OL | Organic Letters

Letter

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

pubs.acs.org/OrgLett

A Domino Aza-Piancatelli Rearrangement/Intramolecular Diels–Alder Reaction: Stereoselective Synthesis of Octahydro-1*H*-cyclopenta[*cd*]isoindole

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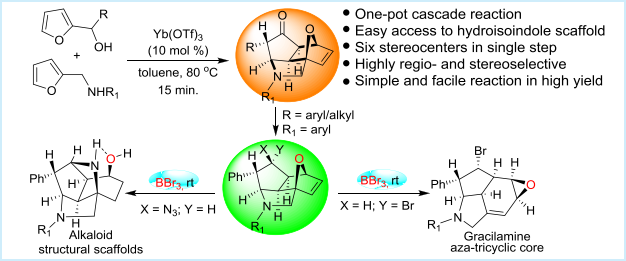
Supporting Information

ABSTRACT: For the first time, an efficient one-pot method for the construction of an angularly fused 5–6–5 aza-tricyclic framework has been developed in a highly stereoselective manner. This domino reaction is a novel combination of aza-Piancatelli rearrangement and intramolecular Diels–Alder reaction, which readily furnishes hexahydro-2a,5-epoxy-cyclopenta[*cd*]isoindole adducts, bearing six contiguous stereogenic centers in very good yields. The BBr_3-mediated cleavage of the oxa-bridged adduct results in the formation of octahydro-1*H*-cyclopenta[*cd*]isoindole, an aza-tricyclic BCE core of a gracilamine alkaloid.



Domino reactions are highly atom-economical processes as multiple events occur in one pot, providing quick access to complex frameworks. The efficiency of this process has inspired much interest among the synthetic community to design and develop novel cascade strategies.[1] The angularly fused 5–6–5 aza-tricyclic core is very common in numerous natural products, exhibiting a broad spectrum of biological activities such as antipyretic,[2] antihypertensive,[3] anti-inflammatory,[4] antitumor,[5] anti-HIV,[6] and anticancer[7] (Figure 1).

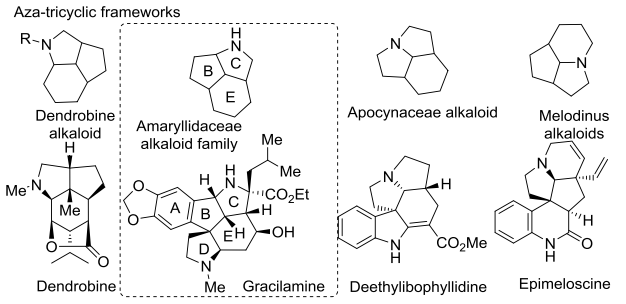


Figure 1. Aza-tricyclic alkaloid framework containing biologically important molecules.

Synthesis of alkaloids having an angularly fused aza-tricyclic core has attracted significant attention due to their structural complexity coupled with the broad spectrum of biological activities.[2−7]

Natural alkaloids such as dendrobine,[2] gracilamine,[3] deethylibophyllidine,[4] and epimeloscine[5] possess the 5–6–5 aza-tricyclic core (Figure 1). As a consequence of their remarkable structural frameworks, various approaches have been developed for the construction of the 5–6–5 aza-tricyclic core, using intramolecular [3+2] cycloaddition, Diels–Alder reaction, Mannich reaction, and radical cyclization as a key step.[3−6] Nevertheless, new synthetic strategies for the construction of functionalized the aza-tricyclic core with remarkable efficiency and exquisite selectivity are urgently being sought.

