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Total Synthesis of (+)-Isatisine A

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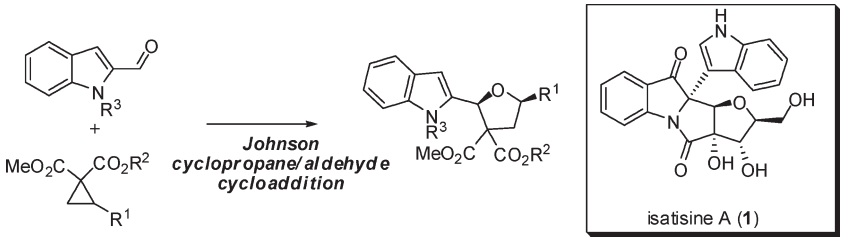

The asymmetric total synthesis of (+)-isatisine A has been accomplished commencing with a Lewis acid-catalyzed cyclization of homochiral (*S*)-vinylcyclopropane diester and *N*-tosylindole-2-carboxaldehyde to construct the tetrahydrofuran ring. A palladium-catalyzed oxidative decarboxylation was utilized to obtain the dihydrofuran required for the subsequent dihydroxylation reaction to install the diol present on the tetrahydrofuran ring. The total synthesis was completed by an indole oxidation and electrophilic aromatic substitution sequence to construct isatisine A acetonide, which was then carried forward to the antipode of the natural product. The absolute configuration of the natural enantiomer (−)-isatisine A was determined to be C2(*S*), C9(*R*), C10(*S*), C12(*R*), and C13(*R*).

Introduction

Isatisine A (**1**) (Figure 1) is a complex bisindole natural product isolated from the leaves of *Isatis indigotica* Fort, a shrub prevalent in the Anhui province of China.[1] The roots and leaves of *I. indigotica* have been used in traditional Chinese medicine for the treatment of viral diseases including influenza, viral pneumonia, mumps, and hepatitis.[2]

During the fractionation process, *Isatis indigotica* Fort leaf extracts were eluted with acetone on silica gel, which yielded isatisine A acetonide (**2**), initially believed to be the natural product; however, it was likely an artifact of the isolation process. Suspecting this, isatisine A (**1**) was prepared by hydrolysis of **2** and matched with an HPLC trace of a crude extract, leading to the supposition that **1** and not **2** was in fact the biogenetic product. Although the relative stereochemistry of **2** (and consequently **1**) was confirmed by single crystal X-ray diffraction studies of acetonide **2**, the absolute stereochemistry remained unknown. The biological activity of isatisine A (**1**) could not be determined due to the small amount obtained from hydrolysis of the acetonide **2**; however, **2** has been shown to possess anti-HIV-1_{IIIB} activity with an $EC_{50} = 37.8\,\mu M$.[1] An enantioselective total synthesis of the natural product from a starting material with known absolute stereochemistry would allow for the determination of the absolute configuration of isatisine A and would also provide material for biological testing. Our initial communication on the total synthesis of (+)-isatisine A (**1**) outlined our successful route, herein we report our overall findings.[3]

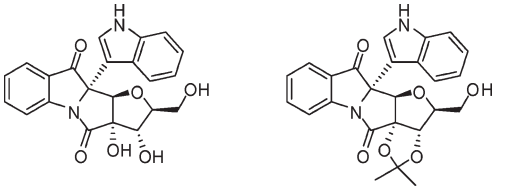

FIGURE 1. Structure of isatisine A (**1**) and its acetonide **2**.

Our interest in isatisine A stemmed from a natural product previously synthesized in our group, namely mersicarpine (**5**).[4] In the final stages of the total synthesis of mersicarpine, indole **3**

(1) Liu, J.-F.; Jiang, Z.-Y.; Wang, R.-R.; Zheng, Y.-T.; Chen, J.-J.; Zhang, X.-M.; Ma, Y.-B. *Org. Lett.* **2007**, *9*, 4127–4129.
(2) Zheng, H. Z.; Dong, Z. H.; Yu, Q. *Modern Study of Traditional Chinese Medicine*; Xueyuan Press: Beijing, China, 1997; Vol. 1, pp 328−334.
(3) Karadeolian, A.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2010**, *49*, 1133–1135.
(4) Magolan, J.; Carson, C. A.; Kerr, M. A. *Org. Lett.* **2008**, *10*, 1437–1440.

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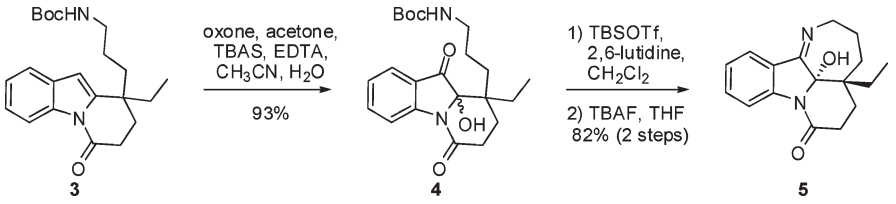
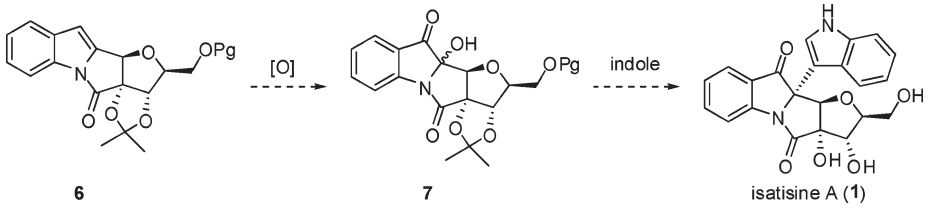
SCHEME 1. Final Steps in the Synthesis of Mersicarpine



SCHEME 2. Proposed Late Stage Route to Isatisine A (1) from Advanced Indole Substrate 6



was oxidized to indoxyl **4** followed by imine formation to yield **5** (Scheme 1). When comparing intermediate **4** and isatisine A, the common indoxyl moiety becomes apparent. Thus, we envisioned that isatisine A could potentially be accessed through oxidation of indole **6** to the indoxyl **7** (by a similar method to that used for mersicarpine), followed by indole addition into this species (Scheme 2).

Oxidation of the indole C2−C3 double bond has been well documented, where the identities of the oxidation products depend on the nature of the substituents on the N1, C2, and C3 positions of the indole. Reagents that have been shown to oxidize indole include (hexamethylphosphoramide)oxodiperoxomolybdenum(VI) ($MoO_5 \cdot HMPA$),[5] bis(acetylacetonato)oxovanadium(IV),[6] dimethyl dioxirane,[7] singlet oxygen,[8] and *m*-CPBA.[9] Important examples within these studies, which are pertinent to our proposed route, are instances where indole oxidation was followed by electrophilic aromatic substitution (EAS) on a second indole molecule with the indoxyl species (Figure 2). Initial reports of such processes came from work by Sakamoto using $MoO_5 \cdot HMPA$ to oxidize 2-phenylindole (eq 1, Figure 2).[5c] Speier has reported the synthesis of a similar dimeric species when oxidizing 2-methylindole with oxygen in the presence of a vanadium catalyst (eq 2, Figure 2).[7] Finally Jimenez, working with oxodiperoxomolybdenum oxidants with trialkylphosphine oxide ligands, has reported the desired EAS in many instances (eqs 3 and 4, Figure 2).[10] Jimenez' studies demonstrated that indoles containing *N*-alkyl subtituents undergo the EAS reaction, while *N*-acyl indoles do not (eq 5, Figure 2). The rationale used to explain this observation relies on the formation of an iminium ion **18** upon oxidation of indole **14** (Scheme 3). This iminium intermediate can be attacked by a second indole moiety to form dimer **15**. An electron-withdrawing substituent on the nitrogen, such as an acyl group, would inhibit the formation of the iminium intermediate, thereby preventing the dimerization process.

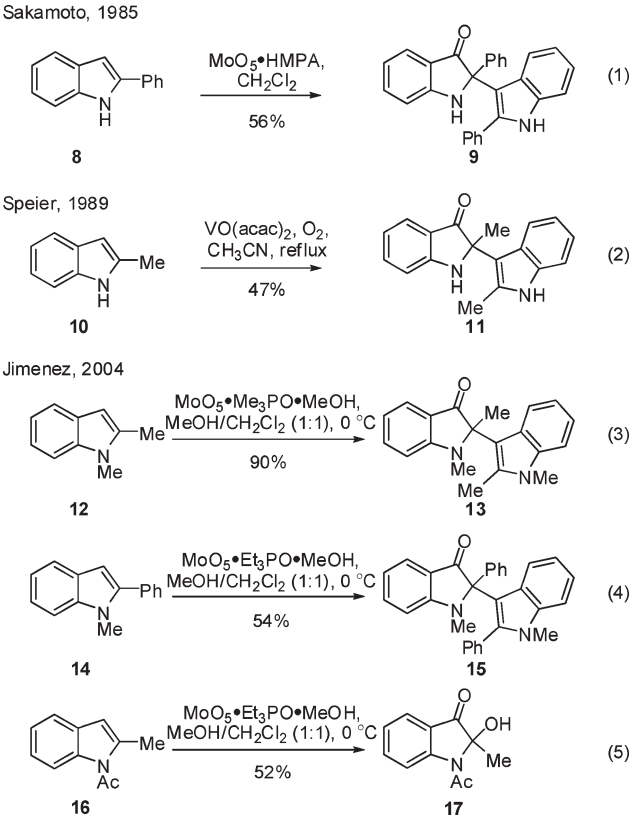


FIGURE 2. Examples of indole oxidation with concomitant EAS of a second indole molecule.

Results and Discussion

To demonstrate the feasibility of the indole oxidation and EAS process toward the synthesis of isatisine A (**1**), two

(5) (a) Kawasaki, T.; Chien, C. S.; Sakamoto, M. *Chem. Lett.* **1983**, 855–858. (b) Chien, C. S.; Suzuki, T.; Kawasaki, T.; Sakamoto, M. *Chem. Pharm. Bull.* **1984**, *32*, 3945–3951. (c) Chien, C. S.; Takanami, T.; Kawasaki, T.; Sakamoto, M. *Chem. Pharm. Bull.* **1985**, *33*, 1843–1848. (d) Chien, C. S.; Hasegawa, A.; Kawasaki, T.; Sakamoto, M. *Chem. Pharm. Bull.* **1986**, *34*, 1493–1496. (e) Wang, Z.; Jimenez, L. S. *Tetrahedron Lett.* **1996**, *37*, 6049–6052.

(6) Balogh-Hergovich, E.; Speier, G. *J. Mol. Catal.* **1989**, *57*, L9–L12.

(7) (a) Zhang, X.; Foote, C. S. *J. Am. Chem. Soc.* **1993**, *115*, 8867–8868. (b) Colandrea, V. J.; Rajaraman, S.; Jimenez, L. S. *Org. Lett.* **2003**, *5*, 785–787.

(8) (a) Carloni, P.; Eberson, L.; Greci, L.; Stipa, P.; Tosi, G. *J. Chem. Soc., Perkin Trans. 2* **1991**, 1779–1783. (b) Zhang, X. J.; Foote, C. S.; Khan, S. I. *J. Org. Chem.* **1993**, *58*, 47–51. (c) Ling, K.-Q. *Synth. Commun.* **1995**, *25*, 3831–3835. (d) Ling, K. Q. *Synth. Commun.* **1996**, *26*, 149–152.

