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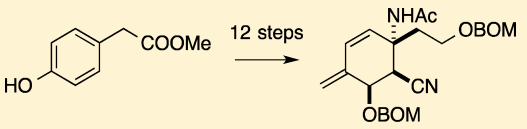
Assembly of a Key Dienic Intermediate for Tetrodotoxin via a Machetti−DeSarlo Reaction

Jaclyn Chau, Sanjia Xu, and Marco A. Ciufolini*

Department of Chemistry, The University of British Columbia, 2036 Main Mall, Vancouver, British Columbia V6T 1Z1, Canada

Supporting Information

ABSTRACT: A route to a racemic diene intermediate for the synthesis of tetrodotoxin is described. Key steps of the sequence leading to such a compound include the oxidative amidation of a phenol, a Cu(II)-catalyzed cyclocondensation of a nitroketone with an olefin (Machetti−DeSarlo reaction), and a nucleophilic fragmentation of the resulting isoxazoline. Several unusual reactions encountered in the course of this study are thoroughly discussed.



INTRODUCTION

Tetrodotoxin (TTX, **1**; Figure 1),[1] a neurotoxic agent[2] initially isolated[3] from puffer fish,[4] remains a privileged target for chemical synthesis on account of complex architecture, high density of reactive functionalities packed into a small framework, and sheer difficulty of a synthetic attack.[5] The first synthesis of (±)-**1** was achieved in 1972;[6] however, enantioselective avenues to the natural product[7] and its congeners[8] began to appear only in the early 2000s. Interestingly, the best contemporary route[7b] to **1** relies on new synthetic technology: the insertion of a nitrenoid into a C−H bond.[9] This suggests that key to an efficient approach is the inclusion of new reactions as elements of the overall strategy.

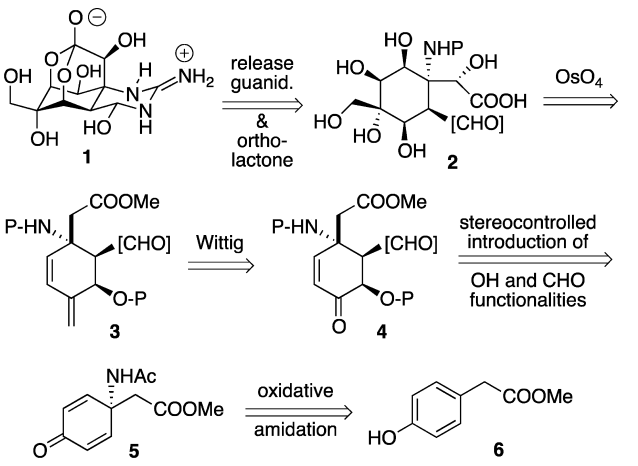
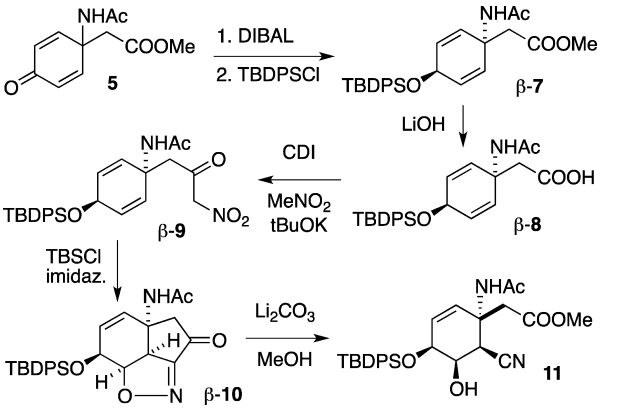


Figure 1. Structure and retrosynthetic analysis of tetrodotoxin.

In that respect, we perceive opportunity in an oxidative amidation of a phenol[10] as an early step toward **1**. To illustrate (Figure 1), the TTX forerunner **2**, where [CHO] indicates an expressed or latent formyl group and P a protecting group, could be made by bis-dihydroxylation of diene **3**, which results upon Wittig reaction of ketone **4**. The latter arises via the stereoselective installation of OH and latent CHO groups on dienone **5**, recognized as the product of oxidative amidation of phenolic ester **6**.[11]

Past efforts[12] demonstrated the elaboration of **5** to nitrile **11**, as shown in Scheme 1. Key steps in this sequence included a Torssell[13] cyclization of nitroketone *β*-**9** and a nucleophilic fragmentation of the resultant isoxazoline *β*-**10**.[14] Compounds *β*-**7**−*β*-**10** in Scheme 1 are so described to underscore the *β* configuration of the *tert*-butyldiphenylsilyloxy (TBDPSO) group. It subsequently transpired that it is advantageous to carry out this sequence with the *α*-epimers of **7**−**10**.[15] Moreover, the Torssell step was found to scale up poorly, complicating material throughput. Herein, we describe remedies to these problems, as well as the elaboration of the *α*-TBDPSO epimer of **11** to a diene of the type **3**. We stress that this work constituted a feasibility-level study, for which issues of enantioselectivity were of secondary importance. Accordingly, all experiments were carried out in the racemic series.[16]

Scheme 1. Previously Described Route[12] to Compound 11



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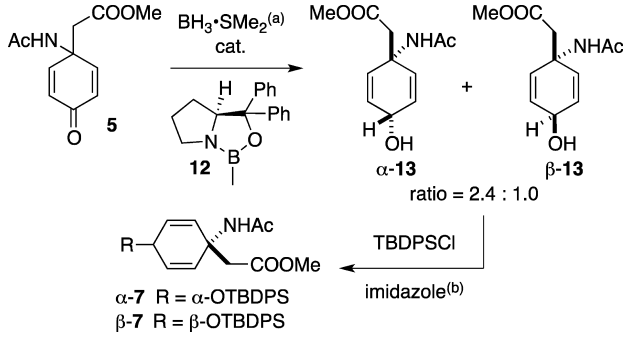
RESULTS AND DISCUSSION

The elaboration of **5** to a nitroketone requires prior reduction of the keto group.[17] Our previous route relied on a DIBAL reduction of **5** that preferentially yielded the alcohol *β*-**13** (Scheme 2).[18] Interestingly, a Corey–Bakshi–Shibata (CBS)[19]

Scheme 2. Reduction of Dienone 5 and Protection of the Resultant Alcohols[a]



[a]Reagents: (a) 1.0 equiv, 1 mol % of **12**, THF, 0 °C, 1 h, >95% yield of crude *α*- + *β*-**13**; (b) 1.0 equiv each, CH_2Cl_2, overnight, 85–90% yield.

reduction[20] preferentially afforded alcohol *α*-**13**,[21] albeit with weak selectivity.[22] While the reason for this stereochemical reversal is unclear, a hypothesis may be advanced as follows. Nucleophiles tend to undergo 1,2- or 1,4-addition to enones of the type **5** from the face of the *π* system *anti* to the heteroatomic group,[23] perhaps due to a Felkin–Anh-type effect[24] created by the electronegative heteroatom.[25] Thus, the stereochemical outcome of the CBS reduction is consonant with the anticipated facial preference of **5**, while the DIBAL reduction occurs with opposite selectivity. Perhaps, the latter reaction proceeds through a complex of the acetamide (or an anionic form thereof) with DIBAL, leading to *β*-**13** via intramolecular hydride delivery to the keto carbonyl (Figure 2).[26]

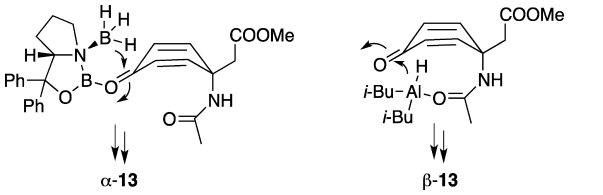
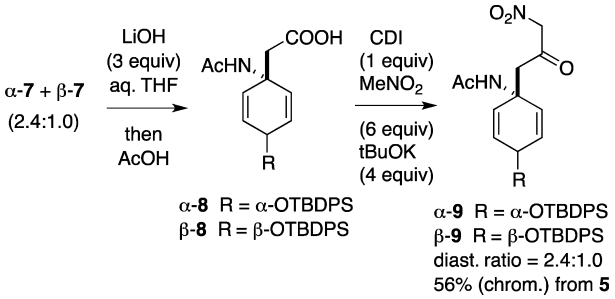


Figure 2. Hypothesis for the stereochemical course of the reduction of **5**.

The mixture of *α*- and *β*-**13** was advanced to the more stable *tert*-butyldiphenylsilyl (TBDPS) ethers[27] *α*- and *β*-**7** (Scheme 2), which were converted into nitroketones[28] *α*-**9** and *β*-**9** as described earlier.[12] It proved expedient to eschew purification of the various intermediates en route to the nitroketones. In this way, dienone **5** produced a 2.4:1 mixture of *α*-**9** (major) and *β*-**9**, in 56% overall yield after chromatography over four steps: CBS reduction, TBDPS protection, ester saponification,[29] and carbonyldiimidazole[30] (CDI)-mediated condensation of the resultant acids with $MeNO_2$[31] (Scheme 3).

