JOC The Journal of Organic Chemistry

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Total Synthesis of (+)-Isatisine A: Application of a Silicon-Directed Mukaiyama-Type [3 + 2]-Annulation

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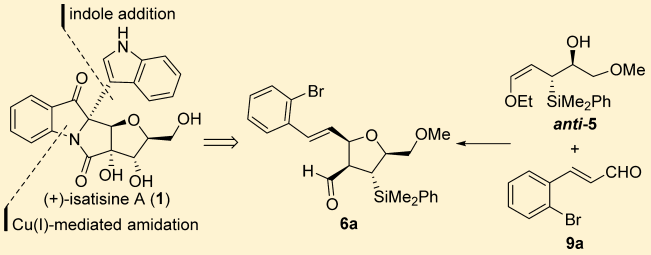
Supporting Information

ABSTRACT: Complete details of an asymmetric synthesis of (+)-isatisine A (**1**) are described. The synthesis highlights the use of a highly diastereoselective Mukaiyama-type [3 + 2]-annulation of allylsilane **5** with the unsaturated aldehyde **9a** to assemble the functionalized tetrahydrofuran core of isatisine A. A convergent route to the framework of the natural product was established that employed a substrate-controlled indole coupling that was followed by a late-stage intramolecular copper(I)-mediated amidation to complete the assembly of the tetracyclic framework of (+)-isatisine A. In addition, the scope of the [3 + 2]-annulation was evaluated and enhanced utilizing diastereomeric allylsilanes *anti*-**5** and *syn*-**5** to establish an efficient route to stereochemically well-defined tetrahydrofurans.



INTRODUCTION

Isatis indigotica Fort. (Cruciferae), which is a plant species widely cultivated in China and East Asia, has been used as a traditional medicine for treatment of viral diseases such as influenza, viral pneumonia, mumps, and hepatitis. Further investigations conducted by Chen and co-workers on *I. Indigotica* to identify potent antiviral compounds resulted in the isolation of isatisne A (**1**, Figure 1) along with 11 other

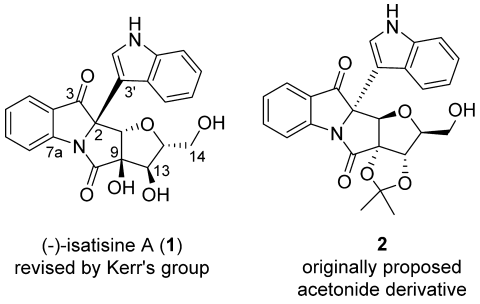


Figure 1. Structures of isatisine A (**1**) and its acetonide derivative **2**.

nonalkaoid species.[1] Initially, isatisine was isolated as an acetonide derivative, which was most certainly generated during the chromatographic purification using acetone as an eluent. However, its unusual dioxolane group that is rarely found in natural products led to further investigation to unambiguously assign the correct structure of the natural product. Biological evaluation of acetonide derivative of isatisine revealed its potent cytotoxicity against C8166 with CC_{50} = 302 μM and anti-HIV activity of EC_{50} = 37.8 μM.

Isatisine A (**1**) is a unique fused-polycyclic alkaloid bearing an indole ring system at the C2 position, of which the intriguing and challenging structure led to significant attention from the synthetic community. In 2010, Kerr and co-worker reported the first total synthesis of (+)-isatisine A and revision of its absolute configuration.[2a,b] This report was followed by two total syntheses from the Panek[2c] and Liang[2d] groups, respectively. Recently, Xie[2e] has disclosed a biomimetic total synthesis of isatisine A, and shortly after, Ramana and co-workers[2f,g] reported their efforts culminating in the synthesis of the natural product and its derivatives.

The present work differs considerably from the previous syntheses. For instance, Kerr and co-worker also reported a [3 + 2] cycloaddition using a vinyl cyclopropane and an aldehyde to generate the tetrahydrofuran core. However, the indole addition to the intermediate aminal turned out to be problematic, which led to a revised route to introduce the indole branch through a cascade reaction sequence including incorporation of indole and lactamization to form the tetracyclic framework of isatisine at the late stage of their synthesis. Additionally, the independent approaches, reported by Xie and Ramana, respectively, demonstrated the use of the "chiral pool" where protected forms of D-glucal and D-ribose were used as the starting materials, respectively.

Herein, we disclose the full details of our efforts toward the total synthesis of (+)-isatisine A (**1**), including the development of Mukaiyama-type [3 + 2]-annulation that led to the assembly of the tetrahydrofuran core and the synthesis of 9-*H*-13-silyl-substituted advanced intermediate **15**.

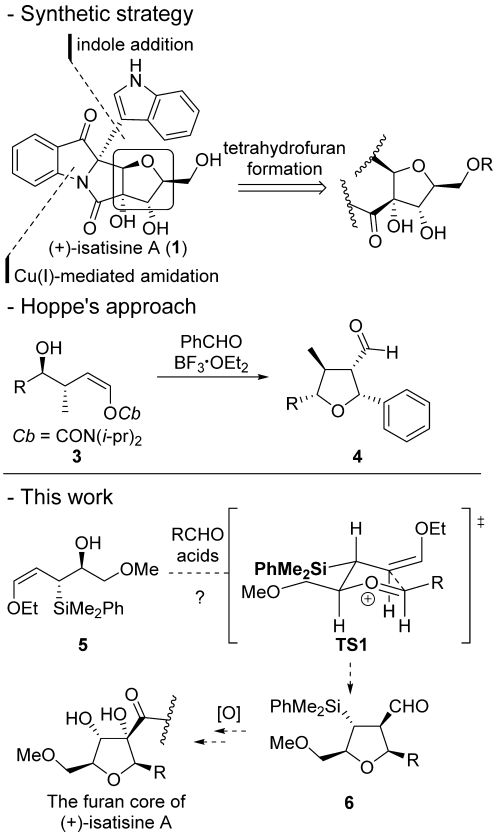
Received: January 9, 2015
Published: March 4, 2015

DOI: 10.1021/acs.joc.5b00051
J. Org. Chem. 2015, 80, 2959−2971

RESULTS/DISCUSSION

Strategy and Methodology Development. Our interest in isatisine originated from its unique tetracyclic ring system, which bears a highly oxygenated tetrahydrofuran. As illustrated in Scheme 1, our synthetic analysis of this alkaloid revealed three crucial transformations required to construct the indole branch and tetracyclic scaffold, including formation of an aryl C−N bond and densely functionalized tetrahydrofuran. Therefore, our strategy set out the preparation of the tetrahydrofuran core as a starting point.

Scheme 1. Synthetic Strategy and Methodology Development for Synthesis of (+)-Isatisine A (1)



Due to the abundance of natural products and bioactive molecules[1,3] bearing a tetrahydrofuran core, methods for the preparation of functionalized tetrahydrofurans have been described.[4] However, the challenging heterocyclic core of isatisine prompted us to develop a stereocontrolled method to access the functionalized tetrahydrofuran, which can be subsequently converted to the isatisine core by straightforward transformations.

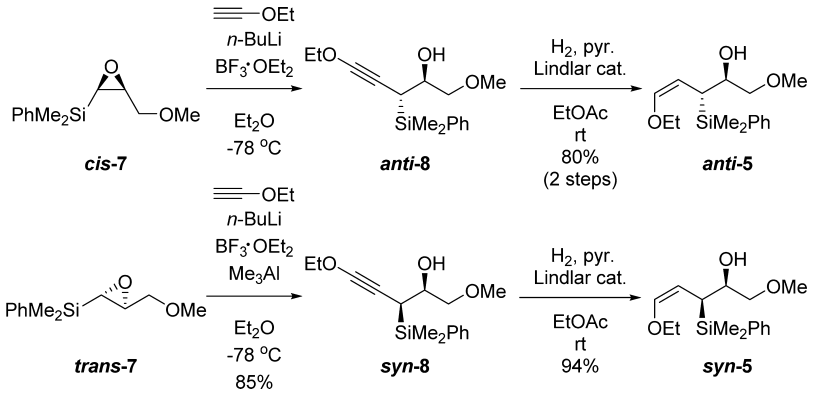
During the course of a search of methods for tetrahydrofuran synthesis, a Mukaiyama-type [3 + 2]-cycloaddition of a carbamoyl enol ether with an aldehyde reported by Hoppe[4j−m] particularly attracted our interest in these possibilities: (1) cyclization is initiated by formation of an oxocarbenium between the homoallylic hydroxyl group and an aldehyde under acidic conditions; (2) the stereochemical course was dictated by the configuration of the allylic stereocenter. Taking advantage of these points, we envisioned that alkoxy-substituted allylsilane **5** bearing allylic C-centered chirality could direct the stereochemical course of a Mukaiyama-type annulation to provide a properly functionalized tetrahydrofuran **6** with useful diastereoselectivity (Scheme 1).[5]

The development of the [3 + 2]-annulation was initiated with the preparation of the allylsilane nucleophiles *anti*-**5** and *syn*-**5**, starting from the known epoxysilanes[6] *cis*-**7** and *trans*-**7**, respectively (Scheme 2). The annulation substrate *anti*-**5** was synthesized through epoxide opening reaction of *cis*-**7** with ethoxy ethynyllithium anion to afford a propargyl silane *anti*-**8** and subsequent Lindlar reduction of the alkyne to the (*Z*)-olefin.[7] Although an epimerization of the secondary hydroxyl group in *anti*-**8**, which arises from the stabilizing effect of a cation by the β-silicon effect, is mechanistically possible, any sign of the epimerization was not observed under the given reaction conditions. Additionally, a prefect level of regioselectivity in the epoxide opening reaction can be explained by bond length difference between C−Si and C−C bond. Si−C bond is ∼1.2 times longer than a normal C−C bond, which may support the highly regioselective attack of a nucleophile at the α-carbon from the silicon group.

In a similar manner, *syn*-**5** was also prepared through nucleophilic epoxide opening of *trans*-**7** and subsequent reduction of the resulting intermediate propargylic silane *syn*-**8**. However, epoxide *trans*-**7** was unreactive under the same conditions used for the epoxide opening reaction of *cis*-**7**. This problem was circumvented by the utilization of an $AlMe_3$−BF_3·OEt_2 mixture to generate the more nucleophilic ethynyl aluminum "ate complex" toward an epoxide opening.[8]

With the availability of reagents *anti*- and *syn*-**5**, the proposed [3 + 2]-annulation of *anti*-**5** with 2-bromocinnamyl aldehyde **9a**[9] was carried to furnish tetrahydrofuran **6a**, which accounts

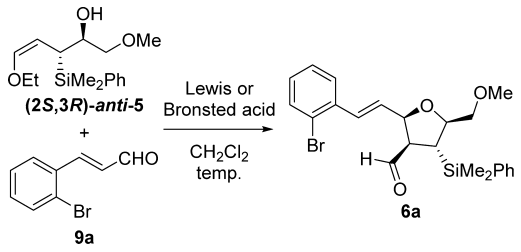
Scheme 2. Preparation of Allylsilanes *anti*-5 and *syn*-5



DOI: 10.1021/acs.joc.5b00051
J. Org. Chem. 2015, 80, 2959−2971

for all of the required carbons of the tetracyclic framework of isatisine. Guided by Hoppe's previous results,[4e] the annulation was promoted with $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at −50 °C (Table 1, entry 1), which provided the desired *trans,trans,cis*-tetrahydrofuran **6a** in moderate yield albeit with excellent diastereoselectivity (>20:1).[2b] Similarly, a series of evaluations utilizing other Lewis acids, such as $In(OTf)_3$ and $Sc(OTf)_3$, afforded **6a** in moderate yields (entries 2 and 3). The series of reactions using Brønsted acids, such as trichloroacetic acid (TCA), trifluoroacetic acid (TFA), and camphorsulfonic acid (CSA), also provided the tetrahydrofuran **6a** in moderate yield. The optimal conditions were found utilizing 1.0 equiv of PTSA at 0 °C, which afforded the desired product in 87% with a high level of diastereoselectivity and within a short reaction time (ca. 10 min). As expected, the observed relative stereochemistry of **6a** suggested that the annulation proceeded through an envelope-like transition state (Scheme 1, **TS1**), where a bulky silane group is positioned at the pseudoequatorial orientation and the enol ether is oriented in such a way as to minimize any developing $A^{1,3}$-allylic strain between the trialkysilane and ethoxy group.

Table 1. Reaction Optimization of the Mukaiyama-Type [3 + 2]-Annulation of *anti*-5 and 9a



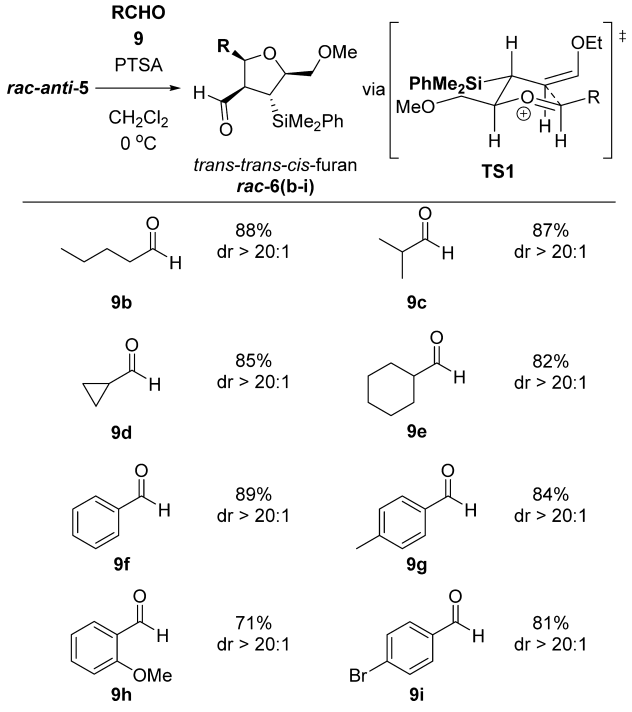
entry[a]	acids (equiv)	temp (°C)	dr[b]	yield[c] (%)
1	$BF_3{\cdot}OEt_2$ (2.0)	−50	>20:1	67
2	$Sc(OTf)_3$ (0.5)	0 to rt	>20:1	58
3	$In(OTf)_3$ (0.5)	0	>20:1	30
4	TCA (1.0)	0	>20:1	53
5	TFA (1.0)	0	>20:1	57
6	CSA (1.0)	0	>20:1	57
7	PTSA (1.0)	0	>20:1	87

[a]The reactions were conducted in a 0.3 M solution of ethoxyl allyl silane *anti*-**5** in CH_2Cl_2. [b]Diastereoselectivities (dr) were determined by ^1H NMR. [c]Purification yield after SiO_2 column chromatography.