(9) Buller, M. J.; Cook, T. G.; Kobayashi, Y. *Heterocycles* **2007**, *72*, 163–166.

(10) Altinis Kiraz, C. I.; Emge, T. J.; Jimenez, L. S. *J. Org. Chem.* **2004**, *69*, 2200–2202.

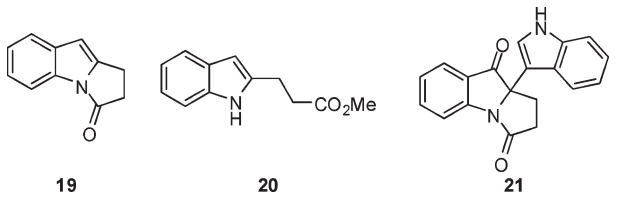
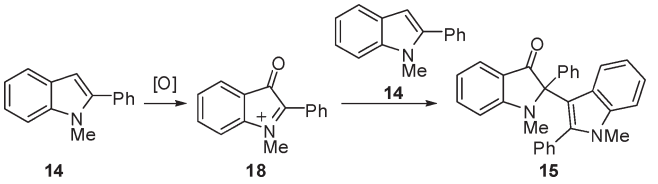


FIGURE 3. Substrates for model study and model target compound **21**.

SCHEME 3. Rationale Explaining Dimerization Process



model studies were conducted to form the western half of **1** by this sequence (Figure 3). In our first study, pyrroloindolone **19** was synthesized and carried onto model substrate **21**. In our second study, 2-substituted indole **20** was utilized to construct model compound **21**.

The oxidation and EAS sequence with pyrroloindolone **19**[11] was investigated with various oxidizing reagents (Figure 4). Oxidation of **19** with in situ generated DMDO led to complete cleavage of the indole C2−C3 bond, producing carboxylic acid **22** in high yield (Figure 4, eq 1).[4] Attempts at preventing the over oxidation by lowering the reaction temperature were unsuccessful due to insolubility of substrate **19**. Use of the milder Vedejs' reagent ($MoO_5 \cdot HMPA \cdot Py$)[12] yielded a mixture of three compounds over a week-long reaction time (Figure 4, eq 2). Our desired indoxyl product **23** accompanied by its methyl aminal **25** were isolated in 17% and 7.6% yield, respectively, with the major product of this reaction consisting of compound **24** in 25% yield. Oxidation of **19** with oxodiperoxomolybdenum bis(triphenylphosphine oxide) complex led to exclusive formation of compound **24** in 48% yield over a shorter 16 h reaction time (Figure 4, eq 3). We were able to further oxidize this species to indoxyl **25** by treatment with IBX in DMSO. Although EAS with indole was not attempted with indoxyl **25**, this two-step oxidation sequence was viewed as an alternative, should the direct oxidation of an indole to the respective indoxyl be unsuccessful during our efforts toward isatisine A.

We were delighted to find that oxidation of **19** with DMDO afforded the desired indoxyl **23** as the sole product (Figure 4, eq 4). Treatment of **23** with methanesulfonyl chloride and triethylamine in the presence of indole facilitated the EAS process to yield a 2:1 mixture of the model compound **21** and indoxyl starting material **23**, respectively. This reaction was not optimized since the purpose of this study was to test the feasibility of the indole oxidation and EAS sequence.

To obviate some of the difficulties encountered in the oxidation of pyrroloindolone **19**, an alternative oxidation substrate, indole **20** was synthesized though a modification of a literature procedure beginning with *o*-nitrotoluene and succinic anhydride.[13] Oxidation of **20** with Vedejs' reagent afforded indoxyl **26** as the methyl aminal in moderate yield (Scheme 4). Stronger oxidants such as *m*-CPBA or in situ generated DMDO did not furnish any indoxyl species. Gratifyingly, EAS of indoxyl **26** with indole took place under very mild reaction conditions and in high yield to produce compound **28**.[14] Construction of the pyrroloindolone ring was more difficult than anticipated; standard conditions for direct lactam formation proved unsuccessful until a two-step procedure involving hydrolysis of the ester to carboxylic acid **29** followed by EDC-induced cyclization was able to furnish the model compound **21** in 66% yield over the two steps. With the successful demonstration of an oxidation/EAS sequence we focused our efforts on the construction of the indole substrate required for the natural product itself.

As described earlier, our final disconnection involves oxidation of indole **6** followed by an electrophilic aromatic substitution onto indole. Scheme 5 shows a full retrosynthesis of isatisine A. Indole **6** would arise from dihydroxylation of an α,β-unsaturated ester, which would be obtained from a compound such as **30**. The unit of unsaturation would be installed by removal of an ester and oxidation, either in a multistep fashion or in one single transformation. Tetrahydrofuran **30** would be obtained by Johnson's[15] Lewis acid-mediated cyclization of indole-2-carboxaldehyde **31** and a suitable cyclopropane diester **32**.

Three 2-substituted 1,1-cyclopropane diesters were selected as possible substrates for the synthesis of isatisine A. We first investigated the reactivity of cyclopropane **32a**,[16] which contains the primary alcohol present in the natural product protected as the benzyl ether (Table 1). Cyclizations with this cyclopropane and electron-rich indole **31a** led to decomposition of the indole with recovery of the cyclopropane diester (entry 1). When an electron-poor indole **31b** was subjected to the same reaction conditions, a very low yield of product was obtained as a 2:1 mixture of 2,5-cis:2,5-trans isomers (entry 2). Attempts at increasing this yield by either increasing the catalyst loading (not shown) or by raising the reaction temperature led to decomposition of the reagents with no product formation (entry 3). Attempts with $Sn(OTf)_2$ also led to substrate decomposition under the reaction conditions (entry 4).

We then turned to Yadav's silylmethyl-substituted cyclopropane diester **32b**.[17] Yadav has demonstrated the successful cyclization of *N*-Boc-indole-3-carboxaldehyde with this substrate. The three aldehydes (entries 5−7) we subjected to his reaction conditions did not yield any product. Performing the reaction at increased temperatures led to decomposition of the cyclopropane diester, as did the use of a stronger Lewis acid (entries 8 and 9).

(11) Crenshaw, M. D.; Zimmer, H. *J. Heterocycl. Chem.* **1984**, *21*, 623–624.
(12) Vedejs, E. *J. Am. Chem. Soc.* **1974**, *96*, 5944–5946.
(13) Arcari, M.; Aveta, R.; Brandt, A.; Cecchetelli, L.; Corsi, G. B.; Dirella, M. *Gazz. Chim. Ital.* **1991**, *121*, 499–504.
(14) Ling, K.-Q. *Synth. Commun.* **1996**, *26*, 149–152.
(15) (a) Pohlhaus, P. D.; Johnson, J. S. *J. Org. Chem.* **2005**, *70*, 1057–1059. (b) Pohlhaus, P. D.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 16014–16015. (c) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 8642–8650. (d) Parsons, A. T.; Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2008**, *10*, 2541–2544. (e) Parsons, A. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 3122–3123. (f) Campbell, M. J.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 10370–10371. (g) Sanders, S. D.; Ruiz-Olalla, A.; Johnson, J. S. *Chem. Commun.* **2009**, 7601–7601.
(16) Burgess, K.; Ke, C.-Y. *Synthesis* **1996**, *12*, 1463–1467.
(17) (a) Yadav, V. K.; Sriramurthy, V. *Org. Lett.* **2004**, *6*, 4495–4498. (b) Yadav, V. K.; Sriramurthy, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 2669–2671. (c) Yadav, V. K.; Kumar, N. V.; Parvez, M. *Chem. Commun.* **2007**, 2281–2283. (d) Yadav, V. K.; Gupta, A. *Tetrahedron Lett.* **2008**, *49*, 3212–3215. (e) Gupta, A.; Yadav, V. K. *Tetrahedron Lett.* **2006**, *47*, 8043–8047. (f) Yadav, V. K.; Gupta, A. *Tetrahedron Lett.* **2009**, *50*, 4647–4650.

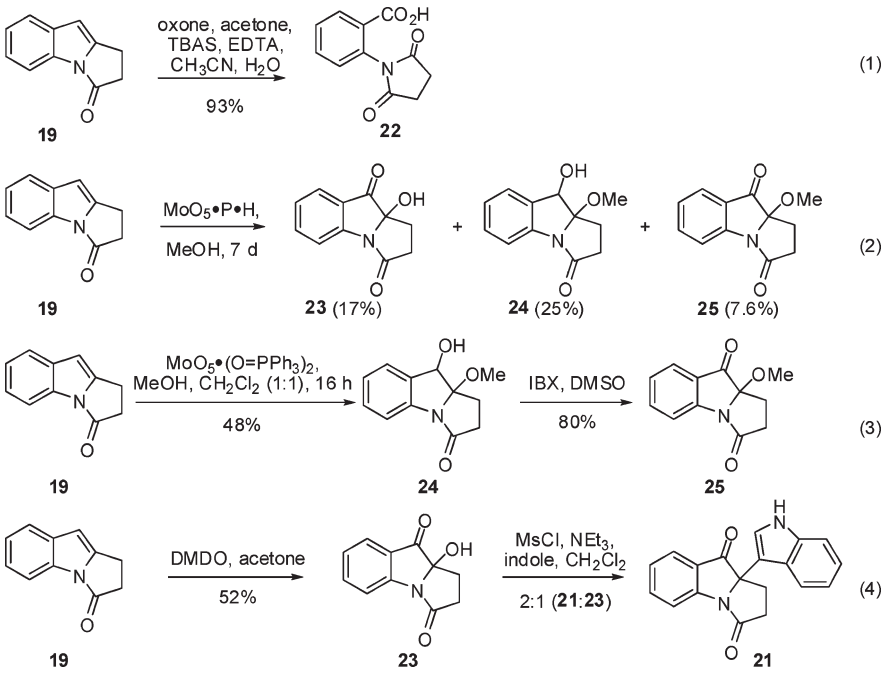
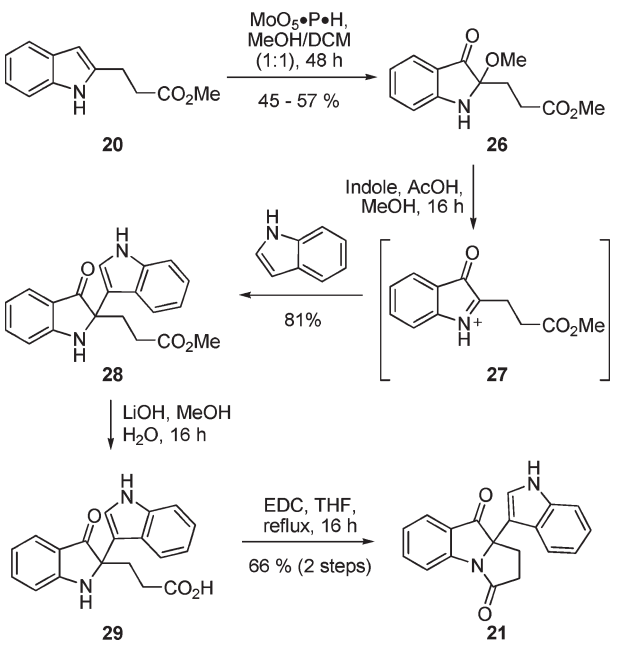
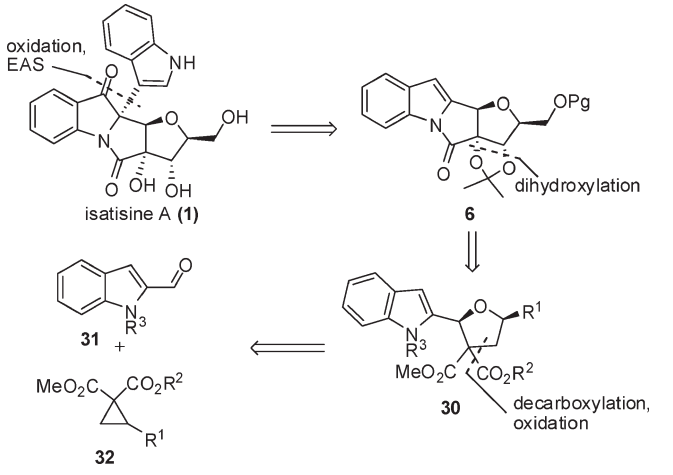


FIGURE 4. Oxidation of pyrroloindolone **19** leading to model compound **21**.