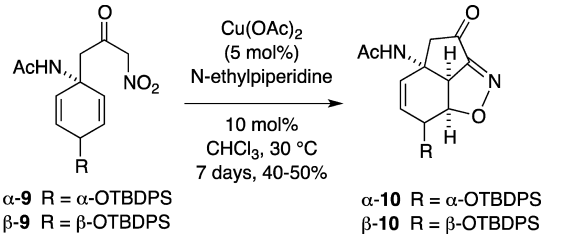
Unfortunately, the separation of *α* and *β* diastereomers at any stage of this sequence was difficult. Therefore, the crucial conversion of the nitroketones into isoxazolines *α*-**10** and *β*-**10**

Scheme 3. Preparation of Nitroketones 9



had to be carried out with a 2.4:1 mixture of *α*- and *β*-**9**. This step was challenging.[32] The Torssell cyclization[13] had performed adequately on a small scale,[12] but it proved unsuitable for processing grams of material. In a search for alternatives, we evaluated a Cu(II)-catalyzed process described by Machetti and DeSarlo,[33] a variant of which (5 mol % of $Cu(OAc)_2$,[34] 10 mol % of *N*-ethylpiperidine,[35] $CHCl_3$,[36] 30 °C,[37] 168 h) advanced the nitroketones to isoxazolines *α*-**10** and *β*-**10** in 40–50% yield (Scheme 4). A substrate

Scheme 4. Cu(II)-Catalyzed Formation of Isoxazolines 10 (Machetti–DeSarlo Reaction)



concentration of 0.2 M minimized byproduct formation, but attempts to accelerate the reaction by using more catalyst, *especially more base*, promoted formation of side products (cf. Scheme 5 for the nature of these). Isoxazoline *α*-**10** was purified to homogeneity, and no further work was done with *β*-**10**.

The Machetti–DeSarlo reaction performed consistently on a scale of up to 6 g of nitroketone; however, it was not free from difficulties. First, the yield of isoxazoline was moderate. Second, the reaction required an induction period of 15–20 h before the isoxazoline would begin to form. Third, the reaction failed to reach completion, unreacted nitroketone remaining even after 7 days. Fourth, it tended to stall, and addition of more catalyst to stalled reactions failed to revive them. Fifth, significant quantities of acids **8** accompanied the desired isoxazolines. The acids could only form by hydrolysis of the nitroketone through a process that would release nitromethane, but because reagents and solvents had been carefully dried, it seemed likely that the water required to cleave **9** was that liberated by the reaction itself.[38] Numerous small-scale reactions were thus carried out in $CDCl_3$ solutions (NMR tube),[39] with monitoring by ^1H NMR,[40] in order to garner a better understanding of the process. These experiments revealed that release of $MeNO_2$ (singlet at 4.33 ppm) began to occur after about 15–20 h, at about the same time that the isoxazoline was becoming apparent in the ^1H NMR spectrum. In an effort to contain/suppress $MeNO_2$ release, i.e., the formation of acids **8**, the effect of adding drying agents to the

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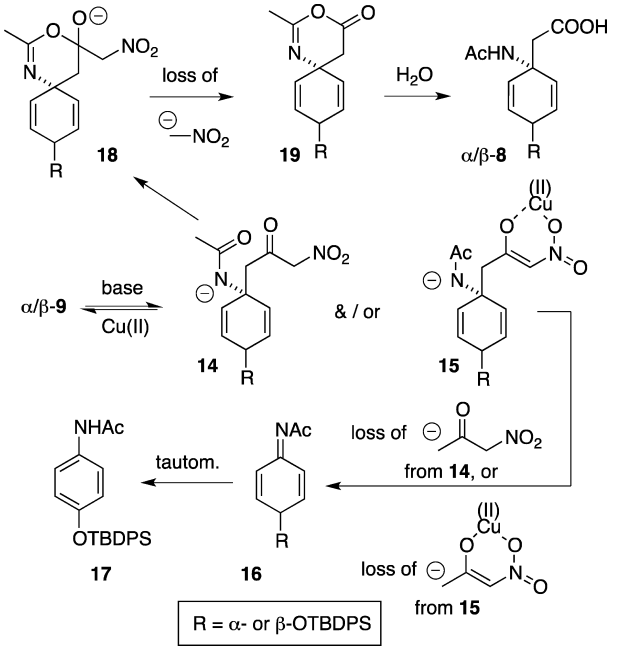
Scheme 5. Side Reactions Observed During the Cyclization of Nitroketones 9

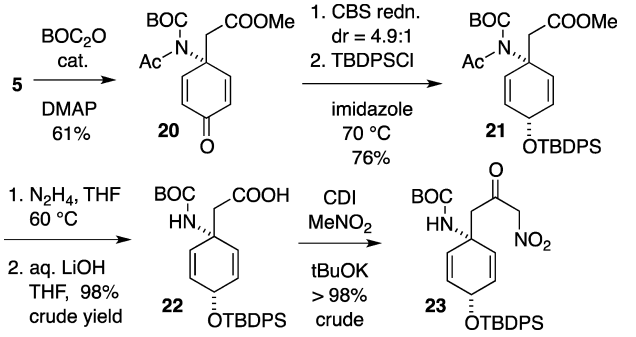


reaction mixture was examined. Molecular sieves inhibited isoxazoline formation. It seems likely that this was due to protonation of *N*-ethylpiperidine by the acidic molecular sieves, an event that would deny the reaction an essential basic agent. Powdered, anhydrous Na_2SO_4 had no effect, but $CaSO_4$ (powdered white Drierite activated by heating under vacuum) significantly diminished $MeNO_2$ formation, without fully suppressing it.[41] However, reactions run in the presence of $CaSO_4$ still tended to stall and could not be resurrected by the addition of more catalyst.

A byproduct detected during NMR monitoring of the reaction, compound **17**[42] (Scheme 5), and the observation that running the reaction at higher temperatures in the presence of $CaSO_4$ induced only a greater extent of formation of **17** without accelerating isoxazoline formation, provided a clue as to the source of the above problems. A sensible mechanism for the formation of **17** starts with reversible deprotonation of the AcNH group, either in the free nitroketone (cf. **14**) or in a Cu(II) chelate thereof (cf. **15**). Such events lead to the release of nitroacetone, a good ligand for Cu(II) that can sequester the metal and bring the catalytic cycle leading to the isoxazolines to a halt. Moreover, the O terminus of the anion of the acetamide could add to the keto carbonyl (cf. **14** → **18**), triggering release of $MeNO_2$ and formation of acids **8** upon hydrolysis of azalactones **19**. On such a basis, it seemed desirable to replace the *N*-acetyl with a less N−H acidifying and less O-nucleophilic BOC group.[43]

N-BOC-protected nitroketone **23** was thus prepared according to Scheme 6, several aspects of which deserve comment. First, the CBS reduction of **20** proceeded with improved selectivity relative to **5** (4.9:1 in favor of the *α* epimer vs 2.4:1). Second, the less polar *N*-BOC compounds were easier to handle and purify than their *N*-acetyl congeners. Finally, and in contrast to the *N*-acetyl series, the epimeric alcohols obtained upon CBS reduction of **20** could be easily separated at the stage of **21**: the latter crystallized from the mixture, enabling also a structural proof by X-ray diffractometry

Scheme 6. Preparation of *N*-BOC Substrate 23



(Figure 3). All subsequent work was therefore carried out with stereochemically homogeneous materials.

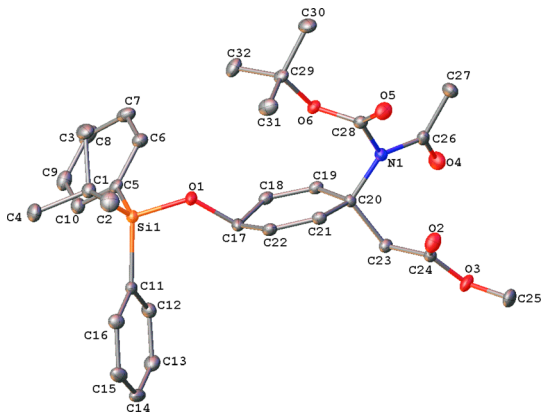
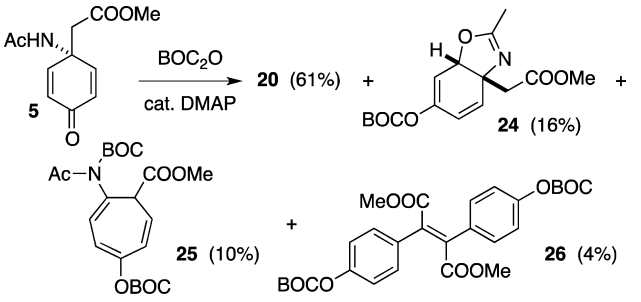


Figure 3. X-ray crystal structure of compound **21**.

