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AN IMPROVED SYNTHESIS OF THE TRICYCLIC CORE OF SARAINS BY A 3-OXIDOPYRIDINIUM BETAINE CYCLOADDITION[1]

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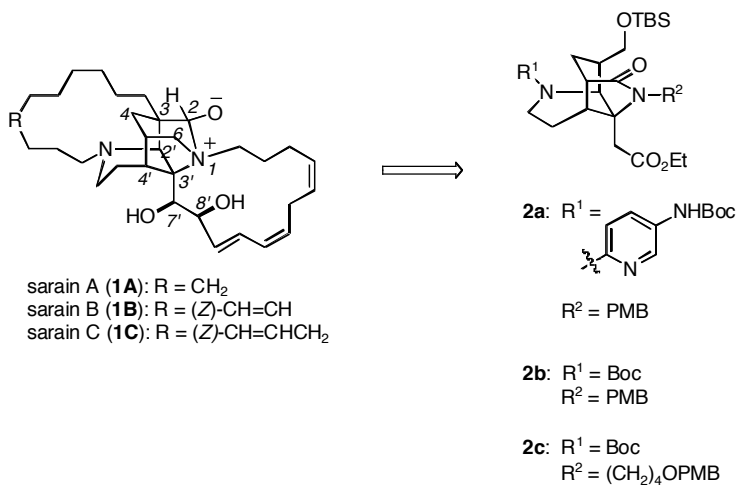
Abstract – An improved synthesis of a suitably functionalized tricyclic core of sarains has been developed by adaptation of Katritzky's cycloaddition using a 3-oxidopyridinium betaine.

INTRODUCTION

From the sponge *Reniera sarai*,[2a,b] Cimino and co-workers isolated the structurally intricate alkaloids sarains A–C (**1A**–**C**) that were reported to show antitumor, antibacterial, and insecticidal activity.[2c] The unusual features of sarains include the unprecedented diazatetracyclic core containing the ammonium alkoxide moiety, the two macrocyclic rings (a functionalized 14-membered "eastern" ring and a 13-membered "western" ring), and also the biosynthetic origin of sarains: the biogenesis of sarains has been

Scheme 1



sarain A (**1A**): R = CH_2
sarain B (**1B**): R = (*Z*)-CH=CH
sarain C (**1C**): R = (*Z*)-CH=$CHCH_2$

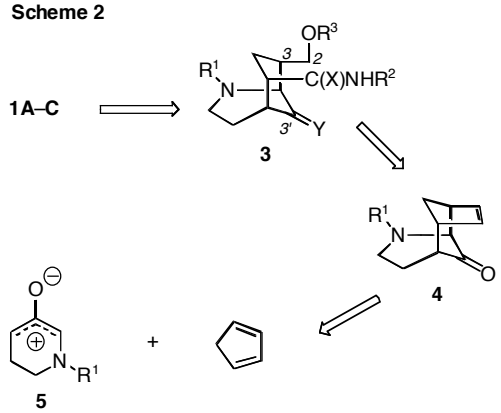
postulated to involve reductive condensation of a dihydropyridinium macrocycle.[3] The extraordinary architecture of sarains has attracted considerable synthetic interest, culminating in several syntheses of their tricyclic core.[1a,4-6] The Weinreb group and, more recently, our laboratory reported annulation of the "western" macrocyclic ring of **1A** by employing a Grubbs' ring-closing olefin metathesis strategy.[4c] Assembly of the "eastern" macrocycle was addressed by the Heathcock group in an appropriately designed model system.[5b] To date none of **1A–C** has succumbed to total synthesis. Toward a total synthesis of **1A**, we report herein an improved synthesis of the tricyclic core (**2c**) of sarains (Scheme 1).[7]

RESULTS AND DISCUSSION

Retrosynthetic analysis.

The pyrrolidine ring of **1A–C** would be readily prepared by intramolecular conjugate addition of a nitrogen nucleophile to a suitable Michael acceptor such as an α,β-unsaturated ester (**3**) (e.g., Y = $CHCO_2Et$) (Scheme 2). A strategic bond connection between the C-6 carbon and the C-2 carbon (the aldehyde of **1A–C**) would unveil the tricycle (**4**) as a key intermediate. The initial [4 + 3] cycloaddition of a six-membered cyclic oxyallyl (**5**) with cyclopentadiene was the cornerstone of our approach to **1A–C**. The synthetic utility of *cyclic* oxyallyls, i.e., oxyallyls embedded within rings, has been amply demonstrated in a convenient preparation of medium-sized carbocycles and heterocycles by virtue of the spectator rings.[8] Of particular note is excellent diastereoselectivity in these [4 + 3] cycloaddition

Scheme 2

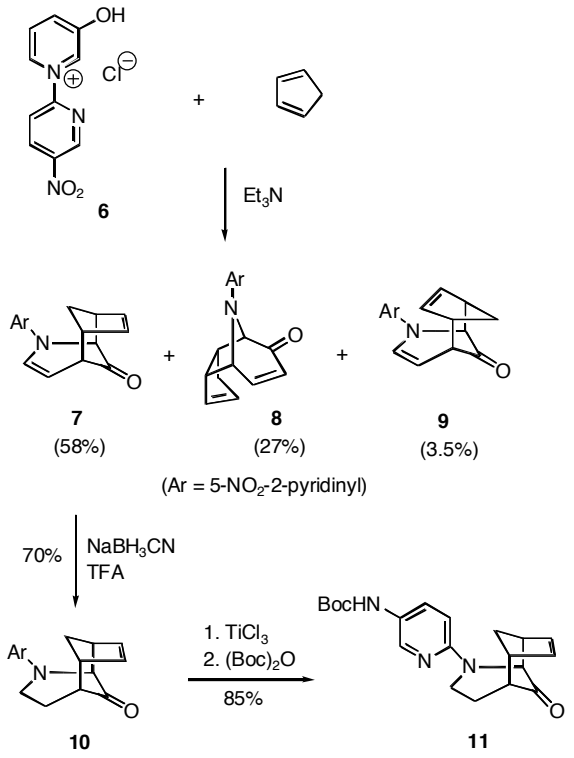


reactions of oxyallyls for the endo-like cycloadduct (**4**). Moreover, the cycloadduct (**4**) contains a well-defined diastereofacial bias, as well as necessary functionalities suitable for subsequent elaboration of the side chains at C-3, C-3', and N-1. We were particularly interested in developing the rarely utilized [4 + 3] cycloaddition reactions of heteroatom-containing oxyallyls to provide a new, conceptually appealing approach to heterocyclic compounds.