Having established optimal reaction conditions, a range of aldehydes was evaluated to explore the scope of the [3 + 2]-annulation with *anti*-**5**. In that regard, we have learned that aliphatic aldehydes **9b−e** were excellent reaction partners in the annulations to afford the *trans,trans,cis*-tetrahydrofurans **6b−e** in high yields and diastereoselectivities (Table 2). Additionally, various aromatic aldehydes **9f−i**, bearing an electron-donating or -withdrawing substituent, were compatible under the defined reaction conditions affording tetrahydrofurans **6f−i** in high yields and diastereoselectivities. The series of annulations shown in Table 2 suggested that ethoxy-terminated allylsilane *anti*-**5** can be an useful reagent for the preparation of a range of 2,4,5-*cis,cis*-tetrahydrofurans.

In studies designed to expand the scope of the tetrahydrofuran annulation, allylsilane *syn*-**5** was employed with the same set of aldehydes **9b−i** to gain access to the diastereomeric tetrahydrofurans. In these experiments, the use of $MeSO_3H$ as a promoter gave superior results in terms of reaction efficiency (up to 96% yield, 20:1 dr) compared to those using PTSA, and the expected *cis,trans,cis*-tetrahydrofurans **10b−i** were produced as the major diastereomer (Table 3). The reactions employing aliphatic aldehydes **9b−e** provided the desired product **10b−e** with attenuating diastereoselectivities regardless of the presence of α-substitutents. However, cyclopropanecarboxylic aldehyde **9d** and aromatic aldehydes **9f−i** gave comparable results to the examples of *anti*-**5**, which imply a presumable π-bond interaction between the enol ether and aryl group to form a more stable transition state (**TS 2**). In fact, it has been documented that the C−C bond of cyclopropane has significantly more π-bond character than a simple sp^3 C−C bond, since the ring strain in a cyclopropane distorts the bonding orbital forming a 104° angle.[10] The observed preservation of diastereoselectivity in the case of cyclopropanecarboxaldehyde **9d** also supports a possible TS stabilization arising from a π-bond interaction in the transition state.

Table 2. Mukaiyama-Type [3 + 2]-Annulation of *anti*-5 with Aldehydes 9b−i[a,b]



[a]Reactions were carried at a 0.3 M concentration, and 2.0 equiv of aldehyde and 1.0 equiv of acid were employed. [b]Diastereoselectivities (dr) were determined by ^1H NMR.

Total Synthesis of (+)-Isatisine A: First-Generation Approach toward the Total Synthesis of (+)-Isatisine A. Having an established synthesis of tetrahydrofuran **6a**, which bears the required stereochemical relationships and carbon atoms for the fused-cyclic framework (C2−C14) of the natural product, our remaining strategy relied on a series of oxidations to furnish the correct oxidation states required for (+)-isatisine. Therefore, our initial retrosynthetic analysis began with disconnection of C7a−N1 to afford an intermediate secondary amide **11**. Further disconnection at the indole side chain C2−C3′ led to an indole and key intermediate lactam **12**, which would be furnished through a series of oxidations of the intermediate tetrahydrofuran **6a** (Scheme 3).

DOI: 10.1021/acs.joc.5b00051
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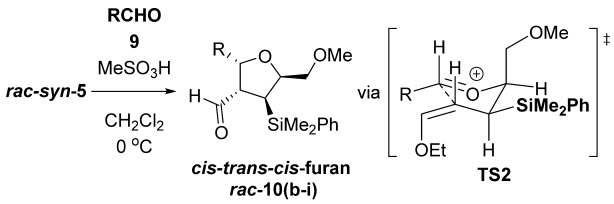
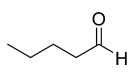
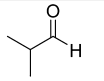
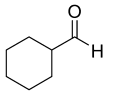
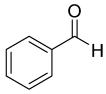
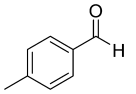
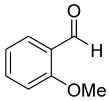
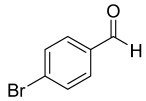
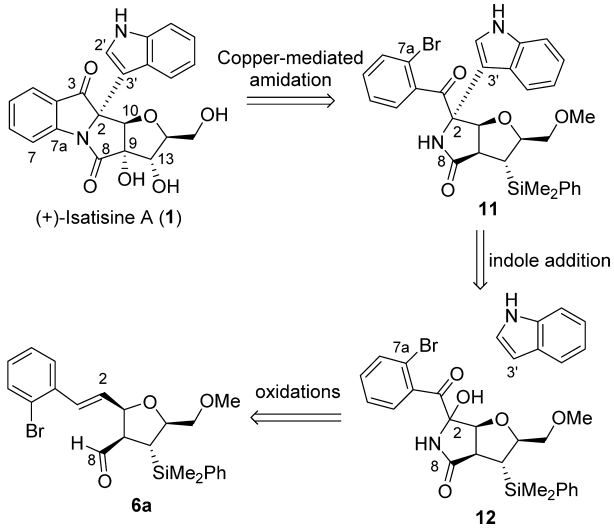
Table 3. Mukaiyama-Type [3 + 2]-Annulation of *syn*-5 with Aldehydes 9b–i[a,b]



 9b	75% dr = 6:1	 9c	74% dr = 3:1
 9d	96% dr > 20:1	 9e	86% dr = 6:1
 9f	83% dr > 20:1	 9g	84% dr > 20:1
 9h	76% dr > 20:1	 9i	70% dr > 20:1

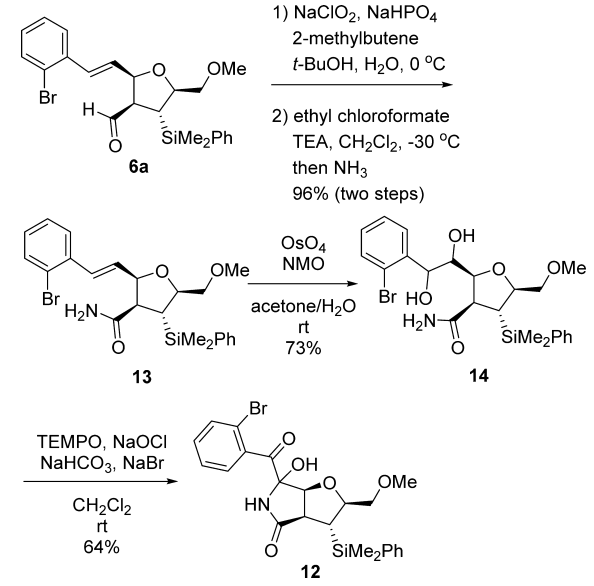
[a]Reactions were carried at 0.3 M concentration, and 2.0 equiv of aldehyde and 1.0 equiv of acid were used. [b]Diastereoselectivities (dr) were determined by ^{1}H NMR.

Scheme 3. Retrosynthetic Analysis of (+)-Isatisine A (1)



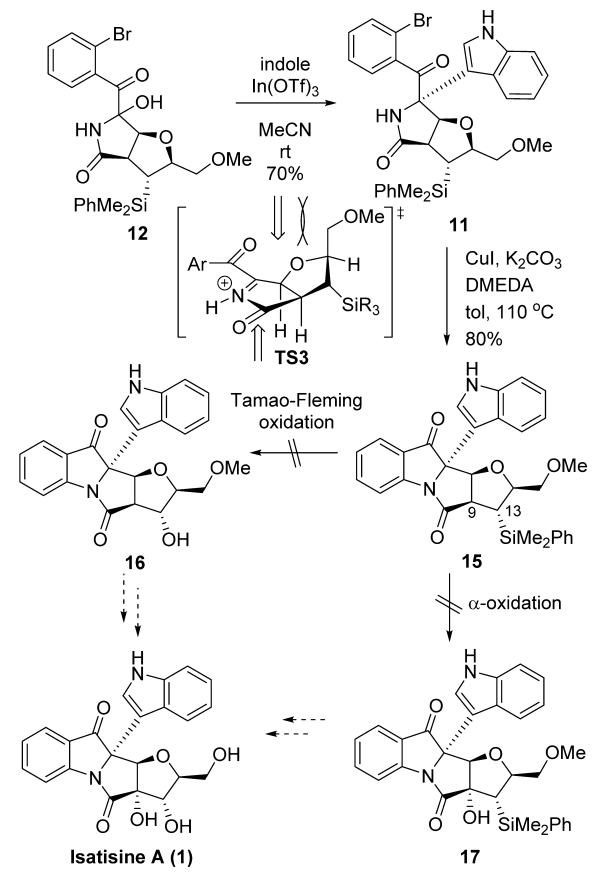
As such, our efforts toward the synthesis of (+)-isatisine were initiated with an oxidation of tetrahydrofuran **6a** to an intermediate carboxylic acid under Pinnick oxidation conditions (Scheme 4). In order to introduce the N1 nitrogen atom in the tetracyclic framework, the carboxylic acid was converted to amide **13** through the intermediate mixed anhydride.[11] Dihydroxylation of the *trans*-disubstituted double bond in **13** afforded the diol **14** as a mixture of diastereomers (dr = 2:1) in 73% yield, which was subjected to another oxidation in the presence of TEMPO to produce the desired cyclic aminal **12** as a 6:1 mixture of diastereomers.[12]

Scheme 4. Preparation of Hydroxy Lactam 12



To introduce the indole moiety at the C2 position, a direct addition to lactam **12** was attempted under Lewis acidic conditions (Scheme 5).[13] Fortunately, the utilization of $In(OTf)_3$ (4.0 equiv) successfully achieved stereoselective addition to provide α-adduct **11**, which was generated by delivering indole from the less hindered convex face of the bicyclic intermediate **12** (**TS3**), without formation of the undesired β-adduct. Construction of the tetracyclic framework

Scheme 5. Construction of 9-*H*-13-Silylisatisine A (15)



DOI: 10.1021/acs.joc.5b00051
J. Org. Chem. 2015, 80, 2959–2971

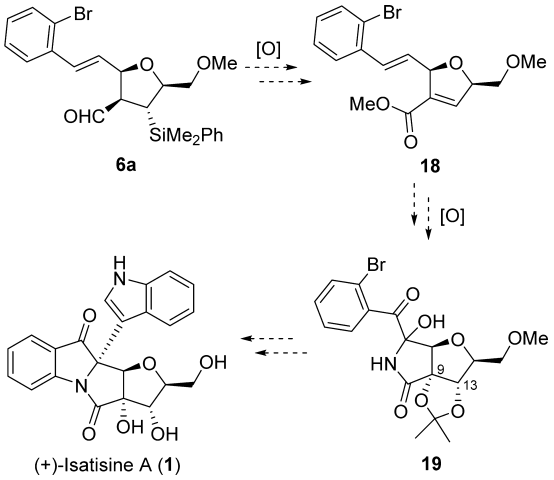
of isatisine was conducted under modified amidation conditions,[11] originally developed by Buchwald.[14] Upon exposure of **11** to the modified Cu(I)-mediated amidation conditions, previously used in our syntheses of macrocyclic lactam natural products, the tetracyclic intermediate **15** was successfully generated in 80% yield.

At this stage of the synthesis, a series of oxidations at C9 and C13 to a diol were necessary to complete the total synthesis. Unfortunately, initial attempts to convert the dimethylphenylsilyl group of **15** into a hydroxyl group under Tamao−Fleming oxidation conditions[15] were unsuccessful and only produced unidentifiable byproducts. With considerable effort, a series of oxidations at C9 to give α-hydroxyl amide **17** was investigated under conventional α-hydroxylation conditions[16] employing hindered, non-nucleophilic bases such as LDA, lithium diethylamide, and KHMDS, with or without the protection of the indole nitrogen, but surprisingly, intermediate **15** was completely unreactive under those conditions.

While intermediate **15** was efficiently accessed from tetrahydrofuran **6a** with a minimized number of protection−deprotection steps, further transformations of **15** to the natural product under oxidative conditions turned out to be problematic and eventually untenable. Considering these difficulties in the late-stage oxidation at C9 and C13, an alternative approach was devised to synthesize (+)-isatisine A.

Second-Generation Approach toward the Total Synthesis of (+)-Isatisine A. Our modified approach shown in Scheme 6 relied on an early-stage oxidation of tetrahydrofuran

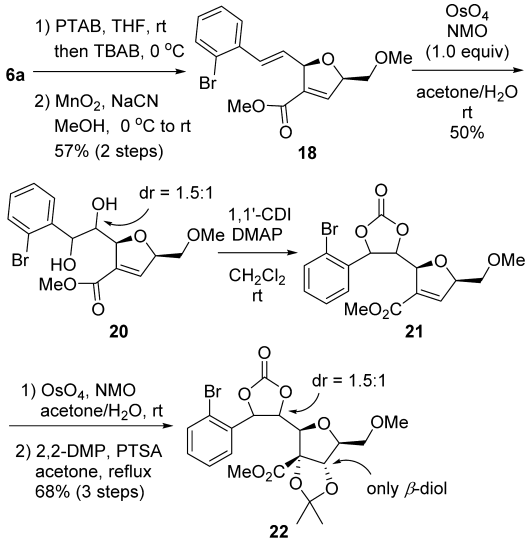
Scheme 6. Revised Strategy for (+)-Isatisine A



6a to intermediate hydroxyl lactam **19**, which also established the required oxidation states present in the natural product. In the course of [3 + 2]-annulation, as we anticipated, the configuration of the dimethylphenyl silane group proved to be a crucial stereocontrol element, which successfully transferred its C-centered chirality to the product tetrahydrofuran with a high level of selectivity (dr ≥20:1). However, our previous attempts revealed that direct oxidation of the silicon group to a hydroxyl group was ineffective under the typically reliable Tamao−Fleming conditions.[15] Meanwhile, a trialkylsilicon group is also known to undergo elimination arising from its σ-donating character to afford an olefin when a leaving group is on the adjacent carbon.[17] Thus, elimination of the silicon group and subsequent dihydroxylation of the resulting olefin at the early stage of the synthesis could serve as an alternative route for the oxidation at C9 and C13 positions (Scheme 6).