SCHEME 4. Synthesis of Model Compound 21 from *N*-H Indole 20



SCHEME 5. Retrosynthetic Analysis of Isatisine A

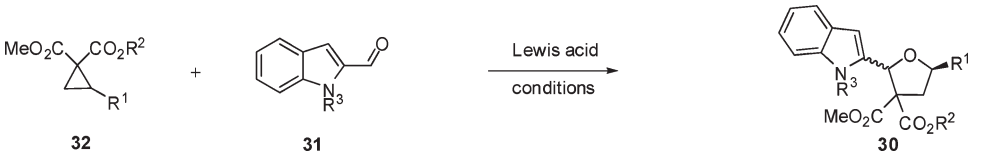


Cyclopropanes containing a vinyl substituent (**32c**,**d**) were then screened with various aldehydes and reactions conditions (entries 10−14). As seen before, electron-rich indoles were not tolerated under the Lewis acidic conditions and decomposed when used alongside vinylcyclopropane diester **32c**. *N*-Boc-indole also decomposed due to cleavage of the Boc group, which is known to occur under these reaction conditions (entry 11).[18] We were delighted to find that indole-2-carboxaldehydes containing electron-withdrawing protecting groups on the nitrogen were good substrates for the cyclization reaction with these vinylcyclopropane diesters (entries 12−14). Under $SnCl_4$ catalysis a 5:2 mixture of 2,5-cis:2,5-trans isomers was obtained in good yield. An attempt at increasing the diastereoselectivity of the reaction by lowering the reaction temperature was unsuccessful; the diastereoselectivity remained unchanged but the yield was substantially lowered (entry 13).

With suitable substrates and reaction conditions in hand for the tetrahydrofuran formation, we moved forward with our synthetic efforts toward isatisine A. Treatment of cyclopropane diester **32c** and aldehyde **31b** with catalytic $SnCl_4$ delivered tetrahydrofuran **30a** in good yield and acceptable diastereoselectivity (Scheme 6). Unfortunately, the diastereomers were inseparable at this point, and were carried forward as a mixture. Krapcho demethoxycarbonylation successfully removed

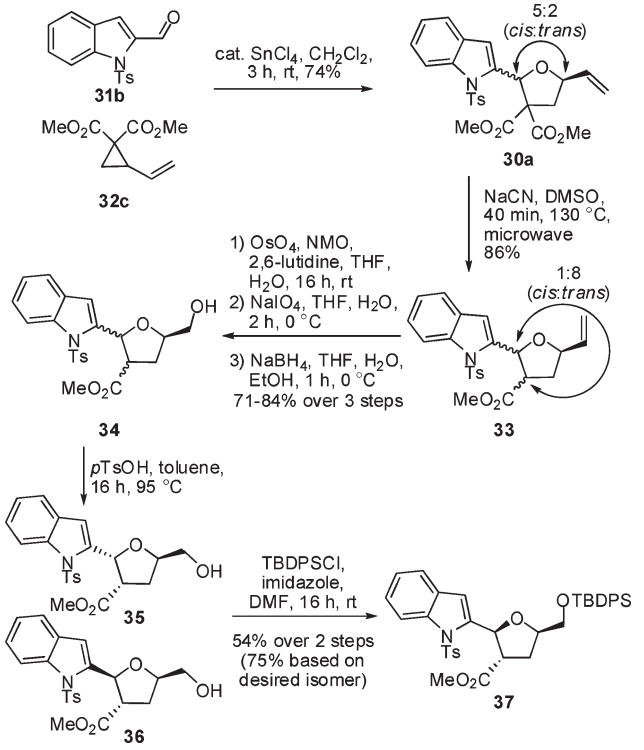
(18) Bose, D. S.; Kumar, K. K.; Reddy, A. V. N. *Synth. Commun.* **2003**, *33*, 445–450.

TABLE 1. Attempts at Cyclization Reaction To Form Tetrahydrofuran Core 30



entry	R^1	R^2	R^3	conditions	outcome
1	CH_2OBn	Me (32a)	Bn (**31a**)	$SnCl_4$, DCE, 45 °C	aldehyde decomposition
2		Me	Ts (**31b**)	$SnCl_4$, DCE, 55 °C	25% yield, 2:1 (cis:trans)
3		Me	Ts (**31b**)	$SnCl_4$, toluene, 110 °C	decomposition
4		Me	Ts (**31b**)	$Sn(OTf)_2$, toluene, 110 °C	decomposition
5	CH_2TBDPS	Me (32b)	H (**31c**)	$Sn(OTf)_2$, CH_2Cl_2, rt	recovered starting material
6		Me	Bn (**31a**)	$Sn(OTf)_2$, CH_2Cl_2, rt	recovered starting material
7		Me	Ts (**31b**)	$Sn(OTf)_2$, CH_2Cl_2, rt	recovered starting material
8		Me	Ts (**31b**)	$Sn(OTf)_2$, CH_2Cl_2, 42 °C	cyclopropane decomoposition
9		Me	Ts (**31b**)	$SnCl_4$, CH_2Cl_2, rt	cyclopropane decomoposition
10	vinyl	Me (32c)	Bn (**31a**)	$SnCl_4$, CH_2Cl_2, rt	aldehyde decomposition
11		Me	Boc (**31d**)	$Sn(OTf)_2$, CH_2Cl_2, rt	aldehyde decomposition
12		Me	Ts (**31b**)	$SnCl_4$, CH_2Cl_2, rt	74% yield, 5:2 (cis:trans)
13		Me	Ts (**31b**)	$SnCl_4$, CH_2Cl_2, 0 °C	55% yield, 5:2 (cis:trans)
14	vinyl	Allyl (32d)	Ts (**31b**)	$SnCl_4$, CH_2Cl_2, rt	81% yield, 2.4:1 (cis:trans)

SCHEME 6. Initial Synthetic Attempt



an ester group, yielding an inseparable 1:8 mixture of diastereomers **33** for both the 2,5-cis and 2,5-trans isomers. The mixture of four diastereomers was subjected to a three-step protocol involving dihydroxylation, oxidative cleavage, and reduction to obtain a mixture of primary alcohols **34**. Heating this mixture in toluene in the presence of *p*-toluenesulfonic acid successfully removed two of the diastereomers by lactone formation leaving **35** and **36**. Protection of the primary alcohols as silyl ethers allowed for separation of the two remaining diastereomers by flash column chromatography, providing **37** in 54% yield from the diastereomeric mixture of **33**. With substrate **37** in hand, we attempted to insert the unit of unsaturation required for the upcoming dihydroxylation by installation of a leaving group followed by elimination. Unfortunately, the requisite leaving group could not be installed in our substrate in this manner. Treatment of **37** with strong base led to instantaneous decomposition of the material, even at low temperatures. Attempts at generating the silyl-enol ether of **37** followed by bromination or oxidation were also unsuccessful.

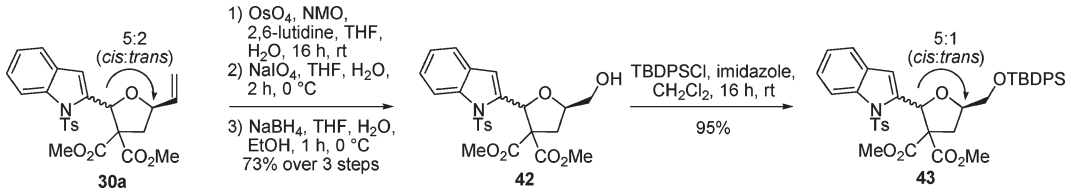
Rather than removing one of the esters followed by oxidation, hydrolysis of one of the esters to its carboxylic acid would yield a substrate that could undergo a radical decarboxylation followed by trapping of the resulting radical with a halide. The synthetic sequence to diester **43** is shown in Scheme 7. Hydrolysis of **43** under various conditions was unsuccessful due to the poor substrate solubility. It was at this junction in our synthetic efforts toward isatisine A that Tsuji's oxidative decarboxylation of allyl β-keto esters[19] was brought to our attention (Scheme 8).[20]

To apply the palladium-catalyzed oxidative decarboxylation reaction to the tetrahydrofuran system, an allyl ester would be required. The previous study with the dimethyl ester substrate **43** (Scheme 7) showed hydrolysis to be difficult. A solution to this issue was to incorporate the allyl ester into the cyclopropane prior to tetrahydrofuran formation. Thus, cyclopropane **32d** was prepared, as a 5:1 diastereomeric mixture, in a two-step sequence from the dimethyl ester by *mono*-saponification followed by alkylation with allyl bromide. $SnCl_4$-catalyzed cyclization with aldehyde **31b** yielded a 2.4:1 mixture of 2,5-cis and 2,5-trans isomers, respectively (Table 1, entry 14) (Scheme 9). An inconsequential 3.5:1 mixture of diastereomers at the diester carbon was also observed. Treatment of **30c** with tris(dibenzylideneacetone)dipalladium(0) in refluxing acetonitrile led to a mixture of three compounds in nearly equal amounts. The three isomers consisted of the 2,5-cis and 2,5-trans isomers of the

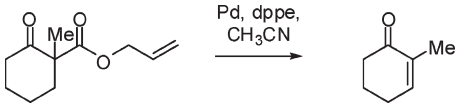
(19) (a) Shimizu, I.; Tsuji, J. *J. Am. Chem. Soc.* **1982**, *104*, 5844–5846. (b) Tsuji, J.; Minami, I.; Shimizu, I. *Chem. Lett.* **1984**, 1721–1724. (c) Minami, I.; Nisar, M.; Yuhara, M.; Shimizu, I.; Tsuji, J. *Synthesis* **1987**, 992–998. (d) Mercier, C.; Mignani, G.; Aufrand, M.; Allmang, G. *Tetrahedron Lett.* **1991**, *32*, 1433–1436.

