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Harnessing the 1,3-azadiene-anhydride reaction for the regioselective and stereocontrolled synthesis of lactam-fused bromotetrahydropyrans by bromoetherification of lactam-tethered trisubstituted tertiary alkenols†

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Halo-cycloetherification of lactam-tethered alkenols enables the construction of oxygen-heterocycles that are fused to nitrogen heterocycles *via* intramolecular halonium-induced nucleophilic addition. Specifically, tetrahydropyrans (THPs) that are fused to a nitrogen heterocycle constitute the core of several bioactive molecules, including tachykinin receptor antagonists and alpha-1 adrenergic antagonists. Although the literature is replete with successful examples of the halo-cycloetherification of simple mono- or disubstituted primary alkenols, methods for the modular, efficient, regioselective, and stereocontrolled intramolecular haloetherification of sterically encumbered trisubstituted tertiary alkenols are rare. Here, we describe a simple intramolecular bromoetherification strategy that meets these benchmarks and proceeds with exclusive 6-*endo* regioselectivity. The transformation employs mild and water-tolerant conditions, which bodes well for late-stage diversification. The hindered ethers contain four contiguous stereocenters as well as one halogen-bearing tetrasubstituted stereocenter.

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Introduction

Functionalized δ- and γ-lactams as well as their deoxygenated variants (*i.e.*, piperidines and pyrrolidines) are prevalent in alkaloid natural products, corrosion inhibitors, fruit preservation agents, ligands, and pharmaceuticals (including antibacterial, antioxidants, appetite suppressants, antitumor and antibiotics).[1–7] Similarly, tetrahydropyrans (THPs) are commonplace topologies in natural products and pharmaceuticals, including those that possess antibiotic, antiproliferative, antifungal, antimicrobial, anti-HIV activity.[8] For example, C2-aryl and polysubstituted THPs can be found in antibacterial agent centrolobine as well as in antifungal agents morinols **A** and **B** (Fig. 1). Importantly, fused bicyclic THPs are present in several bioactive molecules, including tachykinin receptor antagonist **A**, alpha-1 adrenergic antagonist **B**, and Lubiprostone **C**.[8] We therefore surmised that a modular strategy that merges a functionalized lactam and a tetrahydropyran motif would undeniably expand the 3D-structural space for the discovery of new small molecules with medicinal value.

Diversity-Oriented Synthesis (DOS) is gradually transitioning from structural diversity to biological as well as functional relevance.[9] A complementary strategy for generating biologically-relevant chemical libraries is to employ complexity-generating transformations that produce compounds with conformationally rigid cyclic frameworks with a high ratio of sp^3 carbon atoms.[10] Increasing the three-dimensional character of a molecule has indeed been associated with a more successful outcome in drug discovery.[11]

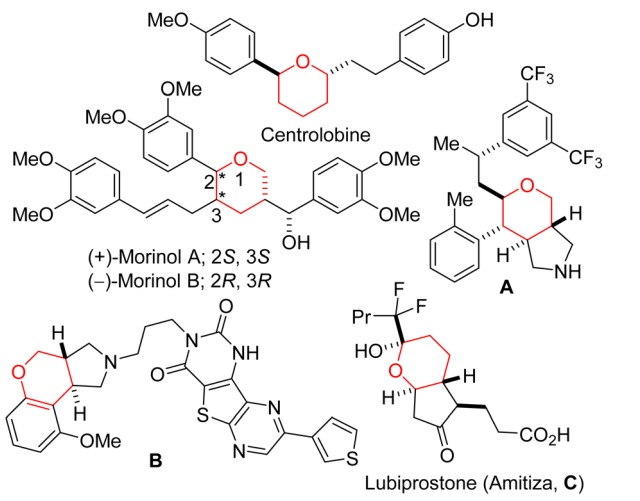

Fig. 1 Examples of bioactive tetrahydropyrans.

