CH_3OH, R_f = 0.80), in addition to some unreacted starting material (R_f = 0.28). The product was purified on a small SiO_2 flash column (17 cm × 1.5 cm) eluted with CH_2Cl_2. Yield of clear glass: 9.5 mg, 0.021 mmol, 24%. [Unreacted starting materials (33 mg) were eluted with CH_2Cl_2/10 to 50% CH_3OH]: UV (hexanes) λ^1_{max} 296 nm, λ^2_{max} 243 nm; ^1H NMR (500 MHz, C_6D_6) δ H_{3e} (3.57, m, 1 H), H_4 (5.44, ddd, J = 10, 5.5, 3.5 Hz, 1 H), H_5 (5.33, br d, J = 10 Hz, 1 H), H_{6a} (1.83, br t, J = 12 Hz, 1 H), H_{7a} (0.87, q,* J = 12 Hz, 1 H), H_{7e} (1.64, br d, J = 12 Hz, 1 H), H_{8a} (1.41, br m, 1 H), H_{9a} (1.36, dddd, J = 12, 12, 12, 3.5 Hz, 1 H), H_{9e} (1.99, br d, J = 12 Hz, 1 H), H_{10a} (1.18, br q,* J = 12 Hz, 1 H), H_{10e} (2.58, br d, J = 12 Hz, 1 H), H_{11a} (1.91, t,* J = 12 Hz, 1 H), H_{12} (1.92, s, 3 H), H_{13}/H_{14} (5.23, m,‡ 2 H), H_{15} (1.21, d, J = 4.5 Hz, 3 H), H_{16} (0.90, d, J = 6.5 Hz, 3 H), $H_{5'}$ (2.82, s, 1 H), $H_{6'}$ (3.97, dd, J = 12, 1.5 Hz, 1 H), $H_{6''}$ (3.40, dd, J = 12, 2.0 Hz, 1 H), $H_{7'}$ (2.32, s, 3 H), H_{ortho} (7.81, d, J = 8.0 Hz, 2 H), H_{meta} (7.43, t, J = 8.0 Hz, 2 H), H_{para} (7.28, t, J = 8.0 Hz, 1 H). (*, partially obscured; ‡, overlapping); ^1H NMR (500 MHz, $CDCl_3$) δ H_{3e} (3.16, m, 1 H), H_4 (5.32, ddd, J = 10, 5.0, 2.5 Hz, 1 H), H_5 (5.37, br d, J = 10 Hz, 1 H), H_{6a} (1.87, br t,* J = 12 Hz, 1 H), H_{7a} (0.88, q, J = 12 Hz, 1 H), H_{7e} (1.81, br d, J = 12 Hz, 1 H), H_{8a} (1.54, br m, 1 H), H_{9a} (1.15, dddd, J =12, 12, 12, 3.5 Hz, 1 H), H_{9e} (1.90, br d, J = 12, 1 H), H_{10a} (0.96, br q,* 1 H), H_{10e} (2.20, br d, J = 12 Hz, 1 H), H_{11a} (1.63, t, J = 12 Hz, 1 H), H_{12} (1.51, s, 3 H), H_{13} (4.93, ddd, J = 15, 8.5, 1.5 Hz, 1 H), H_{14} (5.08, dq, J = 15, 6.5 Hz, 1 H), H_{15} (1.23, d, J = 6.5 Hz, 3 H), H_{16} (0.96, d, J = 6.5 Hz, 3 H), $H_{5'}$ (3.50, br s, 1 H), $H_{6'}$ (3.97, dd, J = 12, 1.5 Hz, 1 H), $H_{6''}$ (3.71, dd, J = 12, 3.0 Hz, 1 H), $H_{7'}$ (3.25, s, 3 H), H_{ortho} (7.54, dd, J = 8.0, 1.5 Hz, 2 H), H_{meta} (7.36, br t, J = 8.0 Hz, 2 H), H_{para} (7.31, br t, J = 8.0 Hz, 1 H). (*, partially obscured); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 194.2 (C_1), 189.6 ($C_{4'}$), 173.9 ($C_{2'}$), 132.1 ($2C_{ortho}$), 131.6 (C_5), 130.6 (C_{para}), 127.8 ($2C_{meta}$), 127.6 (C_4 or C_{13} or C_{14}), 126.8 (C_4 or C_{13} or C_{14}), 126.6 (C_4 or C_{13} or C_{14}), 101.2 ($C_{3'}$), 69.6 ($C_{5'}$), 60.8 ($C_{6'}$), 48.9 (C_2), 46.0 (C_3), 42.7 (C_7), 40.9 (C_{11}), 39.1 (C_6), 36.4 (C_9), 34.1 (C_8), 28.8 (C_{10}), 28.3 ($C_{7'}$), 22.7 (C_{16}), 17.6 (C_{15}), 14.0 (C_{12}); CI(-) MS (NH_3) m/z 459 (16), 357 (54), 355 (100), 343 (38), 341 (37), 339 (31), 337 (23), 327 (22), 195 (32), 181 (41), 167 (31), 153 (20); CI(-) MS (NH_3), CAD (N_2) m/z 459 (M^-, 100), 355 (28), 337 (51).

