide intermediate.[4]

Although quinagolide is sold in its racemic form, the dopaminomimetic activity is entirely associated with the (−) enantiomer[5] and it would be desirable to use the (−) enantiomer for medicinal use. Also, the synthesis of the *trans*-fused amino piperidine skeleton poses a challenge to synthetic chemists. The medicinal use of quinagolide and necessity to make it available in enantiomerically pure form prompted us to undertake its synthesis under our research program, directed toward the expedient synthesis of drug molecules[6] having societal importance.

3-Aminopiperidine scaffolds constitute an integral part of several natural products and biologically active compounds.[7] For the synthesis of 3-aminopiperidine scaffolds, azidoalkoxylation of endocyclic enecarbamate is a well-established method.[8] In this context, a methodology of CAN-mediated azidoalkoxylation of enol ethers was previously reported by our group.[9] In the present work, the idea was to utilize this methodology for the synthesis of the 3-aminopiperidine

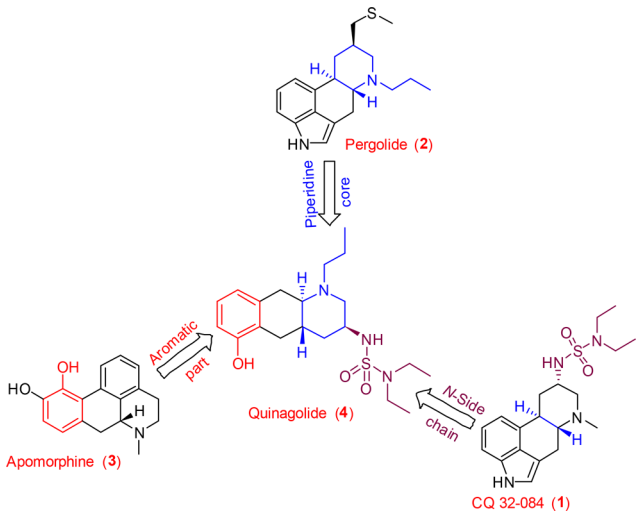


Figure 1. Quinagolide (**4**) showing combined structural features of both ergolines and apomorphine.

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skeleton of quinagolide, as this route would enable quick access to the piperidine ring, as well as the nitrogen-containing side chain of quinagolide (see Figure 2).

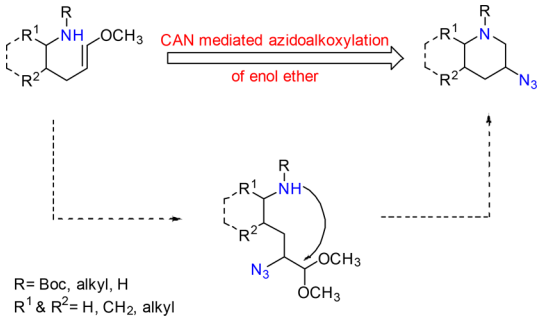
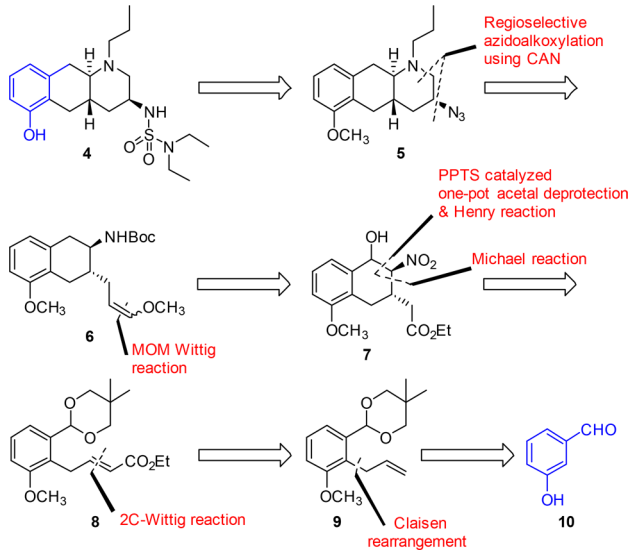


Figure 2. Initial hypothesis for 3-azidopiperidine synthesis (based on our previous work).

Accordingly, a retrosynthetic plan proposed for (±)-quinagolide **4** is depicted in Scheme 1.