(20) We would like to thank Professor Jeffrey M. Manthorpe for this suggestion.

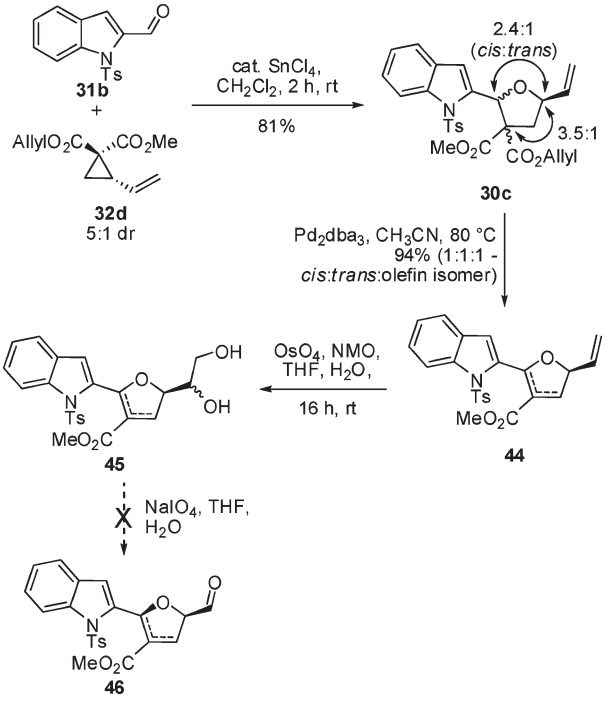
SCHEME 7. Synthesis of Diester 43



SCHEME 8. Tsuji's Palladium(0)-Catalyzed Oxidative Decarboxylation of β-Keto Allyl Esters



SCHEME 9. Palladium-Catalyzed Oxidative Decarboxylation of Diester 32d



unsaturated ester along with the olefin isomer in which the double bond lay between C2 and C3 of the tetrahydrofuran. The observed ratio of products was later found to be due to the selective β-hydride elimination of the 2,5-trans isomer producing exclusively the C3−C4 double bond, whereas the 2,5-cis isomer yielded roughly equal amounts of the double bond isomers. Considering that diester **30c** is almost a 2:1 mixture of cis and trans isomers, this would account for the observed ratio of the three olefin isomers.

During our optimization attempts for the oxidative decarboxylation reaction, we found acetonitrile to be the only suitable solvent. Dimethylformamide showed initial promise with an increased selectivity for the 2,5-cis C3−C4 olefin; however, the reaction did not reach completion and upon scale-up, stopped at less than 20% conversion. Attempts at changing the ligands on the metal were also unsuccessful; amine ligands stopped the reaction completely and phosphine ligands induced the competitive allylation reaction rather than oxidative decarboxylation.

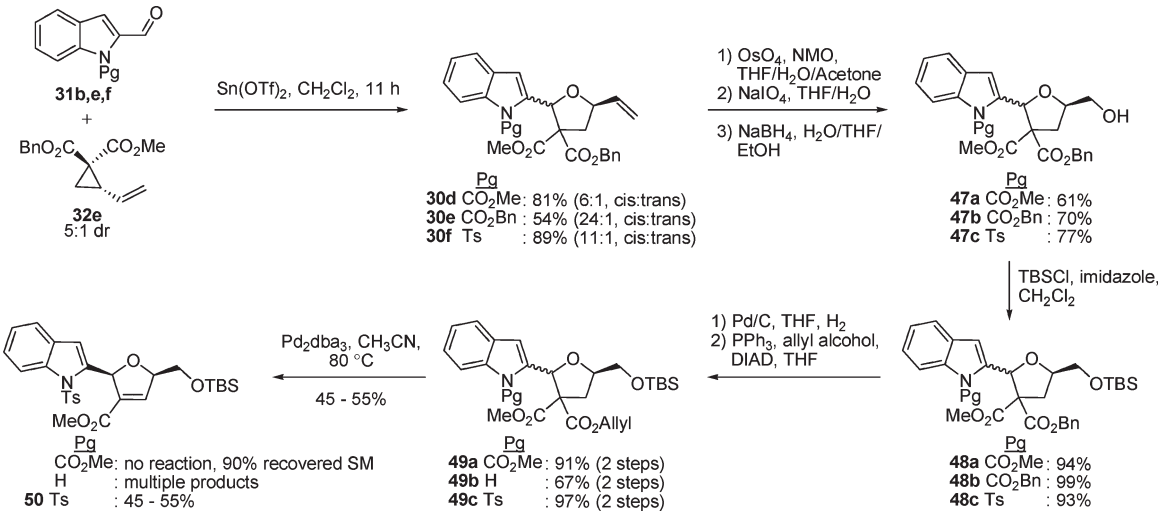
We attempted to carry the mixture of **44** forward to the primary alcohol through the three-step sequence shown previously. Dihydroxylation of the vinyl group was successful, but the following oxidative cleavage led to decomposition of the material. Dihydroxylation of both olefins in **44** was also attempted without success. The incompatibility of the vinyl substituent and the α,β-unsaturated ester forced us to devise a route where the allyl ester could be installed after conversion of the vinyl group to the primary alcohol.

The use of a benzyl ester in place of the allyl ester on the cyclopropane was explored whereby hydrogenation could reveal the carboxylic acid, which could then be allylated to yield the requisite allyl ester. Benzyl methyl cyclopropane diester **32e** was prepared by using the same protocol as for the allyl methyl cyclopropane diester **32d**. By this time in our study of the Lewis acid-catalyzed cyclization reaction of aldehydes and cyclopropane diesters, we had begun employing $Sn(OTf)_2$ as a preferred Lewis acid. Three different aldehydes (methylcarbamate **31e**, benzylcarbamate **31f**, and *p*-toluenesulfonamide **31b** protected indole-2-carboxadehydes) were subjected to the cyclization conditions and carried forward through the sequence shown in Scheme 10. Upon cyclization, a three-step procedure involving dihydroxylation of the vinyl group and oxidative cleavage of the diol followed by reduction of the resulting aldehyde yielded primary alcohols **47**. Protection of the primary alcohol led to **48** in which conversion of a benzyl ester to an allyl ester was required to provide the substrate for oxidative decarboxylation. Treatment of **48** with palladium on carbon under a hydrogen atmosphere removed the benzyl group and the resulting carboxylic acid was allylated under Mitsunobu conditions to yield esters **49**. In the case of **48b**, the benzyl carbamate was also removed under the hydrogenation conditions and the lower yield of allyl ester **49b** is due to competitive lactamization of the indole and the carboxylic acid under the reaction conditions.

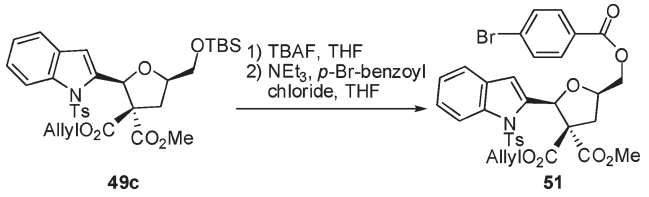
Of the three allyl ester substrates, only **49c** (Pg = Ts) was an acceptable candidate for the oxidative decarboxylation reaction. Substrate **49a** did not furnish any olefin and was recovered in high yield. This result may be explained by coordination of the palladium species to the carbonyl of the carbamate, thus preventing progression of the catalytic cycle. When **49b** was subjected to the oxidative decarboxylation conditions, an inseparable mixture of products containing olefin isomers along with proto-decarboxylation isomers was obtained. Substrate **49c** on the other hand furnished the desired olefin **50** in moderate but acceptable yield, with the remaining mass balance consisting of the trans isomer and the olefin regioisomer.

To confirm the relative stereochemistry of the substituents on the tetrahydrofuran ring, a crystalline derivative of the major diastereomer of **49c** was obtained (Scheme 11). Removal of the silyl ether followed by esterification with *p*-bromobenzoyl chloride furnished **51**, which could be recrystallized from CH_2Cl_2 and hexanes to provide single crystals suitable for X-ray diffraction analysis. As expected, the major isomer consisted of the

SCHEME 10. Successful Route to Dihydrofuran 50



SCHEME 11. Synthesis of Crystalline Derivative 51



2,5-cis relative geometry of the substituents on the tetrahydrofuran ring.

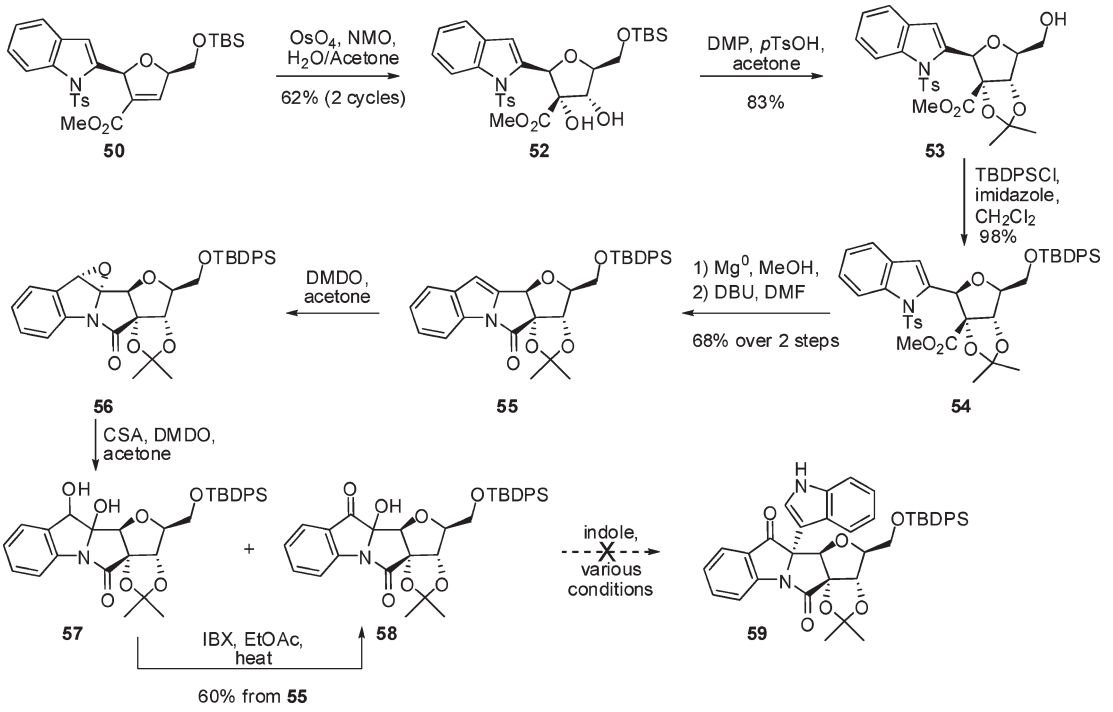
With the successful installation of an olefin in our tetrahydrofuran, we repeated the reaction sequence employing homochiral vinylcyclopropane[20] and used enantiopure material from this point forward. At this junction, our initial aim was to construct the lactam ring to form the pyrroloindolone, followed by oxidation of the indole species and EAS onto indole. With this in mind, dihydroxylation of **50** provided diol **52** in moderate yield (Scheme 12). Acetonide formation occurred with concomitant silyl deprotection to yield primary alcohol **53**. The TBS group was found to be very labile and was cleaved under the mildest reaction conditions. Therefore, the primary alcohol was protected again, this time as the TBDPS ether in nearly quantitative yield. Removal of the tosyl group was achieved under standard conditions, followed by DBU-induced lactam formation to provide **55**. Single crystals of **55** were obtained by slow evaporation of CH_2Cl_2 from hexanes which were suitable for X-ray crystal analysis to confirm the relative structure of **55**.