Our revised synthesis began with the oxidation of tetrahydrofuran **6a** to the dihydrofuran **18** (Scheme 7). On

Scheme 7. Preparation of Intermediate 22



that account, selective α-bromination of aldehyde **6a** in the presence of the styrene-like olefin was conducted using phenyltrimethylammoniumtribromide (PTAB), which was directly treated with TBAF at 0 °C to form an intermediate unsaturated aldehyde.[18] Due to the instability of the aldehyde, it was immediately subjected to the venerable Corey−Ganem oxidation using MnO_2 in the presence of NaCN to directly afford the unsaturated methyl ester **18** in 57% yield from tetrahydrofuran **6a**.[19]

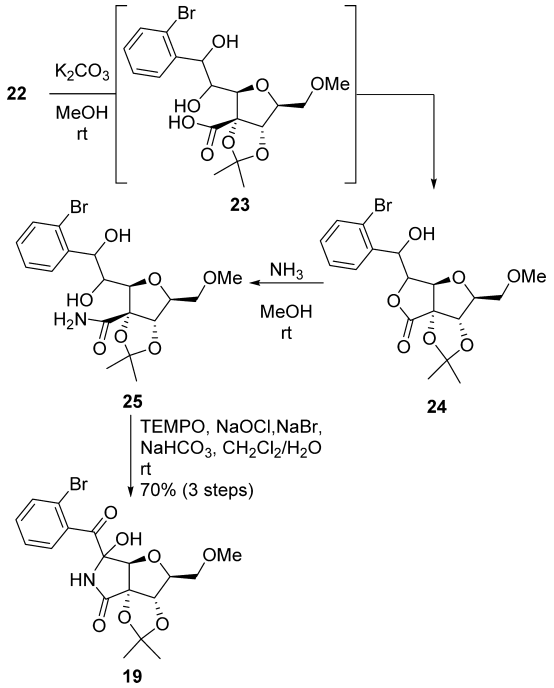
Initially, we planned a stepwise dihydroxylation−protection sequence to secure the formation of the key intermediate hydroxyl lactam **19**. In this approach, the more nucleophilic styrene-like olefin in **18** chemoselectively underwent dihydroxylation using 1.0 equiv of NMO to furnish diol **20** as a 1.5:1 mixture of diastereomers. Protection of the mixture of diols as a cyclic carbonate and subsequent dihydroxylation of the unsaturated ester in **21** provided an intermediate diol with a perfect level of selectivity favoring the α-face, which was followed by an acetonide formation to produce oxolane **22** in 67% yield (three steps) from diol **20**. At this stage, the relative configuration of the diol was assigned by NOE measurements of **22** after separation and purification of the individual diastereomers.[2b]

Removal of the carbonate protecting group in **22** under basic (hydrolysis) conditions also resulted in the cleavage of the methyl ester to form the intermediate dihydroxy acid **23**, which underwent spontaneous lactonization to give the bicyclic lactone **24** (Scheme 8). Treatment of this material with a solution of anhydrous NH_3 in MeOH provided intermediate amide **25**, which was subjected to oxidation with TEMPO and NaOCl at room temperature.[12] As anticipated, the oxidation of the dihydroxy amide **25** resulted in a spontaneous cyclization to afford the key advanced intermediate hydroxyl lactam **19**, which possessed the required oxidation states to be converted to the natural product.

The intermediate hydroxyl lactam can also be prepared through a four-step reaction sequence from diene **18** with an

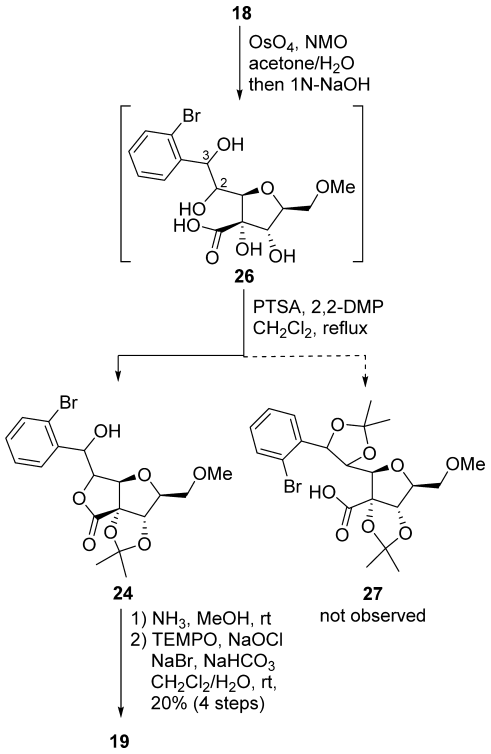
DOI: 10.1021/acs.joc.5b00051
J. Org. Chem. 2015, 80, 2959−2971

Scheme 8. Preparation of Hydroxy Lactam 19



equal level of efficiency (Scheme 9). Both the styrene-like olefin and unsaturated ester were concomitantly dihydroxylated by

Scheme 9. Alternative Route to Hydroxyl Lactam 19

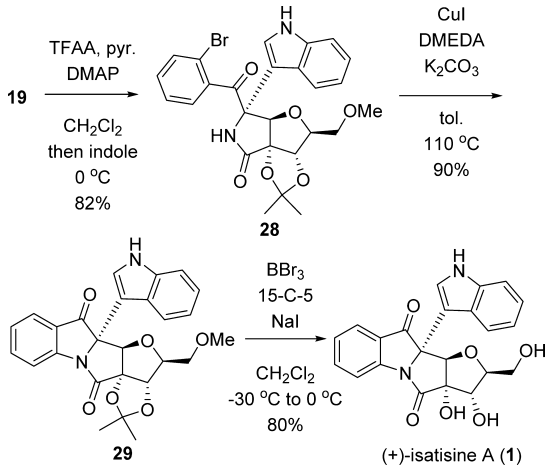


catalytic OsO_4 using an excess amount of NMO, which was subsequently treated with 1.0 N solution of NaOH to produce intermediate tetraol **26** as a mixture of diastereomers (dr = 3:2−6:1) arising from the benzylic 1,2-diol. Interestingly, this tetraol was totally inactive under conditions intended to produce a lactone, possibly due to the attenuating nucleophilicity of the oxygen atoms by a complicated hydrogen-bonding network between the hydroxyl groups.

Accordingly, we attempted a cascade-like protection and lactonization sequence as an alternative pathway to lactone **24** (Scheme 9). In this approach, we presumed that isopropylidene formation is a completely reversible process and forms the thermodynamically more stable lactone **24** rather than bis-acetonide **27**. In order to validate this hypothesis, the dihydrofuran **18** was converted to the intermediate carboxylic acid **26**, which was directly treated with 2,2-dimethoxypropane (2,2-DMP) under reflux conditions. Fortunately, the reaction sequence furnished the desired lactone **24** as a mixture of diastereomers at C2 and C3 without detectable formation of bis-acetonide **27**. For experimental simplification, the resulting mixture of diastereomeric lactones was directly subjected to aminolysis and subsequent TEMPO oxidation without purification to afford spectroscopically clean **19** in 20% yield as a single diastereomer.[20]

With access to intermediate hydroxyl lactam **19**, we turned our attention to the stereoselective incorporation of the branching indole nucleus.[13] Surprisingly, in this case, **19** was revealed to be totally unreactive under the previously reported reaction conditions [4.0 equiv of $In(OTf)_3$] (Scheme 10). After

Scheme 10. Completion of the Total Synthesis of (+)-Isatisine A (1)



extensive screening of reaction conditions, we learned that treatment of **19** with TFAA (1.2 equiv) and pyridine at 0 °C readily activated the hydroxyl lactam to an intermediate acyl iminium ion, and subsequent addition of a solution of the indole (5.0 equiv) in CH_2Cl_2 produced the desired adduct **28** in 82% yield as a single diastereomer. The stereochemistry and absolute configuration of the indole branched quaternary carbon center of **28** was confirmed by single-crystal X-ray crystallographic analysis.[2b]

At the final stage of this synthesis, the assembly of the fused tetracyclic framework was carried out by employing a copper(I)-mediated intramolecular amidation under the conditions that were used in our first-generation synthesis.[11] As anticipated, the advanced tetracyclic intermediate **29** was successfully generated through Cu(I)-mediated coupling in 90% yield. Subsequent cleavage of the methyl ether[5b,21] and acetonide with an excess amount of 1.0 M solution of BBr_3 in CH_2Cl_2 in the presence of 15-crown-5 and NaI (3.0 equiv) successfully provided (+)-isatisine A (**1**) in 80% yield.

DOI: 10.1021/acs.joc.5b00051
J. Org. Chem. 2015, 80, 2959−2971

CONCLUSION

We have developed a silicon-directed Mukaiyama-type [3 + 2]-annulation to construct highly functionalized tetrahydrofurans. This reaction displayed remarkable compatibility with a several types of aromatic and aliphatic aldehydes and provided an access to a wide range of functionalized tetrahydrofurans with considerable structural and stereochemical variation. A total synthesis of (+)-isatisine A (**1**) has been achieved starting from the highly functionalized tetrahydrofuran **6a**, which was generated through this silicon-directed Mukaiyama-type [3 + 2]-annulation. Additionally, this synthesis represents another application of a Buchwald-type amidation culminating the assembly of the 3-indolone moiety of the complex natural product. Further studies to synthesize naturally occurring materials, which bear a complex tetrahydrofuran core, employing this annulation methodology are in progress and may be reported at a later time.

EXPERIMENTAL SECTION

General Experimental Procedures. All reactions were carried out in oven or flame-dried glassware under argon atmosphere. Triethylamine and 2,6-lutidine were distilled and stored over potassium hydroxide. *n*-Butyllithium was purchased and standardized by titration with menthol/2,2′-dipyridyl. All other reagents were used as supplied. Dichloromethane, toluene, diethyl ether, benzene, tetrahydrofuran, and acetonitrile were obtained from an anhydrous solvent system (alumina) and used without further drying. Unless otherwise noted, reactions were magnetically stirred and monitored by thin-layer chromatography with 0.20 mm silica gel 60 Å plates. Flash chromatography was performed on 32−63 μm 60 Å silica gel. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise noted. ^{1}H NMR spectra were taken in $CDCl_3$, methanol-d_4, and CD_3CN at 400 or 500 MHz (as indicated), respectively. ^{13}C NMR spectra were also taken in $CDCl_3$, methanol-d_4, and CD_3CN at 100 or 125 MHz (as indicated), respectively. Chemical shifts are reported in parts per million relative to $CDCl_3$ (^{1}H, δ 7.24; ^{13}C, δ 77.0), methanol-d_6 (^{1}H, δ 3.31; ^{13}C, δ 49.0), and acetonitrile-d_3 (^{1}H, δ 1.94; ^{13}C, δ 118.7). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept = septuplet m = multiplet, br = broad, obsc = obscured), coupling constant, integration. Diastereomeric ratios were determined by ^{1}H NMR (500 MHz) analysis of crude mixtures, operating at signal/noise ratio of 200:1. Infrared resonance spectra were recorded as a thin film on KBr plate. High-resolution mass spectra (HRMS) were obtained by electrospray ionization using a Q-TOF mass spectrometer in positive-ion mode (M + H or M + Na) as indicated.

*(2S,3R,Z)-3-(Dimethyl(phenyl)silyl)-5-ethoxy-1-methoxypent-4-en-2-ol (anti-**5**).* A solution of ethoxy acetylene (50 wt % in hexane, 2.5 mL, 12.8 mmol) in diethyl ether (60 mL) was cooled to −78 °C under an atmosphere of Ar. *n*-BuLi (2.5 M in hexane, 5.1 mL, 12.8 mmol) was added dropwise for 5 min at −78 °C, and stirring was continued for 1 h at the same temperature. A solution of *cis*-**7**[6a] (1.91 g, 6.75 mmol) in ethyl ether (20 mL) and $BF_3{\cdot}OEt_2$ (1.7 mL, 13.5 mmol) were successively added, and the reaction mixture was stirred for 30 min at −78 °C before addition of satd $NaHCO_3$ (80 mL). Ethyl acetate (80 mL) was added, and the resulting layers were separated. The organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo to obtain a yellowish residue. Purification over silica gel with hexanes/ethyl acetate (10/1) afforded an inseparable mixture of *anti*-**8** and unidentified byproduct (2.25 g): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.58−7.56 (m, 2H), 7.35−7.31 (m, 3H), 4.00 (q, J = 7.0 Hz, 2H), 3.73 (m, 1H), 3.38 (dd, J = 9.5, 7.0 Hz, 1H), 3.30 (dd, J = 9.5, 5.0 Hz, 1H), 3.27 (s, 3H), 2.07 (d, J = 3.0 Hz, 1H), 2.02 (d, J = 7.0 Hz, 1H), 1.30 (t, J = 7.5 Hz, 3H), 0.42 (s, 3H), 0.41 (s, 3H).

To a solution of *anti*-**8** (2.25g, 7.69 mmol) and pyridine (1.3 mL, 15.4 mmol) in ethyl acetate (50 mL) was added Lindlar's catalyst (157 mg). The air in the reaction vessel was substituted with H_2 gas employing vacuum (three times) and stirring was continued for 1 h. The mixture was then filtered through a pad of Celite, and the solution was concentrated under reduced pressure to give a yellow residue. Purification over silica gel with hexanes/ethyl acetate (10/1) afforded *anti*-**5** as a colorless oil (2.0 g, 80%, two steps): $[\alpha]_D^{20}$ = −34.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.57−7.55 (m, 2H), 7.32−7.29 (m, 3H), 5.99 (d, J = 6.5, 1H), 4.42 (dd, J = 11.0, 5.2 Hz, 1H), 3.85 (m, 1H), 3.66 (qd, J = 7.2, 6.8 Hz, 2H), 3.28−3.20 (m, 2H), 3.25 (s, 3H), 2.36 (dd, J = 3.5, 1.0 Hz, 1H), 2.30 (dd, J = 10.5, 3.5 Hz, 1H), 1.15 (t, J = 7.0 Hz, 3H), 0.34 (s, 3H), 0.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.3, 138.4, 134.0, 128.7, 127.4, 101.9, 77.0, 69.9, 67.2, 58.6, 28.4, 15.1, −3.5, −3.9; IR (film) ν_{max} 3465, 2976, 2895, 1652, 1427, 1251 cm^{-1}; HRMS (CI, NH_3) m/z [M + Na]$^+$ calcd for $C_{16}H_{26}NaO_3Si$ 317.1549, found 317.1577.