It should also be noted that the step leading to **20** afforded byproducts **24**–**26** in 16%, 10%, and 4% yields, respectively (Scheme 7). The isolation of **24** underscores the notion

Scheme 7. Byproducts Formed in the Step Leading to 20



advanced in Scheme 5 that deprotonation of the acetamide is relatively facile and that such an event may be at the root of many undesirable side reactions. In fact, **24** arguably arose through Michael cyclization of the N anion of **5** at the O terminus and interception of the emerging enolate by BOC_2O. The formation of the noteworthy cycloheptatriene **25** indicates that deprotonation of the ester segment in **5** and/or **20** is also facile. Indeed, the work of Carreno and collaborators[44] supports the sequence of events depicted in Scheme 8 for the formation of **25**. Finally, compound **26** reflects the tendency of enolate **27** to eliminate the anion of *N*-BOC-acetamide, leading to quinone methide **29**. The genesis of **26** may be accounted for by

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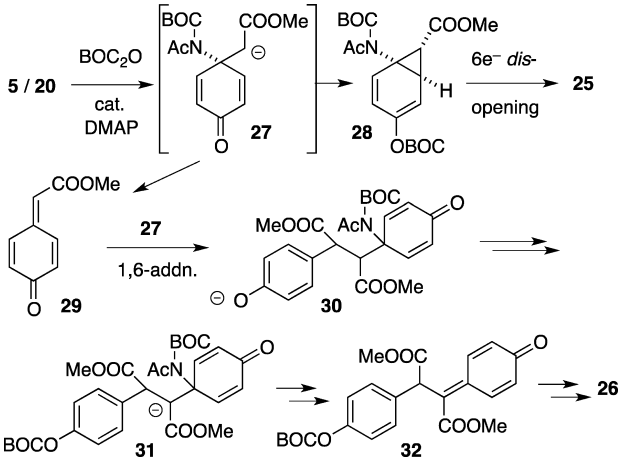
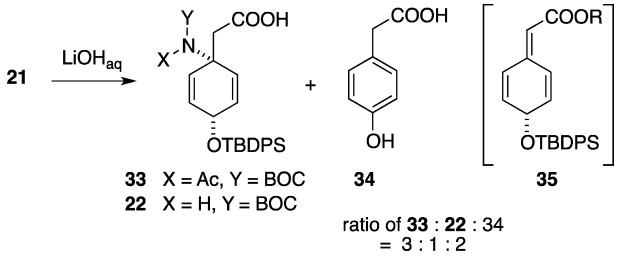
Scheme 8. Presumed Sequence of Events Leading to the Formation of Byproducts 25 and 26



invoking a 1,6-addition of **27** to **29** and evolution of the resultant **30** as per Scheme 8.

Elimination of *N*-BOC-acetamide seems responsible also for the formation of significant quantities of **34** (Scheme 9) during

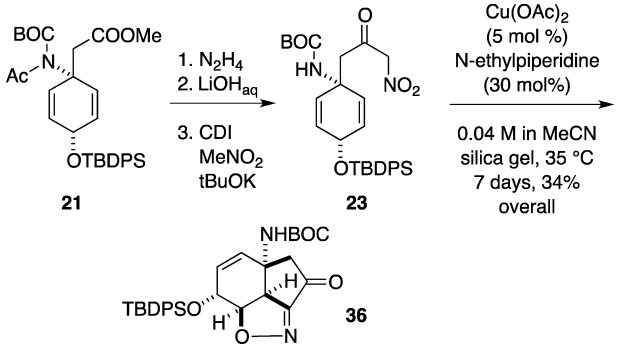
Scheme 9. Proposed Mechanism of Formation of 34 during Hydrolysis of 21



attempts to reach **22** by simultaneous ester saponification/*N*-deacetylation of **21** with aqueous LiOH. Compound **34** probably arose upon tautomerization of elimination product **35**, followed by release of the silyl group under basic conditions. It is this problem that mandated the *N*-deacetylation of **21** with $N_2H_4{\cdot}H_2O$ prior to basic hydrolysis (Scheme 6).

The behavior of *N*-BOC nitroketone **23** under the Machetti–DeSarlo conditions of Scheme 4 paralleled that of the *N*-acetyl congener. However, and in sharp contrast to the case of **9**, an increase in the amount of base (30 mol % of *N*-ethylpiperidine vs the original 10 mol %) accelerated the conversion of **23** into the desired isoxazoline with no significant increase in formation of the byproducts shown in Scheme 5. This it is consistent with the diminished N–H acidity and O nucleophilicity of the *N*-BOC compounds relative to *N*-Ac materials. As before, an increase in the amount of $Cu(OAc)_2$ (10 mol % vs 5 mol %) resulted only in the formation of more of the *N*-BOC analogue of compound **17**, while the addition of $CaSO_4$ diminished the extent of $MeNO_2$ release without affecting rates and yields. More beneficial was the use of MeCN as a solvent in lieu of $CHCl_3$, a modification that induced the reaction to proceed to completion. Finally, the addition of silica gel to the reaction medium and—more importantly—the conduct of the reaction in more dilute solutions (0.04 M) produced the best results. Just as seen earlier in the *N*-acetyl series, compound **21** was reproducibly advanced to isoxazoline **36** in 34% overall yield (after chromatography) over a four-step sequence encompassing N-deacetylation, ester saponification, nitroketone synthesis, and Cu(II)-catalyzed cyclization (76% average yield per step), without purification of intermediate products (Scheme 10). Chromatography of the final **36** also

Scheme 10. Preparation of Compound 36 in Four Steps from 21 without Intermediate Purification



returned quantities of acid **22** (typically 25–30% yield based on **21**), which was conveniently recycled into the sequence. However, we emphasize that the stated yield of **36** refers to the actual yield of the process outlined in Scheme 10, and it is not based on recovered or recycled **22**.

The previously described[12] nucleophilic isoxazoline fragmentation (Li_2CO_3/MeOH)[45] advanced *α*-**10** to **37** (the structure of which had been confirmed earlier by X-ray diffractometry; Figure 4)[46] in 98% yield after chromatography (Scheme 11).

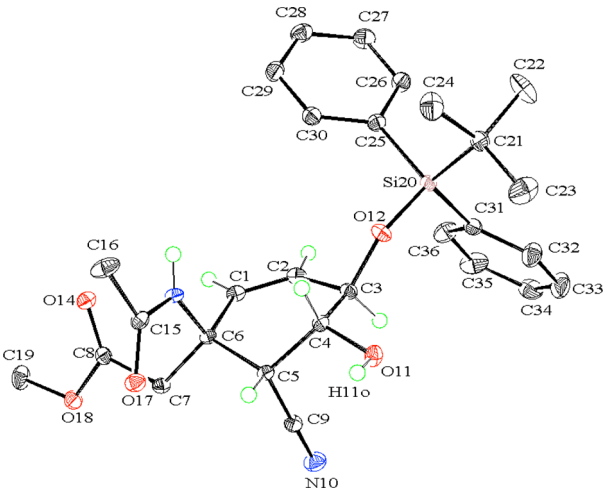


Figure 4. X-ray crystal structure of compound **37**.[46]

The fragmentation of **36** occurred as efficiently to afford **38**, which was free from contaminants (NMR) and therefore required no further purification.[47]

The quantities of acetamido intermediates accumulated in the course of these investigations served to explore one more transformation: the elaboration of **37** into a diene of the type **3**.[48] This effort started with the protection of the free OH group as a BOM derivative[49] in preparation for release of the TBDPS group, oxidation to a ketone, and a Wittig reaction (Scheme 12). Desilylation of **32** and Parikh–Doering oxidation[50] of the resultant alcohol afforded ketone **40**,[51]

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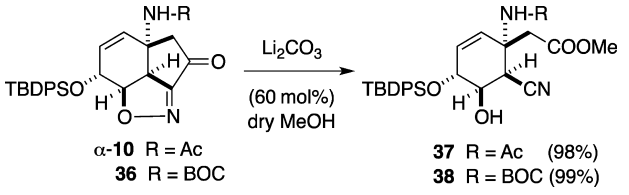
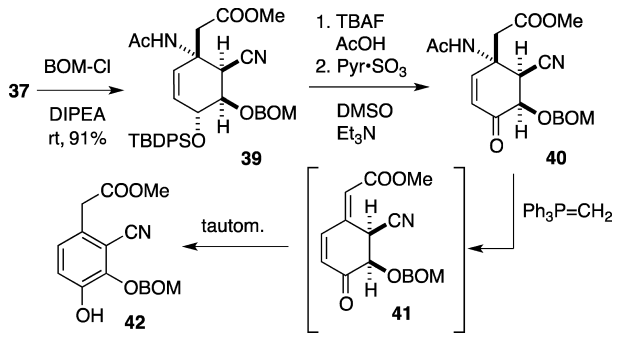
Scheme 11. Nucleophilic Fragmentation of Isoxazolines α-10 and 36

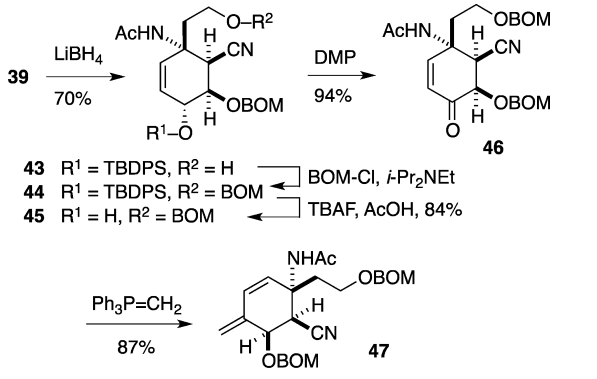


Scheme 12. Aromatization of Ketone 63 under Wittig Conditions



contact of which with $Ph_3P{=}CH_2$ at −78 °C triggered rapid aromatization to **42**.[52] Previous observations (Schemes 8 and 9) suggested that suppression of the ester functionality would resolve the problem. Therefore, the ester was selectively reduced ($LiBH_4$)[53] and the resultant primary alcohol was blocked with a second BOM group (Scheme 13). Release of the

Scheme 13. Preparation of Diene 47



TBDPS group in **44** was best achieved with TBAF buffered with acetic acid,[54] while Dess–Martin periodinane (DMP) was the reagent of choice for the oxidation of **45** to ketone **46**, which, to our relief, underwent smooth Wittig olefination to furnish diene **47** in 87% yield.