Treatment of **55** with DMDO did not yield the indoxyl species as we had seen for the model study; instead, epoxide **56** was obtained in nearly quantitative yield and was stable at room temperature, which is uncommon for such compounds.[8b] Epoxide **56** was not stable to silica gel and was characterized without purification. After many trials, we found that addition of CSA to the DMDO solution after consumption of **55** led to a mixture of two products: diol **57** and indoxyl **58**. This mixture was treated with IBX in refluxing ethyl acetate to obtain indoxyl **58** in 60% yield from pyrroloindolone **55**. Just as oxidation of **55** was more complicated than in the model study, indoxyl **58** would not participate in the EAS reaction with indole to yield TBDPS protected isatisine A acetonide **59**. A variety of reaction conditions were employed to promote the EAS reaction but only recovered starting material or decomposition was observed. At this point we changed direction and attempted a route involving oxidation of an N−H indole that would presumably be more susceptible to the EAS reaction.

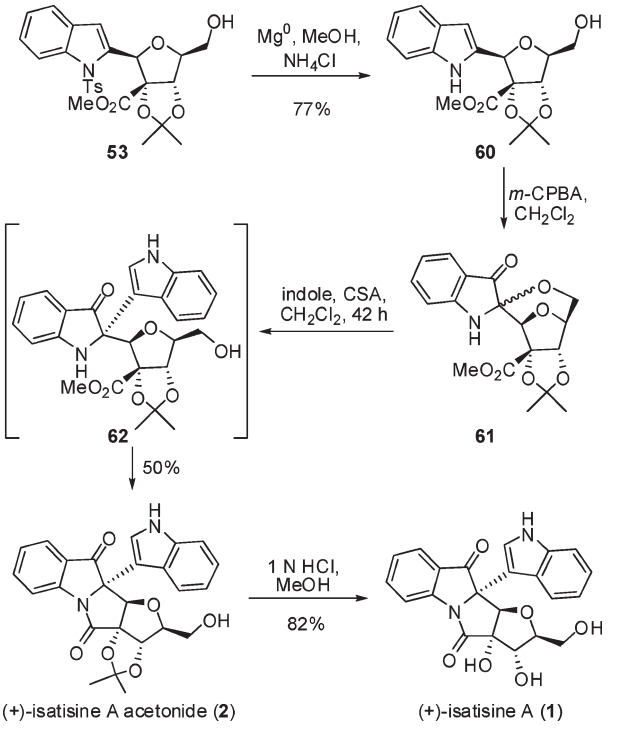
Beginning with primary alcohol **53**, tosyl deprotection took place in good yield to provide free indole **60** (Scheme 13). Oxidation of **60** with *m*-CPBA[9] yielded a mixture of aminals **61**. Surprisingly, these intermediates were stable to silica gel and were isolable for characterization. For the synthetic sequence, the aminals were used as a crude mixture (after removal of the *m*-chlorobenzoic acid byproduct by extraction with ethyl acetate from a basic aqueous solution). Treatment of the aminals with indole and CSA over a 42 h reaction period provided isatisine A acetonide **2** in 50% yield from indole **60**. Isatisine A was obtained in 82% yield by hydrolysis of acetonide **2** with acidic methanol. The specific rotation of synthetic isatisine A acetonide **2** and isatisine A **1** was $[\alpha]^{25}_{D}$ +271 and $[\alpha]^{25}_{D}$ +274, respectively. The specific rotation of isolated isatisine A acetonide is $[\alpha]^{14}_{D}$ −283, which is almost equal in magnitude but opposite in direction to that of the synthetic material. Since we know the absolute configuration of our product, which is antipodal to the isolated compound, the absolute configuration of the isolated natural product must be C2(*S*), C9(*R*), C10(*S*), C12(*R*), and C13(*R*). A synthesis employing (*R*)-vinylcyclopropane **32e** would thus yield the natural enantiomer.

The indole oxidation and EAS cascade reaction requires further discussion. Intermediate **62** (which was isolated in our initial efforts) was not in fact the first product formed upon treatment of **61** with indole and an acid catalyst. In fact, the diastereomeric (and undesired) indole adduct **64** was the kinetic product (formed almost instantly) and isomerized over time to the desired **62**, which in turn was converted to isatisine A acetonide **2** and subsequently to isatisine A **1**. This was monitored by ^{1}H NMR spectroscopy and is shown in Figure 5. Aminals **61** were purified as the diastereomeric mixture and their ^{1}H NMR spectrum is shown in Figure 5 at $t = 0$ h. Within 15 min of adding 1 equiv of indole and CSA both aminal starting materials were consumed and EAS diastereomer **64** was the major product (▲) with a small amount of diastereomer **62** (■). After 1 h the amount of **62** had increased and after 12 h **62** become the major diastereomer. Furthermore, a small amount of isatisine A acetonide **2** (●) was present after 12 h. By 36 h the

SCHEME 12. Pyrroloindolone Route



SCHEME 13. Successful Route to (+)-Isatisine A



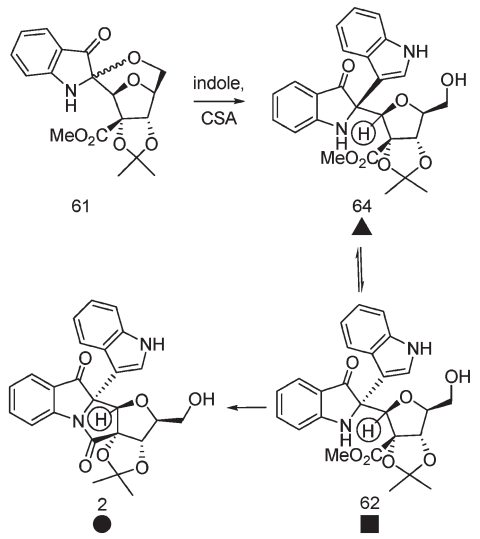
major product was **2** with the other two intermediates still present. After 72 h the reaction was nearly complete with less than 5% of the material as **62**.

Figure 6 shows, in graphical form, the progress of the reaction beginning with the kinetic adduct **64**. Its disappearance is concomitant with the production of diastereomer **62**, the concentration of which peaks at about 10 h under our reaction conditions. The amount of **62** decreases in concert with the appearance of the isatisine A acetonide **2**. Inspection of simple molecular models indicates that lactam formation via **64** would be difficult and so it seems that lactam formation from the desired **62** fortunately provides an irreversible sink to the process. With 2 equiv of indole and CSA, the progress of the reaction increased slightly.

A more detailed mechanistic picture is shown in Scheme 14. The acid catalyst facilitates formation of iminium ion **63**, a willing electrophile for the nucleophilic indole. While other mechanistic possibilities are not unreasonable, we postulate that the isomerizaiton of **64** to **62** may proceed via a gramine-type fragmentation via intermediate **65**. Reclosure of the aniline onto the indole methide provides access to useful quantities of **62**, which in turn may be trapped as the desired lactam **2**.

Conclusion

In summary, we have completed the total synthesis of (+)-isatisine A (**1**) via its acetonide **2** in a 14-step process, with a 5.8% overall yield from homochiral cyclopropane diester **32e** and aldehyde **31b** using a Lewis acid-catalyzed cyclization reaction to construct the tetrahydrofuran ring. A palladium-catalyzed oxidative decarboxylation reaction was used to install a unit of unsaturation directly from the diester species. Lastly, an oxidation and electrophilic aromatic substitution reaction was employed to furnish acetonide **2** in a cascade process involving an equilibrium between EAS substrate diastereomers which converge to acetonide **2**. Importantly, the absolute configuration of isatisine A has been determined by our enantioselective synthesis of the antipode of the natural product. Efforts are underway to determine the biological activity of (+)-isatisine A (**1**) along with its acetonide **2**.



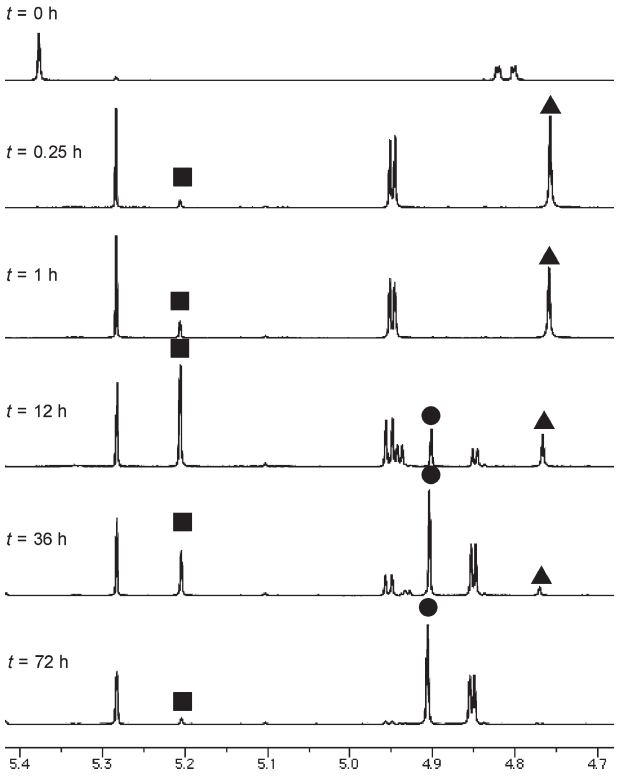


FIGURE 5. EAS cascade reaction monitored by ^{1}H NMR (circled hydrogen indicated in the spectrum).

Experimental Section

General Considerations. Melting points were determined with a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were obtained as thin films on NaCl plates. HPLCs were conducted with a dual λ-absorbance detector set to 256 nm. NMR experiments were conducted in $CDCl_3$ (referenced to 7.26 ppm for ^{1}H and 77.0 for ^{13}C) or d_4-MeOD (referenced to 3.31 ppm for ^{1}H or 49.15 ppm for ^{13}C). Coupling constants (J) are in Hz. The multiplicities of the signals are described by using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br = broad. High-resolution mass spectra (HRMS) were obtained at 70 eV. Toluene, THF, ether, DMF, and methylene chloride were dried and deoxygenated by passing the nitrogen-purged solvents through activated alumina columns. All other reagents and solvents were used as purchased from the supplier. The progress of reactions was followed by thin layer chromatography (TLC) (silica gel 60 F254) and the developed plates stained with acidic anisaldehyde, phosphomolybdic acid, or basic potassium permanganate. Flash column chromatography was performed with silica gel (230−400 mesh).