*(2S,3S,Z)-3-(Dimethyl(phenyl)silyl)-5-ethoxy-1-methoxypent-4-en-2-ol (syn-**5**).* A solution of ethoxy acetylene (40 wt % in hexane, 3.2 mL, 13.5 mmol) in diethyl ether (25 mL) was cooled to −78 °C under an atmosphere of Ar. *n*-BuLi (2.5 M in hexane, 5.4 mL, 13.5 mmol) was added dropwise, and stirring was continued at −78 °C for 1 h. A 2.0 M solution of Me_3Al in heptane (6.75 mL, 13.5 mmol) and a solution of *trans*-**7**[6a] (1.5 g, 6.75 mmol) in ethyl ether (9 mL) were successively added, which was followed by $BF_3{\cdot}OEt_2$ (1.7 mL, 13.5 mmol). After 30 min at −78 °C, satd $NaHCO_3$ (34 mL) was added, and the mixture was diluted with ethyl acetate (50 mL). The resulting layers were separated, and the organic layer were dried over magnesium sulfate, filtered, and concentrated in vacuo to obtain a yellowish residue. Column chromatography over silica gel with hexanes/ethyl acetate (10/1) afforded *syn*-**8** as a yellowish oil (1.67 g, 85%): $[\alpha]_D^{20}$ = −45.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.65−7.63 (m, 2H), 7.37−7.34 (m, 3H), 3.95 (q, J = 6.8 Hz, 2H), 3.79−3.73 (m, 1H), 3.57 (dd, J = 9.6, 2.8 Hz, 1H), 3.38 (dd, J = 9.6, 7.6 Hz, 1H), 3.33 (s, 3H), 2.55 (d, J = 4.8 Hz, 1H), 2.11 (d, J = 8.8 Hz, 1H), 1.29 (t, J = 6.8 Hz, 3H), 0.47 (s, 3H), 0.46 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.5, 134.0, 128.9, 127.4, 92.2, 76.4, 58.7, 35.3, 22.3, 14.2, −3.2, −3.3; IR (film) ν_{max} 3453, 2896, 2258, 1427, 1247 cm^{-1}.

A solution of *syn*-**8** (1.57g, 5.37 mmol) and pyridine (0.9 mL, 10.7 mmol) in ethyl acetate (50 mL) was treated with Lindlar's catalyst (157 mg). The air in the reaction vessel was substituted with H_2 gas through a vacuum-H_2 reload process (three times), and stirring was continued for 6 h. The mixture was then filtered through a pad of Celite, and the solution was concentrated under reduced pressure to give a yellow residue. Purification over silica gel with hexanes/ethyl acetate (10/1) afforded *syn*-**5** as a colorless oil (1.45 g, 92%): $[\alpha]_D^{20}$ = −32.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.57−7.55 (m, 2H), 7.31−7.29 (m, 3H), 5.91 (d, J = 6.5 Hz, 1H), 4.10 (dd, J = 11.0, 6.0 Hz, 1H), 3.75−3.71 (m, 1H), 3.70 (q, J = 7.0 Hz, 1H), 3.64 (q, J = 6.5 Hz, 1H), 3.15 (t, J = 9.0 Hz, 1H), 2.44 (dd, J = 11.0, 9.0 Hz, 1H), 2.32 (d, J = 3.5 Hz, 1H), 1.16 (t, J = 7.0 Hz, 3H), 0.35 (s, 3H), 0.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): 144.4, 135.5, 134.0, 128.5, 127.2, 103.3, 76.9, 71.9, 67.2, 58.6, 29.3, 15.1, −2.8, −3.3; IR (film) ν_{max} 3461, 2977, 2894, 1653, 1245 cm^{-1}; HRMS (CI, NH_3) m/z [M + Na]$^+$ calcd for $C_{16}H_{26}NaO_3Si$ 317.1549, found 317.1579.

General Procedure for the Silicon-Directed Mukaiyama-Type [3 + 2]-Annulation of *anti*-5. Ethoxy allyl silane (±)-*anti*-**5** (40 mg, 0.136 mmol) and aldehyde **9** (0.271 mmol) were dissolved with methylene chloride (0.45 mL) in a round-bottom flask. The mixture was cooled to 0 °C, and PTSA monohydrate (26 mg, 0.136 mmol) was added in one portion. The solution was allowed to stir for 10 min at 0 °C before addition of satd $NaHCO_3$ solution (1.0 mL). The mixture was diluted with methylene chloride (3.0 mL), and the resulting layers were separated. The organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo to obtain a crude product. Purification over silica gel with hexanes/ethyl acetate (20/1 to 10/1) provided product tetrahydrofuran **6**:

*(±)-(2R,3R,4R,5S)-2-Butyl-4-(dimethyl(phenyl)silyl)-5-(methoxymethyl)tetrahydrofuran-3-carbaldehyde (**6b**).* Aldehyde **9b** (29 μL, 0.271 mmol) was used following the general procedure. Tetrahydrofuran **6b** was obtained as a colorless oil (40 mg, 88% yield):

DOI: 10.1021/acs.joc.5b00051
J. Org. Chem. 2015, 80, 2959−2971

^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.52 (d, J = 5.0 Hz, 1H), 7.47−7.45 (m, 2H), 7.37−7.32 (m, 3H), 3.96 (ddd, J = 9.0, 6.5, 2.5 Hz, 1H), 3.60 (ddd, J = 8.0, 6.0, 6.0 Hz, 1H), 3.27−3.19 (m, 2H), 3.25 (s, 3H), 2.68 (ddd, J = 6.0, 4.5, 4.5 Hz, 1H), 2.68 (ddd, J = 6.0, 4.5, 4.5 Hz, 1H), 1.67 (dd, J = 9.0, 4.5 Hz, 1H), 1.65−1.60 (m, 1H), 1.54−1.47 (m, 1H), 1.40−1.33 (m, 1H), 1.25−1.20 (m, 3H), 0.82 (t, J = 7.0 Hz, 3H), 0.33 (s, 3H), 0.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.8, 135.9, 133.7, 129.6, 128.0, 82.0, 80.3, 74.7, 59.2, 56.3, 30.3, 28.6, 28.0, 22.4, 13.7, −4.1, −4.7; IR (film) ν_{max} 3069, 2955, 1718, 1427, 1252, 1114 cm^{-1}; HRMS (CI, NH_3) m/z [M + Na]$^+$ calcd for $C_{19}H_{30}NaO_3Si$ 357.1862, found 357.1852.

*(±)-(2R,3R,4R,5S)-4-(Dimethyl(phenyl)silyl)-2-isopropyl-5-(methoxymethyl)tetrahydrofuran-3-carbaldehyde (**6c**).* Aldehyde **9c** (25 μL, 0.271 mmol) was used following the general procedure. Tetrahydrofuran **6c** was obtained as a colorless oil (38 mg, 87% yield): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.53 (d, J = 5.4 Hz, 1H), 7.52−7.42 (m, 2H), 7.42−7.27 (m, 3H), 3.95 (ddd, J = 8.5, 6.0, 2.4 Hz, 1H), 3.28 (dd, J = 10.7, 2.4 Hz, 1H), 3.26 (s, 3H), 3.19 (dd, J = 10.7, 6.0 Hz, 1H), 3.11 (dd, J = 10.3, 5.5 Hz, 1H), 2.69 (td, J = 5.4, 3.5 Hz, 1H), 1.84 (dp, J = 10.3, 6.5 Hz, 1H), 1.61 (dd, J = 8.6, 3.5 Hz, 1H), 0.97 (d, J = 6.4 Hz, 3H), 0.81 (d, J = 6.7 Hz, 3H), 0.34 (d, J = 7.7 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 206.2, 138.6, 132.8, 93.3, 85.1, 81.8, 79.4, 64.1, 60.2, 33.8, 33.1, 25.9, 23.3, 0.6, 0.0; IR (film) ν_{max} 3049, 2875, 1716, 1470, 1252 cm^{-1}; HRMS (CI, NH_3) m/z [M + Na]$^+$ calcd for $C_{18}H_{28}NaO_3Si$ 343.1705, found 343.1708.

*(±)-(2R,3R,4R,5S)-2-Cyclopropyl-4-(dimethyl(phenyl)silyl)-5-(methoxymethyl)tetrahydrofuran-3-carbaldehyde (**6d**).* Aldehyde **9d** (20 μL, 0.271 mmol) was used following the general procedure. Tetrahydrofuran **6d** was obtained as a colorless oil (37 mg, 85% yield): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.70 (dd, J = 3.9, 0.6 Hz, 1H), 7.50−7.39 (m, 2H), 7.41−7.26 (m, 3H), 3.92 (dddd, J = 9.5, 6.1, 2.8, 0.6 Hz, 1H), 3.27−3.23 (m, 5H), 0.31−0.29 (m, 4H), 3.02 (dd, J = 9.1, 7.1 Hz, 1H), 1.84 (ddd, J = 9.5, 6.4, 0.6 Hz, 1H), 0.32−0.29 (m, 7H), 2.82 (dddd, J = 7.0, 6.3, 3.9, 0.6 Hz, 1H), 0.91−0.82 (m, 1H), 0.63−0.54 (m, 1H), 0.48 (ddd, J = 9.2, 8.4, 5.5 Hz, 1H), 0.39−0.32 (m, 2H), 0.38−0.32 (m, 2H), 0.32 (s, 3H), 0.30 (s, 3H), 0.17−0.10 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.5, 136.0, 133.8, 129.6, 128.0, 86.1, 80.7, 74.8, 59.2, 57.2, 27.7, 11.2, 5.3, 1.8, −4.1, −4.7; IR (film) ν_{max} 3048, 2884, 1718, 1456, 1252 cm^{-1}; HRMS (CI, NH_3) m/z [M + Na]$^+$ calcd for $C_{18}H_{26}NaO_3Si$ 341.1549, found 341.1538.

*(±)-(2R,3R,4R,5S)-2-Cyclohexyl-4-(dimethyl(phenyl)silyl)-5-(methoxymethyl)tetrahydrofuran-3-carbaldehyde (**6e**).* Aldehyde **9e** (33 μL, 0.271 mmol) was used following the general procedure. Tetrahydrofuran **6e** was obtained as a colorless oil (40 mg, 82% yield): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.53 (d, J = 5.4 Hz, 1H), 7.50−7.43 (m, 2H), 7.40−7.30 (m, 3H), 3.93 (ddd, J = 8.5, 6.0, 2.5 Hz, 1H), 3.28 (dd, J = 10.7, 2.5 Hz, 1H), 3.26 (s, 1H), 3.18 (ddd, J = 10.1, 9.2, 5.7 Hz, 3H), 2.69 (td, J = 5.4, 3.4 Hz, 1H), 2.06−1.94 (m, 1H), 1.64−1.52 (m, 7H), 1.23−1.00 (m, 4H), 0.93−0.74 (m, 2H), 0.34 (d, J = 7.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.4, 136.0, 133.8, 129.6, 128.0, 87.0, 80.0, 74.6, 59.3, 55.0, 38.2, 31.3, 28.6, 28.1, 26.1, 25.4, 25.2, −4.2, −4.8; IR (film) ν_{max} 2924, 2851, 1716, 1450, 1252 cm^{-1}; HRMS (CI, NH_3) m/z [M + Na]$^+$ calcd for $C_{21}H_{32}NaO_3Si$ 383.2018, found 383.2010.

*(±)-(2S,3R,4R,5S)-4-(Dimethyl(phenyl)silyl)-5-(methoxymethyl)-2-phenyltetrahydrofuran-3-carbaldehyde (**6f**).* Aldehyde **9f** (28 μL, 0.271 mmol) was used following the general procedure. Tetrahydrofuran **6f** was obtained as a colorless oil (43 mg, 89% yield): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.99 (d, J = 3.5 Hz, 1H), 7.54−7.51 (m, 2H), 7.40−7.34 (m, 3H), 7.29−7.19 (m, 5H), 4.83 (d, J = 7.5 Hz, 1H), 4.14 (ddd, J = 9.5, 5.5, 3.5 Hz, 1H), 3.40−3.39 (m, 2H), 3.33 (s, 3H), 3.07 (ddd, J = 7.0, 5.5, 3.5 Hz, 1H), 1.94 (dd, J = 9.5, 6.0 Hz, 1H), 0.39 (s, 3H), 0.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.8, 136.6, 135.8, 133.8, 129.7, 128.4, 128.0, 127.8, 125.9, 82.1, 81.0, 74.6, 59.2, 58.1, 27.9, −3.9, −4.6; IR (film) ν_{max} 3068, 2878, 1719, 1427, 1252, 1110 cm^{-1}; HRMS (CI, NH_3) m/z [M + H]$^+$ calcd for $C_{21}H_{27}O_3Si$ 355.1729, found 355.1727.

*(±)-(2S,3R,4R,5S)-4-(Dimethyl(phenyl)silyl)-5-(methoxymethyl)-2-(p-tolyl)tetrahydrofuran-3-carbaldehyde (**6g**).* Aldehyde **9g** (32 μL, 0.271 mmol) was used following the general procedure. Tetrahydrofuran **6g** was obtained as a colorless oil (42 mg, 84% yield): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.01 (dd, J = 3.8, 0.7 Hz, 1H), 7.55−7.49 (m, 2H), 7.42−7.33 (m, 3H), 7.15 (d, J = 8.0 Hz, 2H), 7.08 (d, J = 8.0 Hz, 2H), 4.82 (d, J = 7.4 Hz, 1H), 4.16−4.09 (m, 1H), 3.42−3.37 (m, 2H), 3.33 (s, 2H), 3.04 (dtd, J = 7.4, 3.8, 1.9 Hz, 1H), 2.28 (s, 3H), 1.93 (ddd, J = 9.5, 5.9, 1.0 Hz, 1H), 0.38 (d, J = 10.5 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.0, 137.4, 135.9, 133.9, 133.6, 129.7, 129.1, 128.1, 125.9, 82.1, 81.0, 74.7, 59.3, 58.1, 28.0, 21.1, −4.0, −4.7; IR (film) ν_{max} 3047, 1715, 1515, 1455, 1252 cm^{-1}; HRMS (CI, NH_3) m/z [M + Na]$^+$ calcd for $C_{22}H_{28}NaO_3Si$ 391.1705, found 391.1700.

