OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Enantioselective Formal Total Synthesis of (−)-Quinagolide

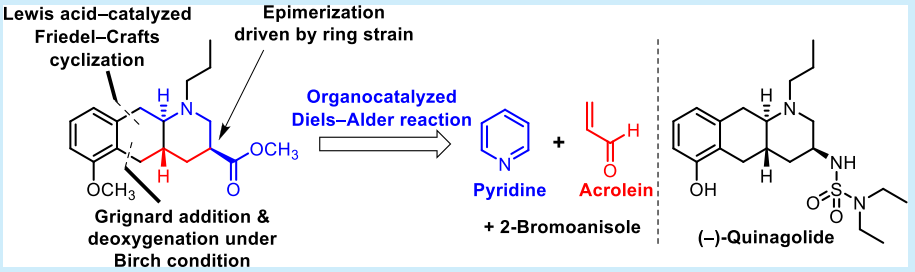
Subhash P. Chavan,*[,†,‡] Appasaheb L. Kadam,[†,‡] and Rajesh G. Gonnade[‡,§]

[†]Division of Organic Chemistry, CSIR-National Chemical Laboratory, Pune 411008, India

[‡]Academy of Scientific and Innovative Research (AcSIR), New Delhi 110025, India

[§]Physical and Materials Chemistry Division, CSIR-National Chemical Laboratory, Pune 411008, India

Supporting Information



ABSTRACT: The enantioselective formal total synthesis of (−)-quinagolide has been accomplished in a linear sequence of 8 purification steps from pyridine. The key steps are (a) organocatalyzed Diels−Alder reaction for fixing all three stereocenters on piperidine ring; (b) protecting group enabled deoxygenation of isoquinuclidine skeleton under Birch reduction condition; (c) Lewis acid ($TiCl_4$) catalyzed intramolecular Friedel−Crafts cyclization of dicarboxylic acid; and (d) one-pot diastereoselective ketone reduction−intramolecular cyclization to form oxazolidinone which enables *trans*-geometry installation. During the course of the synthesis, an interesting reductive cleavage of the C−N bond in the electron-deficient isoquinuclidine skeleton under the Birch reduction conditions has been observed. This is the first synthetic effort to access the core skeleton of (−)-quinagolide.

The isoquinuclidine (2-azabicyclo[2.2.2]octane) ring system is found in a wide number of natural products, namely iboga-type alkaloids.[1] Elegant methods for the synthesis of chiral isoquinuclidines have been developed, especially since Fukuyama's synthesis of oseltamivir using organocatalyzed Diels−Alder reaction.[2] Despite the high functionalization ability of isoquinuclidine to provide complex scaffolds in chiral fashion, its applications for the synthesis of natural products and bioactive compounds are scarce.[1] To date, there are only three synthetic approaches (total synthesis of oseltamivir by Fukuyama[2] and (+)-luciduline by Charette[3] and formal synthesis of catharanthine by Batey[4]) reported in the literature in which application of the chiral isoquinuclidine skeleton constructed via organocatalyzed Diels−Alder reaction has been demonstrated.

Due to our continued interest in the synthesis of biologically active compounds, we were interested in the enantioselective synthesis of (−)-quinagolide (**1**) by taking advantage of the chiral isoquinuclidine skeleton. Quinagolide (**1**), a selective D_2 receptor agonist used for the treatment of elevated levels of prolactin, has combined structural features of well-known dopamine agonists, namely ergolines CQ 32-084 (**2**), pergolide (**3**), and apomorphine (**4**) (Figure 1). Furthermore, quinagolide (**1**) has distinct advantages over bromocriptine (**5**) and cabergoline (**6**), which are currently available medications for the treatment of hyperprolactinemia.[5] Quinagolide hydrochloride as its racemate is marketed by