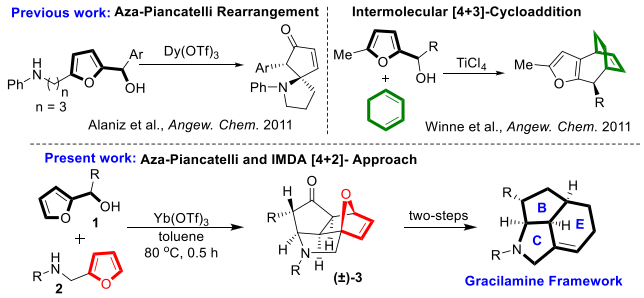
Furan and its derivatives have served as powerful synthons for the creation of structurally diverse natural and unnatural molecules.[8] Intriguingly, 2-furfurylcarbinol derivatives undergo a wide variety of chemical transformations, including metalation, cycloaddition, oxidation, and rearrangement reactions.[8−10] In particular, Piancatelli rearrangement is one of the most efficient synthetic methods available for the construction of 4-hydroxy-2-cyclopentenone from 2-furfurylcarbinol.[10] These functionalized intermediates served as valuable building blocks in the synthesis of a wide variety of biologically important molecules.[11,12] Alaniz et al. described a diastereoselective synthesis of azaspiro-fused cyclopentanone using aza-Piancatelli rearrangement as a key step,[13] whereas Winne and co-workers developed a novel Lewis acid-mediated [4+3] cycloaddition reaction of 2-furfurylcarbinol with 1,3-diene (Scheme 1).[14a] Moreover, Gou et al. have reported a [3+2] cycloaddition of 2-furfurylcarbinol with alkyl azide, leading to a new class of heterocyclic scaffolds.[14b]

Our continued interest in the development of novel domino strategies for the synthesis of biologically relevant molecules[15] has resulted in the design and synthesis of the bridged aza-tricyclic core of immunosuppressant FR901483.[16] Herein, we report for the first time a simple and highly efficient one-pot approach for the stereoselective construction of hexahydro-

Received: April 11, 2019

DOI: 10.1021/acs.orglett.9b01267
Org. Lett. XXXX, XXX, XXX–XXX

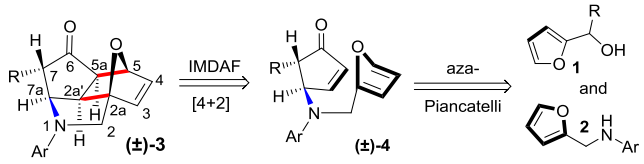
Scheme 1. Furfurylcarbinol-Based Novel Synthesis of the Aza-Tricyclic BCE Core of Gracilamine Alkaloid



2a,5-epoxy-cyclopenta[*cd*]isoindole, an aza-tricyclic core of gracilamine alkaloid, using a novel domino strategy based on aza-Piancatelli rearrangement coupled with intramolecular Diels–Alder (IMDA) reaction as a key step.

We anticipated that *N*-furfurylaniline **2** could serve as a nitrogen nucleophile in the aza-Piancatelli rearrangement of 2-furfuryl carbinol **1**, resulting in the formation of 4-amino-5-alkyl/aryl-cyclopentenone (±)-**4**, which in turn could undergo IMDA reaction with tethered furan to give oxa-bridged aza-tricyclic derivative (±)-**3** (Scheme 2).

Scheme 2. Domino Strategy for the Construction of the Angularly Fused 5–6–5 Aza-Tricyclic Core of Gracilamine

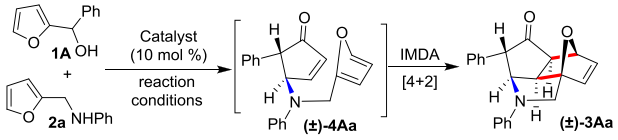


Thus, to test our hypothesis, furan-2-yl-(phenyl)methanol **1A** was treated with *N*-(furan-2-yl-methyl)aniline **2a** and camphor sulfonic acid (CSA, 10 mol %) in toluene and the resultant mixture was stirred at 80 °C for 1.5 h. The reaction mixture upon workup afforded the desired 5–6–5 fused aza-tricyclic adduct (±)-**3Aa** in 50% yield, and the structure of (±)-**3Aa** was unambiguously established on the basis of ^{1}H NMR, ^{13}C NMR, 2D NMR, and HRMS analyses.

To optimize the reaction condition, furan-2-yl-(phenyl)-methanol **1A** was allowed to react with *N*-(furan-2-yl-methyl)aniline **2a** in the presence of various Lewis and Brønsted acid catalysts in different solvents, and the results are summarized in Table 1. In the case of TfOH, TFA, $BF_3{\cdot}OEt_2$, and TMSOTf, the reaction was found to be very facile even at −10 °C in DCM; however, the desired product was isolated in low yield (Table 1, entries 2–5, respectively).