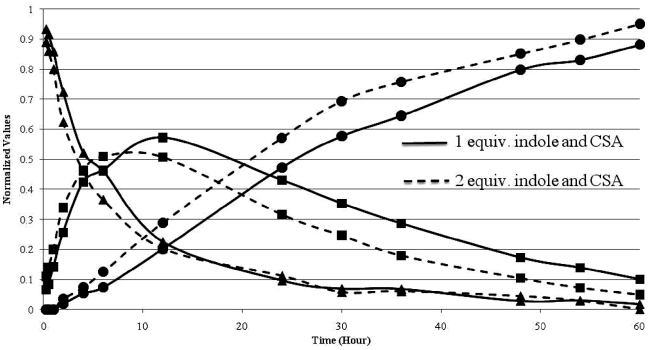


FIGURE 6. EAS Cascade at Various Time Intervals.

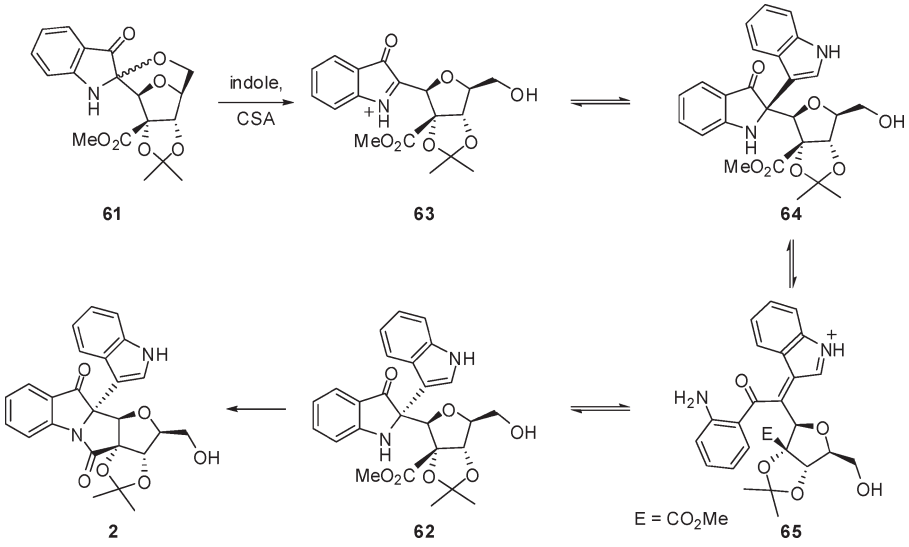
Experimental Procedures. Compound 32e. To a stirring solution of dimethyl (*S*)-2-vinylcyclopropane 1,1-diester[21] (**32c**) (3.01 g, 16.34 mmol) (racemic material was prepared according to literature procedures[22]) in methanol (12.5 mL) was added 12.5 mL of an aqueous 1.7 N NaOH solution. The resulting solution was stirred for 1.5 h after which time TLC analysis showed complete consumption of the starting material. The reaction was poured into a separatory funnel containing 5% aqueous HCl and extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to yield 2.78 g of a clear colorless oil. The resulting acid was dissolved in DMF (125 mL) and K_2CO_3 (2.48 g, 17.97 mmol) was added followed by 2.15 mL (17.97 mmol) of benzyl bromide. The solution was stirred under argon for 48 h then added to H_2O and extracted with Et_2O (4×). The combined organic extracts were washed with H_2O (2×) and brine, dried over $MgSO_4$, and filtered. Concentration in vacuo yielded 4.04 g (95% over 2 steps) of **32e** as a clear colorless oil that was used without further purification (R_f 0.44, 30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.29 (m, 5H), 5.49−5.06 (m, 5H), 3.72 (s, 3H), 2.61 (q, J = 8.4 Hz, 1H), 1.74 (dd, J = 4.8, 7.2 Hz, 1H), 1.60 (dd, J = 4.8, 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 167.7, 135.5, 132.9, 128.5, 128.2, 127.8, 118.7, 67.1, 52.5, 35.9, 31.4, 20.6; IR (thin film, cm^{-1}) ν_{max} 3090, 3067, 2954, 1729, 1639, 1457, 1381, 1271, 1209, 1129, 991, 747, 698; HRMS calcd for $C_{15}H_{16}O_4$ 260.1049, found 260.1056.

Compound 30f. $Sn(OTf)_2$ (0.35 g, 0.84 mmol) was placed in a flask equipped with a stir bar and purged with argon. Cyclopropane **32e** (2.2 g, 8.45 mmol) and aldehyde **31b** (3.5 g, 11.8 mmol) were dissolved in 9 mL of CH_2Cl_2 and added to the flask.[14c] An additional 3 mL of CH_2Cl_2 was used to quantify the transfer of cyclopropane and aldehyde. After being stirred for 11 h the reaction was passed through a small plug of silica gel and the resulting solution was concentrated in vacuo. Purified by flash column chromatography (5−13% EtOAc/hexanes) yielded 4.2 g (89%) of **30f** as a yellow foam. ^{1}H NMR showed **30f** to be a mixture of 4 diastereomers (1:0.23:0.07:0.04) with an 11:1, 2,5-cis: 2,5-trans ratio, respectively. The diastereomers at the esters (3.5:1) are inconsequential since they will converge

(21) Carson, C. A.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 6560–6563.

(22) Kierstead, R. W.; Linstead, R. P.; Weedon, B. C. L. *J. Chem. Soc.* **1952**, *74*, 3610–3616.

SCHEME 14. Mechanism of EAS Cascade



further on in the synthesis (R_f 0.26 and 0.34, 30% EtOAc/hexanes); for ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) see spectra in the Supporting Information; HRMS calcd for $C_{31}H_{29}NO_7S$ 559.1651, found 559.1665.

Compound 47c. To the diastereomeric mixture of **30f** (14.3 g, 25.5 mmol) dissolved in THF (175 mL), H_2O (140 mL), and acetone (35.5 mL) was added methanesulfonamide (2.42 g, 25.5 mmol), NMO (3.28 g, 28.0 mmol), and a large crystal of OsO_4. The reaction was monitored by TLC and upon completion sodium sulfite was added to the reaction, which was then stirred for a further 30 min. The reaction was then filtered through Celite and the volatile components were removed in vacuo. The remaining solution was added to brine and extracted with EtOAc (4×), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield a white foam (R_f 0.23 and 0.35, 70% EtOAc). The resulting foam was dissolved in THF (180 mL) and H_2O (180 mL), then cooled to 0 °C, and after addition of $NaIO_4$ (7.63 g, 35.7 mmol) the reaction flask was removed from the ice bath and the solution was stirred at room temperature. The reaction was monitored by TLC and upon completion 300 mL of EtOH was added and the solution was filtered through Celite rinsing the filter cake with 100 mL of EtOH (R_f 0.55 streak, 70% EtOAc). $NaBH_4$ (1.64 g, 43.4 mmol) was added to the filtrate and the solution was stirred at room temperature. TLC monitoring showed consumption of the aldehyde after 45 min at which time the reaction was quenched with dropwise addition of a saturated aqueous solution of NH_4Cl. The organic solvents were removed under reduced pressure and the remaining solution was added to H_2O and extracted with EtOAc (4×). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography (30−50% EtOAc/hexanes) yielded 12.5 g of the diastereomeric mixture of primary alcohols as a white foam (87% over 3 steps). A small amount of the major isomer of **47c** (shown above, R_f 0.60, 70% EtOAc/hexanes) was isolated and used for characterization; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.07 (d, J = 8.8 Hz, 1H), 7.70 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 7.6 Hz, 1H), 7.27 (ddd, J = 1.6, 7.2, 7.2 Hz, 1H), 7.21−7.12 (m, 6H), 7.04−7.01 (m, 2H), 6.80 (s, 1H), 6.76 (s, 1H), 4.94 (d, J = 12.4 Hz, 1H), 4.57 (d, J = 12.4 Hz, 1H), 4.21 (dddd, J = 3.0, 4.8, 4.8, 11.4 Hz, 1H), 3.95−3.91 (m, 1H), 3.77 (s, 3H), 3.77−3.72 (m, 1H), 2.92 (dd, J = 11.2, 13.2 Hz, 1H), 2.39 (dd, J = 5.2, 13.2 Hz, 1H), 2.27 (s, 3H), 2.04 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 167.8, 144.7, 138.7, 136.9, 135.3, 134.7, 129.6, 129.1, 128.1, 128.0, 126.6, 124.8, 123.6, 121.1, 114.9, 111.6, 78.8, 77.4, 67.5, 66.1, 63.2, 53.1, 35.8, 21.4; IR (thin film, cm^{-1}) ν_{max} 3474, 3068, 3036, 2955, 2886, 1734, 1452, 1374, 1274, 1188, 1060, 735, 580; HRMS calcd for $C_{30}H_{29}NO_8S$ 563.1614, found 563.1598.

Compound 48c. A mixture of alcohols **47c** (12.5 g, 22.1 mmol) was dissolved in CH_2Cl_2 (220 mL) followed by the successive addition of TBSCl (4.67 g, 31.0 mmol) and imidazole (2.11 g, 31 mmol). The reaction was stirred for 12 h after which time it was added to H_2O and extracted with CH_2Cl_2 (2×). The combined organic extracts was washed with brine, dried over $MgSO_4$, and filtered. Purification via flash column chromatography (5% EtOAc/hexanes) yielded 14.2 g (94%) of the diastereomeric mixture as a white foam. A small amount of the major isomer of **48c** (shown above, R_f 0.42, 30% EtOAc/hexanes) was isolated and characterized; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.05 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 7.6 Hz, 1H), 7.24−7.05 (m, 10 H), 6.76 (s, 1H), 4.95 (d, J = 12.4 Hz, 1H), 4.68 (d, J = 12.4 Hz, 1H), 4.10 (dddd, J = 11.6, 4.0, 4.0, 4.0 Hz, 1H), 3.98 (dd, J = 11.2, 3.6 Hz, 1H), 3.81 (dd, J = 11.2, 4.0 Hz, 1H), 3.78 (s, 3H), 2.94 (t, J = 12.4 Hz, 1H), 2.34 (dd, J = 12.8, 4.4 Hz, 1H), 2.29 (s, 3H), 0.93 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 167.6, 144.6, 139.5, 137.1, 135.3, 135.0, 129.6, 129.5, 128.2, 128.1, 127.9, 126.6, 124.6, 123.6, 121.0, 114.9, 112.4, 79.0, 77.6, 67.4, 66.1, 63.4, 53.1, 35.6, 25.9, 21.5, 18.4, −5.3, −5.5; IR (thin film, cm^{-1}) ν_{max} 2956, 2930, 2858, 1736, 1598, 1472, 1451, 1175, 1091, 813, 703, 581; HRMS calcd for $C_{36}H_{43}NO_8SSi$ 677.2479, found 677.2473.