*(±)-(2S,3R,4R,5S)-4-(Dimethyl(phenyl)silyl)-5-(methoxymethyl)-2-(2 methoxyphenyl)tetrahydrofuran-3-carbaldehyde (**6h**).* Aldehyde **9h** (37 mg, 0.271 mmol) was used following the general procedure. Tetrahydrofuran **6h** was obtained as a colorless oil (37 mg, 71% yield): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.00 (d, J = 3.5 Hz, 1H), 7.57−7.51 (m, 2H), 7.49 (ddd, J = 7.7, 1.8, 0.9 Hz, 1H), 7.42−7.35 (m, 3H), 7.23−7.14 (m, 1H), 6.94−6.85 (m, 1H), 6.79 (dd, J = 8.2, 1.0 Hz, 1H), 5.03 (dd, J = 7.1, 0.9 Hz, 1H), 4.11 (ddd, J = 9.5, 5.7, 3.1 Hz, 1H), 3.79 (s, 3H), 3.43−3.34 (m, 2H), 3.32 (s, 3H), 3.30−3.22 (m, 2H), 1.86 (dd, J = 9.5, 5.9 Hz, 1H), 0.39 (d, J = 16.9 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.1, 155.3, 136.2, 133.9, 129.6, 128.5, 128.0, 126.4, 125.3, 120.5, 109.7, 80.5, 77.6, 74.9, 59.3, 55.7, 55.2, 27.9, −3.9, −4.7; IR (film) ν_{max} 2979, 2837, 1719, 1602, 1491, 1246 cm^{-1}; HRMS (CI, NH_3) m/z [M + Na]$^+$ calcd for $C_{22}H_{28}NaO_4Si$ 407.1655, found 407.1661.

*(±)-(2S,3R,4R,5S)-2-(4-Bromophenyl)-4-(dimethyl(phenyl)silyl)-5-(methoxymethyl)tetrahydrofuran-3-carbaldehyde (**6i**).* Aldehyde **9i** (50 mg, 0.271 mmol) was used following the general procedure. Tetrahydrofuran **6i** was obtained as a colorless oil (48 mg, 81% yield): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.98 (d, J = 3.9 Hz, 1H), 7.51 (dd, J = 7.4, 1.9 Hz, 2H), 7.45−7.31 (m, 5H), 7.18−7.11 (m, 2H), 4.78 (d, J = 7.4 Hz, 1H), 3.46−3.33 (m, 3H), 4.13 (ddd, J = 9.5, 5.9, 2.5 Hz, 1H), 3.43−3.33 (m, 2H), 3.32 (s, 3H), 1.93 (dd, J = 9.5, 6.0 Hz, 1H), 0.38 (d, J = 9.9 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 200.5, 135.8, 135.7, 133.8, 131.6, 129.8, 128.1, 127.9, 127.7, 121.7, 103.1, 81.4, 81.2, 74.5, 59.3, 58.0, 28.1, −4.0, −4.7; IR (film) ν_{max} 2979, 2884, 1718, 1488, 1399, 1253 cm^{-1}. HRMS (CI, NH_3) m/z [M + Na]$^+$ calcd for $C_{21}H_{25}BrNaO_3Si$ 455.0654, found 455.0649.

General Procedure for Silyl-Directed Mukaiyama-Type [3 + 2]-Annulation of *syn*-5. Ethoxy allyl silane (±)-*syn*-**5** (40 mg, 0.136 mmol) and aldehyde **9** (0.271 mmol) were added into a round-bottom flask followed by methylene chloride (0.45 mL). The mixture was cooled to 0 °C, and methansulfonic acid (9.0 μL, 0.136 mmol) was added in one portion. The reaction was allowed to stir for 10 min at 0 °C before being quenched with satd $NaHCO_3$ solution (1.0 mL). Upon warming to room temperature, the layers were separated and the aqueous phase was extracted with methylene chloride (3.0 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to obtain a crude product. Purification over silica gel with hexanes/ethyl acetate (20/1 to 10/1) afforded a furan **10** as an oil:

*(±)-(2S, 3S, 4S, 5S)-2-Butyl-4-(dimethyl(phenyl)silyl)-5-(methoxymethyl)tetrahydrofuran-3-carbaldehyde (**10b**).* Aldehyde **9b** (29 μL, 0.271 mmol) was used following the general procedure. Tetrahydrofuran **10b** was obtained as a colorless oil (34 mg, 75% yield): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.42 (d, J = 4.5, 1H), 7.48−7.35 (m, 2H), 7.35−7.30 (m, 3H), 4.43 (ddd, J = 8.0, 6.0, 3.5 Hz, 1H), 4.21 (ddd, J = 9.0, 9.0, 4.5 Hz, 1H), 3.24 (dd, J = 10.0, 3.5 Hz, 1H), 3.18−3.13 (m, 1H), 3.16 (s, 3H), 3.05 (ddd, J = 13.5, 9.0, 4.5 Hz, 1H), 2.21 (dd, J = 9.0, 8.5 Hz, 1H), 1.57−1.49 (m, 1H), 1.45−1.40 (m, 2H), 1.29−1.24 (m, 3H), 0.84 (t, J = 7.5 Hz, 3H), 0.34 (s, 3H), 0.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 202.5, 137.3, 133.6, 129.3, 127.9, 80.6, 80.5, 74.0, 58.6, 56.3, 31.4, 30.8, 28.7, 22.6, 13.8, −2.4, −3.1; IR (film) ν_{max} 3069, 2929, 1719, 1427, 1251, 1111 cm^{-1}; HRMS (CI, NH_3) m/z [M + Na]$^+$ calcd for $C_{19}H_{30}NaO_3Si$ 357.1862, found 357.1857.

*(±)-(2S,3S,4S,5S)-4-(Dimethyl(phenyl)silyl)-2-isopropyl-5-(methoxymethyl)tetrahydrofuran-3-carbaldehyde (**10c**).* Aldehyde **9c** (25 μL, 0.271 mmol) was used following the general procedure. Tetrahydrofuran **10c** was obtained as a colorless oil (32 mg, 74%

DOI: 10.1021/acs.joc.5b00051
J. Org. Chem. 2015, 80, 2959−2971

yield): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.52 (dd, J = 5.0, 0.6 Hz, 1H), 7.52−7.42 (m, 2H), 7.38−7.31 (m, 3H), 4.46 (ddd, J = 8.3, 6.3, 3.7 Hz, 1H), 3.73 (dd, J = 9.1, 7.2 Hz, 1H), 3.26 (dd, J = 10.3, 3.7 Hz, 1H), 1.89−1.77 (m, 1H), 3.22−3.18 (m, 1H), 3.18 (s, 3H), 2.97 (td, J = 7.0, 5.0 Hz, 1H), 2.14 (dd, J = 8.4, 6.9 Hz, 1H), 1.91−1.74 (m, 1H), 0.97 (d, J = 6.5 Hz, 3H), 0.87 (d, J = 6.6 Hz, 3H), 0.36 (s, 3H), 0.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.7, 137.5, 133.6, 129.4, 127.9, 86.1, 80.6, 73.9, 58.7, 56.0, 31.0, 29.2, 20.3, 19.3, −2.2, −3.0; IR (film) ν_{max} 2958, 2890, 1718, 1470, 1389, 1252 cm^{-1}; HRMS (CI, NH_3) m/z [M + Na]$^+$ calcd for $C_{18}H_{28}NaO_3Si$ 343.1705, found 343.1704.

*(±)-(2S,3S,4S,5S)-2-Cyclopropyl-4-(dimethyl(phenyl)silyl)-5-(methoxymethyl)tetrahydrofuran-3-carbaldehyde (**10d**).* Aldehyde **9d** (20 μL, 0.271 mmol) was used following the general procedure. Tetrahydrofuran **10d** was obtained as a colorless oil (42 mg, 96% yield): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.57 (d, J = 4.4 Hz, 1H), 7.50−7.46 (m, 2H), 7.37−7.31 (m, 3H), 4.43 (ddd, J = 7.8, 5.3, 3.5 Hz, 1H), 3.59 (t, J = 8.9 Hz, 1H), 3.25−3.18 (m, 2H), 3.12 (s, 3H), 2.36−2.31 (m, 1H), 0.88 (dddd, J = 12.5, 10.7, 6.1, 2.9 Hz, 1H), 0.66−0.56 (m, 1H), 0.48−0.36 (m, 2H), 0.34 (s, 3H), 0.30 (s, 3H), 0.22−0.13 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 202.1, 137.3, 133.7, 129.4, 127.9, 85.1, 81.2, 74.5, 58.6, 56.8, 31.1, 12.4, 4.9, 2.1, −2.5, −3.2; IR (film) ν_{max} 2980, 2828, 1772, 1394, 1251 cm^{-1}; HRMS (CI, NH_3) m/z [M + Na]$^+$ calcd for $C_{18}H_{26}NaO_3Si$ 341.1549, found 341.1548.

*(±)-(2S,3S,4S,5S)-2-Cyclohexyl-4-(dimethyl(phenyl)silyl)-5-(methoxymethyl)tetrahydrofuran-3-carbaldehyde (**10e**).* Aldehyde **9e** (33 μL, 0.271 mmol) was used following the general procedure. Tetrahydrofuran **10e** was obtained as a colorless oil (42 mg, 86% yield): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.52 (dt, J = 5.0, 0.9 Hz, 1H), 7.52−7.43 (m, 2H), 7.37−7.30 (m, 3H), 4.45 (ddd, J = 8.8, 6.4, 3.7 Hz, 1H), 3.77 (dd, J = 8.9, 7.1 Hz, 1H), 3.27−3.22 (m, 1H), 3.21−3.17 (m, 1H), 3.17 (s, 3H), 2.96 (td, J = 6.9, 5.0 Hz, 1H), 2.11 (ddd, J = 7.6, 6.5, 1.0 Hz, 1H), 1.95−1.88 (m, 1H), 1.71−1.57 (m, 5H), 1.22−1.07 (m, 4H), 0.35 (s, 3H), 0.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.7, 137.5, 133.6, 129.4, 128.0, 85.1, 80.4, 73.8, 58.7, 55.8, 38.7, 30.8, 30.5, 29.6, 26.2, 25.7, 25.5, −2.1, −3.0; IR (film) ν_{max} 2924, 2852, 1718, 1450, 1251, 1110 cm^{-1}; HRMS (CI, NH_3) m/z [M + Na]$^+$ calcd for $C_{21}H_{32}NaO_3Si$ 383.2018, found: 383.2042.

*(±)-(2R,3S,4S,5S)-4-(Dimethyl(phenyl)silyl)-5-(methoxymethyl)-2-phenyltetrahydrofuran-3-carbaldehyde (**10f**).* Aldehyde **9f** (28 μL, 0.271 mmol) was used following the general procedure. Tetrahydrofuran **10f** was obtained as a colorless oil (40 mg, 83% yield): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.65 (d, J = 4.5, 1H), 7.51−7.48 (m, 2H), 7.36−7.33 (m, 3H), 7.30−7.27 (m, 2H), 7.25−7.19 (m, 3H), 5.40 (d, J = 9.0 Hz, 1H), 4.68 (ddd, J = 8.0, 5.0, 3.5 Hz, 1H), 3.40 (ddd, J = 11.0, 9.0, 4.5 Hz, 1H), 3.35 (dd, J = 10.0, 3.5 Hz, 1H), 3.25 (dd, J = 10.0, 5.0 Hz, 1H), 3.19 (s, 3H), 2.34 (dd, J = 10.5, 8.0 Hz, 1H), 0.37 (s, 3H), 0.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.0, 138.1, 137.0, 133.7, 133.6, 129.4, 129.0, 128.4, 127.9, 127.8, 127.7, 126.1, 82.2, 81.5, 74.4, 58.6, 57.8, 30.7, −2.4, −3.2; IR (film) ν_{max} 2923, 1719, 1427, 1251, 1111 cm^{-1}; HRMS (CI, NH_3) m/z [M + Na]$^+$ calcd for $C_{21}H_{26}NaO_3Si$ 377.1549, found 377.1555.

*(±)-(2R,3S,4S,5S)-4-(Dimethyl(phenyl)silyl)-5-(methoxymethyl)-2-(p-tolyl)tetrahydrofuran-3-carbaldehyde (**10g**).* Aldehyde **9g** (32 μL, 0.271 mmol) was used following the general procedure. Tetrahydrofuran **10g** was obtained as a colorless oil (42 mg, 84% yield): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.66 (d, J = 4.6 Hz, 1H), 7.54−7.48 (m, 2H), 7.37−7.32 (m, 3H), 7.13 (d, J = 8.1 Hz, 2H), 7.09 (d, J = 7.7 Hz, 2H), 5.38 (d, J = 9.0 Hz, 1H), 4.68 (ddd, J = 8.1, 5.4, 3.6 Hz, 1H), 3.42−3.33 (m, 2H), 3.25 (dd, J = 10.1, 5.3 Hz, 1H), 3.20 (s, 3H), 2.35 (dd, J = 10.8, 7.9 Hz, 1H), 2.29 (s, 3H), 0.37 (s, 3H), 0.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 202.2, 137.4, 137.1, 135.1, 133.7, 129.4, 129.1, 128.0, 126.0, 82.1, 81.5, 74.5, 58.7, 57.8, 30.7, 21.1, −2.4, −3.2; IR (film) ν_{max} 2980, 2829, 1718, 1427, 1251, 1111 cm^{-1}; HRMS (CI, NH_3) m/z [M + Na]$^+$ calcd for $C_{22}H_{28}NaO_3Si$ 391.1705, found 391.1694.