Among the catalysts screened, $Yb(OTf)_3$ was found to be the most ideal choice. Similarly, among the solvents screened, toluene was found to be the most suitable medium to carry out this reaction (Table 1, entry 10). Moreover, an extended reaction time or an elevated temperature did not improve the yield of the product (Table 1, entries 11 and 12). Thus, under the optimized conditions using $Yb(OTf)_3$ (10 mol %) in toluene at 80 °C, the desired aza-tricyclic adduct (±)-**3Aa** was isolated in 87% yield along with a small amount (~5%) of the uncyclized intermediate as an inseparable mixture (Table 1, entry 10).

Table 1. Optimization of the Domino Reaction Conditions[a]



entry	catalyst (10 mol %)	solvent	temp (°C)	time (h)	yield (%)[b]
1	CSA	toluene	80	1.5	50
2	TfOH	DCM	−10	0.15	42
3	TFA	DCM	−10	0.15	44
4	$BF_3{\cdot}OEt_2$	DCM	−10	0.15	50
5	TMSOTf	DCM	−10	0.15	50
6	$Yb(OTf)_3$	CH_3CN	70	7.0	70
7	$Yb(OTf)_3$	DCE	70	2.0	55
8	$Yb(OTf)_3$	toluene	28	32.0	40
9	$Yb(OTf)_3$	toluene	50	4.0	57
10	$Yb(OTf)_3$	toluene	80	0.25	87
11	$Yb(OTf)_3$	toluene	80	0.5	70
12	$Yb(OTf)_3$	toluene	90	0.25	55
13	$In(OTf)_3$	toluene	80	0.25	80
14	$Sc(OTf)_3$	toluene	80	0.5	68
15	$Zn(OTf)_2$	toluene	80	0.5	70

[a]Reaction conditions: **1** (0.5 mmol, 1.0 equiv), **2a** (0.55 mmol, 1.1 equiv), and $Yb(OTf)_3$ (10 mol %) in toluene (5 mL) at 80 °C. [b]Isolated yield.

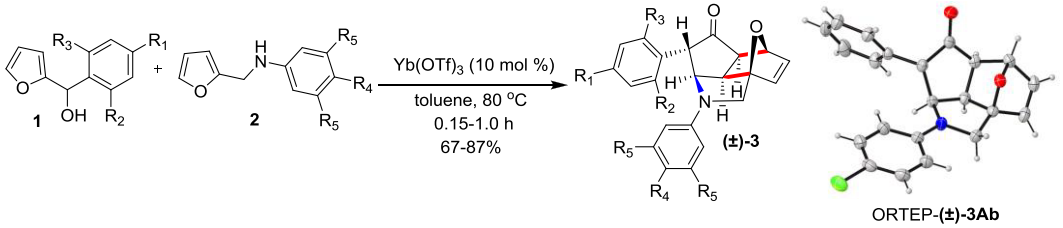
The scope of this domino reaction involving aza-Piancatelli rearrangement followed by IMDA reaction was investigated with different furfuryl alcohols and furfurylamine derivatives, and the results are summarized in Table 2. Initially, *ortho*- and *para*-substituted 2-furfurylcarbinols (**1A**–**1H**) were allowed to react with *N*-(2-furanyl)aniline derivatives bearing electron-donating and electron-withdrawing groups, and the corresponding adducts were isolated in good yields (Table 2, entries 1 and 2). The structure of the cyclized products was established using ^{1}H NMR, ^{13}C NMR, 2D NMR, and HRMS data, and the relative stereochemistry of adduct (±)-**3Ab** was further unambiguously confirmed by single-crystal X-ray analysis (Table 2).[17] Several functional groups such as halides, -^{t}Bu, -OMe, and -CO_2Et are found to be stable under the reaction conditions.

Moreover, sterically demanding 2-furfurylcarbinol **1I** also reacted readily with *N*-(2-furanyl)aniline derivatives **2a**, **2c**, and **2d** to furnish the corresponding aza-tricyclic adducts (±)-**3Ia**, (±)-**3Ic**, and (±)-**3Id**, respectively, in very good yields (Table 2, entry 3). Similarly, 3,5-dimethyl-*N*-furanylaniline derivative **2e** underwent smooth reaction with furylcarbinols **1A** and **1I** to furnish the corresponding adducts (±)-**3Ae** and (±)-**3Ie**, respectively, in good yields with a high degree of stereoselectivity (Table 2, entry 4). As anticipated, electron-deficient substrates (**2d** and **2e**) required slightly longer reaction times (Table 2). Moreover, 2-furfurylcarbinol bearing thiophene (**1J**) and isopropyl (**1K**) reacted readily with *N*-furfurylaniline derivatives (**2a** and **2b**) to furnish the aza-tricyclic adducts (±)-**3Ja** and (±)-**3Jb** and (±)-**3Ka** and (±)-**3Kb**, respectively, in good yields (Scheme 3).