First-generation synthesis.

An expedient synthetic equivalent to **5** was found in a 3-oxidopyridinium betaine (Scheme 3). Many years ago, Katritzky discovered an interesting dual reactivity of oxidopyridinium betaines: with a 1,3-diene, a 3-oxidopyridinium betaine functions as an oxyallyl to undergo [4 + 3] cycloaddition, whereas it functions as an azomethine ylide with an olefin (e.g., acrylate).[9] A slight modification of Katritzky's method involving slow addition (*via* syringe pump) of triethylamine to a mixture of readily available **6** and cyclopentadiene at room temperature afforded the [2+4] endo-like cycloadduct (**7**) in 58% yield, along with **8** (27%) (from cyclopentadiene acting as a conjugated olefin) and the exo-like cycloadduct (**9**) (3.5%).[9a,10] Thus, Katritzky's cycloaddition allowed us to prepare **7** in large quantities. Reduction of **7** with $NaBH_3CN$ gave tricyclic amine (**10**) (Cf. **4**) in 70% yield. The nitro compound was then converted to *N-tert*-butoxycarbamate (**11**) (85%) for ease of handling; although comparable results were obtained for other 5-nitro-2-pyridine substituted compounds in subsequent transformations, these nitro-containing compounds were found to possess very poor solubility in typical organic solvents.

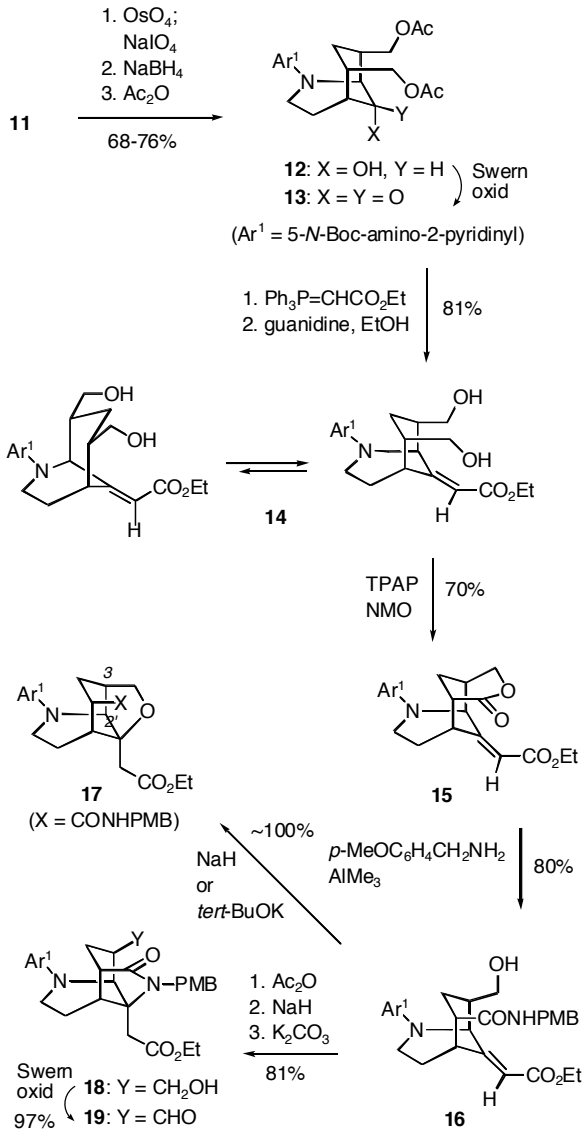
Scheme 3



For oxidative cleavage of the double bond in **11**, this compound was subjected sequentially to osmylation, periodate oxidation, reduction with $NaBH_4$, and acetylation to deliver alcohol (**12**) in 68–76% overall yield (Scheme 4). Swern oxidation of **12**, subsequent Wittig olefination of the resulting ketone (**13**), and deacetylation (guanidine, EtOH) then afforded α,β-unsaturated ester (**14**), as one geometrical isomer, in

81% yield. On the basis of difference NOE measurements, the configuration of the double bond was tentatively assigned to be *Z*. Our next task was differentiation of the two nearly identical hydroxyl groups of **14** in order to install the pyrrolidine ring of sarains. Oxidation of diol (**14**) with TPAP[11] gave lactone (**15**) (70%) as a single regioisomer; unequivocal structural determination of the indicated regiochemistry was possible by ^{1}H–^{1}H COSY (*vide infra*). The two hydroxymethyl substituents in **14** are in somewhat different steric environment which could be attributed to the presence of the *Z*-double bond and the carbamate group, where the less hindered alcohol undergoes selective oxidation. In a similar vein,

Scheme 4



acylation or silylation of **14** with pivaloyl chloride, *p*-toluenesulfonyl chloride, and TBSCl was also regioselective under standard reaction conditions. No attempt was made to ascertain the regiochemistry of the resulting products, but these reactions were presumed to display the regiochemistry identical to **14**