CONCLUSION

The elaboration of **5** to isoxazoline **36** under the modified Machetti–DeSarlo conditions detailed above alleviated material throughput issues that affected the original route to **11**. An avenue to diene **47** is also described. Observations recorded in the course of this research are key to the success of ongoing synthetic efforts toward the natural product.

EXPERIMENTAL SECTION

Experimental Protocols. Unless otherwise indicated, ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were obtained from $CDCl_3$ solutions at room temperature. Chemical shifts are reported in parts per million (ppm) on the δ scale, coupling constants, J, in hertz (Hz), and multiplicities as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), m (multiplet), c (complex), br (broad), ABq (AB quartet), and app (apparent). Infrared (IR) spectra (cm^{-1}) were recorded from thin films deposited on NaCl plates. Mass spectra (m/z) were obtained in the electrospray (ESI) or atmospheric pressure chemical ionization (APCI) modes on a time-of-flight mass spectrometer equipped with an electrospray ion source. Melting points (uncorrected) were measured on a Mel-Temp apparatus. Commercial reagents and solvents were used without further purification except for THF (freshly distilled from Na/benzophenone under N_2), CH_2Cl_2 (freshly distilled from CaH_2 under N_2), $CHCl_3$ (washed with H_2O, treated with solid K_2CO_3, freshly distilled from Na_2SO_4 under Ar), MeOH (freshly distilled from Mg/I_2 under Ar), 1,2-dichloroethane and acetone (freshly distilled from $CaSO_4$ under Ar), and i-Pr_2NEt and MeCN (distilled from CaH_2 under Ar). Commercial n-BuLi was titrated against $Ph_2CHCOOH$.[55] Flash chromatography was performed on Silicycle 230–400 mesh silica gel. All reactions were performed under an Ar atmosphere in oven-dried flasks fitted with rubber septa for the introduction of substrates/reagents/solvents via syringe and equipped with Teflon stirring bars.

Preparation of α-9 without Purification of the Various Intermediates. Commercial $BH_3{\cdot}SMe_2$ (~10 M solution, 2.7 mL, 27 mmol, 1.0 equiv) was *carefully* added dropwise, via syringe, to a rapidly stirred solution of **5** (6.0 g, 27 mmol, 1.0 equiv) and (*S*)-CBS catalyst (0.075 g, 0.27 mmol, 0.01 equiv) in dry THF (135 mL) maintained under Ar in a 500 mL round-bottom flask immersed in an ice bath. The mixture was stirred for 45 min, during which time it was warmed to room temperature; then it was cooled back to 0 °C, the flask was opened, and MeOH (3.3 mL, 81 mmol, 3.0 equiv) was *carefully* added dropwise via syringe at 0 °C (*Caution!* H_2 evolution). The solution was warmed to room temperature, and the solvent was removed under reduced pressure. The residue of crude α-**13** (major component of a 2.4/1 mixture with β-**13**) was dried under high vacuum, and then it was taken up in dry CH_2Cl_2 (100 mL); to this solution were added imidazole (1.83 g, 27 mmol, 1.0 equiv) and TBDPSCl (7.0 mL, 27 mmol, 1.0 equiv). The mixture was stirred for 12 h (overnight) at room temperature under Ar, and then 0.05 N HCl (100 mL) was added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The extracts were combined, dried (Na_2SO_4), filtered, and concentrated. The residue of crude α-**7** (major component of a 2.4:1 mixture with β-**7**) was dissolved in THF (100 mL) and treated with H_2O (100 mL) and $LiOH{\cdot}H_2O$ (3.4 g, 81 mmol, 3.0 equiv). The solution was stirred for 1.5 h at room temperature, and then most of the THF was removed by rotary evaporation. Diethyl ether (100 mL) was added to the aqueous suspension, and the layers were separated to remove organic byproducts from previous steps (the desired carboxylic acids were dissolved in the aqueous layer as the Li carboxylates). The aqueous layer was acidified with 50% aqueous AcOH (30 mL) and extracted with EtOAc (3 × 100 mL, check pH of aqueous layer). The combined extracts were dried (Na_2SO_4), filtered, and concentrated. The residue was resuspended in toluene, and the resulting mixture was again concentrated (rotary evaporation) to remove AcOH. Coevaporation with toluene was repeated three to four times until all AcOH had been removed. The residue of crude α-**8** (major component of a 2.4:1 mixture with β-**8**) was taken up in dry THF (70 mL) and treated with CDI (4.36 g, 27 mmol, 1.0 equiv). The solution was stirred at room temperature under Ar for 1 h, and then $MeNO_2$ (8.5 mL, 0.16 mol, 6.0 equiv) and t-BuOK (12.0 g, 0.11 mol, 4.0 equiv) were added at room temperature and the resulting mixture was stirred at room temperature for 2 h. Aqueous 50% AcOH (30 mL) was added, and the volatiles were removed under reduced pressure. The residue was partitioned between H_2O (70 mL) and CH_2Cl_2 (100 mL), the layers were separated, and the aqueous phase was extracted with more CH_2Cl_2 (2 × 100 mL). The combined extracts were dried

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(Na_2SO_4), filtered, and concentrated, and the residue was purified by gradient column chromatography (1/1−7:/3 EtOAc/hexanes) to furnish nitroketone α-**9** (7.9 g, 16 mmol, 56% over four steps), light yellow oil, as the major component of a 2.4/1 mixture with diastereomer β-**9**. Data for α-**9** are as follows ^{1}H NMR (acetone-d_6): 7.75−7.72 (m, 4H); 7.53−7.37 (m, 6H); 6.20−6.14 (m, 2H); 5.88−5.82 (m, 2H); 5.57 (s, 2H); 4.61−4.59 (m, 1H); 3.22 (s, 2H); 1.88 (s, 3H); 1.07 (s, 9H). Signals arising from diastereomer **9**[12] were apparent at 5.67 (s, 2H), 3.30 (s, 2H), 1.78 (s, 3H), and shoulder at 1.07 (s, 9H). ^{13}C NMR (acetone-d_6): 195.3, 170.8, 136.6, 134.5, 130.9, 130.2, 129.7, 128.8, 85.1, 64.4, 52.6, 48.4, 27.4, 23.7, 19.8. Signals arising from diastereomer **9**[12] were apparent at 195.5, 170.4, 130.8, 128.7, 52.2, 48.7, 27.3, 23.5, and 19.7. IR: 1736, 1700, 1656, 1558. MS: 515 [M + Na]$^+$; negative mode: 491 [M − H]$^-$. HRMS: calcd for $C_{27}H_{32}N_2O_5SiNa$ [M + Na]$^+$ 515.1978; found 515.1962.

Preparation of α-10. A solution of α-**9** (major component of a 2.4/1 mixture with diastereomer β-**9**; 226 mg, 459 μmol, 1 equiv), $Cu(OAc)_2{\cdot}H_2O$ (5 mg, 25 μmol, 5.4 mol %), and *N*-ethylpiperidine (8 μL, 6.7 mg, 59 μmol, 13 mol %) in dry $CHCl_3$ (3 mL) was stirred at 30 °C (oil bath temperature) under Ar for 7 days, and then it was concentrated. The residue was dissolved in EtOAc (10 mL) and washed three times with 0.01 M aqueous HCl solution (5 mL). The organic phase was rinsed with brine, dried (Na_2SO_4), and evaporated, and the residue was purified by flash column chromatography on silica gel (50% EtOAc in hexanes) to give pure α-**10** (60 mg, 27%, white powder, mp 74−75 °C), plus a fraction containing α-**10** and β-**10** (12 mg, 6%), and pure isoxazoline β-**10**[12] (30 mg, 14%), for an overall 47% yield of isoxazolines. ^{1}H NMR: 7.71−7.60 (m, 4H); 7.53−7.37 (m, 6H); 6.18 (dd, *J* = 9.96, 5.94, 1H); 5.6 (d, *J* = 9.96, 1H); 5.75 (br, 1H); 5.05 (app s, 2H); 4.24 (d, *J* = 5.94, 1H); 4.06 (d, *J* = 18.4, 1H); 2.97 (d, *J* = 18.4, 1H); 1.95 (s, 3H); 1.10 (s, 9H). ^{13}C NMR: 191.4, 170.8, 161.7, 135.8, 135.6, 135.5, 134.9, 133.4, 132.6, 132.4, 130.5, 130.4, 128.1, 128.0, 85.1, 63.2, 54.2, 52.3, 27.0, 24.0, 19.1. IR: 3289, 1747, 1651, 1596, 1530. MS: 475 [M + H]$^+$. HRMS: calcd for $C_{27}H_{31}N_2O_4Si$ [M + H]$^+$ 475.2053; found 475.2059.

Larger Scale Preparation of α-10 Contaminated with Acids α- and β-8. A solution of α-**9** (major component of a 2.4/1 mixture with diastereomer β-**9**; 3.5 g, 7.1 mmol, 1.0 equiv), $Cu(OAc)_2{\cdot}H_2O$ (0.072 g, 0.36 mmol, 0.05 equiv), and *N*-ethylpiperidine (0.10 mL, 0.71 mmol, 0.10 equiv) in dry $CHCl_3$ (25 mL) was stirred at 30 °C (oil bath temperature) under Ar for 168 h, and then it was concentrated. The residue was dissolved in a minimal volume of EtOAc and filtered through a short plug of silica gel, rinsing with more EtOAc. The solvent was evaporated, and the residue was purified by flash column chromatography on silica gel (EtOAc/Et_2O 1/4) to give α-**10** as the major component of a 5/1 mixture with acids α- and β-**8**. The mass of this material amounted to 2.0 g of a pale yellow foam, which therefore consisted of 84% (mass-wise) of α-**10** and 16% of acids, making the yield of oxazoline equal to 1.68 g, 3.5 mmol, 49%.