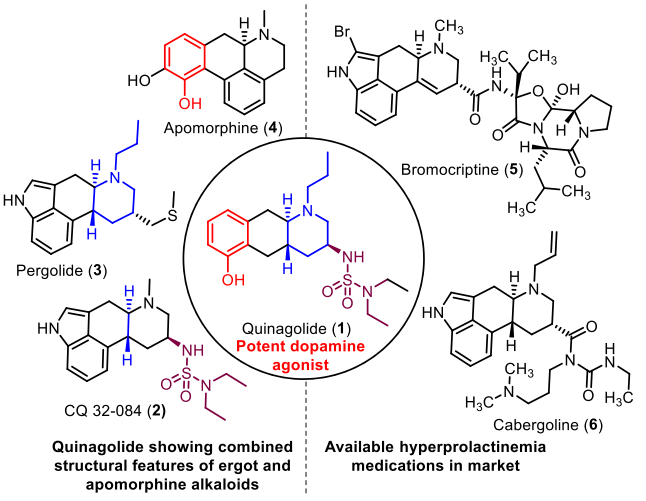


Figure 1. Available hyperprolactinemia medications on the market and structural features of quinagolide (**1**).

Ferring Pharmaceuticals, Switzerland, under the trade name Norprolac.

Received: October 1, 2019

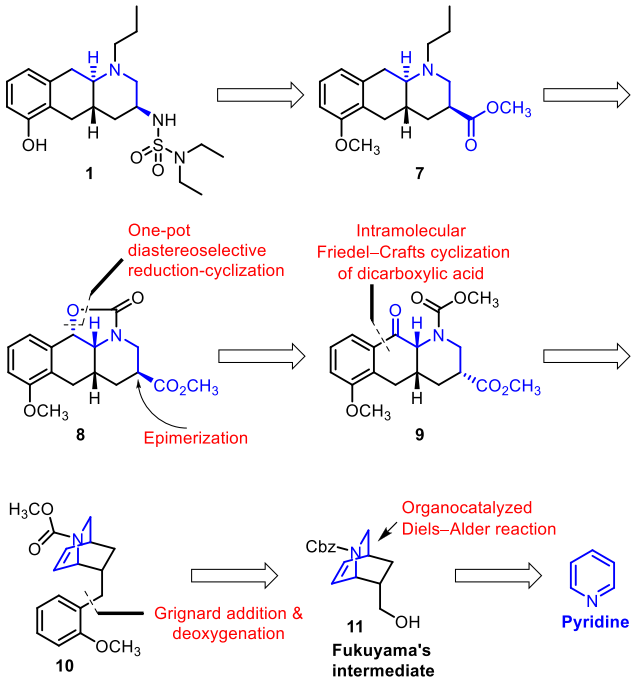
DOI: 10.1021/acs.orglett.9b03477
Org. Lett. XXXX, XXX, XXX−XXX

In the year 1985, Nordmann et al. from Sandoz Ltd. reported the synthesis and biological activity of quinagolide.[6] Subsequently, in 2000, scalable synthesis of quinagolide intermediate was reported by Banziger et al. from Novartis Ltd.[7] Recently, our group reported the entirely different approach for the total synthesis of (±)-quinagolide.[8] Though Nordmann et al. resolved the intermediate of (±)-quinagolide and found that the dopaminomimetic activity is entirely associated with the (−)-enantiomer,[6b] to date, enantioselective total synthesis of (−)-quinagolide is not reported in the literature. In this context, the development of a new synthetic route for the enantioselective synthesis of (−)-quinagolide is highly desirable.

From the last few decades, pyridine has served as an ideal choice of starting material for the effective total synthesis of alkaloids in enantioselective fashion while also providing the basic nitrogen atom as well.[2−4,9] In this context, the nitrogen atom and the three necessary stereocenters on the piperidine ring of quinagolide could be introduced from pyridine via organocatalyzed Diels−Alder reaction of the corresponding dihydropyridine and acrolein.[10] Further, the tricyclic ring skeleton of quinagolide could be constructed by Grignard addition followed by Friedel−Crafts cyclization.

On the basis of these deliberations, retrosynthetic analysis for target molecule **1** is outlined in Scheme 1. We envisioned