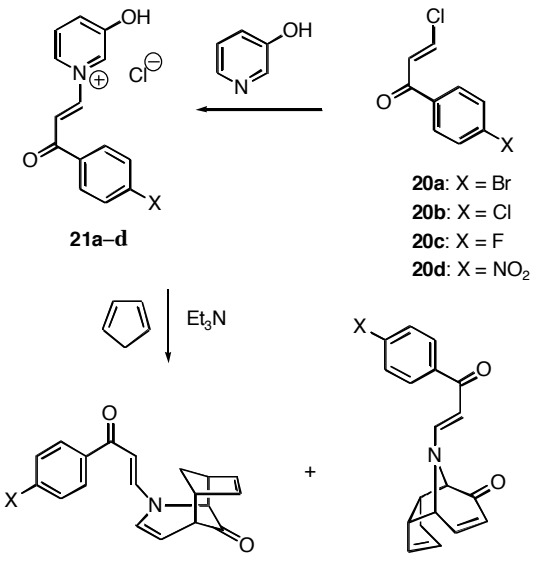
 15. In sharp contrast, the corresponding diol (structure not shown), prepared from hydrolysis (by guanidine in ethanol) of ketone (**13**), yielded a 1:1 mixture of both regioisomers in low yields, when treated with pivaloyl chloride or TBSCl. These results, taken together, are indicative of a significant influence the *Z*-,-unsaturated ester exerts on the requisite differentiation of the two hydroxyl groups.
In order to install the pyrrolidine ring, the lactone (**15**) was converted to *N*-*p*-methoxybenzylamide (**16**) (80%).[12] Treatment of **16** with NaH or potassium *tert*-butoxide resulted in exclusive formation of **17** (quantitative yield); the COSY spectrum clearly shows coupling of the methine proton at C-2' (4.63 ppm, J = 4.3 Hz) to the proton (2.62) at C-3, which is in turn coupled to one of –CH_2O– [3.91 (dd) and 3.56 (d)]. Protection of the primary hydroxyl group in **16** as the acetate, followed by treatment with NaH and subsequent deacetylation, afforded the desired pyrrolidinone (**18**) in 81% overall yield. Aldehyde (**19**) was readily prepared (97%) by Swern oxidation. Next, removal of the *N*-Boc-5-amino-2-pyridinyl moiety in alcohol (**18**) and its acetate was examined by exhaustive hydrogenation so as to construct the western macrocycle. Despite several attempts under different conditions, this deprotection step (H_2, Pd/C) was capricious and afforded the desired free amine in only poor yields.

Second-generation synthesis.

The disappointing result on removal of the *N*-Boc-5-amino-2-pyridinyl group prompted us to search for a more easily removable substituent under mild conditions. In addition to ease of removal, there are two equally important prerequisites for an ideal 3-hydroxypyridium salt: it should be readily prepared from 3-hydroxypyridine and its betaine should undergo the desired [4 + 3] addition with cyclopentadiene, preferably with minimal formation of an unwanted 2,6-cycloadduct (i.e. **8**). -Aroylvinyl seemed to satisfy these essentials as a nearly perfect *N*-substituent. In 1980, in fact, Katritzky and co-workers reported the cycloaddition between **21a** and cyclopentadiene by the action of triethylamine (in MeCN) to provide **22a** and **23a** in 23% and 16%, respectively (Scheme 5).[9b] However, we were convinced that optimization should be possible by the above-mentioned modification of slow addition (to avoid the otherwise facile dimerization of the betaine) and also the variation of the electronic property of the aryl moiety. Of some concern was the reported instability of these cycloadducts. In any event, the pyridinium salt (**21a**) was prepared in nearly quantitative yield by Katrizky's published procedure for coupling of known and readily available **20a** and 3-hydroxypyridine. The key cycloaddition reaction of **21a** in MeCN under our modified conditions resulted in an improved (41%) yield of **22a**. A brief survey of various solvents was first undertaken: comparable yields were obtained by use of methylene chloride, but other solvents proved to be unsuitable. Because of an improved product ratio of **22a** to **23a** so as to facilitate the purification task, methylene chloride was chosen as the reaction solvent in subsequent studies. Electronic effects on the cycloaddition reaction were next investigated by changing the substituent at the

para position of the phenyl ring. Among the four different pyridinium salts (**21a–d**) examined, best yields were obtained with *p*-fluoro- and *p*-nitro derivatives (**21c**,**d**). Thus, an electron-withdrawing substituent appeared to be beneficial for the [4 + 3] cycloaddition. Further refinement might be possible with systematic studies, but we decided to forge ahead with **22c**.

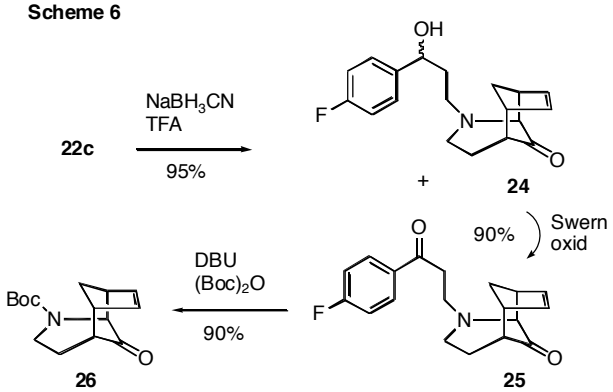
Scheme 5



21a	solvent	22a	23a
	MeCN (ref 9b)	23%	16%
	MeCN	41%	10%
	CH_2Cl_2	40%	5%
	THF	10%	2%
	DMF	15%	1%
	CF_3CH_2OH	7%	1%

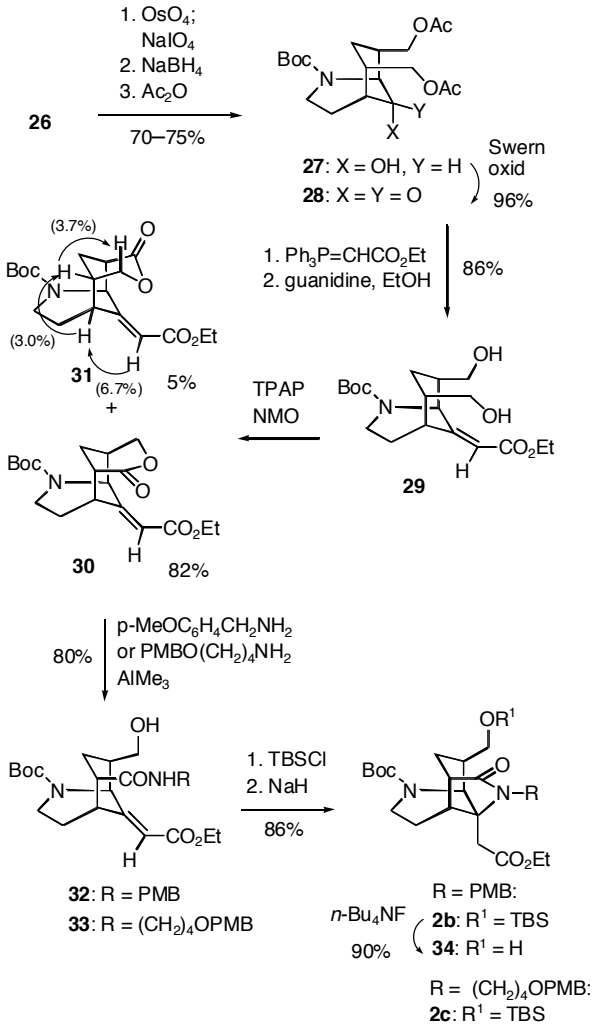
substrate	22b–d	23b–d
21b: X = Cl	41%	5%
21c: X = F	60%	15-25%
21d: X = NO_2	48%	15%