Evidently, the intramolecular Diels–Alder reaction of the tethered furan (±)-**4** afforded the *exo* adduct as the only product. The exclusive formation of the *exo* adduct is further supported by the density functional theory (DFT) calculations. The DFT calculations showed that the formation of the *exo*

DOI: 10.1021/acs.orglett.9b01267
Org. Lett. XXXX, XXX, XXX–XXX

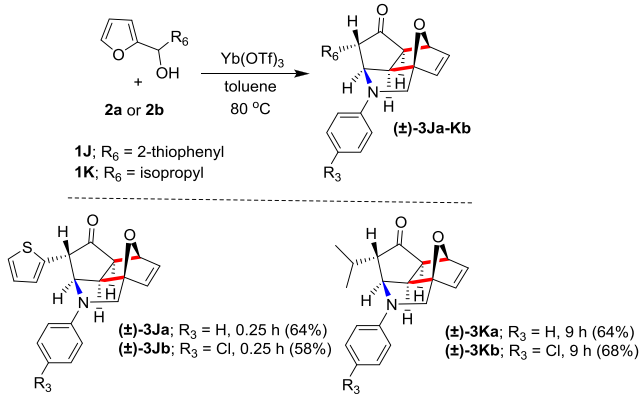
Table 2. Domino One-Pot Synthesis of Aza-Tricyclic Adducts



entry	2-furylcarbinol (**1**)	*N*-(2-furanyl)aniline (**2**)	time (h)	product [(±)-3]	yield (%)[a]
1	**1A**, R_1, R_2, R_3 = H	**2a**, R_4, R_5 = H	0.15	**3Aa**, R_1, R_2, R_3, R_4, R_5 = H	87
		2b, R_4 = Cl, R_5 = H	0.33	**3Ab**, R_1, R_2, R_3, R_5 = H, R_4 = Cl	81
		2c, R_4 = OMe, R_5 = H	0.15	**3Ac**, R_1, R_2, R_3, R_5 = H, R_4 = OMe	80
		2d, R_4 = CO_2Et, R_5 = H	0.75	**3Ad**, R_1, R_2, R_3, R_5 = H, R_4 = CO_2Et	75
2	**1B**, R_1 = Me, R_2, R_3 = H		0.25	**3Ba**, R_1 = Me, R_2, R_3, R_4, R_5 = H	87
	1C, R_1 = OMe, R_2, R_3 = H	**2a**, R_4, R_5 = H	0.15	**3Bb**, R_1 = Me, R_2, R_3, R_5 = H, R_4 = Cl	82
	1D, R_1 = F, R_2, R_3 = H	**2b**, R_4 = Cl, R_5 = H	0.25	**3Ca**, R_1 = OMe, R_2, R_3, R_4, R_5 = H	86
	1E, R_1 = Ph, R_2, R_3 = H		0.25	**3Cb**, R_1 = OMe, R_2, R_3, R_5 = H, R_4 = Cl	83
	1F, R_1 = ^{t}Bu, R_2, R_3 = H		0.5	**3Da**, R_1 = F, R_2, R_3, R_4, R_5 = H	81
	1G, R_1, R_3 = H, R_2 = OMe		0.5	**3Db**, R_1 = F, R_2, R_3, R_5 = H, R_4 = Cl	75
	1H, R_1, R_3 = H, R_2 = Cl		0.25	**3Ea**, R_1 = Ph, R_2, R_3, R_4, R_5 = H	80
			0.25	**3Eb**, R_1 = Ph, R_2, R_3, R_5 = H, R_4 = Cl	77
			0.25	**3Fb**, R_1 = ^{t}Bu, R_2, R_3, R_5 = H, R_4 = Cl	74
			0.15	**3Gb**, R_1, R_3, R_5 = H, R_2 = OMe, R_4 = Cl	84
			0.15	**3Hb**, R_1, R_3, R_5 = H, R_2, R_4 = Cl	80
3	**1I**, R_1, R_2, R_3 = Me	**2a**, R_4, R_5 = H	0.25	**3Ia**, R_1, R_2, R_3 = Me, R_4, R_5 = H	73
		2c, R_4 = OMe, R_5 = H	0.15	**3Ic**, R_1, R_2, R_3 = Me, R_4 = OMe, R_5 = H	78
		2d, R_4 = CO_2Et, R_5 = H	1.0	**3Id**, R_1, R_2, R_3 = Me, R_4 = CO_2Et, R_5 = H	70
4	**1A**, R_1, R_2, R_3 = H	**2e**, R_4 = H, R_5 = Me	0.25	**3Ae**, R_1, R_2, R_3 = H, R_4 = H, R_5 = Me	80
	1I, R_1, R_2, R_3 = Me		1.0	**3Ie**, R_1, R_2, R_3, R_5 = Me, R_4 = H	67