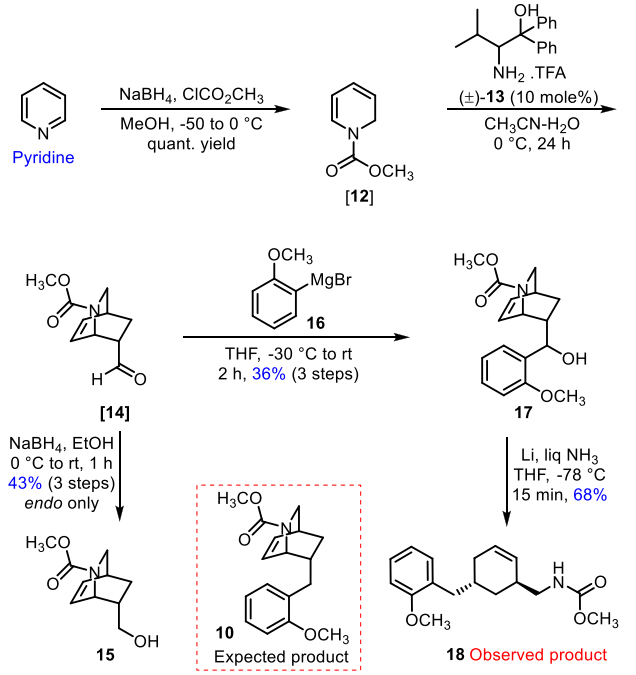
Scheme 1. Retrosynthetic Analysis



that bicyclic precursor **10** could be effectively converted to tricyclic skeleton **7** of quinagolide (**1**) via functionalization of olefin part of bicyclic precursor **10** into keto-ester **9**. The steps involved could be Lewis acid catalyzed intramolecular Friedel−Crafts cyclization of dicarboxylic acid followed by epimerization at tetracyclic intermediate **8**, which in turn could be synthesized from keto-ester **9** through one-pot reductive cyclization. Bicyclic precursor **10** could be successively constructed via Grignard addition on bicyclic aldehyde corresponding to Fukuyama's intermediate **11**,[2] which in turn could be synthesized using organocatalyzed Diels−Alder reaction followed by benzylic deoxygenation under Birch reduction condition.

In initial attempts to establish a synthetic strategy toward **7**, our efforts commenced with pyridine, acrolein, and racemic β-amino alcohol **13**[10] as an organocatalyst (Scheme 2).

Scheme 2. Initial Attempt



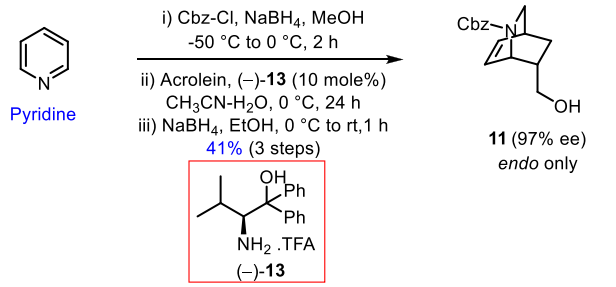
Pyridine was treated with methyl chloroformate and $NaBH_4$ in MeOH to afford dihydropyridine **12** in quantitative yield. The Diels−Alder reaction of dihydropyridine **12** with acrolein using (±)-**13** as an organocatalyst furnished the desired adduct **14**. For the characterization purpose, aldehyde **14** was reduced using $NaBH_4$ to corresponding bicyclic alcohol **15** (*endo* only) in 43% yield over three steps. In the next step, the crude aldehyde **14** was subjected for addition reaction of Grignard reagent **16** derived from 2-bromoanisole to provide the inseparable mixture of diastereomeric alcohol **17** in 36% yield over three steps. At this stage, deoxygenation of **17** would have provided bicyclic alkene **10**. For deoxygenation of **17**, literature known reaction conditions were screened, but either complex reaction mixture or desired product formation in very poor yield was observed. Under the Birch reduction conditions, instead of obtaining the expected product **10**, ring-opened carbamate **18** was isolated as a major product in 68% yield. The structure of **18** was confirmed by detailed 2D-NMR analysis, and the ring-opening of isoquinuclidine **17** under the Birch reduction conditions could be explained on the basis of the mechanism proposed (see the SI).[11] It is noteworthy to mention that this type of ring-opening of isoquinuclidine under the Birch reduction conditions is the first of its kind and hopefully will find more applications in the context of the total synthesis of alkaloids and drug development.