Scheme 6



Treatment of **22c** with $NaBH_3CN$ and TFA afforded an easily separable mixture of **24** (45%) and **25** (40%) (Scheme 6). Most conveniently, however, the crude reaction mixture was subjected, without separation, to Swern oxidation to furnish **25** in excellent yield. Treatment of **25** with DBU and $(Boc)_2O$ gave *N*-Boc-carbamate (**26**) in 90% yield. Thus, the initial concern about the instability of **22c** proved to be unwarranted by performing straightforward reduction of the enamine functionality.

Scheme 7



With large quantities of **26** in hand, the reaction sequence analogous to **11** → **18** was applied to uneventfully deliver the *N*-Boc protected tricyclic core (**34**) in multigram quantities (Scheme 7). Starting with **26**, oxidative cleavage of the double bond and Wittig olefination of **28** afforded **29** in comparable yield. TPAP oxidation of **29** gave the desired lactone (**30**) in 82% yield, along with a small (5%) amount of the regioisomer (**31**). The ^1H NMR spectrum of **30** was too complicated to extract all key structural data due to the presence of the two *N*-Boc rotamers. However, the ^1H NMR spectrum of **31** was

amenable to detailed analysis; ^1H–^1H COSY and difference NOE measurements allowed unequivocal confirmation of the regiochemistry of the lactone and the configuration of the double bond. Informative NOE data are shown in parentheses in Scheme 7.[13] As in the case of the first-generation synthesis of **18**, internal conjugate addition of **32**, after formation of the acetate as a temporary protecting group, proceeded without incident to yield **34**, following straightforward deprotection. The Boc protecting group was removed (90%) by TFA; the ^1H–^1H COSY experiment of the resulting amine (having the acetate group instead of the TBS moiety) was also performed as additional corroboration of the assigned structure. To aid later investigations on the construction of the 14-membered eastern ring of **1A**, a more robust protecting (e.g., *tert*-butyldimethylsilyl) was desirable. To this end, the TBS-protected tricyclic core (**2b**) was prepared in 86% overall yield. Also, the tricyclic core (**2c**) was prepared, *via* **33**, in comparable yield.

Conclusion

In summary, we have achieved an efficient synthesis of an *N*-Boc-protected tricyclic core of sarains in multigram quantities. Particularly noteworthy is the use of the *E*-□-(4'-fluorobenzoyl)vinyl moiety in 3-oxidopyridinium betaines. This *N*-substituent is not only easy to install and remove, but also well suited for the pivotal [4 + 3] cycloaddition reaction. Additionally, the *N*-substituent on pyridinium salts appears to exert significant electronic effects on the efficiency and partitioning of the two (2,4 and 2,6) cycloadditions. Mechanistic studies and further refinement will be reported in due course.

EXPERIMENTAL

[4 + 3] Cycloaddition of 21c to cyclopentadiene. To a mixture of **21c** (15.9 g, 57 mmol) and cyclopentadiene (150 mL, 1.8 mol) in CH_2Cl_2 (150 mL) was added triethylamine (8.8 mL, 63 mmol) *via* a syringe pump over 20 h at rt. After the addition was complete, the resulting black reaction mixture was stirred for an additional 24 h. Water (200 mL) was then added, and the reaction mixture was extracted with CH_2Cl_2 (2 x 200 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (aluminum oxide, activated basic, 1:3 hexane/EtOAc) to give cycloadduct (**22c**) (10.5 g, 60%) as a pale yellow solid, along with **23c** (15%).

Spectral data for **22c**: mp 133–135 ºC; IR (KBr) 1747, 1651, 1610 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) □ 7.92 (dd, *J* = 8.7, 5.4 Hz, 2H), 7.68 (d, *J* = 12.5 Hz, 1H), 7.10 (dd, *J* = 8.7, 8.6 Hz, 2H), 6.61 (d, *J* =

7.3 Hz, 1H), 6.24 (dd, *J* = 5.7, 2.6 Hz, 1H), 6.06 (d, *J* = 12.5 Hz, 1H), 6.00 (dd, *J* = 5.7, 2.6 Hz, 1H), 5.06 (dd, *J* = 7.3, 7.2 Hz, 1H), 4.11 (br s, 1H), 3.55 (br s, 1H), 3.03 (br s, 1H), 2.96 (m, 1H), 2.46 (d, *J* = 11.8 Hz, 1H), 1.73 (dt, *J* = 11.8, 4.0 Hz, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) 203.5, 187.5, 165.0 (d, *J* = 251 Hz, C–F), 147.2, 138.8, 135.5, 132.7, 130.1 (d, *J* = 9 Hz, C–C–C–F), 115.3 (d, *J* = 21 Hz, C–C–F), 105.2, 95.5, 65.3, 49.6, 47.3, 46.0, 36.3.

$NaCNBH_3$ Reduction of Cycloadduct (22c). To a solution of **22c** (10.0 g, 32.3 mmol) in CH_2Cl_2 (200 mL) were added sequentially at –78 °C sodium cyanoborohydride (8.1 g, 129 mmol) and trifluoroacetic acid (19.9 mL, 258 mmol). The reaction mixture was stirred at –20 °C for 1 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (200 mL), and extracted with CH_2Cl_2 (3 x 100 mL). The combined extracts were washed with brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (aluminum oxide, activated basic, 1:1 hexane/EtOAc) to afforded **25** (4.5 g, 45%). The alcohol (**24**) (4.1 g, 40%, as a pale yellow oil) was then obtained as a mixture of diastereomers upon elution with hexane/EtOAc (1:3).