*(±)-(2R,3S,4S,5S)-4-(Dimethyl(phenyl)silyl)-5-(methoxymethyl)-2-(2-methoxyphenyl)tetrahydrofuran-3-carbaldehyde (**10h**).* Aldehyde **9h** (37 mg, 0.271 mmol) was used following the general procedure. Tetrahydrofuran **10h** was obtained as a colorless oil (40 mg, 76% yield): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.74 (d, J = 4.7 Hz, 1H), 7.54 (dd, J = 4.8, 2.5 Hz, 2H), 7.50 (dd, J = 7.7, 1.9 Hz, 1H), 7.38 (s, 3H), 7.24 (td, J = 7.8, 1.9 Hz, 1H), 6.97 (t, J = 7.4 Hz, 1H), 6.80 (d, J = 8.2 Hz, 1H), 5.62 (dd, J = 8.6, 2.4 Hz, 1H), 4.74−4.59 (m, 1H), 3.79 (s, 3H), 3.50−3.42 (m, 1H), 3.36 (dd, J = 10.2, 3.5 Hz, 1H), 3.29 (ddd, J = 10.2, 6.1, 2.0 Hz, 1H), 3.24 (s, 3H), 2.28−2.19 (m, 1H), 0.41 (s, 3H), 0.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.6, 155.0, 137.2, 133.7, 129.3, 128.5, 127.9, 126.7, 126.6, 120.5, 109.6, 81.6, 76.4, 74.1, 58.8, 56.2, 55.0, 30.5, −2.3, −3.1; IR (film) ν_{max} 2980, 2835, 1720, 1600, 1589, 1284 cm^{-1}; HRMS (CI, NH_3) m/z [M + Na]$^+$ calcd for $C_{22}H_{28}NaO_4Si$ 407.1655, found 407.1670.

*(±)-(2R,3S,4S,5S)-2-(4-Bromophenyl)-4-(dimethyl(phenyl)silyl)-5-(methoxymethyl)tetrahydrofuran-3-carbaldehyde (**10i**).* Aldehyde **9i** (50 mg, 0.271 mmol) was used following the general procedure. Tetrahydrofuran **10i** was obtained as a colorless oil (42 mg, 70% yield): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.65 (d, J = 4.7 Hz, 1H), 7.52−7.45 (m, 2H), 7.44−7.39 (m, 2H), 7.35 (dd, J = 5.0, 2.1 Hz, 3H), 7.15−7.10 (m, 2H), 5.35 (d, J = 9.0 Hz, 1H), 4.66 (ddd, J = 8.3, 5.1, 3.4 Hz, 1H), 3.37−3.33 (m, 1H), 3.40 (ddd, J = 10.8, 9.0, 4.7 Hz, 1H), 3.35 (dd, J = 10.2, 3.4 Hz, 1H), 3.24 (dd, J = 10.2, 5.2 Hz, 1H), 3.19 (s, 2H), 2.29 (dd, J = 10.8, 7.9 Hz, 1H), 0.37 (s, 3H), 0.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.6, 137.3, 136.8, 133.7, 131.6, 129.5, 128.0, 127.9, 121.6, 82.3, 81.0, 74.5, 65.8, 58.7, 57.8, 30.9, 15.2, −2.5, −3.3; IR (film) ν_{max} 2980, 2831, 1718, 1507, 1395, 1251 cm^{-1}. HRMS (CI, NH_3) m/z [M + Na]$^+$ calcd for $C_{21}H_{25}BrNaO_3Si$ 455.0654, found 455.0679.

First-Generation Approach toward the Total Synthesis of (+)-Isatisine A. *(2R,3R,4R,5S)-2-(2-Bromostyryl)-4-(dimethyl-(phenyl)silyl)-5-(methoxymethyl)tetrahydrofuran-3-carbaldehyde (**6a**).* Ethoxy allyl silane *anti*-**5** (1.3 g, 4.41 mmol) and aldehyde **9a** (1.86 g, 8.82 mmol) were dissolved with methylene chloride (15 mL) in a round-bottom flask. The mixture was cooled to 0 °C, and PTSA monohydrate (0.83 g, 4.41 mmol) was added in one portion. The solution was allowed to stir for 10 min at 0 °C before addition of satd $NaHCO_3$ solution (10 mL). The mixture was diluted with methylene chloride (10 mL), and the resulting layers were separated. The organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo to obtain an oil. Purification over silica gel with hexanes/ethyl acetate (20/1 to 10/1) provided product tetrahydrofuran **6a** as a colorless oil (1.76 g, 87% yield): $[\alpha]_D^{20}$ = −3.6 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.53 (d, J = 3.5 Hz, 1H), 7.50−7.48 (m, 3H), 7.40−7.35 (m, 4H), 7.29 (dt, J = 7.5, 1.0 Hz, 1H), 7.07 (dt, J = 8.0, 2.0 Hz, 1H), 6.97 (d, J = 16.0 Hz, 1H), 6.09 (dd, J = 16.0, 7.0 Hz, 1H) 4.49 (td, J = 7.5, 1.0 Hz, 1H), 4.07 (ddd, J = 8.5, 6.5, 2.5 Hz, 1H), 3.34 (dd, J = 10.5, 2.5, 1H), 3.299 (s, 3H), 3.297 (dd, J = 11.0, 2.0 Hz, 1H), 3.01 (ddd, J = 10.5, 7.0, 3.5 Hz, 1H), 1.92 (dd, J = 9.5, 7.0 Hz, 1H), 0.38 (s, 3H), 0.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.7, 136.0, 135.8, 133.7, 132.8, 131.7, 129.7, 129.1, 128.0, 127.8, 127.4, 127.2, 123.6, 81.3, 81.2, 74.6, 59.2, 58.2, 28.0, −3.9, −4.6; IR (film) ν_{max} 2881, 2729, 1719, 1466, 1428, 1254 cm^{-1}; HRMS (CI, NH_3) m/z [M + Na]$^+$ calcd for $C_{23}H_{27}BrNaO_3Si$ 481.0811, found 481.0790.

*(2R,3R,4R,5S)-2-((E)-2-Bromostyryl)-4-(dimethyl(phenyl)silyl)-5-(methoxymethyl)tetrahydrofuran-3-carboxamide (**13**).* The aldehyde **6a** (586 mg, 2.07 mmol) was dissolved in *tert*-butyl alcohol (12.8 mL). The mixture was cooled to 0 °C, and 2-methylbutane (6.7 mL, 63.8 mmol) was added quickly into the reaction followed by slow addition of freshly prepared $NaClO_2$−NaH_2PO_4−H_2O (2g-2g-20 mL) solution (12.8 mL). The yellow reaction mixture was stirred at rt for 3 h before being concentrated under reduced pressure. The residue was diluted with ethyl acetate and water (ca. 10.0 mL each). The aqueous layer was acidified with 1 N HCl until pH = 5.0 and extracted with diethyl ether (3 × 10.0 mL). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give a crude acid as a colorless oil. The crude acid was used for the next amidation step without purification: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.53−7.43 (m, 3H), 7.43−7.32 (m, 4H), 7.19−7.13 (m, 1H), 7.04 (td, J = 7.7, 1.7 Hz, 1H), 6.89 (d, J = 15.7 Hz, 1H), 6.06 (dd, J = 15.7, 7.4 Hz, 1H), 4.40 (td, J = 7.3, 1.1 Hz, 1H), 4.06 (ddd, J = 9.4, 4.8, 2.2 Hz, 1H), 3.49−3.42 (m, 1H), 3.33 (d, J = 0.7 Hz, 3H), 3.29−3.21

DOI: 10.1021/acs.joc.5b00051
J. Org. Chem. 2015, 80, 2959−2971

(m, 1H), 3.16 (t, J = 7.1 Hz, 1H), 1.97 (dd, J = 9.4, 6.9 Hz, 1H), 0.39 (s, 3H), 0.36 (s, 3H).

A mixture of the crude acid and TEA (0.38 mL, 1.92 mmol) in methylene chloride (60 mL) was treated with ethyl chloroformate (0.18 mL, 1.92 mmol) at −30 °C. After 30 min, anhydrous NH_3 gas was bubbled through the reaction mixture at the same temperature for 10 min. Then the reaction was warmed to rt, diluted with ethyl acetate (10.0 mL), and washed with H_2O (5.0 mL). The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give a yellowish oil. Purification over silica gel with CH_2Cl_2/MeOH (50/1) afforded amide **13** as a viscous oil (586 mg, 96%): $[\alpha]_D^{20}$ = +1.3 (c 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.53−7.49 (m, 2H), 7.48−7.42 (m, 2H), 7.40−7.33 (m, 3H), 7.18 (tt, J = 7.9, 1.8 Hz, 1H), 7.06−7.01 (m, 1H), 6.90 (dt, J = 16.0, 1.6 Hz, 1H), 6.78 (s, 1H), 6.12 (ddd, J = 15.7, 7.2, 1.9 Hz, 1H), 5.40 (s, 1H), 4.18 (ddt, J = 8.4, 6.6, 1.6 Hz, 1H), 4.12−4.05 (m, 1H), 4.01 (ddd, J = 9.1, 3.4, 2.1 Hz, 1H), 3.59 (dd, J = 10.7, 2.2 Hz, 1H), 3.32 (s, 3H), 3.05 (dd, J = 10.7, 3.1 Hz, 1H), 2.95−2.89 (m, 1H), 2.07−2.00 (m, 1H), 0.41 (s, 3H), 0.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 175.7, 136.4, 135.9, 133.9, 132.6, 132.2, 129.7, 129.0, 128.1, 127.8, 127.7, 127.4, 123.5, 81.8, 80.2, 73.1, 59.2, 30.8, 14.5, −4.1, −5.2; IR (film) ν_{max} 3340, 3188, 2922, 1671, 1467, 1428, 1255 cm^{-1}; HRMS (CI, NH_3) m/z [M + Na]$^+$ calcd for $C_{23}H_{28}BrNNaO_3Si$ 496.0920, found 496.0943.

*(2S,3R,3aR,6aS)-6-(2-Bromobenzoyl)-3-(dimethyl(phenyl)silyl)-6-hydroxy-2-(methoxymethyl)tetrahydro-2H-furo[2,3-c]pyrrol-4(5H)-one (**12**).* Amide **13** (560 mg, 1.18 mmol) was dissolved in a 9:1 mixture (12 mL) of acetone and H_2O at rt. NMO (193 mg, 1.65 mmol) was added to the solution, which was stirred for 5 min at rt. OsO_4 (4 wt % solution in H_2O, 0.3 mL, 0.0340 mmol) was then added, and the reaction mixture was stirred for 14 h at rt. Aqueous satd $Na_2S_2O_3$ (12 mL) was added, and the mixture was stirred for additional 10 min at rt. Ethyl acetate (20 mL) was added, and the resulting layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo to obtain a brown oil. Purification over silica gel with hexanes/ethyl acetate (1/1) afforded diol **14** (2:1 mixture of diastereomers) as a viscous oil (440 mg, 73%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.55 (s, 1H) 7.52 (dd, J = 7.9, 1.7 Hz, 1H), 7.50−7.45 (m, 3H), 7.40−7.34 (m, 3H), 7.30- 7.25 (m, 1H), 7.11−7.06 (m, 1H), 5.40 (s, 1H), 5.22 (s, 1H), 3.97 (dt, J = 8.3, 2.1 Hz, 1H), 3.86 (dd, J = 9.3, 5.7 Hz, 1H), 3.80 (dd, J = 9.2, 1.9 Hz, 1H), 3.53 (dd, J = 10.9, 1.8 Hz, 1H), 3.29 (s, 3H), 3.01 (dd, J = 5.7, 3.0 Hz, 1H), 2.96 (dd, J = 11.0, 2.4 Hz, 1H), 1.94 (dd, J = 8.3, 3.1 Hz, 1H), 0.37 (d, J = 5.9 Hz, 6H).

The diol **14** (440 mg, 0.865 mmol) was dissolved in methylene chloride (8.0 mL), and NaBr (267 mg, 2.60 mmol) and TEMPO (68 mg, 0.433 mmol) were added. A premixed solution of NaOCl (5% in H_2O, 17 mL) and $NaHCO_3$ (272 mg) was added at rt, and the resulting brown mixture was stirred until it turned light yellow (∼30 min). Methylene chloride (20 mL) and water (5 mL) were added, and the layers were separated. The organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo to obtain a yellowish solid. Purification over silica gel with hexanes/ethyl acetate (2/1) afforded hydroxyl lactam **12** as a white solid (260 mg, 64%): $[\alpha]_D^{20}$ = +29.6 (c 1.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.60−7.54 (m, 2H), 7.52−7.48 (m, 2H), 7.39−7.31 (m, 5H), 7.28 (td, J = 7.8, 1.8 Hz, 1H), 6.52 (s, 1H), 5.62 (s, 1H), 4.71 (d, J = 7.6 Hz, 1H), 4.21 (ddd, J = 8.3, 4.2, 2.7 Hz, 1H), 3.40 (dd, J = 10.5, 2.8 Hz, 1H), 3.22 (s, 3H), 3.10 (t, J = 7.6 Hz, 1H), 2.90 (dd, J = 10.5, 4.3 Hz, 1H), 1.96 (dd, J = 8.4, 7.6 Hz, 1H), 0.44 (d, J = 4.4 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 200.0, 175.2, 138.2, 135.7, 133.9, 133.3, 131.6, 129.8, 128.9, 128.1, 126.9, 119.5, 88.8, 84.5, 80.5, 73.1, 58.9, 49.4, 30.8, −3.6, −5.5; IR (film) ν_{max} 3247, 3069, 2923, 1705, 1427, 1281 cm^{-1}; HRMS (CI, NH_3) m/z [M + Na]$^+$ calcd for $C_{23}H_{26}BrNNaO_5Si$ 526.0661, found 526.0663.