We thought that the methylcarbamate protecting group played a vital role in the opening of bicyclic intermediate **17** under the Birch reduction condition. Synthesis of a bicyclic amine having a protecting group like *N*-Cbz would solve our problem as *N*-Cbz can be easily deprotected under Birch

DOI: 10.1021/acs.orglett.9b03477
Org. Lett. XXXX, XXX, XXX−XXX

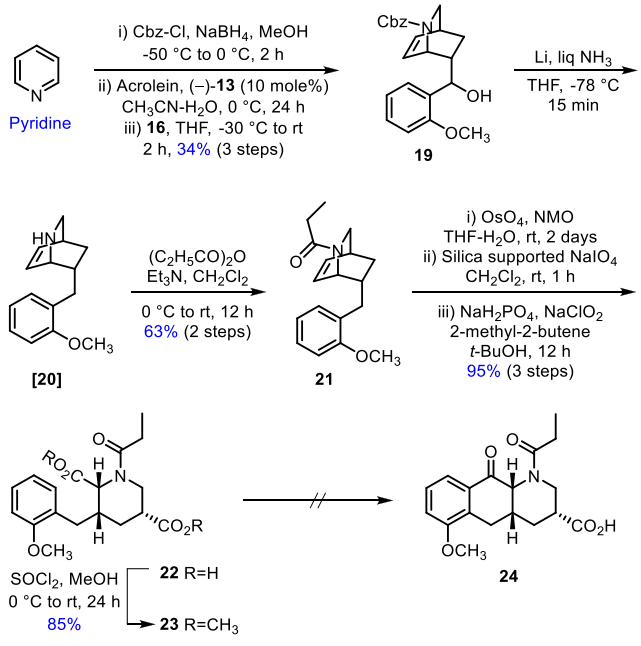
reduction conditions, and thus, ring opening will be prevented. Thus, Fukuyama's intermediate **11** was successfully synthesized on a gram scale (41% yield over three steps) and in high enantiomeric excess (97% ee) following Nakano-type Diels–Alder reaction using (−)-**13** derived from L-valine as an organocatalyst (Scheme 3).[10]

Scheme 3. Synthesis of Fukuyama's Intermediate 11



In the next step, the bicyclic aldehyde obtained from the Diels–Alder reaction was subjected to the addition reaction of Grignard reagent **16** derived from 2-bromoanisole to obtain bicyclic intermediate **19** in 34% yield over three steps (Scheme 4).

Scheme 4. Attempted Synthesis of Tricyclic Skeleton



At this stage, deoxygenation of bicyclic intermediate **19** under the Birch reduction conditions worked well according to our observations to furnish bicyclic amine **20**. The next step was the protection of bicyclic amine with a suitable group which can be easily converted to tertiary propylamine in the final product. Accordingly, bicyclic amine **20** was protected as its amide derivative **21** using propionic anhydride in 63% yield over two steps. The amide **21** was then dihydroxylated using OsO_4–NMO, and the crude diol was subjected to cleavage using silica-supported $NaIO_4$ to provide the corresponding dialdehyde. The crude dialdehyde was immediately subjected to Pinnick oxidation to afford dicarboxylic acid **22** in 95% yield over three steps.[12] For the purpose of characterization, dicarboxylic acid **22** was converted into the corresponding methyl diester **23** in 85% yield. At this stage, as per our plan, intramolecular Friedel–Crafts cyclization of dicarboxylic acid **22** using Lewis acid would have provided tricyclic keto-acid **24**. But unfortunately, several attempts failed to cyclize dicarboxylic acid **22** into tricyclic core **24**.

Detailed literature analysis revealed that the methylcarbamate protection of α-amino acid might be essential for its intramolecular Friedel–Crafts cyclization.[13] Accordingly, bicyclic amine **20** was protected as it is methylcarbamate derivative **10** using methyl chloroformate in 64% yields (Scheme 5). Following the same sequence of dihydroxylation–diol cleavage and Pinnick oxidation used in Scheme 4, olefin **10** was converted into the corresponding dicarboxylic acid **20** in 95% yield over three steps.

Intramolecular Friedel–Crafts cyclization was found to be the crucial step in this synthesis. Several attempts for the intramolecular Friedel–Crafts cyclization of the dicarboxylic acid **25** were made to arrive at an optimized condition as shown in Table 1.