Spectral data for **25**: IR (film) 1731, 1684, 1585 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) 7.97 (dd, *J* = 8.7, 5.4 Hz, 2H), 7.14 (dd, *J* = 8.7, 8.6 Hz, 2H), 6.14 (dd, *J* = 5.7, 2.2 Hz, 1H), 5.98 (dd, *J* = 5.7, 2.6 Hz, 1H), 3.07–2.88 (m, 7H), 2.66 (br s, 2H), 2.49 (td, *J* = 12.1, 5.4 Hz, 1H), 2.44 (m, 1H), 2.08 (td, *J* = 12.1, 6.2 Hz, 1H), 1.89 (ddd, *J* = 12.1, 10.8, 5.4 Hz, 1H), 1.67 (dt, *J* = 11.1, 4.2 Hz, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) 211.0, 197.5, 165.7 (d, *J* = 253 Hz, C–F), 139.1, 134.8, 133.4, 130.6 (d, *J* = 9 Hz, C–C–C–F), 115.7 (d, *J* = 22 Hz, C–C–F), 71.4, 53.9, 47.8, 46.8, 46.5, 45.2, 36.7, 35.8, 26.4; HRMS (M^+) calcd for $C_{19}H_{20}NO_2F$ 313.1473, found 388.1461.

Spectral data for **24**: IR (film) 3426, 1731 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) 7.36 (m, 2H), 7.22 (dd, *J* = 8.7, 8.6 Hz, 2H), 6.20 (dd, *J* = 5.7, 2.3 Hz, 1H), 6.03 (dd, *J* = 5.7, 2.6 Hz, 1H), 4.96–4.88 (m, 1H), 3.20–3.10 (m, 1H), 3.04 (m, 1H), 2.95 (br s, 2H), 2.85–2.70 (m, 3H), 2.53 (m, 1H), 2.42 (td, *J* = 12.5, 5.6 Hz, 1H), 2.32–2.14 (m, 2H), 2.00 (m, 1H), 1.95–1.82 (m, 2H), 1.77 (m, 1H).

To a solution of oxalyl chloride (2.27 mL, 26 mmol) in CH_2Cl_2 (30 mL) was added a solution of DMSO (3.7 mL, 52 mmol) in CH_2Cl_2 (30 mL) at –78 °C. After the mixture had been stirred for 15 min, a solution of **24** (4.05 g, 12.9 mmol) in CH_2Cl_2 (30 mL) was added dropwise at –78 °C. The reaction mixture was stirred for 30 min and a solution of Et_3N (14.5 mL, 104 mmol) was then added. The mixture was then allowed to warm to 0 °C, quenched with water (100 mL), and extracted with CH_2Cl_2 (2 x 100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (aluminum oxide,

activated basic, 1:1 hexane/EtOAc) to afford **25** (3.63 g, 90%).

Carbamate (26). To a solution of **25** (7.42 g, 48.1 mmol) in CH_2Cl_2 (70 mL) were added sequentially di-*tert*-butyl dicarbonate (41.99 g, 192 mmol) and DBU (14.6 mL, 96 mmol). The reaction mixture was heated at reflux under a nitrogen atmosphere for 30 h and then cooled to rt. The reaction was quenched with water (50 mL), and the reaction mixture was extracted with CH_2Cl_2 (2 x 50 mL). The combined extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (silica gel, 3:1 hexane/EtOAc) afforded **26** (5.61 g, 90%) as a white solid: mp 127–128 °C; IR (film) 1743, 1697 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.14 (m, 1H), 6.04 (dd, *J* = 5.6, 2.7 Hz, 1H), 4.16 (dd, *J* = 13.9, 7.3 Hz, 0.7H), 4.03 (br s, 0.3H), 3.98 (dd, *J* = 13.9, 7.3 Hz, 0.3H), 3.94 (br s, 0.7H), 3.37 (m, 0.3H), 3.21 (m, 0.7H), 2.95 (td, *J* = 13.9, 5.9 Hz, 0.3H), 2.88 (td, *J* = 13.9, 5.9 Hz, 0.7H), 2.78 (br s, 1H), 2.60 (m, 1H), 2.52 (d, *J* = 11.5 Hz, 0.7H), 2.49 (d, *J* = 11.5 Hz, 0.3H), 2.13 (td, *J* = 13.9, 7.3 Hz, 1H), 2.01–1.88 (m, 1H), 1.78 (td, *J* = 11.5, 4.0 Hz, 1H), 1.47 (s, 9H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 209.4, 208.9, 154.4, 154.2, 139.2, 138.6, 135.0, 134.5, 80.3, 65.1, 64.8, 46.9, 46.7, 46.1, 45.3, 44.5, 40.8, 39.5, 35.6, 35.4, 28.4, 26.0, 25.6; HRMS (M^+) calcd for $C_{15}H_{21}NO_3$ 263.1516, found 263.1508.

Bisacetate (27). To a solution of **26** (5.32 g, 20.22 mmol) in 10:1 THF/H_2O (99 mL) were added 4-methylmorpholine *N*-oxide (7.11 g, 60.7 mmol) and osmium tetroxide (94.6 mL of a 2.5 wt. % solution in 2-methyl-2-propanol). The reaction mixture was stirred for 4 h and quenched with 10% aqueous sodium hydrosulfite solution (100 mL). The mixture was extracted with EtOAc (2 x 100 mL). The combined extracts were washed with brine (50 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 1:3 hexane/EtOAc) to afford the diol (5.23 g, 87%) as a colorless oil: IR (film) 3408, 1737, 1696 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.08 (dd, *J* = 13.5, 6.5 Hz, 0.6H), 3.99–3.88 (m, 3.6H), 3.69 (d, *J* = 4.1 Hz, 0.4H), 3.51 (d, *J* = 3.6 Hz, 0.4H), 3.28 (dd, *J* = 8.7, 4.1 Hz, 1H), 2.88 (m, 0.4H), 2.77 (m, 0.6H), 2.68 (td, *J* = 13.5, 5.7 Hz, 1H), 2.60 (m, 1H), 2.34 (m, 1H), 2.21–1.96 (m, 3H), 1.79 (m, 1H), 1.46 (s, 5.4H), 1.45 (s, 3.6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 211.1, 154.4, 80.9, 80.8, 72.5, 72.4, 70.6, 70.1, 66.1, 65.6, 52.4, 52.2, 51.2, 50.4, 47.7, 47.6, 40.1, 38.8, 28.4, 27.1, 26.7, 22.6, 22.5; HRMS (M^+) calcd for $C_{15}H_{23}NO_5$ 297.1576, found 297.1573.