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In the last decade, our group has sought to harness the 1,3-azadiene-anhydride reaction for the stereocontrolled synthesis of lactam-bearing 5-aryl-4(*E*)-pentenoic acids and subsequent post-diversification.[12] For example, we previously disclosed that the direct oxidative alkoxylation of appropriately tethered alkenols of type **1** proceeds with 6-*endo* selectivity under Pd- or Cu-catalysis (Fig. 2A, see **2**).[13] Additionally, we showed that Fe- or Ru-catalyzed dehydrative coupling of **1** furnishes the C–C cross-coupling products (see **3**).[14]

In the current studies, we seek to explore the amenability of these lactam-tethered trisubstituted tertiary alkenols to stereocontrolled and regioselective bromoetherification, in view of constructing lactam-fused bromotetrahydropyrans of type **4**/**5** (Fig. 2B). Halonium-promoted addition of nucleophiles such as alcohols to alkenes is one of the most fundamental reactions in organic chemistry. The intramolecular variant enables the creation of a new ring and the construction of new tetrahedral stereogenic centers. The reaction also introduces a requisite halogen group for subsequent functionalizations. Although the literature is inundated with successful examples of halocycloetherification of simple mono- or disubstituted primary alkenols,[15] such as those depicted in Fig. 2C, methods for efficient, regioselective, and stereocontrolled haloetherification of sterically encumbered trisubstituted tertiary alkenols are relatively rare. This is hardly surprising given that tertiary alcohols are significantly less nucleophilic than primary alcohols. Additionally, the regioselectivity of attack of the tethered alcohol group on the trisubstituted alkene can hardly be predicted *a priori*, especially when the more substituted carbon of the alkene does not harbor an aryl substituent (as is the case in alkenol **1**).[15] Herein, we describe an efficient intramolecular bromoetherification process that meets the aforementioned benchmarks. The reaction proceeds under water-tolerant conditions.

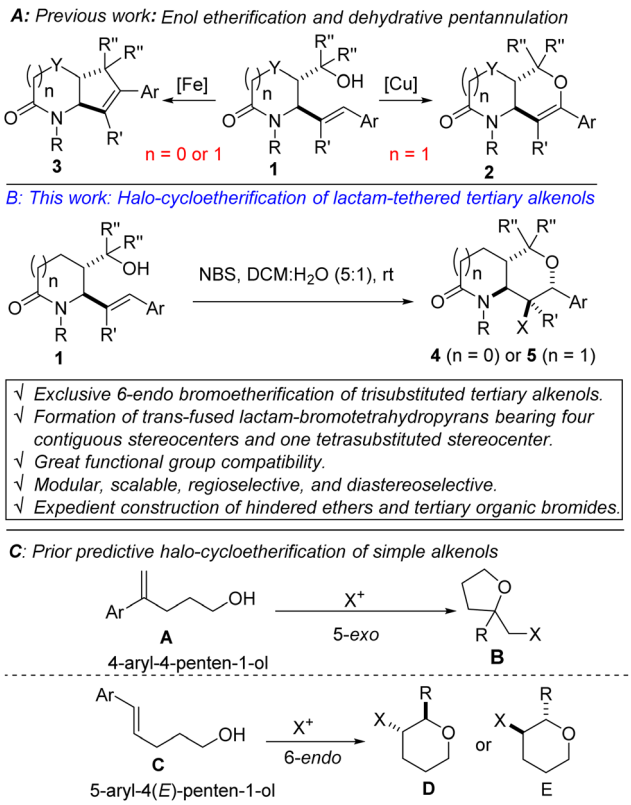


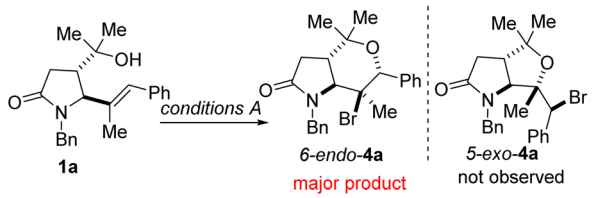
Fig. 2 (A) Prior cyclizations utilizing lactam-tethered alkenol **1**, (B) proposed plan for accessing lactam-fused bromotetrahydropyrans from **1**, (C) reported predictive approaches for halo-cycloetherification of simple alkenols.

Results and discussion

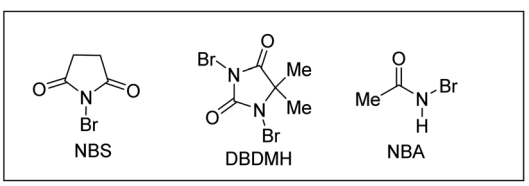
Studies on the bromoetherification of lactam-tethered alkenols of type **1** commenced with model γ-lactam-tethered alkenol **1a** (Table 1) and *N*-bromosuccinimide (NBS).