Compound 49c. To a diastereomeric mixture of **48c** (14.1 g, 20.8 mmol) in THF (250 mL) was added 1.4 g of 10% Pd/C. The reaction vessel was purged with hydrogen gas (4×) then placed under 1 atm of hydrogen for 3 h after which time TLC analysis showed consumption of the diester. The solution was filtered through a pad of Celite and the Celite was rinsed with THF (200 mL). Triphenylphosphine (8.06 g, 30.7 mmol) and allyl alcohol (2.1 mL, 30.7 mmol) were added to the solution along with a magnetic stir bar. With stirring DIAD (6.0 mL, 30.7 mmol) was added to the solution and stirring was continued for 50 min after which time a further 0.3 equiv of all the reagents was added. After 40 min TLC analysis showed consumption of the acid substrate. Purification by flash column chromatography (60−100% CH_2Cl_2/hexanes) yielded 12.9 g (99%) of a diastereomeric mixture of products as a white foam. A small amount of the major isomer of **49c** was isolated and used for characterization (R_f 0.38, 30% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.07 (dd, J = 8.0, 0.4 Hz, 1H), 7.68−7.65 (m, 2H),

7.40−7.38 (m, 1H), 7.24 (ddd, J = 7.6, 7.6, 1.6 Hz, 1H), 7.17 (dd, J = 7.6, 1.2 Hz, 1H), 7.14−7.12 (m, 2H), 7.03 (s, 1H), 6.75 (d, J = 0.8 Hz, 1H), 5.55 (dddd, J = 16.4, 10.8, 6.0, 6.0 Hz, 1H), 5.04 (dq, J = 17.2, 1.2 Hz, 1H), 4.95 (dq, J = 10.4, 1.2 Hz, 1H), 4.33 (ddt, J = 12.8, 6.0, 1.2 Hz, 1H), 4.17 (ddt, J = 11.6, 6.0, 1.2 Hz, 1H), 4.11 (dq, J = 12.0, 4.0 Hz, 1H), 3.99 (dd, J = 11.2, 3.6 Hz, 1H), 3.87 (s, 3H), 3.83 (dd, J = 11.2, 3.6 Hz, 1H), 2.96 (dd, J = 12.8, 11.6 Hz, 1H), 2.33 (dd, J = 13.2, 4.4 Hz, 1H), 2.28 (s, 3H), 0.95 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 167.5, 144.6, 139.4, 137.1, 135.3, 131.0, 129.7, 129.5, 126.6, 124.5, 123.6, 121.0, 118.6, 114.8, 112.4, 78.9, 77.6, 66.5, 66.1, 63.4, 53.2, 35.8, 26.0, 21.5, 18.4, −5.3, −5.4 ; IR (thin film, cm^{-1}) ν_{max} 2956, 2930, 2859, 1737, 1451, 1261, 1175, 1092, 914, 837, 749, 581; HRMS calcd for $C_{32}H_{41}NO_8SSi$ 627.2322, found 627.2340; $[\alpha]^{25}_D$ +201 (c 2.6, MeOH).

Compound 50. To the diastereomeric mixture of ally esters **49c** (2.36 g, 3.8 mmol) in acetonitrile (125 mL) was added Pd_2dba_3 (0.18 g, 0.19 mmol).[20] The reaction was heated to 80 °C for 10 h after which time it was filtered through a pad of Celite. Flash column chromatography (5−20% EtOAc/hexanes) yielded 1.0 g of **50** as a white foam (49%, typically yield ranges from 45% to 55%). The remaining mass balance consists of 2,5-trans isomer **G** and the undesired olefin isomer **H**. **50**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 8.0 Hz, 2H), 7.42 (d, 7.6 Hz, 1H), 7.31−7.27 (m, 1H), 7.21−7.17 (m, 4H), 6.83 (t, J = 2.4 Hz, 1H), 6.46 (s, 1H), 5.09−5.03 (X of ABX, 1H), 3.70 (A/B of ABX, J = 10.0, 4.8 Hz, 1H), 3.67 (s, 3H), 3.50 (A/B of ABX, J = 10.0, 7.2 Hz, 1H), 2.32 (s, 3H), 0.83 (s, 9H), −0.03 (s, 3H), −0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 144.6, 142.5, 136.8, 135.8, 133.7, 129.4, 128.8, 127.2, 125.0, 123.5, 121.3, 114.9, 110.3, 87.1, 78.1, 65.5, 51.9, 25.8, 21.5, 18.3, −5.46; IR (thin film, cm^{-1}) ν_{max} 2955, 2929, 2858, 1727, 1451, 1375, 12691, 1177, 1150, 1121, 1091, 1057, 837, 782, 673, 581; HRMS calcd for $C_{28}H_{35}NO_6SSi$ 541.1954, found 541.1958; $[\alpha]^{25}_D$ +131 (c 0.57, MeOH); R_f 0.40, 30% EtOAc/Hexanes. **G**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.12 (dd, J = 8.4, 0.8 Hz, 1H), 7.92 (d, J = 12.6 Hz, 2H), 7.41 (d, J = 8.0 Hz, 1H), 7.29 (ddd, J = 8.4, 7.2, 1.2 Hz, 1H), 7.20−7.16 (m, 2H), 6.89 (dd, J = 8.4, 5 Hz, 1H), 6.46 (s, 1H), 4.99−4.94 (m, 1H), 3.90 (dd, J = 10.4, 4.8 Hz, 1H), 3.72 (dd, J = 10.0, 6.8 Hz, 1H), 3.68 (s, 3H), 2.32 (s, 3H), 0.91 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 144.6, 142.7, 139.7, 137.0, 135.7, 134.3, 129.5, 128.8, 127.3, 125.0, 123.5, 121.2, 114.9, 109.8, 85.5, 78.3, 65.1, 51.9, 25.8, 21.5, 18.3, −5.4 (2C); IR (thin film) ν_{max} 2954, 2929, 2885, 2857, 1726, 1598, 1472, 1375, 1257, 1175, 1150, 1121, 1091, 1055, 837, 815, 779, 749; R_f 0.45, 30% EtOAc/hexanes. **H**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.04 (d, J = 8.4 Hz, 1H), 7.73 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.0 Hz, 1H), 7.32 (t, J = 8.0 Hz, 1H), 7.21 (t, J = 8.0 Hz, 1H), 7.13 (d, J = 8.0 Hz, 2H), 6.86 (s, 1H), 4.99−4.92 (m, X of ABX, 1H), 3.92 (A/B of ABX, J = 10.8, 7.2 Hz, 1H), 3.85 (A/B of ABX, J = 10.8, 7.2 Hz, 1H), 3.56 (s, 3H), 3.16 (dd, J = 14.8, 10.8 Hz, 1H), 3.00, (dd, J = 14.8, 8.8 Hz, 1H), 2.30 (s, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 157.1, 144.6, 137.0, 135.1, 129.4, 129.1, 127.2, 125.7, 123.7, 121.7, 115.8, 115.0, 107.6, 83.4, 77.2, 64.5, 51.0, 32.6, 25.9, 21.5, 18.3, − 5.2 (2C); IR (thin film, cm^{-1}) ν_{max} 2953, 2930, 2900, 2886, 2858, 1706, 1375, 1258, 1190, 1176, 1123, 1093, 1056, 837, 813, 780, 750; HRMS calcd for $C_{28}H_{35}NO_6SSi$ 541.1954, found 541.1809; R_f 0.40, 30% EtOAc/hexanes.

Compound 52. (Note well, complete separation of the regioisomeric double bond compounds was difficult and in most cases a mixture of the two compounds was obtained from the previous step and used in the dihydroxylation.) A 2:1 mixture of enoates **50** and **H** (6.21 g, 11.3 mmol total, 4.14 g, 7.5 mmol of desired isomer) was dissolved in acetone/H_2O (44 mL, 10:1) and to it were added NMO (1.94 g, 16.6 mmol), methanesulfonamide (1.25 g, 12.1 mmol), and a large crystal of osmium tetraoxide. The reaction was stirred until it became black at which point sodium sulfite was added to the reaction then the mixture was stirred for a further 30 min. The solution was filtered through Celite, added to water, and extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography (8−22% EtOAc/hexanes) yielded 2.15 g of **52** (49%) and 1.96 g of a 1:0.7 mixture of enoate starting material (in favor of the desired isomer). The enoate mixture was resubjected to the reaction conditions in acetone/H_2O (16.5 mL, 10:1), with NMO (0.5 g, 4.2 mmol), methanesulfonamide (0.4 g, 4.2 mmol), and catalytic osmium tetraoxide to yield a further 0.58 g of **52** and 0.74 g of a 1:1 mixture of enoates. Overall yield after 2 cycles was 2.63 g (62%) (R_f 0.16, 30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 7.2 Hz, 1H), 7.28−7.12 (m, 5H), 7.73 (s, 1H), 4.58 (s, 1H), 4.50 (dd, J = 10.8, 8.8 Hz, 1H), 4.17−4.13 (m, 1H), 3.96−3.92 (m, 2H), 3.39 (s, 3H), 2.62 (d, 11.2 Hz, 1H), 2.30 (s, 3H), 0.98 (s, 9H), 0.19 (s, 3H), 0.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 145.1, 138.6, 137.0, 134.9, 129.9, 129.7, 126.4, 124.6, 123.9, 121.1, 114.4, 111.8, 84.6, 83.2, 82.4, 73.3, 61.7, 53.3, 26.0, 51.5, 18.5, −5.3, −5.4 ; IR (thin film, cm^{-1}) ν_{max} 3477, 2954, 2929, 2857, 1735, 1452, 1371, 1268, 1229, 1175, 836, 764, 750, 581; HRMS calcd for $C_{28}H_{37}NO_8SSi$ 575.2009, found 575.1992; $[\alpha]^{25}_D$ +182 (c 2.3, MeOH).

Compound 53. To a solution of **52** (0.61 g, 1.06 mmol) in acetone (15 mL) were added 2,2-dimethoxypropane (0.9 mL, 7.5 mmol) and p-toluenesulfonic acid (0.21 g, 1.06 mmol). The reaction was stirred for 16 h then a small amount of a saturated aqueous solution of $NaHCO_3$ was added to the reaction and the acetone was removed under reduced pressure. The resulting mixture was added to water, then extracted with EtOAc (3×), and the combined organics were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (15−40% EtOAc/hexanes) yielded **53** (0.45 g, 83%) as a white foam (R_f = 0.09, 30% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 (d, J = 8.4 Hz, 1H), 7.68 (apparent d, J = 8.4 Hz, 2H), 7.42 (d, J = 7.8 Hz, 1H), 7.27 (t, J = 8.4 Hz, 1H), 7.19 (t, J = 7.8 Hz, 1H), 7.15 (apparent d, J = 8.4 Hz, 2H), 6.78 (s, 1H), 6.12 (s, 1H), 5.10 (d, J = 4.8 Hz, 1H), 4.32 (apparent q, J = 4.2 Hz, 1H), 4.06−3.95 (m, 2H), 3.32 (s, 3H), 2.42 (br s, 1H), 2.30 (s, 3H), 1.75 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 144.8, 137.4, 135.9, 135.0, 129.6, 129.3, 126.7, 125.0, 123.9, 121.0, 117.4, 115.3, 112.2, 94.8, 84.7, 84.3, 82.1, 62.6, 52.4, 27.4, 25.6, 21.5; IR (thin film, cm^{-1}) ν_{max} 3448, 2991, 2951, 1735, 1375, 1255, 1217, 1175, 1091, 914, 734; HRMS calcd for $C_{25}H_{27}NO_8S$ 501.1457, found 501.1476; HPLC (Phenomenex Lux 3u Cellulose-2, 30% i-PrOH/hexanes, 1.0 mL/min, (±) RT = 11.65, 17.67 min, (+) RT = 17.63 min; ee >98%; $[\alpha]^{25}_D$ +106 (c 2.3, MeOH); mp (+)-**53** 169−172 °C (recrystallized from MeOH).