Preparation of 20. Solid DMAP (82 mg, 0.67 mmol, 0.04 equiv) and solid Boc_2O (6.6 g, 30.3 mmol, 1.8 equiv) were added to a solution of **5** (3.75 g, 16.8 mmol, 1.0 equiv) in THF (100 mL). The mixture was stirred under Ar at room temperature for 48 h, and then it was concentrated under vacuum. The residue was dissolved in EtOAc (50 mL), and the resulting solution was washed with 0.02 M HCl solution (2 × 30 mL), DI water (10 mL), and brine (10 mL), and then dried (Na_2SO_4) and concentrated. The residue was purified with gradient chromatography (3/7−1/1−7/3 EtOAc/hexanes) to afford, in order of elution: **25** (0.72 g, 1.7 mmol, 10%; R_f = 0.50 in 3/7 EtOAc/hexanes) as a pale yellow oil; **26** (0.17 g, 0.3 mmol, 4%; R_f = 0.34 in 3:7 EtOAc/hexanes) as white plates, mp 171 °C (dec); the desired **20** (3.20 g, 9.9 mmol, 61%; R_f = 0.24 in 3/7 EtOAc/hexanes) as a pale yellow oil; **24** (0.88 g, 2.7 mmol, 16%; R_f = 0.52 in EtOAc) as a reddish oil.

Data for compound **20** are as follows. ^{1}H NMR: 7.26 (d, *J* = 10.2 Hz, 2H); 6.24 (d, *J* = 10.2 Hz, 2H); 3.66 (s, 3H); 3.22 (s, 2H); 2.28 (s, 3H); 1.46 (s, 9H). ^{13}C NMR: 184.6, 172.2, 169.0, 152.7, 148.4, 128.0, 85.2, 58.7, 52.0, 42.5, 27.5, 26.3. IR: 1740, 1690, 1670, 1631. MS: 346 [M + Na]$^+$. HRMS: calcd for $C_{16}H_{21}NO_6Na$ [M + Na]$^+$ 346.1267; found 346.1265.

Data for compound **24** are as follows. ^{1}H NMR: 5.85 (d, *J* = 9.8 Hz, 1H); 5.77 (dd, *J* = 10.2 Hz, 1.9 Hz, 1H); 5.67 (app d, *J* = 5.1 Hz, 1H); 5.77 (d, *J* = 5.1 Hz, 1H); 3.64 (s, 3H); 2.79, 2.64 (ABq, J_{AB} = 14.9 Hz, 2H); 1.96(s, 3H); 1.49 (s, 9H). ^{13}C NMR: 170.0, 166.1, 150.8, 148.1, 132.4, 120.8, 106.3, 84.0, 80.4, 69.0, 52.0, 45.5, 27.8, 14.1. IR: 1754, 1739, 1662. MS: 346 [M + Na]$^+$. HRMS: calcd for $C_{16}H_{22}NO_6$ [M + H]$^+$ 324.1447; found 324.1453.

Data for compound **25** are as follows. ^{1}H NMR: 6.36 (dd, *J* = 7.0 Hz, 1.2 Hz, 1H); 6.21 (app d, *J* = 9.7 Hz, 1H); 6.05 (d, *J* = 7.0 Hz, 1H); 5.63 (dd, *J* = 9.7 Hz, 6.7 Hz, 1H); 3.69 (s, 3H); 3.28 (d, *J* = 6.7 Hz, 1H); 2.47 (s, 3H); 1.51(s, 9H); 1.43 (s, 9H). ^{13}C NMR: 173.3, 170.9, 152.3, 151.5, 151.3, 124.2, 123.9, 122.8, 122.3, 117.2, 83.8, 83.7, 52.3, 47.8, 27.9, 27.7, 26.1. IR: 1739, 1708 (shoulder). MS: 446 [M + Na]$^+$. HRMS: calcd for $C_{21}H_{29}NO_8Na$ [M + Na]$^+$ 446.1791; found 446.1793.

Data for compound **26** are as follows. ^{1}H NMR: 7.10, 7.03 (app AB q, J_{AB} = 8.8 Hz, 8H); 3.82 (s, 6H); 1.54 (s, 18H). ^{13}C NMR: 168.2, 151.5, 151.2, 138.2, 131.5, 131.0, 121.2, 83.9, 52.9, 27.8. IR: 1752, 1718. MS: 551 [M + Na]$^+$. HRMS: calcd for $C_{28}H_{32}O_{10}Na$ [M + Na]$^+$ 551.1893; found 551.1888.

Preparation of 21. Commercial $BH_3{\cdot}SMe_2$ complex (1.0 mL, 10.0 mmol, 1.0 equiv) was carefully syringed over 5 min into a cold (0 °C) solution of **20** (3.20 g, 9.9 mmol, 1.0 equiv) and (S)-CBS catalyst (28 mg, 0.1 mmol, 0.01 equiv) in THF (74 mL), with good stirring under Ar. The ice bath cooling the mixture was removed, and stirring was continued for an additional 50 min. The reaction was quenched by careful dropwise addition of MeOH (1.5 mL, 37 mmol, 3.7 equiv) (*Caution!* H_2 evolution). When gas evolution stopped, more MeOH (10 mL) was added and stirring was continued for another 15 min. The solution was concentrated, the residue was redissolved in MeOH (15 mL), and the solution was again concentrated to dryness. The latter operation was repeated once to ensure complete decomposition of organoboron species. The residue was then filtered through a short silica gel plug with 50% EtOAc/hexanes until no product (R_f = 0.13 in 30% EtOAc/hexanes) was observed in the eluate by TLC. The filtrate was concentrated to dryness under vacuum, and the residue was azeotroped with toluene (15 mL) and then dried under high vacuum to constant mass (3.0 g). The crude reduction product was dissolved in dry DMF (20 mL) and treated with imidazole (1.30 g, 19.1 mmol, 1.9 equiv) and TBDPSCl (2.9 mL, 10.0 mmol, 1.0 equiv). The reaction flask was then immersed into an oil bath maintained at 70 °C and the solution stirred for 24 h. The mixture was then cooled to room temperature, and most of the DMF was removed under vacuum. The residue was taken up in EtOAc (60 mL), and the solution was successively washed with 0.02 M HCl solution (3 × 30 mL), DI water (15 mL), and brine (15 mL), dried (Na_2SO_4), and concentrated. The residue was redissolved in MeOH (15 mL), and the solution was again concentrated to dryness. The latter operation was repeated once to ensure complete removal of volatiles. The residue thus obtained was dissolved in refluxing MeOH (15 mL) and the hot solution was allowed to stand overnight, whereupon **21** crystallized as transparent prisms. This solid was filtered and rinsed with cold MeOH (2 × 5 mL) and then recrystallized again from MeOH (10 mL) to afford pure **21** (2.82 g, 5.0 mmol, 51%) as white prisms, mp 94−95 °C. The combined mother liquors from such recrystallizations were concentrated and the residue was subjected to gradient chromatography (1/9−1/4 EtOAc/hexanes) to obtain more **21** (0.45 g, 0.8 mmol, 8%; R_f = 0.38 in 1/4 EtOAc/hexanes), its β epimer (0.44 g, 0.8 mmol, 8%; R_f = 0.31 in 1:4 EtOAc/hexanes) as a pale yellow oil, and a mixture of the two (0.56 g, 1.0 mmol, 10%; containing 48% of **21**). In summary, a 76% yield of both diastereomers was obtained with a 4.9/1 diastereomeric ratio.

Data for compound **21** are as follows. ^{1}H NMR: 7.71−7.67 (m, 4H); 7.46−7.36 (m, 6H); 6.16 (dd, *J* = 10.3 Hz, 1.8 Hz, 2H); 5.81 (dd, *J* = 10.3 Hz, 2.9 Hz, 2H); 4.46−4.42 (m, 1H); 3.53 (s, 3H); 3.08 (s, 2H); 2.16 (s, 3H); 1.53 (s, 9H); 1.07 (s, 9H). ^{13}C NMR: 170.5, 170.1, 153.9, 134.0, 133.7, 130.0, 129.5, 128.0, 127.9, 84.5, 63.1, 57.3, 51.6, 44.0, 27.6, 27.0, 25.2, 19.3. IR: 1741, 1682. MS: 586 [M + Na]$^+$. HRMS: calcd for $C_{32}H_{41}NO_6NaSi$ [M + Na]$^+$ 586.2601; found 586.2600.

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Data for the β-epimer of **21** are as follows: mp 82−84 °C (MeOH). ^{1}H NMR: 7.71−7.66 (m, 4H); 7.44−7.35 (m, 6H); 6.20 (dd, J = 10.3 Hz, 2.1 Hz, 2H); 5.89 (dd, J = 10.3 Hz, 2.7 Hz, 2H), 4.58−4.53 (m, 1H); 3.67 (s, 3H); 3.19 (s, 2H); 2.04 (s, 3H); 1.29 (s, 9H); 1.07 (s, 9H). ^{13}C NMR: 170.4, 169.8, 153.6, 136.0, 133.9, 132.3, 129.9, 128.4, 127.9, 84.1, 63.8, 57.1, 51.8, 43.1, 27.4, 27.1, 24.9, 19.3. IR: 1741, 1682. MS: 586 [M + Na]$^+$. HRMS: calcd for $C_{32}H_{41}NO_6SiNa$ [M + Na]$^+$ 586.2601; found 586.2598.