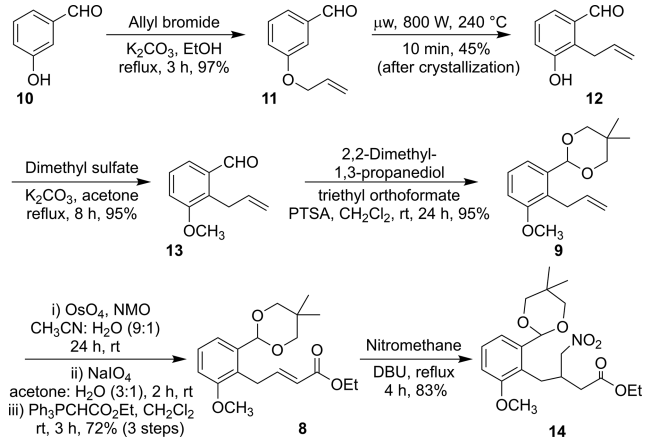
Scheme 1. Retrosynthetic Plan



Thus, quinagolide **4** could be obtained from enol ether **6** by employing a CAN-mediated regioselective azidoalkoxylation of enol ether, followed by necessary functional group interconversions. Enol ether **6** could be obtained from nitroester **7** by double hydrogenation and ester to enol ether conversion using a Wittig reaction. Nitroester **7** could be accessed from unsaturated ester **8** by Michael addition of nitromethane and PPTS-catalyzed concomitant acetal deprotection, followed by a diastereoselective Henry reaction. The unsaturated ester **8** could be obtained from *meta*-hydroxybenzaldehyde **10**, using Claisen rearrangement and two carbon Wittig reaction on compound **9** as the key steps.

Accordingly, synthesis of quinagolide **4** began with the synthesis of Henry reaction precursor nitroester **14** from commercially available *meta*-hydroxybenzaldehyde as the starting material. *meta*-Hydroxybenzaldehyde **10** (Scheme 2) was treated with allyl bromide and K_2CO_3 under reflux conditions to obtain allyl ether **11** in 97% yield. Compound **11** when irradiated in a microwave for 10 min, undergoing Claisen rearrangement to furnish the rearranged phenol **12** in 45%

Scheme 2. Synthesis of Henry Reaction Precursor Nitroester 14



yield. The other byproduct was a *para*-allyl derivative, which was separated by crystallization. Then, the free hydroxyl group of **12** was methylated using dimethyl sulfate and K_2CO_3 to afford compound **13** in 95% yield. Aldehyde **13** was protected as its acetal derivative **9**, using 2,2-dimethyl-1,3-propanediol in 95% yield.

The olefin **9** was dihydroxylated using OsO_4-NMO, followed by diol cleavage using $NaIO_4$ and a two-carbon Wittig reaction on the resulting aldehyde to furnish unsaturated ester **8** in 72% yield over three steps. Unsaturated ester **8** on Michael addition of nitromethane under reflux conditions using DBU as the base furnished nitroester **14**, as a Henry reaction precursor in 83% yield.[10]

When nitroester **14** was subjected to acetal deprotection using PTSA in acetone−water under reflux conditions followed by treatment with catalytic pyridine in CH_2Cl_2, nitrostyrene **7c**[11] was isolated in 66% yield (see Table 1). Alternatively, acetal deprotection was achieved using $FeCl_3$ and the corresponding aldehyde was subjected to a Henry reaction using catalytic DBU or alumina. In both cases, nitrostyrene **7c** was isolated as a major product. It was realized that commercially available PPTS gave variable results, whereas freshly prepared PPTS exclusively furnished nitroalcohols **7a** and **7b** in a 1:1 diastereomeric ratio in 82% combined yield. Both of the diastereomers were separated by repeated column chromatography, and the structure of **7a** was confirmed by single-crystal X-ray analysis, wherein the nitro group and ester were found to be *trans*, as required in quinagolide **4**. The structure of **7b** was confirmed by ^{1}H NMR analysis (Figure 3), via a comparison with ^{1}H NMR of **7a** (coupling constant between three contiguous stereocenters for **7a** are 9.5 and 11.6 Hz, whereas, for **7b**, the corresponding coupling constants are 3.2 and 11.0 Hz).