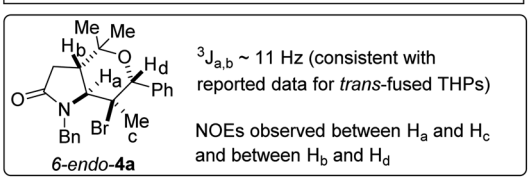
After screening several reaction media (*i.e.*, dichloromethane (DCM), 1,2-dichloroethane, acetonitrile, 1,4-dioxane, hexafluoroisopropanol (HFIP), diethylether, tetrahydrofuran (THF), 2-methyltetrahydrofuran (2-MeTHF), and toluene), a cosolvent

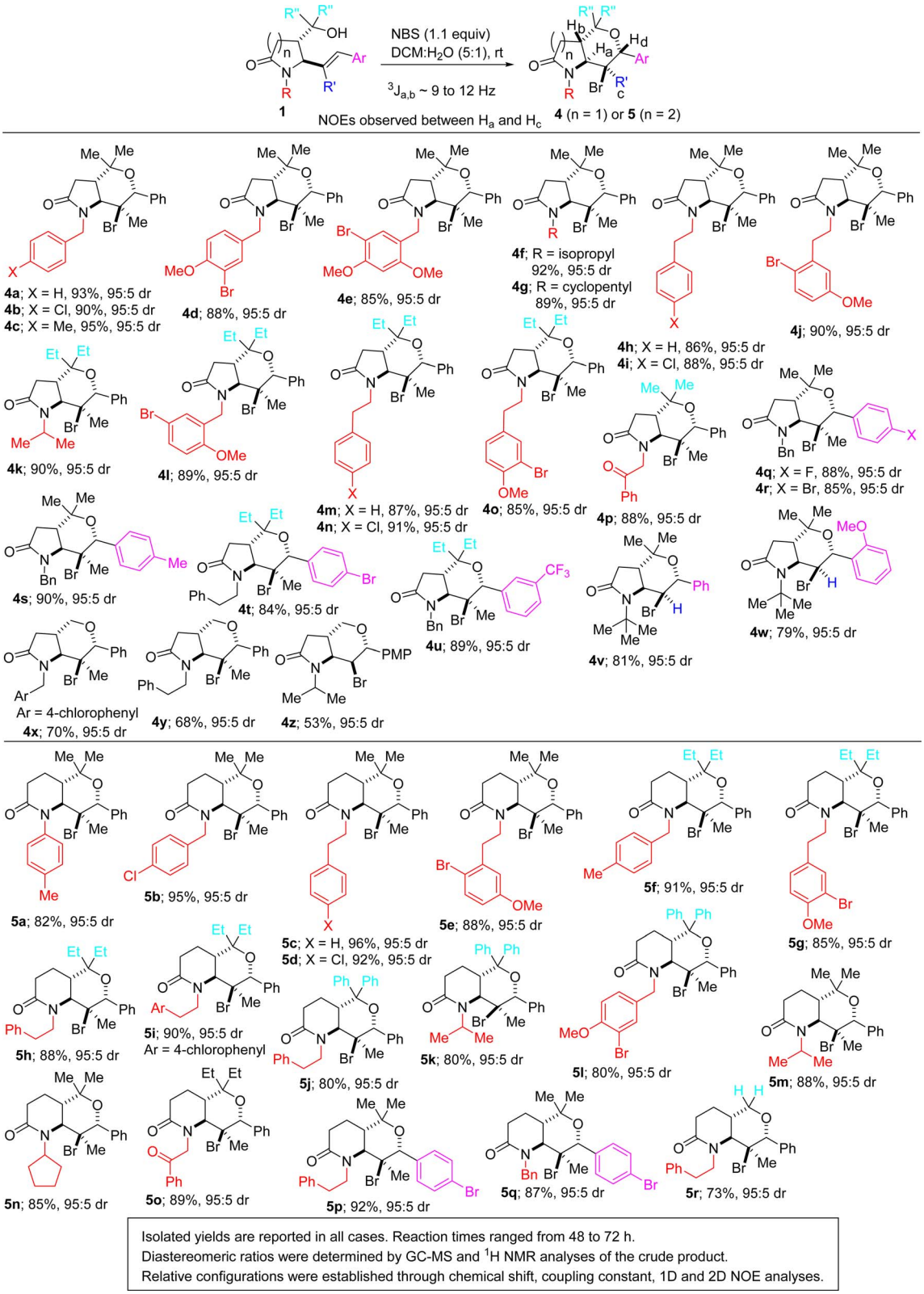
Table 1 Optimization of the bromoetherification of lactam-tethered alkenol **1a**