Preparation of 36 without Purification of Intermediates. Hydrazine hydrate (225 μL, 4.4 mmol, 1.7 equiv) was added (syringe) to a suspension of **21** (1.47 g, 2.61 mmol, 1.0 equiv) in THF (26 mL) maintained under Ar in a heavy-walled glass tube fitted with a screw-cap container. The mixture was heated to 60 °C and stirred for 24 h, and then it was cooled to room temperature and concentrated in vacuo and the residue was filtered through a short silica gel plug (10 mL) with 1/1 EtOAc/hexanes until no deacetylated product (R_f = 0.72 in 3/7 EtOAc/hexanes) eluted. The filtrate was concentrated to dryness, and the residual light yellow oil was dissolved in THF (14 mL). Deionized water (14 mL) was added with good stirring, followed by solid LiOH·H_2O (332 mg, 7.90 mmol, 3.0 equiv, added in one portion). The resulting suspension became a clear monophasic solution within 4 h. Stirring was continued for another 1 h until all starting ester had been consumed, and then the mixture was cooled in an ice bath and acidified with 0.4 M HCl solution (20 mL, 8.0 mmol, 3.1 equiv), added slowly with vigorous stirring. The acidic solution was extracted with EtOAc (2 × 35 mL), and the combined extracts were washed with DI water (20 mL) and brine (20 mL) and then dried (Na_2SO_4) and concentrated. The residue of crude **22** was dissolved in THF (17 mL) and treated with carbonyldiimidazole (467 mg, 2.88 mmol, 1.1 equiv). After 3 h, to the mixture were added $MeNO_2$ (840 μL, 15.6 mmol, 6.0 equiv) and t-BuOK (1.17 g, 10.4 mmol, 4.0 equiv), and then the reaction flask was immersed in an oil bath maintained at 40 °C for 30 min. The mixture was cooled to room temperature and quenched by adding 1/9 HOAc/H_2O (20 mL) solution, and then it was extracted with CH_2Cl_2 (30 mL, 2 × 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Complete removal of AcOH was achieved by azeotroping with toluene (3 × 10 mL). The residue was filtered through a short silica gel plug (10 mL) with 1/1 EtOAc/hexanes (removal of imidazonium salts) until no more **23** (R_f = 0.46 in 3/7 EtOAc/hexanes, streak) eluted. Concentration of the filtrate afforded crude **23**,[56] which was dissolved in freshly distilled MeCN (64 mL) containing $Cu(OAc)_2$·H_2O (25 mg, 0.13 mmol, 0.05 equiv), silica gel (14 mg), and N-ethylpiperidine (105 μL, 0.76 mmol, 0.3 equiv). The resulting suspension was stirred (Ar) at 35 °C (oil bath) for 168 h, whereupon TLC indicated complete consumption of **23**. The mixture was concentrated under vacuum, the residue was dissolved in EtOAc (70 mL), and the solution was washed with 0.02 M HCl (3 × 20 mL) and brine (20 mL), dried (Na_2SO_4), filtered, and concentrated. Purification of the residue by flash chromatography (1/9−1/4 EtOAc/hexanes) furnished **36** as an off-white foam (470 mg, 0.88 mmol, 34%; R_f = 0.56 in 3/7 EtOAc/hexanes). Further elution with with 1/1 EtOAc/hexanes returned acid **22** (340 mg, 0.67 mmol, 26%; R_f = 0.37 in 7/3 EtOAc/hexanes, streak), mp 157−158 °C (CH_2Cl_2),[57] which was conveniently recycled.

Data for **36** are as follows. ^{1}H NMR: 7.70−7.61 (m, 4H); 7.52−7.38 (m, 6H); 6.15 (dd, J = 9.9 Hz, 6.0 Hz, 1H); 5.81 (dd, J = 9.9 Hz, 1.0 Hz, 1H); 5.09−5.02 (m, 2H); 4.83 (d, J = 11.1 Hz, 1H); 4.17 (dd, J = 6.0 Hz, 2.0 Hz, 1H); 3.91, 3.40 (ABq, J_{AB} = 18.5 Hz, 2H); 1.45 (s, 9H); 1.09 (s, 9H). ^{13}C NMR: 191.5, 161.7, 155.01, 135.8, 135.7, 134.7, 134.5, 132.6, 132.5, 130.6, 130.4, 128.2, 128.1, 85.1, 80.7, 62.9, 55.4, 54.7, 52.0, 28.4, 27.1, 19.1. IR: 1747, 1711. MS: 555 [M+Na]$^+$, 587 [M + MeOH + Na]$^+$. HRMS: calcd for $C_{30}H_{36}N_2O_5NaSi$ [M + Na]$^+$ 555.2291; found 555.2300.

Preparation of 37. A solution of α-**10** (major component of a 5/1 mixture with acids **8**, 1.50 g, corresponding to 1.26 g of α-**10**, 2.65 mmol, 1.0 equiv) and Li_2CO_3 (117 mg, 1.58 mmol, 0.6 equiv) in dry MeOH (63.0 mL; freshly distilled from Mg turnings) was stirred under argon at room temperature for 1.5 h, and then the solvent was removed under vacuum. The residue was purified by flash chromatography (EtOAc/hexanes 1/1) to give **37** (1.32 g, 2.60 mmol, 98%) as an off-white solid, mp 166−168 °C.

Data for **37** are as follows. ^{1}H NMR: 7.72−7.68 (m, 4H); 7.50−7.39 (m, 6H); 5.84 (br d, J = 10.29, 1H); 5.76 (br s, 1H); 5.72 (dd, J = 10.2, 2.6, 1H); 4.45−4.41 (m, 1H); 4.35 (d, J = 3.12, 1H); 4.07−4.03 (m, 1H); 3.67 (s, 3H); 3.45 (d, J = 16.08, 1 H); 2.87 (d, J = 16.08, 1 H); 1.98 (s, 3H); 1.10 (s, 9H). ^{13}C NMR: 170.6, 170.3, 135.9, 135.7, 133.1, 132.0, 130.2, 130.2, 128.0, 127.9, 127.8, 117.4, 71.6, 70.2, 55.1, 51.9, 39.17, 38.7, 26.9, 24.1, 19.2. IR: 3370, 3304, 2252, 1720, 1641. MS: 529 [M + Na]$^+$. HRMS: calcd for $C_{28}H_{34}N_2O_5SiNa$ [M + Na]$^+$ 529.2135; found 529.2122.

Preparation of 38. Solid Li_2CO_3 (5 mg, 0.07 mmol, 0.5 equiv) was added to a solution of **36** (72 mg, 0.14 mmol, 1.0 equiv, dried to constant weight under high vacuum and then stored in a desiccator overnight) in dry MeOH (2.5 mL). The suspension was stirred under Ar for 1 h, and then it was diluted with CH_2Cl_2 (2.5 mL), filtered through Celite with more CH_2Cl_2 (10 mL), and concentrated in vacuo. Compound **38** (76 mg, 0.13 mmol, 99%; R_f = 0.46 in 3/7 EtOAc/hexanes) was obtained as an off-white foam. The NMR spectra of this material reveal the presence of no impurities; consequently, no further purification was carried out.

Data for **38** are as follows. ^{1}H NMR: 7.73−7.69 (m, 4H); 7.48−7.38 (m, 6H); 5.85 (d, J = 10.3 Hz, 1H); 5.68 (dd, J = 10.2 Hz, 2.4 Hz, 1H); 4.77 (br, 1H); 4.46 (dd, J = 4.8, 2.0, 1H); 4.13−4.09 (m, 2H); 3.67 (s, 3H); 3.39, 2.82 (ABq, J_{AB} = 15.4 Hz, 2H); 2.14 (d, J = 3.5, 1H) ; 1.45 (s, 9H); 1.10 (s, 9H). ^{13}C NMR: 170.4, 153.9, 136.4, 135.8, 133.3, 133.3, 132.1, 130.4, 130.3, 128.2, 128.1, 127.9, 117.53, 80.8, 72.2, 70.2, 54.8, 51.9, 40.00, 39.8, 28.4, 27.1, 19.4. IR: 3418, 2246, 1721 (broad). MS: 571 [M + Li]$^+$. HRMS: calcd for $C_{31}H_{40}N_2O_6NaSi$ [M + Na]$^+$ 587.2553; found 587.2551.

Preparation of 39. A solution of **37** (0.303 g, 0.60 mmol, 1.0 equiv), BOMCl (0.12 mL, 0.90 mmol, 1.5 equiv), and DIPEA (0.19 mL, 1.08 mmol, 1.8 equiv) in 1,2-dichloroethane (3.0 mL) was stirred at 75 °C under Ar for 48 h, and then it was cooled to room temperature, diluted with CH_2Cl_2 (40 mL), and partitioned between saturated aqueous NH_4Cl solution (50 mL). The organic layer was separated, and the aqueous phase was extracted with more CH_2Cl_2 (2 × 30 mL). The combined extracts were washed with H_2O (150 mL), dried (Na_2SO_4), and concentrated under vacuum, and the residue was purified by column chromatography on silica gel (Et_2O/hexanes 7/3) to give **39** (0.341 g, 0.55 mmol, 91%) as a colorless oil.