To a solution of the diol (5.22 g, 17.57 mmol) in 10:1 THF/H_2O (110 mL) was added sodium periodate (4.51 g, 21 mmol). The mixture was stirred for 30 min and diluted with EtOAc (200 mL). The mixture was filtered through a pad of Celite, and the filter cake was rinsed with EtOH (50 mL). After the solvent had been removed under reduced pressure, the residue was

dissolved in 1:10 MeOH/CH_2Cl_2 (70 mL). The solution was dried over Na_2SO_4 and concentrated in vacuo to afford the crude dialdehyde (5.15 g, *ca.* 90%), which was used for the next step without further purification.

To a solution of the dialdehyde (5.15 g, 17.1 mmol) in MeOH (150 mL) was added sodium borohydride (2.66 g, 70.3 mmol) at –78 °C. The mixture was stirred at rt overnight, quenched by addition of aqueous saturated NH_4Cl solution (14 mL), and diluted with EtOAc (200 mL). The mixture was dried over Na_2SO_4 and concentrated in vacuo. The residue was dissolved with 1:10 MeOH/CH_2Cl_2 (150 mL), dried over Na_2SO_4, and concentrated in vacuo to give the crude triol (4.52 g, *ca.* 95%) which was used for the next step without further purification.

To a solution of the triol (4.52 g, 15.0 mmol) in CH_2Cl_2 (70 mL) and pyridine (6.0 mL, 74 mmol) were added at 0 °C acetic anhydride (3.2 mL, 34 mmol). The reaction mixture was stirred for 12 h under 15 °C. The mixture was quenched with water (70 mL) and extracted with CH_2Cl_2 (2 x 70 mL). The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 2:1 hexane/EtOAc) to give **27** (5.48 g, 95%) as a colorless oil: IR (film) 3457, 1740, 1690 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) □ 4.27 (br s, 0.5H), 4.15 (br s, 0.5H) 4.05 (br s, 2H), 3.99 (d, *J* = 6.7 Hz, 2H), 3.82 (m, 0.5H), 3.67 (br s, 1.5H), 2.89 (m, 1.5H), 2.50 (br s, 0.5H), 2.03 (s, 6H), 2.00–1.85 (m, 3H), 1.67 (br s, 2H), 1.54 (m, 1H), 1.42 (s, 4.5H), 1.40 (s, 4.5H); ^{13}C NMR (90 MHz, $CDCl_3$) □ 171.1, 154.5, 80.0, 79.8, 71.7, 70.0, 68.9, 52.0, 50.9, 37.0, 35.3, 34.4, 33.9, 31.7, 31.1, 28.3, 23.8, 23.4, 21.0, 20.9; HRMS (M^+) calcd for $C_{19}H_{31}NO_7$ 385.2101, found 385.2085.

Diol (29). To a solution of oxalyl chloride (3.6 mL, 41.3 mmol) in CH_2Cl_2 (60 mL) was added dropwise at –78 °C a solution of DMSO (5.8 mL, 81.7 mmol) in CH_2Cl_2 (20 mL). After the mixture had been stirred for 15 min at –78 °C, a solution of **27** (5.23 g, 13.58 mmol) in CH_2Cl_2 (30 mL) was added. The resulting mixture was then stirred at –78 °C for 20 min. A solution of triethylamine (17 mL, 122 mmol) in CH_2Cl_2 (40 mL) was added dropwise, and the mixture was slowly allowed to warm to 0 °C. The reaction was quenched with water, and the mixture was extracted with CH_2Cl_2 and washed with brine. The extract was dried over Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (silica gel; 3:1 hexane/EtOAc) gave ketone **28** (4.99 g, 96%) as a colorless oil: IR (film) 1742, 1693, 1237 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) □ 4.19 (br s, 1H), 4.05 (d, *J* = 6.1 Hz, 2H), 4.01 (dd, *J* = 11.0, 6.2 Hz, 1H), 3.92 (dd, *J* = 11.0, 6.9 Hz, 1H), 3.43 (m, 1H), 2.54–2.41 (m, 2H), 2.39 (br s, 1H), 2.12 (m, 1H), 2.06 (s, 6H),

1.98–1.85 (m, 2H), 1.60 (m, 1H), 1.46 (s, 9H), 0.98 (m, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 209.4, 170.6, 154.0, 80.8, 67.4, 66.4, 60.3, 45.5, 41.3, 39.3, 35.5, 32.2, 28.1, 25.4, 20.6.

A solution of **28** (4.81 g, 12.55 mmol) in toluene (70 mL) was treated with (carbethoxymethylene)triphenylphosphorane (6.56 g, 18.8 mmol). The reaction mixture was heated at reflux overnight. The solution was cooled to rt, diluted with water (50 mL), extracted with EtOAc (90 mL), and washed with brine. The organic extract was dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography (silica gel, 3:1 hexane/EtOAc) furnished the α,β-unsaturated ester (5.12 g, 90%) as a colorless oil: IR (film) 1742, 1716, 1693, 1244 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.04 (br s, 1H), 5.69 (s, 1H), 4.16 (q, *J* = 7.0 Hz, 2H), 4.09 (m, 1H), 4.02–3.95 (m, 2H), 3.94 (dd, *J* = 10.9, 6.4 Hz, 1H), 3.88 (dd, *J* = 10.9, 7.4 Hz, 1H), 3.25 (m, 1H), 2.28 (m, 2H), 2.24 (m, 2H), 2.14 (m, 1H), 2.04 (s, 3H), 2.02 (s, 3H), 1.90 (m, 1H), 1.78 (m, 1H), 1.69 (m, 1H), 1.45 (s, 9H), 1.27 (t, *J* = 7.0 Hz, 3H), 0.83 (m, 1H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 170.9, 164.9, 155.8, 154.6, 116.1, 80.1, 68.0, 67.0, 60.1, 49.2, 40.5, 40.3, 38.6, 35.8, 32.8, 28.3 25.5, 20.9, 20.8, 14.2; HRMS (M^+) calcd for $C_{22}H_{35}NO_8$ 453.2363, found 453.2357.