The same was accomplished by converting dicarboxylic acid **25** into the corresponding acid chloride followed by $TiCl_4$-mediated Friedel–Crafts cyclization to afford tricyclic keto-ester **9** in 62% yield. The relative stereochemistry of **9**, which is found to be *cis*, was determined by single-crystal X-ray analysis of the corresponding acid **26**. At this stage, our plan was the two-center epimerization at the tricyclic core **9** to obtain the desired stereochemistry. Many attempts for the epimerization of **9** failed. Also, the deprotection of methyl carbamate was not realized mainly because of either aromatization or decomposition of starting material. When ketone **9** was subjected to reduction using $LiBH_4$ in THF, tetracyclic carbamate **27** was isolated as a single diastereomer in 68% yield (Scheme 5). The structure and absolute stereochemistry of compound **27** were confirmed by single-crystal X-ray analysis. In the next step, epimerization at the ester center of compound **27** was performed using $NaOCH_3$ in MeOH to obtain tetracyclic skeleton **8** in 70% yield with the required stereochemistry. At this stage also, the structure and absolute stereochemistry of compound **8** were confirmed by single-crystal X-ray analysis.

The next task was the installation of a *trans*-ring junction. To this end, the opening of tetracyclic carbamate **8** was performed by refluxing in ethanolic NaOH[14] and subsequent esterification with diazomethane furnished corresponding tricyclic amino alcohol **28** in 53% yield (Scheme 6). The amino-alcohol **28** was treated with PTSA under reflux in toluene[15] in order to form intermediate enamine followed by its reduction with $NaBH_3CN$ and *N*-alkylation of the corresponding amine using propyl iodide to afford compound **7** in 61% yield over two steps. Compound **7** showed ^1H and ^{13}C NMR spectra, identical with those of a racemic sample reported in the literature,[7,8b] and since the synthesis of (−)-quinagolide (**1**) from compound **7** was reported by Nordmann et al.,[6] the present work constitutes the formal total synthesis of (−)-quinagolide.

In summary, we have accomplished the enantioselective formal total synthesis of (−)-quinagolide in a linear sequence of eight purification steps from pyridine. The key steps used in the synthesis were organocatalyzed Diels–Alder reaction for fixing all three stereocenters on piperidine ring, Birch deoxygenation, Lewis acid ($TiCl_4$) catalyzed intramolecular Friedel–Crafts cyclization of diacarboxylic acid, and one-pot diastereoselective ketone reduction–intramolecular cyclization

DOI: 10.1021/acs.orglett.9b03477
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 5. Successful Synthesis of the Core Skeleton of Quinagolide

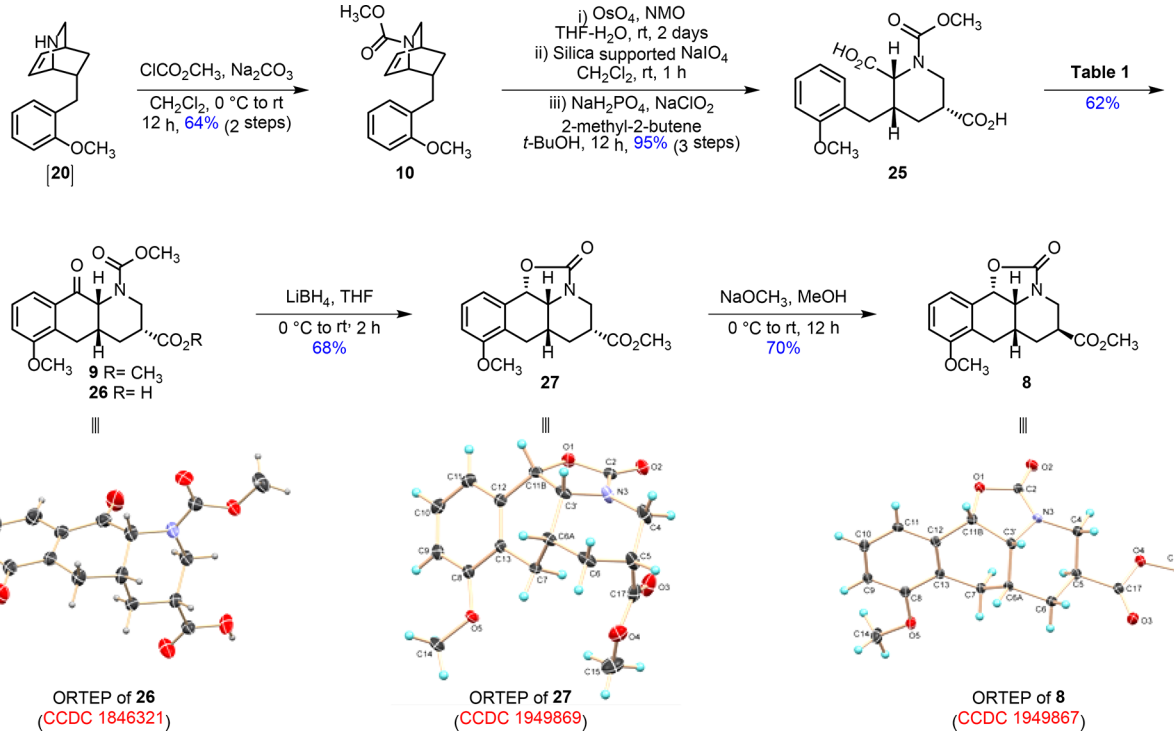
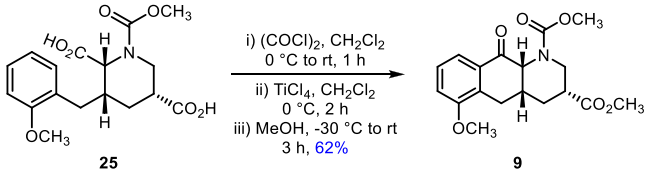