[a]Isolated yield.

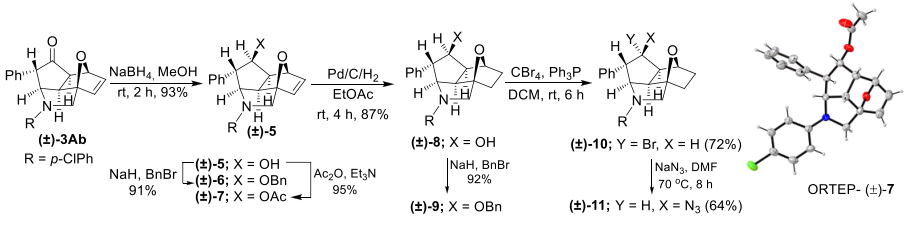
Scheme 3. Scope of Domino Aza-Piancatelli Rearrangement and IMDA Reaction



product (ΔG = −3.23 kcal/mol) is thermodynamically more favored than that of the *endo* product (ΔG = 22.73 kcal/mol).[18]

The synthetic usefulness of the aza-Piancatelli−IMDA adduct was further explored in a divergent manner with respect to the stereoselective synthesis of novel oxa- and aza-bridged aza-polycyclic frameworks [(±)-**12**−**14**][19] and the BCE−aza-tricyclic core of gracilamine (±)-**16** (Scheme 1).[3b] Our initial efforts to cleave the oxa bridge of (±)-**3Ab** under a variety of acidic and basic reaction conditions have met with failure. To gain additional insight into the reactivity of the oxa bridge, the carbonyl group in **3Ab** was further functionalized. Thus, adduct (±)-**3Ab** upon exposure to $NaBH_4$ underwent a highly stereoselective reduction to furnish 6β-hydroxy derivative (±)-**5** in very good yield, which was subsequently converted to the corresponding benzyl ether (±)-**6** and acetate derivative (±)-**7**, respectively, in very good yields (Scheme 4). The β stereochemistry of the hydroxyl group in (±)-**5** was unequivocally established by single-crystal X-ray analysis of the

Scheme 4. Stereoselective Functionalization of Hexahydro-2a,5-epoxy-cyclopenta[*cd*]isoindole 3Ab

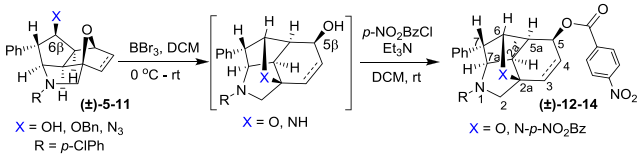


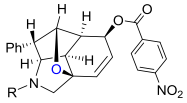
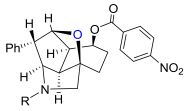
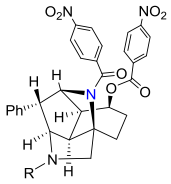
DOI: 10.1021/acs.orglett.9b01267
Org. Lett. XXXX, XXX, XXX−XXX

corresponding acetate (±)-**7** (Scheme 4).[17] The catalytic hydrogenation of (±)-**5** afforded dihydro derivative (±)-**8**, which was further converted to 6*β*-azido dihydro derivative (±)-**11** via 6*α*-bromo derivative (±)-**10** (Scheme 4).