Entry	Deviation from conditions **A**	o/o yield of **4a** (isolated)
1	Water omitted	85
2	1,2-Dichloroethane in place of DCM	80
3	Aceton itrile in place of DCM	79
4	1,4-Dioxane in place of DCM	83
5	HFIP in place of DCM	69
6	Diethylether in place of DCM	83
7	THF in place of DCM	88
8	2-MeTHF in place of DCM	9
9	Toluene in place of DCM	0
10	Br_2 in place of NBS	86
11	DBDMH inplace of NBS	73
12	NBA in place of NBS	77







Scheme 1 Scope of bromoetherification of lactam-tethered alkenols.

of DCM and H_2O (5 : 1) emerged as the optimum reaction medium with respect to the yield, regioselectivity and stereoselectivity. Thus, after stirring a mixture of **1a** (1 mmol) and NBS (1.1 equiv.) in dichloromethane (5 mL) and water (1 mL) for 3 days at room temperature, ^{1}H and ^{13}C NMR analyses of the crude mixture prior to extractive workup revealed the presence of **4a**. Of note, the bromocycloetherification performed reasonably in anhydrous DCM (entry 1). Presumably, the role of

water is to enhance the solubility of NBS. These studies have revealed that THF out-performs sterically encumbered 2-MeTHF (entry 7 *vs.* entry 8). Other electrophilic bromine sources did not perform as well as NBS (entries 9–12).

With the optimized conditions in hand, the scope of the bromocycloetherification was next explored (Scheme 1). It is well established that the nitrogen substituent present on a nitrogen heterocycle can have a profound effect on its reactivity and biological activity.[16] Thus, the effect of the *N*-substituent on the cyclization reaction was first explored. Encouragingly, lactam-tethered alkenols harboring electronically diverse *N*-benzyl substituents undergo satisfactory cyclization (see **4a–e**). *N*-alkyl lactam-alkenols are also competent substrates for the bromoetherification (see **4f**/**g**). The successful construction of lactam-bromotetrahydropyrans harboring the *N*-phenethyl group (see **4h–j**) is noteworthy given that the latter often serves as a precursor to the indolizidine/quinolizidine scaffold.[17] Ketone-bearing alkenols are competent substrates for the bromocycloetherification (see **4p**). Halogenated arenes are well tolerated (see **4b**, **4d**, **4e**, **4l**, **4n**, and **4x**), which bodes well for late-stage diversification as the halogen group may be utilized as a functional handle for cross-coupling purposes. The incorporation of a fluorinated moiety into organic molecules generally increases the solubility, lipophilicity and metabolic stability of the parent molecules.[18] Specifically, the CF_3 group enjoys a privileged role because its incorporation often enhances efficacy by promoting electrostatic interactions with targets, improving cellular membrane permeability, and increasing robustness toward oxidative metabolism of the drug.[18a] It is therefore noteworthy that fluorinated products **4q** and **4u** are obtainable in satisfactory yields. As a testament to the generality of the transformation, when the phenyl group on the styrenyl unit is replaced by electron-deficient aryl groups (see **4q**, **4r**, **4t**, and **4u**) or electron-rich aryl substituents (see **4s** and **4w**), the efficacy of the transformation is not compromised. In addition to the trisubstituted γ-lactam-tethered alkenols that have been interrogated, we have found that intramolecular bromoalkoxylation of γ-lactam-tethered disubstituted alkenols unsurprisingly proceeds regioselectively in favor of the 6-*endo* cyclization pathway (see **4v**/**w**).

Medicinal chemists have widely explored the *gem*-dimethyl group in developing bioactive molecules because of the possibility to (1) mitigate toxicity, (2) obtain superior DMPK profile, (3) modulate the pKa of nearby functionality, (4) induce symmetry into a monomethyl substituted chiral center, (5) increase target engagement, potency, and selectivity through van der Waals interactions and entropically favorable restriction to a bioactive conformation, and (6) apply the Thorpe–Ingold conformational effect, to achieve difficult ring-forming transformations.[19] As of 2017, 3.7% FDA-approved drugs in the US contained the *gem*-dimethyl group.[20] The successful regioselective and stereocontrolled synthesis of the *gem*-dimethylated lactam-fused bromotetrahydropyrans depicted in Scheme 1 (see **4a–j**, **4q–s**, **4v**, and **4w**) is therefore noteworthy.‡ In a succinct manifestation of the Thorpe–Ingold effect, inherently more reactive primary alkenols are less competent than their tertiary alkenol counterparts in this bromocycloetherification protocol (see **4b** *vs.* **4x** and **4h**/**m** *vs.* **4y**). The remaining mass balance in these primary alkenol cases was accounted for by the 5-*exo* cyclization products, which are separable by chromatography.