*(2S,3R,3aR,6R,6aS)-6-(2-Bromobenzoyl)-3-(dimethyl(phenyl)-silyl)-6-(1H-indol-3-yl)-2-(methoxymethyl)tetrahydro-2H-furo[2,3-c]pyrrol-4(5H)-one (**11**).* A solution of hydroxyl lactam **12** (200 mg, 0.396 mmol) in anhydrous MeCN (4.0 mL) was cooled to 0 °C under an atmosphere of Ar, and $In(OTf)_3$ (0.8 g, 1.58 mmol) was added to the solution. After 10 min, indole (232 mg, 0396 mmol) was added to the reaction mixture, which was warmed to rt and stirred for 24 h before addition of satd $NaHCO_3$ (5 mL). Ethyl acetate (10 mL) was added, the resulting layers were then separated, and the organic layer was dried over anhydrous magnesium sulfate. After filtration, the organic layer was concentrated in vacuo. The resultant residue was purified over silica gel with hexanes/ethyl acetate (2/1) to give **11** as a fine yellow solid (167 mg, 70%): $[\alpha]_D^{20}$ = −23.0 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.26 (s, 1H), 7.68−7.55 (m, 2H), 7.51−7.42 (m, 2H), 7.41−7.25 (m, 6H), 7.22−7.14 (m, 2H), 7.11 (t, J = 2.4 Hz, 1H), 7.04 (ddd, J = 8.3, 7.0, 1.1 Hz, 1H), 6.55 (s, 1H), 4.80 (dd, J = 4.7, 1.6 Hz, 1H), 4.21 (td, J = 6.7, 3.5 Hz, 1H), 3.25 (s, 3H), 3.24−3.12 (m, 2H), 2.80 (dd, J = 4.9, 2.8 Hz, 1H), 1.88 (dd, J = 7.1, 2.9 Hz, 1H), 0.31 (d, J = 10.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.8, 177.7, 140.3, 136.9, 135.9, 133.9, 132.9, 131.0, 129.6, 128.6, 128.0, 127.0, 124.7, 123.3, 122.4, 120.7, 120.2, 118.8, 113.6, 111.5, 85.9, 82.3, 75.5, 72.6, 59.0, 49.1, 29.7, −4.3, −4.8; IR (film) ν_{max} 3287, 2925, 1699, 1427, 1251 cm^{-1}; HRMS (CI, NH_3) m/z [M + Na]$^+$ calcd for $C_{31}H_{31}BrN_2NaO_4Si$ 625.1134, found 625.1124.

*(2S,3R,3aR,10aR,10bS)-3-(Dimethyl(phenyl)silyl)-10a-(1H-indol-3-yl)-2-(methoxymethyl)-3,3a-dihydro-2H-furo[2′,3′:3,4]pyrrolo-[1,2-a]indole-4,10(10aH,10bH)-dione (**15**).* A solution of **11** (220 mg, 0.364 mmol) in anhydrous toluene (7.0 mL) was added into a sealed tube under an atmosphere of Ar. CuI (35 mg, 0.182 mmol), potassium carbonate (150 mg, 1.09 mmol), and *N*,*N*-dimethylenediamine (39 μL, 0.364 mmol) were successively added under Ar atmosphere. Then the mixture was warmed to 110 °C and stirred for 12 h. The purple reaction mixture was cooled to rt and filtered through a short pad of silica gel with ethyl acetate (20 mL). The filtrate was concentrated under reduced pressure to give a yellowish solid. Purification over silica gel with hexanes/ethyl acetate (2/1) afforded **15** as a light yellow solid (150 mg, 80%): mp 232−234 °C; $[\alpha]_D^{20}$ = +174.2 (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.15 (s, 1H), 8.00 (ddt, J = 17.8, 8.1, 0.7 Hz, 2H), 7.68−7.58 (m, 2H), 7.45 (dd, J = 7.9, 1.5 Hz, 2H), 7.35−7.25 (m, 4H), 7.22−7.13 (m, 4H), 4.76 (dd, J = 4.0, 0.4 Hz, 1H), 4.17−4.09 (m, 1H), 3.25 (dd, J = 4.0, 2.3 Hz, 1H), 3.05 (dd, J = 10.8, 3.3 Hz, 1H), 2.96 (dd, J = 10.9, 5.1 Hz, 1H), 2.85 (s, 3H), 2.06−2.01 (m, 1H), 0.28 (d, J = 12.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 195.6, 176.1, 151.0, 137.0, 136.4, 135.8, 133.8, 129.7, 128.0, 125.4, 125.3, 125.0, 124.5, 122.8, 122.2, 120.9, 120.5, 116.4, 111.5, 111.3, 83.6, 82.6, 75.6, 74.9, 59.0, 54.3, 30.0, −4.4, −4.7; IR (film) ν_{max} 3352, 2925, 1710, 1601, 1465, 1341, 1250 cm^{-1}; HRMS (CI, NH_3) m/z [M + H]$^+$ calcd for $C_{31}H_{31}N_2O_4Si$ 523.2053, found 523.2050.

Second-Generation Approach toward the Total Synthesis of (+)-Iatisine A. *(2R, 5R)-Methyl 2-(2-bromostyryl)-5-(methoxymethyl)-2,5-dihydrofuran-3-carboxylate (**18**).* To a solution of tetrahydrofuran **6a** (0.86 g, 1.87 mmol) in THF (18 mL) was added phenyltrimethyl tribromide (1.0 g, 2.8 mmol) at rt. The solution was allowed to stir for 12 h at rt before being cooled to 0 °C. TBAF (1 M in THF, 1.87 mL, 1.87 mmol) was added dropwise, and the reaction mixture was stirred for 10 min at 0 °C. Ethyl acetate (50 mL) and water (10 mL) were added, and the layers were separated. The organic layer was washed with H_2O (3 × 10 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo (temperature of water bath must keep below 30 °C) to obtain an unsaturated aldehyde as a yellowish oil. Since this intermediate aldehyde was unstable under acidic conditions, it was directly used for the next reaction without purification: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.82 (s, 1H), 7.60−7.40 (m, 2H), 7.29−7.17 (m, 1H), 7.14−7.02 (m, 2H), 6.89 (td, J = 2.0, 0.8 Hz, 1H), 6.29 (ddd, J = 15.8, 5.7, 0.8 Hz, 1H), 5.65 (dq, J = 3.8, 1.8 Hz, 1H), 5.16 (ddt, J = 3.9, 2.0, 0.9 Hz, 1H), 3.69 (ddd, J = 10.0, 5.1, 0.9 Hz, 1H), 3.59 (ddd, J = 9.9, 5.3, 0.8 Hz, 1H), 3.43 (s, 3H).

To a solution of the unsaturated aldehyde (1.87 mmol, based on **6a**) and NaCN (458 mg, 9.35 mmol) in MeOH (37 mL) was added MnO_2 (dried at 150 °C for 12 h, 4 g, 46.7 mmol) in one portion at 0 °C. The reaction mixture was warmed to rt over a period of 1 h and stirred for an additional 3 h at rt. The mixture was then filtered through a pad of Celite, and MeOH was removed under reduced pressure to give a yellow residue. Ethyl acetate (50 mL) and water (10

DOI: 10.1021/acs.joc.5b00051
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mL) were added, and the layers were separated. The organic layer was washed with H_2O (3 × 10 mL), dried over magnesium sulfate, filtered, and concentrated in vacuo to obtain an oil. Purification over silica gel with hexanes/ethyl acetate (10/1) afforded unsaturated methyl ester **18** as an colorless oil (376 mg, 57%, two steps): $[\alpha]_D^{20}$ = +700 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.50 (td, *J* = 7.0, 1.5 Hz, 2H), 7.24−7.21 (m, 1H), 7.08−7.04 (m, 2H), 6.08 (t, *J* = 2.0 Hz, 1H), 6.25 (dd, *J* = 16.0, 6.5 Hz, 1H), 5.60−5.57 (m, 1H), 5.09−5.06 (m, 1H), 3.74 (s, 3H), 3.60 (dd, *J* = 10.0, 5.5 Hz, 1H), 3.54 (dd, *J* = 10.0, 4.5 Hz, 1H), 3.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 162.5, 138.8, 136.5, 135.4, 132.7, 131.4, 130.1, 128.7, 127.2, 127.1, 123.7, 84.9, 84.9, 74.8, 59.3, 51.7; IR (film) ν_{max} 2882, 1720, 1465, 1436, 1260 cm^{-1}; HRMS (CI, NH_3) *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{17}BrNaO_4$ 375.0208, found 375.0193.

*(2S,5R)-Methyl 2-(2-(2-Bromophenyl)-1,2-dihydroxyethyl)-5-(methoxymethyl)-2,5-dihydrofuran-3-carboxylate (**20**).* Methyl ester **18** (300 mg, 0.849 mmol) was dissolved in an 8:1 mixture (8.0 mL) of acetone and H_2O at rt. NMO (100 mg, 0.849 mmol) was added to the solution, which was stirred for 5 min at rt. OsO_4 (4 wt % solution in H_2O, 207 μL, 0.0340 mmol) was then added, and the reaction mixture was stirred for 10 h at rt. Aqueous satd $Na_2S_2O_3$ (8.0 mL) was added, and the mixture was stirred for an additional 10 min at rt. Ethyl acetate (20 mL) was added, and the resulting layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo to obtain a crude oil. Purification over silica gel with hexanes/ethyl acetate (1/1) afforded diol **20** as a viscous oil (164 mg, 50%): ^{1}H NMR ($CDCl_3$, 500 MHz, major isomer): δ 7.60 (dd, *J* = 11.5, 1.5 Hz, 1H), 7.45 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.31 (td, *J* = 7.5, 1.5 Hz, 1H), 7.09 (td, *J* = 8.0, 1.5 Hz, 1H), 6.86 (t, *J* = 2.0 Hz, 1H), 5.32−5.30 (m, 1H), 5.25 (d, *J* = 6.0 Hz, 1H), 5.03−5.00 (m, 1H), 4.14 (d, *J* = 6.0 Hz, 1H), 4.04 (dd, *J* = 7.5, 3.5 Hz, 1H), 3.91 (d, *J* = 7.0 Hz, 1H), 3.76 (s, 3H), 3.06 (dt, *J* = 10.5, 2.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.8, 162.5, 141.5, 141.1, 140.3, 139.1, 135.0, 134.5, 132.9, 132.7, 129.6, 129.4, 129.1, 129.1, 127.8, 127.8, 122.9, 121.7, 88.7, 88.0, 85.5, 84.9, 74.4, 73.9, 73.5, 73.2, 73.0, 70.2, 59.8, 59.7, 52.5, 52.3; IR (film) ν_{max} 3420, 2892, 1723, 1649, 1468, 1267 cm^{-1}; HRMS (CI, NH_3) *m*/*z* $[M + Na]^+$ calc'd for $C_{16}H_{19}BrNaO_6$ 409.0263, found 409.0250.

*(3aR,4R,6S,6aS)-Methyl 4-(5-(2-Bromophenyl)-2-oxo-1,3-dioxolan-4-yl)-6-(methoxymethyl)-2,2-dimethyltetrahydrofuro[3,4-d]-[1,3]dioxole-3a-carboxylate (**22**).* Diol **20** (130 mg, 0.336 mmol) and DMAP (41 mg, 0.336 mmol) were dissolved in anhydrous methylene chloride (3.4 mL) under an atmosphere of Ar and cooled to 0 °C. Carbonyldiimidazole (272 mg, 1.68 mmol) was introduced into the reaction, which was warmed to rt. After 3 h, methylene chloride (10 mL) and water (5 mL) were added, and layers were separated. The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to obtain crude carbonate **21** (138 mg) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.55 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.37−7.32 (m, 1H), 7.29 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.22 (ddd, *J* = 8.0, 7.2, 1.9 Hz, 1H), 7.01 (t, *J* = 1.6 Hz, 1H), 6.26 (d, *J* = 4.2 Hz, 1H), 5.37 (dt, *J* = 5.2, 2.2 Hz, 1H), 5.12−5.08 (m, 2H), 3.70 (d, *J* = 3.4 Hz, 3H), 3.60 (s, 3H), 3.38 (s, 3H).

A solution of crude **21** (138 mg, 0.334 mmol) was dissolved in a 8:1 mixture (3.3 mL) of acetone and H_2O at rt. NMO (60 mg, 0.501 mmol) was added to the solution, which was stirred for 5 min at rt. OsO_4 (4 wt % solution in H_2O, 1.0 mL, 0.167 mmol) was then added, and the reaction mixture was stirred for 14 h at rt. Aqueous satd $Na_2S_2O_3$ (8.0 mL) was added and the mixture was stirred for additional 10 min at rt. Ethyl acetate (20 mL) was added, and the resulting layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated in vacuo to obtain a crude diol as a brown oil (135 mg): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.62 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.40−7.35 (m, 2H), 7.32 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.28−7.25 (m, 1H), 5.88 (d, *J* = 4.7 Hz, 1H), 4.75 (dd, *J* = 9.1, 4.7 Hz, 1H), 4.37 (d, *J* = 8.7 Hz, 1H), 4.15 (d, *J* = 9.1 Hz, 1H), 3.87−3.84 (m, 1H), 3.83 (s, 3H), 3.51 (dd, *J* = 10.8, 2.6 Hz, 1H), 3.40 (dd, *J* = 10.8, 4.4 Hz, 1H), 3.08 (s, 3H).