Data for **39** are as follows. ^{1}H NMR: 7.73−7.69 (m, 4H); 7.48−7.30 (m, 11H); 6.27 (br s, 1H); 5.77 (d, J = 10.32, 1H); 5.56 (dd, J = 10.32, 3.42, 1H); 4.74−4.67 (m, 4H); 4.53−4.49 (m, 1H); 4.46−4.43 (m, 1H); 4.16−4.13 (m, 1H); 3.68 (s, 3H); 3.28 (d, J = 15.63, 1H); 2.94 (d, J = 15.63, 1H); 1.99 (s, 3H); 1.10 (s, 9H). ^{13}C NMR: 170.8, 170.2, 137.3, 136.0, 135.88, 133.6, 133.0, 130.4, 130.1, 130.0, 129.0, 128.5, 128.0, 127.9, 127.8, 127.8, 118.1, 94.5, 77.5, 76.4, 69.9, 68.2, 54.7, 54.5, 51.9, 40.0, 36.7, 30.4, 27.0, 24.0, 19.3. IR: 3291, 2247, 1737, 1665. MS: 649 [M + Na]$^+$. HRMS: calcd for $C_{36}H_{42}N_2O_6SiNa$ [M + Na]$^+$ 649.2710; found 649.2710.

Preparation of 43. Solid $LiBH_4$ (0.079 g, 3.6 mmol, 10.0 equiv) was added to a dry THF (3.0 mL) solution of **39** (0.227, 0.36 mmol, 1.0 equiv). The mixture was stirred at room temperature under Ar for 24 h, and then it was cooled to 0 °C and saturated aqueous NH_4Cl solution (2.0 mL) was carefully added (*Caution!* H_2 evolution). The solution was stirred at room temperature for a further 30 min, and then it was diluted with EtOAc (20 mL). The layers were separated, and the aqueous phase was extracted with more EtOAc (2 × 20 mL). The combined extracts were dried (Na_2SO_4) and concentrated under vacuum, and the residue was purified by column chromatography on silica gel (100% EtOAc) to give **43** (0.152 g, 0.25 mmol, 70%) as a colorless oil.

Data for **43** are as follows. ^{1}H NMR: 7.73−7.68 (m, 5H); 7.44−7.24 (m, 10H); 6.73 (br s, 1H); 5.82 (d, J = 10.4, 1H); 5.52 (dd, J = 10.4, 3.54, 1H); 4.74−4.45 (m, 5H); 4.35−4.33 (br m, 1H); 4.15−4.12 (br m, 1H); 3.90−3.68 (br m, 2H); 2.42−2.33 (m, 1H); 2.20−2.12 (m, 1H); 1.97 (s, 3H); 1.09 (s, 9H). ^{13}C NMR: 170.6, 137.3, 136.0, 135.9, 133.6, 133.1, 131.2, 130.1, 130.0, 128.5, 128.2, 127.9, 127.9, 127.8, 127.8, 119.1, 94.3, 77.4, 77.1, 69.9, 67.3, 58.4, 55.9, 39.2, 36.3, 27.0,

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24.2, 19.3. IR: 3332 (broad), 2245, 1662. MS: 621 $[M + Na]^+$. HRMS: calcd for $C_{35}H_{42}N_2O_5SiNa$ $[M + Na]^+$ 621.2761; found 621.2759.

Preparation of 45. A 1,2-dichloroethane (7.0 mL) solution of **43** (0.473 g, 0.79 mmol, 1.0 equiv), DIPEA (0.34 mL, 1.98 mmol, 2.5 equiv), and BOMCl (0.22 mL, 1.58 mmol, 2.0 equiv) was stirred under Ar at 50 °C for 24 h, and then it was cooled to room temperature, diluted with CH_2Cl_2 (20 mL), and partitioned with saturated aqueous NH_4Cl solution (15 mL). The organic layer was separated, and the aqueous phase was extracted with more CH_2Cl_2 (2 × 20 mL). The combined extracts were washed with H_2O (50 mL), dried (Na_2SO_4), and concentrated under vacuum to afford crude **44** as a pale yellow oil. This material was taken up in THF (5.0 mL) at room temperature under Ar and treated with a 1 M solution of AcOH in THF (2.0 mL, 1.98 mmol, 2.5 equiv) followed by a 1 M solution of TBAF in THF (2.0 mL, 1.98 mmol, 2.5 equiv). The mixture was stirred at room temperature for 15 h, and then it was diluted with saturated aqueous $NaHCO_3$ solution (10 mL) (*Caution!* CO_2 evolution) and diluted with EtOAc (20 mL). The layers were separated, and the aqueous phase was extracted with more EtOAc (2 × 20 mL). The combined extracts were dried (Na_2SO_4) and concentrated under vacuum, and the residual pale yellow oil was purified by column chromatography on silica gel (EtOAc) to give **45** (0.329 g, 0.66 mmol, 84% over two steps) as a colorless oil.

Data for **45** are as follows. ^{1}H NMR: 7.40−7.28 (m, 10H); 6.64 (br s, 1H); 6.00 (dd, J = 10.23, 4.44, 1H); 5.81 (d, J = 10.23, 1H); 4.87 (br s, 2H); 4.78 (br s, 2H); 4.67 (br s, 2H); 4.62 (br s, 2H); 4.53 (d, J = 3.0, 1H); 4.28−4.18 (m, 1H); 4.14−4.11 (m, 1H); 3.89−3.63 (m, 3H); 2.58−2.49 (m, 1H); 2.28−2.20 (m, 1H); 1.92 (s, 3H). ^{13}C NMR: 170.4, 137.4, 137.0, 130.2, 128.6, 128.5, 128.3, 128.0 (2 signals), 127.7, 118.5, 95.0, 94.8, 70.3, 70.0, 65.4, 63.9, 54.8, 36.8, 35.8, 24.1. IR: 3335, 2244, 1658. MS: 503 $[M + Na]^+$. HRMS: calcd for $C_{27}H_{32}N_2O_6Na$ $[M + Na]^+$ 503.2158; found 503.2155.

Preparation of 46. Solid Dess−Martin periodinane (0.874 g, 2.06 mmol, 1.5 equiv) was added at room temperature to a CH_2Cl_2 (10 mL) solution of **45** (0.660 g, 1.37 mmol, 1.0 equiv), and the mixture was stirred for 30 min. An aqueous solution of $Na_2S_2O_3$/$NaHCO_3$ (7/1, 20 mL) was added, and the mixture was diluted with Et_2O (20 mL) and stirred until the layers turned clear (ca. 15 min). The layers were separated, and the aqueous phase was extracted with more Et_2O (2 × 20 mL). The combined extracts were dried (Na_2SO_4) and concentrated under vacuum, and the residue was purified by column chromatography on silica gel (EtOAc/hexanes 7/3) to give **46** (0.618 g, 1.29 mmol, 94%) as a colorless oil.

Data for **46** are as follows. ^{1}H NMR: 7.42−7.30 (m, 10H); 7.16 (br s, 1H); 6.92 (d, J = 10.59, 1H); 6.07 (d, J = 10.59, 1H); 5.03 (d, J = 6.99, 1H); 4.88−4.83 (m, 4H); 4.73 (d, J = 4.29, 1H); 4.67−4.63 (m, 3H); 4.45 (d, J = 4.29, 1H), 3.93−3.78 (m, 2H); 2.53−2.48 (m, 2H); 1.95 (s, 3H). ^{13}C NMR: 191.0, 170.7, 154.3, 137.5, 137.3, 128.8, 128.6, 128.4, 128.3, 128.1, 127.9, 126.8, 117.1, 95.3, 93.9, 71.5, 70.7, 70.4, 64.1, 55.5, 39.8, 38.3, 23.8. IR: 3347, 2246, 1678, 1660 (shoulder). MS: 501 $[M + Na]^+$. HRMS: calcd for $C_{27}H_{30}N_2O_6Na$ $[M + Na]^+$ 501.2002; found 501.1989.

Preparation of 47. Commercial *n*-BuLi solution (2.5 M in hexanes, 0.50 mL, 1.25 mmol, 3.0 equiv) was carefully added (syringe) to a THF (3.0 mL) suspension of Ph_3PCH_3Br (0.747 g, 2.09 mmol, 5.0 equiv) at room temperature, under Ar, with good stirring. After 1 h, the mixture was cooled to −78 °C, and a THF (3.0 mL) solution of **46** (0.200 g, 0.42 mmol, 1.0 equiv) was added dropwise (syringe). Upon completion of the addition, the reaction was stirred at −78 °C for 5 min, and then it was warmed to 0 °C and stirred for 2.5 h. The mixture was carefully treated with saturated aqueous NH_4Cl solution (20 mL), and then it was warmed to room temperature and diluted with Et_2O (20 mL). The layers were separated, and the aqueous phase was extracted with more Et_2O (2 × 20 mL). The combined extracts were dried (Na_2SO_4) and concentrated under vacuum, and the residual pale yellow oil was purified by column chromatography on silica gel (Et_2O) to give **47** (0.173 g, 0.36 mmol, 87%) as a colorless oil.

Data for **47** are as follows. ^{1}H NMR: 7.41−7.28 (m, 10H); 6.91 (br s, 1H); 6.23 (d, J = 10.3, 1H); 5.80 (d, J = 10.3, 1H); 5.32 (br s, 1H); 5.27 (br s, 1H); 4.89−4.78 (m, 5H); 4.71−4.59 (m, 5H); 3.86−3.82 (m, 2H); 2.50−2.47 (m, 2H); 1.95 (s, 3H). ^{13}C NMR: 170.1, 137.4, 137.3, 136.4, 131.3, 128.6, 128.5, 128.2, 128.0, 127.9, 127.8, 127.8, 119.4, 118.6, 94.9, 91.1, 71.6, 69.9, 69.9, 64.3, 55.6, 38.6, 37.2, 24.2. IR: 3300, 2244, 1659. MS: 499 $[M + Na]^+$. HRMS: calcd for $C_{28}H_{32}N_2O_5Na$ $[M + Na]^+$499.2209; found 499.2189.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text giving additional characterization data, figures giving proton and ^{13}C NMR spectra, and CIF files giving X-ray crystallographic data for **21** and **37**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail for M.A.C.: ciufi@chem.ubc.ca.