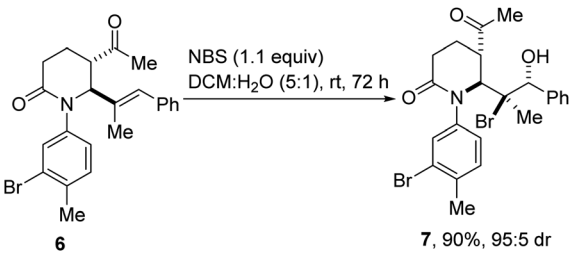
Primarily due to conformational differences, extending reactivity trends from one class of heterocycle to another class can be quite daunting and even foolhardy at times. It was therefore gratifying to find that δ-valerolactam-tethered alkenols also react regioselectively and diastereoselectively with NBS to afford the 2-piperidinone-fused bromotetrahydropyrans depicted in Scheme 1 (see **5a–r**). There are high incentives for the construction of these bicyclic piperidine derivatives since the piperidine motif is arguably the most prevalent in pharmaceuticals and the strategic placement of substituents about this three-dimensional scaffold is ideally suited for structure–activity relationship studies.[11c] The successful deployment of a lactam-tethered tertiary alkenol harboring an *N*-aryl substituent (see **5a**) is noteworthy given that *N*-aryl piperidines and 2-oxopiperidines are embedded in several pharmacologically pertinent targets, including Factor Xa inhibitors and phosphodiesterase-10 inhibitors.[21] Sterically encumbered δ-valerolactam-tethered alkenols bearing two phenyl substituents on the alcohol-containing carbon have been interrogated in this bromoetherification protocol. They reacted sluggishly but still furnished the lactam-fused bromotetrahydropyrans in synthetically attractive yields and diastereoselectivities (see **5j–l**).

In the synthesis of potential drug candidates, scalability is often a significant factor as it serves to provide sufficient amounts for clinical tests. A potentially beneficial aspect of this methodology is therefore the scalable nature of the reactions given that products such as **3c13** have been prepared in gram scale, with little to no compromise in efficiency and diastereoselectivity.

The ^{1}H NMR spectra of **4**/**5** revealed coupling constants for the ring-fusion positions ($^3J_{A,B}$) ranging from 9.0 to 12.0 Hz for protons H_a and H_b (where a refers to the α-amino proton and b refers to the β-amino proton, see Scheme 1 and Table 1). The observed values of $^3J_{a,b}$ for the bicyclic THPs depicted in Scheme 1 fall in the range typical for *trans*-fused THPs. NOESY experiments confirmed that the *anti*-diastereomer is the predominant stereoisomer.

A widely accepted mechanism for this electrophilic halocycloetherification is that an electrophilic halogen is first transferred from a halogen source (NBS in this case) to the alkene to form a halonium ion, followed by an intramolecular attack by the pendant alcohol group. The observed *6-endo* regioselective addition in a Markovnikov sense is the expected outcome for such 5-aryl-4(*E*)-penten-1-ols, characterized by an unsymmetrical build-up of positive charge next to the aryl group in the transition state.[22] The stereocontrolled *anti*-addition (with respect to the newly formed C–O and C–X bonds) is consistent with intramolecular attack of the transient halonium ion by the pendant alcohol group from the opposite side. The possibility of formation of a bromohydrin intermediate prior to attack by the tethered alcohol motif cannot be ruled out at this stage given that such a product was isolated when the tertiary alcohol motif resident in **1** was replaced by a methyl ketone (Scheme 2).

‡ All other lactam-fused bromotetrahydropyrans depicted in Scheme 1 were prepared as described above. Spectroscopic data can be found in the ESI.†



Scheme 2 Evidence of formation of a bromohydrin from homoallylic ketone **6** under similar reaction conditions.