It was noteworthy that acetal deprotection, followed by a diastereoselective Henry reaction, was performed in one pot in which two out of three stereocenters were incorporated into the product in the desired configuration. A diastereoselective Henry reaction using PPTS to fix three contiguous stereocenters on tetrahydronaphthalene was an important finding, in context to the total synthesis of natural product having this structural requirement.[12]

Our next aim was the synthesis of enolether **6** for the key azidoalkoxylation reaction. To this end, reduction of the mixture of nitroesters **7a** and **7b** to corresponding amine and

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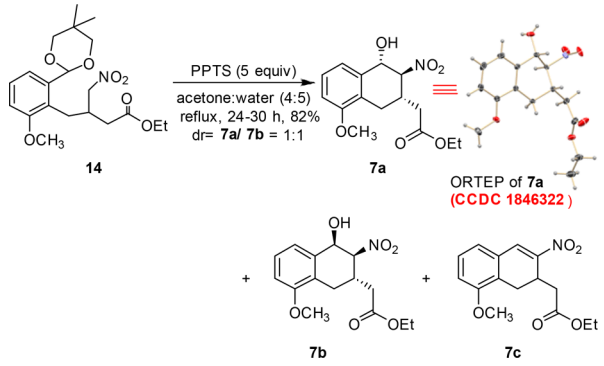
Table 1. PPTS-Catalyzed One-Pot Acetal Deprotection: Diastereoselective Henry Reaction



entry	conditions	yield (7a + 7b + 7c)	ratio (7a:7b:7c)
1	(i) PTSA, acetone−water (1:1), reflux, 24 h	66%	0:0:1
	(ii) pyridine (cat.), CH_2Cl_2, rt, 1 h	(2 steps)	
2	(i) $FeCl_3$, CH_2Cl_2, reflux, 20 min	80%	0:0:1
	(ii) DBU (cat.), rt, 10 min	(2 steps)	0:0:1
3	(i) $FeCl_3$, CH_2Cl_2, reflux, 20 min	86%	0:0:1
	(ii) Neutral alumina, CH_2Cl_2, rt, 2 h	(2 steps)	0:0:1
4	PPTS (commercial, 3 equiv), acetone:water (1:1), reflux, 24 h	61% + 25% (14)	1:1:0
5	PPTS (commercial, 5 equiv), acetone:water (4:5), reflux, 24 h	75%	1:1:0.5
6	PPTS (fresh, 5 equiv), acetone:water (4:5), reflux, 24−30 h	82%	1:1:0

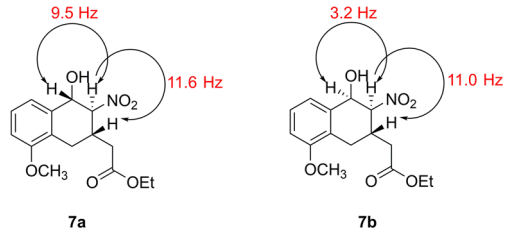
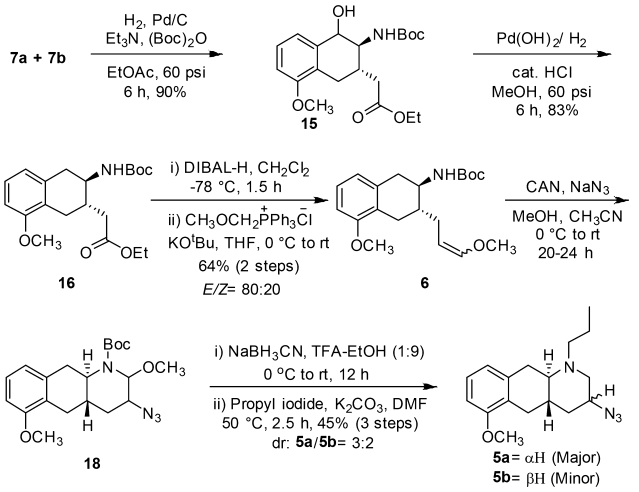


Figure 3. Coupling constants between protons of three contiguous stereocenters for **7a** and **7b**.

its concomitant Boc protection was achieved by hydrogenation using Pd/C and Boc anhydride to afford compound **15** as a diastereomeric mixture in 90% yield (see Scheme 3). Benzylic deoxygenation of **15** was performed using $Pd(OH)_2$ under hydrogenation conditions to furnish ester **16** as a single diastereomer in 83% yield. One-pot nitro reduction, concomitant protection of resulting amine and benzylic deoxygenation under hydrogenation condition could not be realized. The next step was synthesis of enol ether **6** from ester **16**, wherein the ester **16** was reduced with DIBAL-H and the corresponding aldehyde was treated with MOM Wittig salt and potassium *t*-butoxide in THF at 0 °C to afford enol ether **6** in 64% yield (E/Z = 80:20) over two steps.[13]