Notes

The authors declare no competing financial interest.

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(32) As described in ref 12, attempted dehydration of the nitroketones to the corresponding α-oxonitrile oxide with, e.g., 4-chlorophenyl isocyanate[32a] or BOC_2O[32b] resulted in formation of the desired isoxazolines as minor components of a complex mixture. We thank our former coworkers, Dr. Cyril Benhaim and Mr. (now Dr.) Brian Mendelsohn, for carrying out exploratory experiments in this area. (a) Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339. (b) Basel, Y.; Hassner, A. *Synthesis* **1997**, 309 .
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(34) Control experiments confirmed that $Cu(OAc)_2$ was required. Although simpler nitroketones related to **9** can be induced to cyclize in the presence of amine bases only, we had previously determined that treatment of **9** with, e.g., plain Et_3N produced no **10**.[12] Cecchi, L.; De Sarlo, F.; Machetti, F. *Tetrahedron Lett.* **2005**, *46*, 7877.
(35) Inferior results were obtained with *N*-methylmorpholine (20% yield of isoxazoline), imidazole (11% yield), or DABCO (no product detected).
(36) The use of freshly distilled $CHCl_3$ (removal of stabilizing EtOH) was key to maximum efficiency.
(37) The published procedure[33] calls for operation at 60 °C. However, α-**9** yielded numerous byproducts at such a temperature. A cleaner reaction was observed at 30 °C, but at the detriment of rate. Interestingly, epimer β-**9** tolerated higher reaction temperatures, advancing to β-**10** in 40% yield after only 2.5 days at 60 °C, with marginal formation of byproducts.
(38) The formation of the isoxazoline from the nitroketone must necessarily generate 1 equiv of H_2O.
(39) These reactions were carried out with ca. 30 mg of nitroketone and 0.6 mg of $Cu(OAc)_2$ (weighed as a solid) dissolved in 0.6 mL of a stock solution of *N*-ethylpiperidine (3.0 μL) in $CDCl_3$ (2 mL). This solution thus contained 0.9 μL of *N*-ethylpiperidine.
(40) The amount of (paramagnetic) Cu(II) present in the mixture induced an insignificant extent of line broadening, enabling close monitoring of the progress of the reaction by 300 MHz ^{1}H NMR.
(41) Nitromethane can be adsorbed/chemisorbed onto strongly basic earth oxides such as CaO or MgO: Kheir, A. A.; Haw, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 817. It seemed unlikely that nonbasic $CaSO_4$ might also adsorb/chemisorb $MeNO_2$. However, if that were the case, the NMR analysis described herein would produce meaningless results. The following experiment unequivocally ruled out such a possibility. Two 0.6 mL aliquots of a stock solution of $MeNO_2$ (3 μL) in $CDCl_3$ (1.5 mL) were separately syringed into two NMR tubes, one of which contained powdered anhydrous $CaSO_4$ (ca. 20 mg). Both solutions were sonicated for 5 min, and a ^{1}H NMR spectrum of each was recorded. The ratio of the integrated areas under the signals of CH_3NO_2 and residual $CHCl_3$ were identical in both solutions, signifying that no sequestration of $MeNO_2$ had occurred. In contrast, the signal of residual H_2O had been largely suppressed in the sample containing $CaSO_4$.
(42) This material was not thoroughly purified, and it was characterized by ^{1}H NMR and low- and high-resolution mass spectrometry. The identity was confirmed by comparison with a sample prepared from commercial 4-acetamidophenol (see the Supporting Information).
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(45) This step occurred much more efficiently when MeOH freshly distilled from Mg turnings was employed as the solvent, instead of commercial dry MeOH.

(46) The X-ray crystal structure of **37** is described in the Ph.D. dissertation of our former co-worker, Mr. (now Dr.) B. Mendelsohn, who prepared it by the Torsell method.[13,22] The compound cocrystallized with one molecule of CH_2Cl_2, but only the structure of **37** is shown in Figure 3. For full details, see the Supporting Information.

(47) Chromatographic purification of batches of isoxazolines obtained from multigram-scale runs of the above sequences would occasionally return product contaminated with 15−20% of acids **8**/**22**. This was somewhat surprising, since acids and isoxazolines exhibit widely differing chromatographic mobilities (e.g., in 70% EtOAc/hexanes: **22**, R_f = 0.00; **36**, R_f = 0.55). Rather than further purification of the isoxazolines, it was expedient to remove the contaminants at the stage of **37**/**38** to minimize losses. Indeed, the basic treatment and subsequent chromatography of **37**/**38** eliminated all traces of residual acids. See the Experimental Section for details.

(48) Recent work has revealed that the *N*-BOC compound **38** can be elaborated to very advanced TTX intermediates without passing through an analogous diene. Therefore, the sequence leading to the latter was studied only in the *N*-acetyl series.

(49) It is worthy of note that while the BOM protection of **37** proceeded efficiently to afford **39** in 91% yield after 48 h, the same reaction of its epimer **11** was slow and could not be forced to completion without incurring unacceptable losses. Furthermore, the chromatographic mobility of the BOM derivative of **11** was similar to that of the starting alcohol, complicating purification. This is one of the reasons it was advantageous to use α-diastereomers **7**−**10**/**21**−**23** in sequences leading to advanced TTX intermediates.

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(51) Because this ketone proved to be a dead-end compound, the sequence leading to it was not optimized, nor was **40** fully characterized.

(52) This substance was not thoroughly purified, and it was characterized only by 300 MHz ^{1}H NMR ($CDCl_3$: δ 7.45−7.32 (m, 5H); 7.15 (d, J = 8.46, 1H); 7.04 (d, J = 8.46, 1H); 5.32 (s, 2H); 4.93 (s, 2H); 3.76 (s, 2H); 3.74 (s, 3H)) and ESI mass spectrometry (m/z 350 $(M + Na)^+$).

(53) This reduction was slow and required occasional addition of more $LiBH_4$ over 24 h.

(54) The action of unbuffered TBAF on **44** returned **45** in only about 20% yield, as did treatment with HF·(pyridine).

(55) Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.

(56) A small amount of nitroketone **23** was purified by flash chromatography (1/9 EtOAc/hexanes). In $CDCl_3$ solution, about 15% of **23** appears to exist as the enol tautomer of the ketone (presumably, internally H-bonded to the NO_2 group) on the basis of ^{1}H and ^{13}C NMR. Data for **23** are as follows. ^{1}H NMR: 7.71−7.67 (m, 4H); 7.46−7.37 (m, 6H); 6.73 (s, 0.15 H, presumed enol tautomer); 5.99 (app dd, J = 10.3 Hz, 1.8 Hz, 2H); 5.81 (app dd, J = 10.3 Hz, 2.6 Hz, 2H); 5.26 (s, 1.7 H); 4.61 (br, 1H); 4.56 (m, 1H); 3.02 (s, 1.7 H); 2.77 (s, 0.3 H, presumed enol tautomer); 1.45 (s, 9H); 1.08 (s, 9H). ^{13}C NMR: 193.3, 171.3 (presumed enol tautomer), 155.1, 154.6 (presumed enol tautomer), 136.0, 133.8, 130.3, 130.0, 128.3, 127.8, 118.1 (presumed enol tautomer), 83.9, 80.5, 63.5 (presumed enol tautomer), 63.4, 52.2 (presumed enol tautomer), 51.1, 48.1, 42.4 (presumed enol tautomer), 28.4, 27.0, 19.3. IR: 3409, 1703, 1560, 1493. MS: 573 $[M + Na]^+$. HRMS: calcd for $C_{30}H_{36}N_2O_5NaSi$ $[M + Na]^+$ 573.2397; found 573.2390.

(57) Chromatographic purification of **22** is quite difficult. A pure sample was obtained by cooling a hot saturated CH_2Cl_2 solution of the acid, whereupon the compound crystallized as a powdery solid, which was filtered and washed twice with CH_2Cl_2, mp 157−158 °C. ^{1}H NMR: 7.71−7.66 (m, 4H); 7.48−7.36 (m, 6H); 5.93 (dd, J = 10.3 Hz, 1.6 Hz, 2H); 5.81 (dd, J = 10.3 Hz, 2.5 Hz, 2H); 4.52 (m, 1H); 2.64 (br, 2H); 1.45 (s, 9H); 1.07 (s, 9H). ^{13}C NMR: 173.1, 136.0, 133.9, 130.0, 129.5 (br, 2 signals), 127.8, 81.2 (br), 63.5, 51.1, 44.2 (br), 28.5, 27.0, 19.32. The carbonyl carbon of the BOC group at ca. 155 ppm was barely visible, presumably due to spin saturation/slow relaxation. No attempt was made to obtain a better spectrum by altering the relaxation delay between pulses. IR: 3325, 1709, 1656. MS: 530 $[M + Na]^+$; negative ion mode 506 $[M - H]^-$. HRMS: calcd for $C_{29}H_{37}NO_5NaSi$ $[M + Na]^+$ 530.2339; found 530.2346.