To a solution of this α,β-unsaturated ester (5.05 g, 11.14 mmol) in EtOH (30 mL) was added guanidine (24.5 mL of a 1 M solution in EtOH). The reaction mixture was stirred at rt for 1 h, directly loaded onto silica gel, and eluted with 50:1 EtOAc/EtOH. The fractions were concentrated in vacuo to afford **29** (3.91 g, 95%) as a colorless oil: IR (film) 3419, 1713, 1668, 1161 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.97 (br s, 1H), 5.73 (s, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.88 (m, 0.5H), 3.78 (m, 0.5H), 3.63 (m, 1H), 3.50–3.40 (m, 3H), 3.30 (td, *J* = 13.1, 4.2 Hz, 1H), 2.36 (br s, 1H), 2.10 (m, 1H), 2.02 (m, 2H), 1.91 (m, 1H), 1.74 (m, 1H), 1.44 (s, 9H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.04 (br s, 0.5H), 0.81 (br s, 0.5H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 166.9, 166.0, 158.8, 157.3, 155.6, 154.7, 115.6, 114.9, 80.3, 67.1, 65.8, 60.5, 50.0, 49.6, 46.0, 44.5, 42.4, 41.7, 39.9, 36.9, 36.3, 32.7, 28.4, 24.4, 14.1.

TPAP Oxidation of 29 to Lactone (30). To a solution of diol **29** (3.85 g, 10.43 mmol) in CH_2Cl_2 (500 mL) were added 4-methylmorpholine *N*-oxide (4.89 g, 41.7 mmol), 4 Å molecular sieves (7.7 g), and tetra-*n*-propylammonium perruthenate (TPAP, 0.16 g, 0.46 mmol). The resulting mixture was stirred at rt for 1.5 h and filtered through a pad of Celite. The filter cake was rinsed several times with EtOAc. Evaporation of the combined filtrates gave the crude oil, which was purified by column chromatography (silica gel, 4:1 hexane/EtOAc) to yield lactone (**30**) (3.12 g, 82%) as a pale yellow oil and the regioisomer (**31**) (0.19 g, 5%) as a colorless oil upon elution with 1:1 hexane/EtOAc.

Spectral data for **30**: IR (film) 1740, 1715, 1694, 1161 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.84 (s,

1H), 5.77 (br s, 1H), 4.39 (m, 2H), 4.20–4.12 (m, 2H), 3.98 (dd, *J* = 13.4, 6.7 Hz, 0.6H), 3.85 (dd, *J* = 13.4, 6.7 Hz, 0.4H), 2.95 (br s, 0.4H), 2.83 (br s, 1H), 2.80 (br s, 0.6H), 2.74 (br s, 2H), 2.56 (br t, *J* = 13.4 Hz, 1H), 2.15 (m, 1H), 1.96 (m, 1H), 1.79 (d, *J* = 13.7 Hz, 1H), 1.47 (s, 5.4H), 1.46 (s, 3.6H), 1.29–1.23 (m, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) □ 171.8, 171.6, 165.0, 155.2, 152.8, 152.4, 119.0, 118.8, 80.5, 80.2, 71.3, 71.0, 60.4, 53.9, 46.4, 41.3, 39.5, 38.6, 34.7, 33.5, 28.4, 28.1, 27.6, 19.3, 19.1, 14.1; HRMS (M^+ + Na) calcd for $C_{19}H_{27}NO_6Na$ 388.1731, found 388.1730.

Spectral data for **31**: IR (film) 1732, 1714, 1690, 1154 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) □ 5.94 (d, *J* = 3.6 Hz, 1H), 5.88 (s, 1H), 4.50 (dd, *J* = 11.6, 4.9 Hz, 1H) 4.24 (d, *J* = 11.6 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 4.01 (dd, *J* = 12.7, 6.7 Hz, 1H), 3.85 (br s, 0.2H), 3.38 (br s, 0.8H), 2.86 (td, *J* = 12.7, 5.6 Hz, 1H), 2.63 (d, *J* = 10.0 Hz, 1H), 2.57 (d, *J* = 13.8 Hz, 1H), 2.14 (m, 1H), 2.09 (br s, 1H), 1.96 (m, 1H), 1.82 (d, *J* = 13.8 Hz, 1H), 1.52 (s, 9H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) □ 169.4, 164.3, 155.2, 152.0, 118.5, 80.9, 74.0, 60.5, 53.1, 44.6, 43.0, 38.6, 36.7, 28.9, 28.4, 19.4, 14.1.

Amide (32). To a solution of 4-methoxybenzylamine (2.2 mL, 16.84 mmol) in CH_2Cl_2 (20 mL) was added slowly trimethylaluminum (8.3 mL of a 2 M solution in hexanes). After being stirred for 0.5 h, a solution of **30** (3.01 g, 8.24 mmol) in CH_2Cl_2 (10 mL) was slowly added at rt. After the reaction mixture had been stirred for 3 h, the reaction was quenched with aqueous saturated NaCl solution (2 mL). The reaction mixture was diluted with EtOAc (100 mL), dried over Na_2SO_4, and filtered through a pad of Celite. The filter cake was rinsed with EtOAc (5 x 20 mL). The combined filtrates were concentrated in vacuo. Purification by column chromatography (silica gel, 1:2 hexane/EtOAc) gave **32** (3.31 g, 80%) as a colorless oil: IR (film) 3309, 1713, 1686, 1655 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) □ 7.15 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 6.25 (br s, 1H), 5.94 (s, 1H), 5.82 (s, 1H), 4.34 (dd, *J* = 14.5, 5.6 Hz, 1H), 4.28 (dd, *J* = 14.5, 5.5 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.82–3.70 (m 1H), 3.79 (s, 3H), 3.56 (m, 1H), 3.49 (m, 1H), 3.23 (m, 1H), 2.90 (br s, 1H), 2.56 (br s, 1H), 2.08 (br s, 1H), 2.08–1.90 (m, 3H), 1.74 (d, *J* = 11.0 Hz, 1H), 1.55 (m, 1H), 1.43 (s, 9H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) □ 174.0, 166.6, 159.0, 156.3, 155.1, 154.6, 130.2, 129.1, 117.0, 116.1, 114.0, 113.8, 80.4, 65.5, 65.1, 60.6, 60.4, 55.2, 49.6, 49.2, 48.2, 46.2, 45.7, 43.9, 43.2, 39.3, 36.8, 36.1, 32.3, 31.6, 28.3, 25.4, 24.8, 14.1.