Compound 60. To compound **53** (0.45 g, 0.89 mmol) in MeOH (15 mL) were added NH_4Cl (0.21 g, 3.92 mmol) and magnesium turnings (0.43 g, 17.69 mmol). The reaction was stirred and monitored by TLC for completion. Upon consumption of the starting material (R_f 0.51, 20% EtOAc/CH_2Cl_2) the solution was poured into a separatory funnel containing a saturated solution of NH_4Cl and extracted with EtOAc (3×). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (30% EtOAc/hexanes) yielded the titled compound **60** (0.24 g, 77%) as a white foam (R_f 0.34, 20% EtOAc/CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.54 (br s, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.33 (d, J = 8.4 Hz, 1H), 7.16 (dt, J = 7.2, 1.2 Hz, 1H), 7.07 (apparent t, J = 7.2 Hz, 1H), 6.51−6.50 (m, 1H), 5.26 (s, 1H), 5.07 (d, J = 3.6 Hz, 1H), 4.35 (apparent q, J = 4.2 Hz, 1H), 4.11−4.07 (m, 1H), 4.01−3.97 (m, 1H), 3.38 (s, 3H), 2.61 (br t, J = 6 Hz, 1H), 1.70 (s, 3H), 1.38 (s, 3H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 171.2, 135.9, 131.9, 127.8, 122.1, 120.6, 119.7, 117.6, 110.9, 101.0, 93.3, 84.8, 84.7, 62.3, 52.7, 27.3, 25.2; IR (thin film, cm^{-1}) ν_{max} 3395, 2992, 2961, 2887, 1734, 1663, 1457, 1437, 1377, 1214, 1118, 1085, 1047, 867, 751; HRMS calcd for $C_{18}H_{21}NO_6$ 347.1369, found 347.1373; $[\alpha]^{25}_D$ +59 (*c* 0.42, MeOH).

Oxidation and EAS Sequence (2). To compound **60** (0.071 g, 0.20 mmol) in CH_2Cl_2 (9 mL) was added a solution of *m*-CPBA[8] (0.11 g of 66% by mass, 0.41 mmol) in CH_2Cl_2 (9 mL) at room temperature. The reaction was monitored by TLC and upon consumption of the starting material (1.5 h) the mixture was added to a separatory funnel containing a saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3×). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated to yield 0.73 g of a yellow foam. This crude mixture contains a 2:1 ratio of diastereomers **61** and was carried onto the next reaction without any further purification (R_f major 0.50, minor 0.41, 50% EtOAc/hexanes). Indole (0.048 g, 0.41 mmol) and CSA (0.094 g, 0.40 mmol) were added to the diastereomeric mixture of intermediates **60** (0.73 g, crude) dissolved in CH_2Cl_2 (9 mL) and the solution was stirred at room temperature. If the reaction was stopped after 12 h indole addition product **62** could be isolated; however, upon longer exposure (42 h) the acetonide of isatisine A (**2**) was obtained as a light yellow solid (0.05 g, 50%) after purification via flash column chromatograph (0.25−0.75% MeOH/CH_2Cl_2) (R_f 0.34, 5% MeOH/CH_2Cl_2). **61**-major isomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.59 (d, J = 7.8 Hz, 1H), 7.45 (t, J = 7.8 Hz, 1H), 6.91 (t, J = 7.8 Hz, 1H), 6.76 (d, J = 8.4 Hz, 1H), 5.39 (s, 1H), 4.83−4.81 (m, 1H), 4.49 (s, 1H), 4.27 (s, 2H), 3.93 (s, 3H), 3.82 (d, J = 11.4 Hz, 1H), 1.53 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.7, 172.0, 159.3, 137.6, 125.4, 121.2, 120.4, 114.5, 113.4, 92.4, 85.9, 83.5, 83.3, 81.1, 77.2, 64.7, 53.0, 29.7, 26.6 (2C′s); IR (thin film, cm^{-1}) ν_{max} 3332, 3001, 2984, 2936, 2853, 1718, 1617, 1487, 1312, 1270, 1255, 1174, 1097, 751; HRMS calcd for $C_{18}H_{19}NO_7$ 361.1162, found 361.1160; $[\alpha]^{25}_D$ −284 (*c* 0.30, MeOH) (R_f 0.50, 50% EtOAc/hexanes). **61**-minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 8.0 Hz, 1H), 7.48 (t, J = 7.6 Hz, 1H), 6.90−6.86 (m, 2H), 5.83 (s, 1H), 5.56 (s, 1H), 4.25−4.22 (m, 2H), 4.09 (s, 1H), 3.94−3.90 (m, 4H), 1.48 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.2, 168.2, 158.0, 138.1, 125.4, 120.7, 120.4, 113.9, 113.0, 91.5, 88.8, 84.7, 84.4, 82.1, 65.1, 52.8, 26.7, 26.4; IR (thin film) ν_{max} 3363, 2988, 2955, 2937, 1745, 1735, 1636, 1487, 1473, 1383, 1323, 1086, 924, 755; HRMS calcd for $C_{18}H_{19}NO_7$ 361.1162, found 361.1163; $[\alpha]^{25}_D$ −45 (*c* 0.31, MeOH) (R_f 0.41, 50% EtOAc/hexanes). **62**: ^{1}H NMR (600 MHz, CD_3OD) δ 7.69 (d, J = 8.4 Hz, 1H), 7.53 (t, J = 8.4 Hz, 1H), 7.45 (d, J = 7.2 Hz, 1H), 7.38 (s, 1H), 7.32 (d, J = 8.4 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 7.06 (t, J = 7.8 Hz, 1H), 6.92 (t, J = 7.2 Hz, 1H), 6.77 (t, J = 7.2 Hz, 1H), 5.21 (s, 1H), 4.78 (proton under solvent peak), 4.03 (d of X of ABX, J = 5.4 Hz, 1H), 3.70 (A/B of ABX, J = 12.0, 6.0 Hz, 1H), 3.53 (A/B of ABX, J = 12.0, 6.0 Hz, 1H), 3.09 (s, 3H), 1.59 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 203.5, 174.0, 164.1, 139.1, 138.4, 126.4, 125.8, 125.3, 122.7, 122.2, 120.5, 119.6, 117.5, 113.7, 112.6, 110.8, 93.6, 92.9, 89.0, 86.8, 71.7, 63.3, 52.8, 28.6, 26.6; IR (thin film, cm^{-1}) ν_{max} 3405, 2926, 2854, 1734, 1706, 1617, 1488, 1466, 1437, 1266, 1092, 1028, 740; HRMS calcd for $C_{26}H_{26}N_2O_7$ 478.1740, found 478.1754 (R_f 0.07, 50% EtOAc/hexanes). **64**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.40 (t, J = 7.8 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 7.18 (s, 1H), 7.12 (t, J = 7.2 Hz, 1H), 7.08 (t, J = 7.2 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 6.78 (t, J = 7.2 Hz, 1H), 5.72 (s, 1H), 4.95 (d, J = 3.0 Hz, 1H), 4.79 (s, 1H), 4.05 (q, J = 3.0 Hz, 1H), 3.88 (s, 1H), 3.52 (br s, 1H), 3.03 (s, 3H), 1.63 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3, 171.4, 159.8, 136.9, 136.7, 125.7, 125.2, 123.8, 122.0, 120.8, 120.3, 119.9, 119.1, 117.1, 112.2, 111.7, 90.0, 89.6, 85.3, 83.4, 69.1, 62.1, 51.9, 27.4, 25.2; IR (thin film, cm^{-1}) ν_{max} 3389, 3058, 2990, 2934, 2249, 1733, 1699, 1618, 1486, 1376, 1249, 1103, 910, 734; HRMS calcd for $C_{26}H_{26}N_2O_7$ 478.1740, found 478.1735 (R_f 0.16, 50% EtOAc/hexanes). **2**: ^{1}H NMR (600 MHz, CD_3OD) δ 8.00 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.76 (m, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.31 (t, J = 7.2 Hz, 1H), 7.24 (s, 1H), 7.14 (t, J = 7.8 Hz, 1H), 7.07 (t, J = 7.8 Hz, 1H), 4.89 (s, 1H), 4.78 (d, J = 3.6 Hz, 1H), 4.15 (d of X of ABX, J = 3.6 Hz, 1H), 3.48 (A/B of ABX, J = 12, 4.8 Hz, 1H), 3.42 (A/B of ABX, J = 12, 4.8 Hz, 1H), 1.49 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 195.8, 171.5, 151.3, 139.2, 138.0, 127.4, 127.1, 126.3, 125.8, 124.4, 123.4, 121.4, 120.9, 119.6, 117.5, 113.1, 111.1, 99.5, 87.9, 87.2, 86.1, 76.4, 62.6, 27.4, 26.4; HRMS calcd for $C_{25}H_{22}N_2O_6$ 446.1478, found 446.1487; HPLC (Phenomenex Lux 3u Cellulose-2, 35% *i*-PrOH/hexanes, 1.0 mL/min, (±) RT = 7.6, 11.04 min, (+) RT = 11.02 min; ee = >98%; $[\alpha]^{25}_D$ +271 (*c* 1.6, MeOH) (R_f 0.34, 5% MeOH/CH_2Cl_2).

(+)-Isatisine A (1). Acetonide **2** (28 mg, 0.063 mmol) was dissolved in 1 N HCl in MeOH (3 mL) and the mixture was stirred for 1.5 h at which point the solvent was removed. The remaining yellow/orange residue was preadsorbed onto silica and purified by flash column chromatography (1−2.5% MeOH/CH_2Cl_2) to yield 21 mg of isatisine A (82%) as a light yellow solid (R_f 0.51, 10% MeOH/CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.98 (d, J = 7.8 Hz, 1H), 7.93 (d, J = 7.8 Hz, 1H), 7.76−7.73 (m, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.34 (d, J = 8.4 Hz, 1H), 7.31−7.28 (m, 2H), 7.13−7.10 (m, 1H), 7.05 (t, J = 7.8 Hz, 1H), 4.90 (s, 1H), 4.07 (d, J = 3.6 Hz, 1H), 3.86 (d of X of ABX, J = 4.2 Hz, 1H), 3.41 (A/B of ABX, J = 11.4, 5.4 Hz, 1H), 3.34 (A/B of ABX, J = 11.4, 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8, 174.7, 151.9, 139.1, 138.0, 127.4, 127.0, 126.3, 126.1, 124.6, 123.2, 121.5, 120.7, 117.8, 112.9, 110.6, 90.0, 89.0, 84.7, 76.8, 74.4, 63.2; HRMS calcd for $C_{22}H_{18}N_2O_6$ 406.1165, found 406.1151; $[\alpha]^{25}_D$ +274 (*c* 1.1, MeOH).

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Supporting Information Available: Complete experimental procedures as well as ^{1}H NMR and ^{13}C NMR, IR, and MS data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.