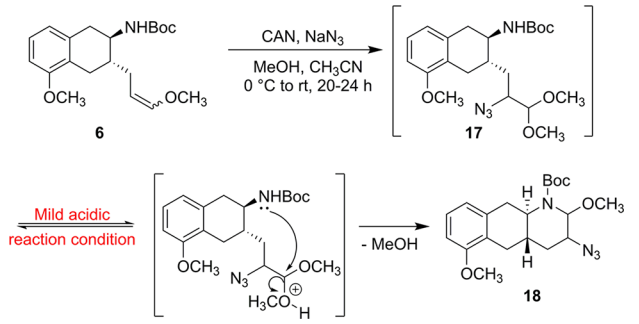
Having enol ether **6** in hand, it was subjected to the methodology of azidoalkoxylation earlier reported by our group.[9] Accordingly, enol ether **6** was treated with NaN_3, CAN and a stoichiometric amount of MeOH in acetonitrile as a solvent. However, instead of conventional azidoalkoxylation product **17**, formation of tricyclic piperidine **18** was observed as a complex diastereomeric mixture. Formation of tricyclic ring **18** can be explained on the basis of regioselective azidoalkoxylation of the enol ether **6** followed by nucleophilic

Scheme 3. CAN-Mediated Azidoalkoxylation of Enol Ether



addition of pendant amine present in **17** under slightly acidic reaction condition on the resulting acetal to obtain compound **18** as a diastereomeric mixture (see Scheme 4).

Scheme 4. Plausible Mechanism for Formation of Tricyclic Piperidine 18 from Enol Ether 6



In the next step, compound **18** was treated with sodium cyanoborohydride in TFA−EtOH (1:9),[14] followed by alkylation of amine using propyl iodide and K_2CO_3 in DMF at 50 °C to afford tricyclic ring system **5a** and **5b** in a 3:2 diastereomeric ratio in 45% combined yield from enol ether **6**. The major diastereomer **5a**, which was found to be the required one, was separated by repeated column chromatography and its structure was confirmed by detailed NMR analysis.[15] To the best of our knowledge, such a type of 3-azidopiperidine synthesis using a CAN-mediated regioselective azidoalkoxylation of enol ether is the first of its kind, which allows rapid access to piperidine-based natural products and biologically active compounds containing such a type of functionality.[7]

The next step was reduction of azide **5a** to amine **19**, which was performed under Staudinger reaction conditions[16] in 83% yield (see Scheme 5). Amine **19** was sulfonated using diethylsulfamoyl chloride and Et_3N in $CHCl_3$ afforded compound **20** in 71% yield. To complete the total synthesis, the last step was demethylation of **20**, which was performed using $AlCl_3$−EtSH to afford quinagolide **4** in 66% yield.[17] The analytical and spectral data obtained for quinagolide **4** were in complete agreement with the reported data.[2]

In summary, total synthesis of (±)-quinagolide was achieved from *meta*-hydroxybenzaldehyde in 14 purification steps. A

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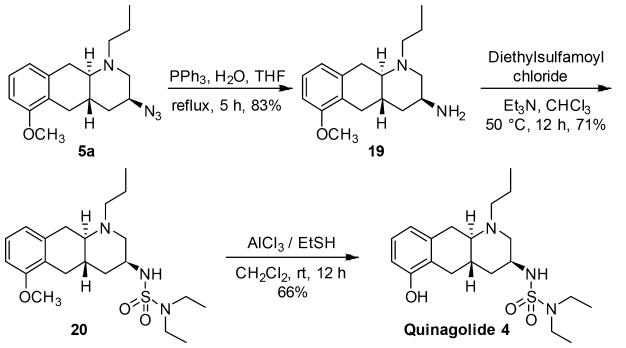
Scheme 5. Completion of the Total Synthesis



PPTS-catalyzed one-pot acetal deprotection, followed by a diastereoselective Henry reaction, which enables construction of required *trans* geometry, and CAN-mediated regioselective azidoalkoxylation of enol ether, which allows quick access to the piperidine ring, as well as nitrogen-containing side chain of quinagolide, are noteworthy features. A diastereoselective Henry reaction using PPTS to fix three contiguous stereocenters on tetrahydronaphthalene and synthesis of 3-azidopiperidines using CAN mediated regioselective azidoalkoxylation of enol ether are important findings of this synthesis and hopefully will find more applications in total synthesis in the near future. The enantioselective total synthesis of quinagolide is currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02900.

NMR spectra, 2D-NMR analysis, detailed experimental procedures, and characterization data (PDF)

Accession Codes

CCDC 1846322 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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