Tricycle (2b). To a solution of **32** (3.11 g, 6.19 mmol) in DMF (30 mL) were added imidazole (1.27 g, 18.7 mmol) and *tert*-butyldimethylsilyl chloride (1.40 g, 9.3 mmol). The reaction mixture was stirred at rt overnight. The mixture was diluted with water (30 mL) and extracted with EtOAc (3 x 30 mL). The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 3:1

hexane/EtOAc) to afford the corresponding silyl ether (3.43 g, 90%) as a colorless oil: IR (film) 3305, 1718, 1690, 1655 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.11 (d, J = 8.6 Hz, 2H), 6.78 (d, J = 8.6 Hz, 2H), 6.59 (br s, 1H), 5.78 (s, 1H), 5.73 (s, 1H), 4.38 (dd, J = 14.6, 6.0 Hz, 1H), 4.22 (dd, J = 14.6, 5.2 Hz, 1H), 4.16–4.07 (m, 2H), 3.80–3.65 (m, 2H), 3.72 (s, 3H), 3.34 (t, J = 10.3 Hz, 1H), 3.24 (m, 1H), 2.99 (br s, 1H), 2.50 (m, 1H), 2.04 (m, 2H), 1.98 (m, 1H), 1.70 (d, J = 13.2 Hz, 1H), 1.41 (s, 9H), 1.36 (m, 1H), 1.24 (t, J = 7.2 Hz, 3H), 0.82 (s, 9H), –0.02 (s, 3H), –0.04 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 174.0, 165.1, 158.8, 155.5, 154.8, 130.4, 128.8, 116.5, 113.9, 79.8, 65.1, 59.8, 55.1, 49.0, 46.6, 43.8, 42.9, 39.7, 36.3, 32.2, 28.3, 25.8, 24.9, 18.1, 14.1, –5.5.

To a solution of this silyl ether (3.12 g, 5.06 mmol) in THF (30 mL) was added at 0 °C NaH (0.41 g, 60 % in mineral oil; 10.1 mmol). After the reaction mixture had been stirred at rt for 8 h, the reaction was quenched by addition of water (30 mL) at 0 °C. The mixture was extracted with EtOAc (2 x 50 mL). The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 3:1 hexane/EtOAc) to give **2b** (2.96 g, 95%) as a colorless oil: IR (film) 1736, 1693 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.18 (d, J = 8.6 Hz, 2H), 6.80 (d, J = 8.6 Hz, 2H), 4.77 (d, J = 15.4 Hz, 1H), 4.49 (s, 1H), 4.05 (br s, 1H), 3.97–3.80 (m, 2H), 3.76 (s, 3H), 3.60 (br s, 0.5 H), 3.42 (br s, 0.5H), 3.27 (t, J = 8.6 Hz, 2H), 3.19 (br s, 1H), 3.05 (br s, 0.5H), 2.84 (br s, 0.5H), 2.67 (s, 1H), 2.62 (br s, 1H), 2.54 (d, J = 4.0, 1H), 2.16–1.98 (m, 3H), 1.85–1.70 (m, 2H), 1.45 (s, 9H), 0.96 (m, 3H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 178.0, 169.3, 158.7, 154.6, 129.8, 129.3, 113.6, 80.1, 66.4, 62.4, 60.2, 55.2, 49.5, 48.9, 43.6, 43.1, 41.4, 38.1, 37.1, 36.8, 35.7, 34.8, 34.4, 28.4, 25.9, 23.2, 20.8, 18.2, 13.7, –5.3; HRMS (M^+) calcd for $C_{33}H_{52}N_2O_7Si$ 616.3544, found 616.3560.

Tricycle (2c). To a solution of **33** (3.5 g, 5.08 mmol) in THF (30 mL) at 0 °C was added NaH (60%, 1.02 g, 25.4 mmol). The reaction mixture was stirred at 0 °C for 30 min, allowed to warm to 40 °C, and stirred for an additional 8 h. After the resulting mixture had been cooled to 0 °C, it was quenched with aqueous saturated solution of NH_4Cl (20 mL) and then diluted with EtOAc (50 mL). The aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography using 3:1 hexanes–EtOAc as eluent provided the tricyclic core (**2c**) (3.19 g, 91%) as a colorless oil: R_f 0.25 (1:3 hexanes–EtOAc); IR (neat) 1736, 1693 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 7.24 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 4.41 (s, 2H), 4.33 (br s, 1H), 4.12–4.00 (m, 2.6H), 3.88 (m, 0.4H), 3.79 (s, 3H), 3.49–3.38 (m, 2H), 3.36–3.04 (m, 5H), 2.85 (s, 0.4H), 2.81 (s, 0.6H), 2.77–2.62 (m, 2H), 2.43 (br s, 1H), 2.21–2.09 (m, 1H), 2.08–1.89 (m, 2H), 1.82–1.53 (m, 6H), 1.45 (s, 9H), 1.19 (t, J = 6.9 Hz, 3H), 0.87 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 177.9, 169.8, 169.6, 159.1, 154.4, 130.6,

129.2, 113.7, 80.2, 80.0, 72.5, 69.5, 66.6, 62.6, 60.7, 55.2, 49.7, 49.3, 43.3, 41.4, 41.0, 38.0, 37.0, 36.5, 36.3, 35.0, 28.4, 27.5, 25.8, 23.4, 23.2, 21.1, 20.8, 18.3, 14.1, –5.3; HRMS (M^+ – *tert*-butyl) calcd for $C_{33}H_{51}N_2O_8Si$ 631.3415, found 631.3392.

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