To a solution of a crude diol (135 mg, 0.302 mmol) and 2,2-dimethoxypropane (0.37 mL, 3.02 mmol) in acetone (3.0 mL) was added PTSA monohydrate (29 mg, 0.151 mmol). The reaction mixture was stirred for 1 h under reflux conditions. After the reaction mixture was cooled to rt, ethyl acetate (10 mL) and H_2O (5 mL) were added and the layers separated. The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to obtain an oil. The resultant residue was purified over silica gel with hexanes/ethyl acetate (5/1) to give dioxolane **22** as a colorless oil (110 mg, 67%, three steps): ^{1}H NMR ($CDCl_3$, 500 MHz, major isomer): δ 7.63 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.41−7.35 (m, 2H), 7.29−7.26 (m, 1H), 5.92 (d, *J* = 6.0 Hz, 1H), 4.93 (d, *J* = 3.0 Hz, 1H), 4.91 (dd, *J* = 7.5, 5.5 Hz, 1H), 4.30 (d, *J* = 7.5 Hz, 1H), 4.23 (td, *J* = 5.0, 3.5 Hz, 1H), 3.82 (s, 3H), 3.41 (dd, *J* = 5.0, 2.0 Hz, 2H), 3.14 (s, 3H), 1.61 (s, 3H), 1.37 (s, 3H); ^{1}H NMR ($CDCl_3$, 500 MHz, minor isomer): δ 7.62 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.43−7.38 (m, 2H), 7.30−7.27 (m, 1H), 5.88 (d, *J* = 4.0 Hz, 1H), 4.96 (d, *J* = 3.0 Hz, 1H), (dd, *J* = 3.5, 1.0 Hz, 1H), 4.52 (d, *J* = 1.5 Hz, 1H), 4.35 (td, *J* = 6.5, 3.5 Hz, 1H), 3.83 (s, 3H), 3.65 (dd, *J* = 6.5, 2.0 Hz, 2H), 3.45 (s, 3H), 1.60 (s, 3H), 1.35 (s. 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.1, 169.8, 153.7, 153.4, 135.8, 134.8, 133.8, 133.4, 131.1, 130.8, 129.2, 128.2, 128.1, 126.7, 122.7, 120.6, 116.6, 116.5, 91.1, 89.4, 86.9, 86.8, 85.2, 84.5, 83.3, 79.7, 79.1, 78.9, 78.3, 71.9, 65.8, 60.3, 59.5, 59.0, 53.2, 53.1, 27.5, 27.4, 25.6, 26.5; IR (film) ν_{max} 2934, 1816, 1745, 1440, 1239 cm^{-1}; HRMS (CI, NH_3) *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{24}BrO_9$ 487.0604, found 487.0607.

*(3aS,4S,6S,6aS)-4-(2-(2-Bromophenyl)-2-oxoacetyl)-6-(methoxymethyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole-3a-carboxamide (**19**).* To a solution of carbonate **22** (110 mg, 0.226 mmol) in MeOH (6 mL) was added potassium carbonate (47 mg, 0.339 mmol) at rt, and the reaction mixture was stirred for 12 h before addition of 1 N HCl (5 mL) and chloroform (20 mL). The layers were separated, and the aqueous layer was extracted with chloroform (2 × 50 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and stored on a bench as a solution in chloroform for 2 h at rt to induce lactonization (screened by TLC). Then the organic layer was concentrated under reduced pressure to give crude **24** as a colorless oil, which was directly used for the next reaction without purification: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.59 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.53 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.33−7.38 (m, 1H), 7.21−7.16 (m, 1H), 5.31−5.25 (m, 1H), 4.77 (dd, *J* = 10.0, 5.5 Hz, 1H), 4.63 (t, *J* = 1.7 Hz, 1H), 4.39−4.34 (m, 1H), 3.72 (dd, *J* = 10.5, 3.0 Hz, 1H), 3.55 (dd, *J* = 10.0, 2.5 Hz, 1H), 3.46 (dd, *J* = 3.6, 3.0 Hz, 2H), 3.29 (s, 2H), 1.59 (s, 3H), 1.58 (s, 3H).

A crude lactone **24** was added to a round-bottom flask followed by anhydrous NH_3 solution (7.0 M in MeOH, 2.3 mL) at rt. The reaction mixture was stirred for 12 h before removing excess NH_3 and MeOH under reduced pressure. Then the resulting crude amide **25** was redissolved in methylene chloride (2.3 mL), and NaBr (70 mg, 0.678 mmol) and TEMPO (17 mg, 0.113 mmol) were added. A premixed solution of NaOCl (5% in H_2O, 4.5 mL) and $NaHCO_3$ (72 mg) was added at rt, and the resulting brown mixture was stirred until it turned light yellow (~30 min). Methylene chloride (20 mL) and water (5 mL) were added, and the layers were separated. The organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo to obtain a yellowish solid. Purification over silica gel with hexanes/ethyl acetate (2/1) afforded aminal **19** as a solid (70 mg, 70%, 3 steps)

Alternative Way to Produce Hydroxyl Lactam 19. Methyl ester **18** (45 mg, 0.127 mmol) was dissolved in a 2:1 mixture (1.3 mL) of *t*-BuOH and H_2O at rt. NMO (45 mg, 0.382 mmol) was added to the solution, which was stirred for 5 min at rt. OsO_4 (2.5 wt % solution in H_2O, 64 μL, 0.005 mmol) was then added, and the reaction mixture was stirred for 48 h at rt. Then 1 N NaOH solution was added to the reaction mixture, which was stirred for an additional 12 h before acidification with 1 M HCl and quenching with satd $Na_2S_2O_3$. Ethyl acetate (10 mL) and H_2O (5 mL) were added and the layers separated. The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to obtain crude acid **26** as a mixture of diastereomers.

DOI: 10.1021/acs.joc.5b00051
J. Org. Chem. 2015, 80, 2959−2971

To a solution of the crude acid **26** and 2,2-dimethoxypropane (16 μL, 0.127 mmol) in methylene chloride (1.3 mL) was added PTSA monohydrate (2.4 mg, 0.013 mmol). The reaction mixture was stirred for 3 h under reflux conditions. After the reaction mixture was cooled to rt, methylene chloride (10 mL) and H_2O (5 mL) were added, and the resulting layers were separated. The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure to obtain a brownish oil. The crude material was directly exposed to the previously described ammonolysis and oxidation conditions to give hydroxyl lactam **19** (12 mg, 20%, four steps): $[\alpha]_D^{20}$ = +70 (*c* 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.59 (td, *J* = 7.5, 1.5 Hz, 2H), 7.33 (td, *J* = 7.5, 1.0 Hz, 1H), 7.28 (td, *J* = 8.0, 2.0 Hz, 1H), 7.01 (s, 1H), 5.77 (s, 1H), 4.81 (d, *J* = 1.5 Hz, 1H), 4.80 (s, 1H), 3.56 (td, *J* = 2.5, 2.0 Hz, 1H) 3.76 (dd, *J* = 10.5, 3.0 Hz, 1H), 3.46 (dd, *J* = 10.5, 3.0 Hz, 1H), 3.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 198.7, 170.3, 137.4, 133.4, 131.8, 129.1, 126.9, 119.8, 116.2, 93.9, 87.2, 87.0, 86.6, 85.9, 72.7, 59.2, 27.0, 26.0; IR (film) ν_{max} 3280, 2936, 1726, 1430, 1233 cm^{-1}; HRMS (CI, NH_3) *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{20}BrNNaO_7$ 464.0321, found 464.0325.

*(3aR,4R,6S,6aS)-4-((S)-2-(2-Bromophenyl)-1-(1H-indol-3-yl)-2-oxoethyl)-6-(methoxymethyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole-3a-carboxamide (**28**).* A solution of aminal **19** (68 mg, 0.153 mmol) in anhydrous methylene chloride (1.5 mL) was cooled to 0 °C under an atmosphere of Ar. DMAP (1.9 mg, 0.0153 mmol) and pyridine (15 μL, 0.184 mmol) were successively added, which was followed by trifluoroacetic anhydride (26 μL, 0.184 mmol), and the formation of trifluoroacetic ester was monitored by TLC (approximately 30 min). A solution of indole (90 mg, 0.765 mmol) in methylene chloride (0.5 mL) was added to the reaction mixture, which was warmed to rt and stirred for 10 h before addition of satd $NaHCO_3$ (5 mL). Methylene chloride (10 mL) was introduced, and the resulting layers were then separated and the organic layer was dried over anhydrous magnesium sulfate. After filtration, the organic layer was concentrated in vacuo, and the residue was purified over silica gel with hexanes/ethyl acetate (2/1) to give **28** as a fine yellow solid (68 mg, 82%): $[\alpha]_D^{20}$ = +52 (*c* 0.50, $CHCl_3$); ^{1}H NMR (CD_3CN, 500 MHz) δ; 9.51 (s, 1H), 7.67−7.65(m, 3H), 7.50 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.41 (d, *J* = 8.5 Hz, 1H), 7.34 (td, *J* = 7.5, 1.0 Hz, 1H), 7.28−7.25 (m, 2H), 7.15 (t, *J* = 8.0 Hz, 1H), 7.02 (t, *J* = 8.0 Hz, 1H), 5.18 (d, *J* = 1.5 Hz, 1H), 4.70 (d, *J* = 4.0 Hz, 1H), 4.26 (q, *J* = 5.0 Hz, 1H), 3.54 (qd, *J* = 11.0, 5.0 Hz, 2H), 3.35 (s, 3H), 1.44 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (CD_3CN, 125 MHz) δ 198.7, 172.7, 140.2, 138.5, 135.0, 133.0, 130.3, 128.3, 125.8, 125.7, 123.6, 121.6, 121.1, 119.1, 114.4, 113.2, 94.5, 86.9, 86.3, 85.9, 73.1, 59.9, 27.7, 26.9; IR (film) ν_{max} 3246, 2931, 1713, 1459, 1246 cm^{-1}; HRMS (CI, NH_3) *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{26}BrN_2O_6$ 541.0974, found 541.0961.

*(3aR,4R,6S,6aS)-4-((S)-1-(1H-Indol-3-yl)-2-oxo-2-phenylethyl)-6-(methoxymethyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole-3a-carboxamide (**29**).* A solution of **28** (54 mg, 0.10 mmol) in anhydrous toluene (5 mL) was added into a sealed tube under Ar atmosphere. CuI (10 mg, 0.05 mmol), potassium carbonate (41 mg, 0.30 mmol), and *N*,*N*-dimethylenediamine (11 μL, 0.10 mmol) were successively added under an atmosphere of Ar. Then the mixture was warmed to 110 °C and stirred for 12 h. The purple reaction mixture was cooled to rt and filtered through a short pad of silica gel with ethyl acetate. The filtrate was concentrated under reduced pressure to give a yellowish solid. Purification over silica gel with hexanes/ethyl acetate (2/1) afforded **29** as a light yellow solid (41 mg, 90%): mp 160−163 °C; $[\alpha]_D^{20}$ = +70.0 (*c* 0.60, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.15−8.13 (m, 2H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.66−7.62 (m, 2H), 7.33−7.31 (m, 1H), 7.24−7.18 (m, 4H), 4.90 (s, 1H), 4.82 (d, *J* = 2.0 Hz, 1H), 4.35 (q, *J* = 2.5 Hz, 1H), 3.34 (dd, *J* = 10.0, 2.5 Hz, 1H), 3.26 (dd, *J* = 10.0, 2.5 Hz, 1H), 2.61 (s, 3H), 1.51 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 195.8, 171.4, 151.5, 139.2, 137.7, 127.5, 127.0, 126.2, 125.7, 124.2, 123.4, 121.3, 120.8, 118.4, 117.6, 113.0, 111.8, 99.7, 88.6, 87.4, 86.0, 76.7, 73.6, 59.2, 27.4, 26.1; IR (film) ν_{max} 3384, 2933, 1719, 1602, 1468, 1217 cm^{-1}; HRMS (CI, NH_3) *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{25}N_2O_6$ 461.1713, found 461.1728.

*(+)-Isatisine A (**1**).* To a solution of methyl ether **29** (9.6 mg, 0.0208 mmol) in anhydrous methylene chloride (1.0 mL) were added NaI (10 mg, 0.0624 mmol) and 15-crown-5 (20 μL, 0.124 mmol) under an atmosphere of Ar. The mixture was cooled to −30 °C, and a 1.0 M solution of BBr_3 in CH_2Cl_2 (187 μL, 0.187 mmol) was added in three portions every 1 h. The reaction mixture was warmed to 0 °C and stirred for 12 h. Diethyl ether (5 mL) was added to the reaction mixture and stirred for 10 min at rt. Ethyl acetate (10 mL) and satd $NaHCO_3$ (5 mL) were added, the resulting layers were then separated, and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over anhydrous magnesium sulfate. After filtration, the organic layer was concentrated in vacuo, and the residue was purified over silica gel with methylene chloride/MeOH (50/1 to 20/1 gradient elution) to give **1** as a fine yellowish solid (6.8 mg, 80%): mp 120−123 °C; $[\alpha]_D^{20}$ = +190 (*c* 0.40, $CHCl_3$) [lit. $[\alpha]_D^{14}$ = −283.15 (*c* 0.46, MeOH)[1] for (−)-isatisine A; $[\alpha]_D^{25}$ = +274 (*c* 1.1, MeOH)[2a,b] for (+)-isatisine A[22]]: ^{1}H NMR (CD_3OD, 500 MHz) δ 7.98 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.93 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.76 (td, *J* = 7.5, 1.0 Hz, 1H), 7.63 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.35−7.31 (m, 2H), 7.29 (s, 1H), 7.12 (td, *J* = 7.0, 1.0 Hz, 1H), 7.05 (td, *J* = 7.0, 1.5 Hz, 1H), 4.89 (s, 1H), 4.06 (d, *J* = 4.0 Hz, 1H), 3.85 (qd, *J* = 4.5, 1.5 Hz, 1H), 3.39 (dd, *J* = 11.5, 5.0 Hz, 1H), 3.32 (dd, *J* = 12.0, 6.0 Hz, 1H); ^{13}C NMR (CD_3OD, 100 MHz) δ 196.8, 174.6, 151.9, 139.1, 137.9, 127.4, 126.9, 126.2, 126.1, 124.6, 123.1, 121.1, 120.6, 117.8, 112.9, 110.6, 89.9, 89.0, 84.7, 76.8, 74.3, 63.2; IR (film) ν_{max} 3389, 2923, 1708, 1610, 1468, 1220 cm^{-1}; HRMS (CI, NH_3) *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{18}N_2NaO_6$ 429.1063, found 429.1082.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Selected spectral data for all new compounds and X-ray crystallographic analysis of compound **28**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to Dr. Paul Ralifo, Dr. Norman Lee, and Dr. Jeffrey Bacon (Chemical Instrumentation Center at Boston University) for helpful discussions and assistance with NMR, HRMS, and X-ray crystallographic analysis experiments.

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DOI: 10.1021/acs.joc.5b00051
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DOI: 10.1021/acs.joc.5b00051
J. Org. Chem. 2015, 80, 2959−2971