Table 1. Intramolecular Friedel–Crafts Cyclization of Dicarboxylic Acid 25

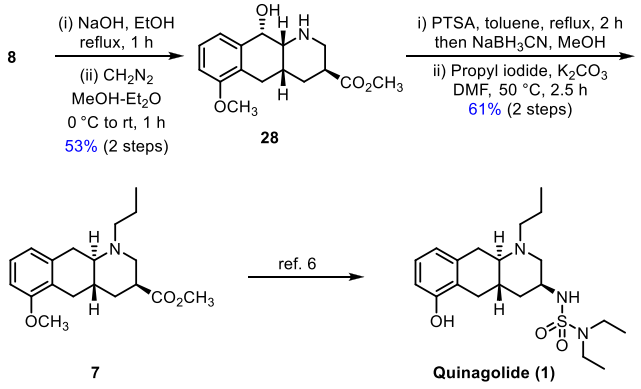


entry	reagents	equiv	temp (°C)	time (h)	yield[a,b] (%)
1	CF_3SO_2H	0.2	45	1.5	*c*
2	TFA/TFAA	2.4	rt	3	NR[d]
3	PPA	5	80	2	*c*
4	BF_3.OEt	2.5	0	3.5	NR[d]
5	TFAA/BF_3.OEt	5	40	4	*c*
6	$FeCl_3$.$MeNO_2$	3.1	0	2	*c*
7	$SnCl_4$	2.2	0	1	*c*
8	$AlCl_3$	4.0	0	0.5	25
9	$AlCl_3$	4.0	0	2	37
10	$TiCl_4$	4.0	0	0.5	40
11	$TiCl_4$	4.0	0	2	52
12	**$TiCl_4$**	**5**	**0**	**2**	**62**

[a]Isolated yield of **9**. [b]Reaction was performed on corresponding acid chloride of **25**. [c]Complex reaction mixture. [d]No reaction.

to form tetracyclic oxazolidinone which provides required *trans*-geometry. The reductive cleavage of C–N bond in an electron-deficient isoquinuclidine skeleton under Birch reduction conditions to access substituted cyclohexenes was an important finding and hopefully will find more applications in total synthesis and drug development programs in the near future.

Scheme 6. Completion of the Formal Synthesis of (−)-Quinagolide



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03477.

Detailed experimental procedures and characterization data, 2D-NMR spectra of **18**, X-ray details of compounds **26**, **27**, and **8**, and ^{1}H, ^{13}C and DEPT NMR spectra of all compounds (PDF)

Accession Codes

CCDC 1846321, 1949867, and 1949869 contain 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

DOI: 10.1021/acs.orglett.9b03477
Org. Lett. XXXX, XXX, XXX–XXX

Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author

*E-mail: sp.chavan@ncl.res.in.