Surprisingly, the oxa bridge present in octahydro-2a,5-epoxy-cyclopenta[*cd*]isoindole derivatives [(±)-**5** and (±)-**6**] was found to be stable under a wide variety of Lewis acid conditions (see the Supporting Information).[20] However, 6*β*-hydroxy derivative (±)-**5** upon exposure to BBr_3 in DCM at 0 °C to rt resulted in a novel [1,3]-transposition of the ether bridge, thus furnishing the 5*β*-hydroxy-2a,6-oxa-bridged aza-tricyclic derivative, which was isolated as the corresponding *p*-nitrobenzoate derivative (±)-**12** (Table 3, entry 1). It is

Table 3. One-Pot Stereoselective Construction of the Novel Oxa- and Aza-Bridged Aza-Tricyclic Framework[a]



entry	starting material	time (h)	product	yield (%)[b]
1	(±)-**5**; X = OH	18	 (±)-**12**	50
2	(±)-**6**; X = OBn	12		67
3	(±)-**8**; X = OH	14	 (±)-**13**	47
4	(±)-**9**; X = OBn	18		63
5	(±)-**11**; X = N_3	7	 (±)-**14**	54

[a]Substrate (1.0 equiv) and BBr_3 (1.5 equiv) in DCM at 0 °C to rt. [b]Isolated yield.

presumed that 6*β*-hydroxy-oxa-bridged derivative (±)-**5** undergoes a BBr_3-assisted regioselective cleavage of the oxa bridge with concomitant trapping of the resultant carbocation by the 6*β*-hydroxy group, leading to the formation of the novel 5*β*-hydroxy-octahydro-2a,6-epoxy-cyclopenta[*cd*]isoindole framework. The structure and relative stereochemistry of oxa-bridged aza-tricyclic derivative (±)-**12** were established by ^{1}H NMR, ^{13}C NMR, 2D NMR, and HRMS data and further unambiguously confirmed by single-crystal X-ray analysis (Figure 2).[17]

The scope of this BBr_3-mediated reaction was further tested with 6*β*-functionalized oxa-bridged derivatives [(±)-**6**, (±)-**8**, and (±)-**9**], and the results are summarized in Table 3. The 6*β*-benzyloxy derivative (±)-**6** also underwent a smooth reaction to furnish 5*β*-hydroxy-oxa-bridged aza-tricyclic derivative (±)-**12** in very good yield (Table 3, entry 2).[21] Similarly, dihydro derivatives (±)-**8** and (±)-**9** reacted with

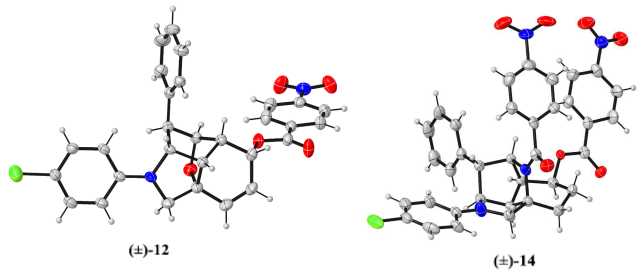


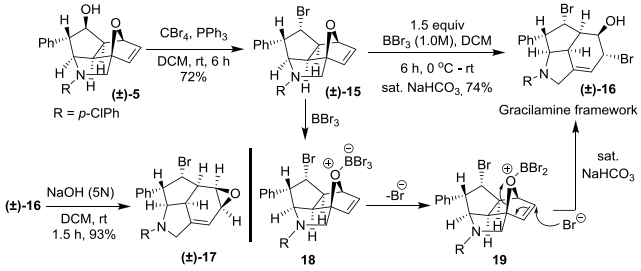
Figure 2. ORTEP diagram of compounds (±)-**12** and (±)-**14**.

BBr_3 to furnish the same rearranged adduct (±)-**13** in good yields (Table 3, entries 3 and 4).