Conclusions

In summary, the site-selective, efficient, and stereocontrolled synthesis of lactam-fused bromotetrahydropyrans has been accomplished through the thermodynamic bromoetherification of sterically imposing lactam-tethered tertiary trisubstituted alkenols. The innate tendency of these lactam-tethered-5-aryl-4(*E*)-penten-1-ols to undergo thermodynamic 6-*endo* cyclization is enforced by the presence of the 5-aryl substituent. These sp^3-rich fused lactam-bromotetrahydropyrans bear four contiguous stereocenters. We anticipate that this efficient strategy would expand the 3D-structural space for the discovery of new lactam-tetrahydropyrans with medicinal value. Efforts to develop an enantioselective variant of this transformation are ongoing and the results will be disclosed in due course.

Experimental

All experiments involving air and moisture-sensitive reagents were carried out under an inert atmosphere of nitrogen and using freshly distilled solvents. Freshly purchased toluene and DMF were stored under 4 Å molecular sieves for several days prior to use. THF and 2-MeTHF were distilled from sodium benzophenone ketyl. All other solvents were used as purchased. All amines, enals, Grignard reagents, and *N*-bromosuccinimide were newly purchased and used without further purification. Column chromatography was performed on silica gel (230–400 mesh). Thin-layer chromatography (TLC) was performed using Silicycle SiliaplateTM glass backed plates (250 μm thickness, 60 Å porosity, F-254 indicator) and visualized using UV (254 nm). Unless otherwise indicated, NMR spectral data were acquired using $CDCl_3$ as solvent, at room temperature. Chemical shifts are quoted in parts per million (ppm). HRMS-EI^+ data were obtained using either electron spray ionization (ESI) or electron impact (EI) techniques. High-resolution ESI was obtained on an LTQ-FT (ion trap; analyzed using Excalibur). High resolution EI was obtained on an Autospec (magnetic sector; analyzed using MassLynx).

General procedure A: bromoetherification of lactam-tethered alkenol 1

An oven-dried vial was equipped with a stir bar and a solution of **1** (1.00 mmol) in dichloromethane (5 mL) was added to the vial followed by deionized water (1 mL) and *N*-bromosuccinimide (1.10 mmol, 1.1 equiv.) at room temperature. After stirring for 3 days at the same temperature, the reaction mixture diluted by the addition of dichloromethane (20 mL) and quenched by the addition of saturated sodium thiosulfate solution (10 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to afford the lactam-fused bromotetrahydropyran.

Typical procedure A

To a solution of alkenol **1a** (349.5 mg, 1.00 mmol) in dichloromethane (10 mL) was added *N*-bromosuccinimide (195.8 mg, 1.10 mmol) at room temperature. After stirring for 3 days at the same temperature, the reaction mixture diluted by the addition of dichloromethane (20 mL) and quenched by the addition of saturated sodium thiosulfate solution (10 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, and concentrated *in vacuo*.

Purification

By flash chromatography on silica eluting with hexane/acetone (90 : 10 to 70 : 30). Yellowish oil. Yield = 398.4 mg, 93%, 95 : 5 dr (*anti:syn*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.39 (m, 2H), 7.39–7.14 (m, 8H), 5.04 (d, J = 15.7 Hz, 1H), 4.89 (s, 1H), 4.73 (d, J = 15.7 Hz, 1H), 4.19 (d, J = 10.8 Hz, 1H), 2.51–2.30 (m, 2H), 2.19–2.08 (m, 1H), 1.47 (s, 3H), 1.33 (s,s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.66, 137.38, 136.01, 129.75, 128.36, 128.33, 127.81, 127.34, 126.98, 80.52, 74.89, 68.08, 67.67, 47.62, 45.20, 33.24, 29.37, 18.19, 17.83. HRMS-EI^+ (*m*/*z*): calc. for $C_{23}H_{26}BrNO_2$ $[M]^+$ 427.1147, found 427.1153. FTIR (KBr): 2965.4, 1727.5, 1696.3, 1604.9, 1511.0, 1448.5, 1414.7, 1384.9, 1357.4, 1298.7, 1247.5, 1179.3, 1135.9, 1031.8, 905.8, 839.0.

Author contributions

I. S. A. – investigation, data curation, methodology; T. K. B. – conceptualization, project administration, supervision, investigation, data curation, methodology, writing – original draft, internal and external funding acquisition.

Conflicts of interest

There are no conflicts of interest to declare.

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