ORCID

Subhash P. Chavan: 0000-0002-2889-3344
Appasaheb L. Kadam: 0000-0002-0452-2901
Rajesh G. Gonnade: 0000-0002-2841-0197

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

A.L.K. thanks UGC, New Delhi, for the award of a research fellowship. The authors thank CSIR, New Delhi for financial support as part of the XII year plan program under title ORIGIN (CSC-0108) and ACT (CSC-0301). We also thank Dr. P. R. Rajamohanan (CSIR-NCL, Pune) for help with 2D NMR analysis and Dr. H. B. Borate (CSIR-NCL, Pune) for carefully evaluating the manuscript.

REFERENCES

(1) Silva, E. M. P.; Rocha, D. H. A.; Silva, A. M. S. *Synthesis* **2018**, *50*, 1773.

(2) Satoh, N.; Akiba, T.; Yokoshima, S.; Fukuyama, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 5734.

(3) Barbe, G.; Fiset, D.; Charette, A. B. *J. Org. Chem.* **2011**, *76*, 5354.

(4) Kim, S. J.; Batey, R. A. *Org. Chem. Front.* **2018**, *5*, 2934.

(5) (a) Di Sarno, A.; Landi, M. L.; Marzullo, P.; Di Somma, C.; Pivonello, R.; Cerbone, G.; Lombardi, G.; Colao, A. *Clin. Endocrinol.* **2000**, *53*, 53. (b) Barlier, A.; Jaquet, P. *Eur. J. Endocrinol.* **2006**, *154*, 187. See also references cited therein.

(6) (a) Nordmann, R.; Petcher, T. J. *J. Med. Chem.* **1985**, *28*, 367. (b) Nordmann, R.; Widmer, A. *J. Med. Chem.* **1985**, *28*, 1540.

(7) Banziger, M.; Cercus, J.; Stampfer, W.; Sunay, U. *Org. Process Res. Dev.* **2000**, *4*, 460.

(8) (a) Chavan, S. P.; Kadam, A. L.; Lasonkar, P. B.; Gonnade, R. G. *Org. Lett.* **2018**, *20*, 7011. (b) Chavan, S. P.; Kadam, A. L.; Kawale, S. A. *ACS Omega* **2019**, *4*, 8231.

(9) (a) Campbell, M. M.; Sainsbury, M.; Searle, P. A.; Davies, G. M. *Tetrahedron Lett.* **1992**, *33*, 3181. (b) Abou-Jneid, R.; Ghoulami, S.; Martin, M. T.; Huu Dau, E. T.; Travert, N.; Al-Mourabit, A. *Org. Lett.* **2004**, *6*, 3933. (c) Lemire, A.; Charette, A. B. *Org. Lett.* **2005**, *7*, 2747. (d) Sales, M.; Charette, A. B. *Org. Lett.* **2005**, *7*, 5773. (e) Schroif-Gregoire, C.; Travert, N.; Zaparucha, A.; Al-Mourabit, A. *Org. Lett.* **2006**, *8*, 2961. (f) Satoh, N.; Akiba, T.; Yokoshima, S.; Fukuyama, T. *Tetrahedron* **2009**, *65*, 3239. (g) Lemire, A.; Charette, A. B. *J. Org. Chem.* **2010**, *75*, 2077.

(10) Suttibut, C.; Kohari, Y.; Igarashi, K.; Nakano, H.; Hirama, M.; Seki, C.; Matsuyama, H.; Uwai, K.; Takano, N.; Okuyama, Y.; Osone, K.; Takeshita, M.; Kwon, E. *Tetrahedron Lett.* **2011**, *52*, 4745.

(11) Compound **18** (major) showed complex ^{1}H and ^{13}C NMR spectra due to the presence of rotamers and minor olefin regioisomer. For similar types of ring opening of 7-azabenzonorbornenes under Birch reduction conditions, see: Hodgson, D. M.; Winning, L. H. *Beilstein J. Org. Chem.* **2008**, *4*, 38.

(12) Maison, W. *Eur. J. Org. Chem.* **2007**, *2007*, 2276.

(13) Melillo, D. G.; Larsen, R. D.; Mathre, D. J.; Shukis, W. F.; Wood, A. W.; Colleluori, J. R. *J. Org. Chem.* **1987**, *52*, 5143.

(14) Steinhagen, H.; Corey, E. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 1928.

(15) Cuevas, J.-C.; Snieckus, V. *Tetrahedron Lett.* **1989**, *30*, 5837.

DOI: 10.1021/acs.orglett.9b03477
Org. Lett. XXXX, XXX, XXX−XXX