Intriguingly, under similar reaction conditions, 6*β*-azido derivative (±)-**11** underwent a smooth rearrangement,[22] and subsequent reduction with $NaBH_4$ followed by benzoylation afforded the corresponding novel aza-bridged aza-tricyclic derivative (±)-**14** in good yield (Table 3, entry 5). The aza-bridged structure was unambiguously confirmed by single-crystal X-ray analysis (Figure 2).[17]

Remarkably, 6*α*-bromo derivative (±)-**15**, derived from (±)-**5**, upon treatment with BBr_3 at room temperature, underwent smooth oxa bridge cleavage, resulting in a novel aza-tricyclic bromohydrin (±)-**16**, a BCE aza-tricyclic core of gracilamine, in 74% yield with a high degree of regio- and stereoselectivity. The stereo- and regioselectivity of bromohydrin (±)-**16** were unambiguously established using ^{1}H NMR, ^{13}C NMR, 2D NMR, and HRMS data. Moreover, exposure of *trans*-bromohydrin (±)-**16** to aqueous NaOH resulted in the formation of functionalized *β*-epoxide derivative (±)-**17** in very good yield (Scheme 5).

Scheme 5. Stereoselective Construction of the Angularly Fused BCE Aza-Tricyclic Core of Gracilamine



The structure and relative stereochemistry of *β*-epoxide derivative (±)-**17**, an aza-tricyclic core of gracilamine, were unequivocally confirmed by single-crystal X-ray analysis (Figure 3).[17] A plausible mechanism for the formation of angularly fused 5−6−5 aza-tricyclic bromohydrin (±)-**16** is also shown in Scheme 5.

In summary, a simple and highly efficient one-pot method for the stereoselective synthesis of functionalized hexahydro-2a,5-epoxy-cyclopenta[*cd*]isoindole derivative (±)-**3** has been developed using aza-Piancatelli rearrangement followed by IMDA reaction as a key step. This cascade reaction is found to be general, and the corresponding oxa-bridged aza-tricyclic adducts are isolated in very good yields. In the presence of BBr_3, 6*β*-hydroxy derivatives of (±)-**3** underwent smooth 1,3-transposition of the ether bridge, leading to oxa-bridged 5*β*-hydroxy-octahydro-2a,6-epoxy-cyclopenta[*cd*]isoindoles

DOI: 10.1021/acs.orglett.9b01267
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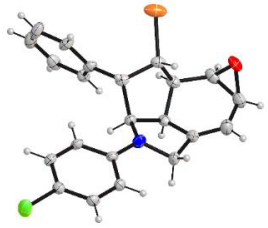

Figure 3. ORTEP diagram of compound (±)-**17**.

(±)-**12** and (±)-**13**, whereas the corresponding 6*β*-azido derivative (±)-**11** furnished a novel aza-bridged aza-tricyclic derivative (±)-**14**. Under similar reaction conditions, 6*α*-bromo derivative (±)-**15** underwent an oxa bridge cleavage and subsequent transformation afforded (±)-**17**, a functionalized BCE aza-tricyclic core of gracilamine. Further application of this domino strategy in the synthesis of biologically relevant molecules will be forthcoming.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01267.

Complete experimental details and characterization data for the synthesized compounds (PDF)

NMR spectra of compounds (PDF)

Accession Codes

CCDC 1856013, 1856052, 1856057−1856058, 1856077−1856078, 1856080, and 1857434 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 Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank DST-SERB (EMR/2016/004040), India, for financial support and DST-FIST for providing instrument facilities. S.G. and N.R.R. thank CSIR-New Delhi for research fellowships. The authors thank Mr. V. Ram Kumar and SAIF, IIT Madras, for single-crystal X-ray analysis.

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(18) DFT calculations were performed at the M06-2X/def2-TZVP-(SMD = toluene)//M06-2X/def2-SVP level of theory with Gaussian 09, and the details are given in the Supporting Information.

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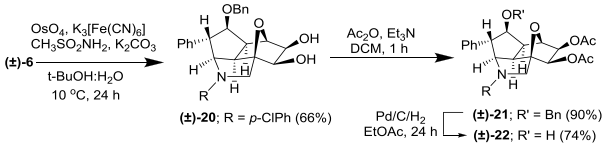
(20) The double bond present in octahydrocyclopenta[*cd*]isoindole derivative **6** underwent stereoselective dihydroxylation with OsO_4 (see below). The structure and relative stereochemistry of product (±)-**22** were established by NMR and HRMS data and further confirmed by single-crystal X-ray analysis (see the Supporting Information).



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