Acetonide Formation. One crystal of pTSA was added to a solution of the *Fusarium* toxin (4.0 mg, 10.7 μmol) in dimethoxypropane (2 mL). After being stirred at room temperature for 2 h, the solution was diluted with 10 mL of $CHCl_3$ and extracted 1× with 2% $NaHCO_3$ and 1× with brine and the organic layer was dried over Na_2SO_4. TLC indicated a mixture of product (SiO_2, benzene/30% CH_3OH, R_f = 0.81) and unreacted starting material (R_f = 0.57). The product was purified on two small SiO_2 columns (pasteur pipets) eluted with benzene/10% CH_3OH and benzene/5% CH_3OH: yield after purification 0.5 mg, 1.21 μmol, 11% (not optimized); GC-MS m/z 413 (19), 395 (8), 355 (18), 337 (17), 336 (18), 250 (38), 239 (44), 203 (37), 192 (30), 182 (39), 181 (57), 180 (46), 175 (42), 152 (100), 119 (29), 105 (65).

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Supplementary Material Available: Experimental details of the spectroscopy experiments and seven figures of fully assigned correlation spectra, variable-temperature ^1H and ^{13}C NMR spectra, mass spectra at different ionization potentials, and parent ion MS/MS data (10 pages). Ordering information is given on any current masthead page.

Total Synthesis of the *Fusarium* Toxin Equisetin: Proof of the Stereochemical Relationship of the Tetramate and Terpenoid Sectors

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Contribution from the Department of Chemistry, Yale University, New Haven, Connecticut 06511. *Received November 29, 1988. Revised Manuscript Received March 6, 1989*

Abstract: A total synthesis of the *Fusarium* mycotoxin equisetin, in a manner that establishes its stereochemistry, is described. The key steps involve a lactonic variation of the ester enolate Claisen rearrangement and a novel construction of a 1-acyltetramic acid from an L-*N*-methylserine derivative and a β-keto ester.

Background and General Synthetic Strategy

The fungal metabolite equisetin, isolated from the white mold *Fusarium equiseti*, is suspected to be a promoter of chronic environmental diseases including certain leukemias.[1] Early investigations indicated equisetin to also be a potent antibiotic.[2] Evidence has already been gathered to the effect that equisetin shows selective toxicity to mammalian cells, and that it binds strongly to DNA.[3] Following the isolation and partial characterization of the *Fusarium* toxin by Burmeister and co-workers, a complete structure assignment has been advanced by Lynn and collaborators.[2,3] The identification of an acyltetramic acid moiety, derivable from L-*N*-methylserine, involved a combination of ultraviolet, magnetic resonance, and polarimetric (Cotton effect) measurements. Extensive NMR experiments allowed the Chicago workers to formulate an octalinoid substructure, with the relative configurations shown in system **1**. Left undefined in a rigorous sense was the stereochemical relationship of this octalinoid ("terpenoid") moiety to the stereogenic center at $C_{5'}$[4] in the tetramate sector. Recently the Chicago workers addressed this issue through the novel use of a phenylboronate ester. Analysis of low-temperature NMR data of the boronate derivative of equisetin revealed several important intramolecular dipolar coupling interactions. On the basis of molecular modeling computations (particularly MM2), it was argued that these interactions would be better rationalized if the overall stereochemistry is that shown in expression **1** rather than that arising from an "ent-terpenoid" diastereomer (see compound **18**). Since the validity of these arguments had not been extensively tested in practice,

(1) (a) Wray, B. B.; O'Steen, K. G. *Arch. Environ. Health* **1975**, *30*, 571. (b) Wray, B. B.; Rushing, E. J.; Boyd, R.; Schindel, A. M. *Arch. Environ. Health* **1979**, *34*, 350.

(2) (a) Burmeister, H. R.; Bennett, G. A.; Vesonder, R. F.; Hesseltine, C. W. *Antimicrob. Agents Chemother.* **1974**, *5*, 634. (b) Vesonder, R. F.; Tjarks, L. W.; Rohwedder, W. K.; Burmeister, H. R.; Laugal, J. A. *J. Antibiot.* **1979**, *32*, 759. (c) Burmeister, H. R. Antibiotic Equisetin and Method of Production. U.S. Patent 3,959,468, May 25, 1976.

(3) (a) Phillips, N. J. Ph.D. Thesis, University of Chicago, Chicago, IL, 1986. At this time, the stereochemical arguments favored the structural assignment of equisetin as that shown in **18**. (b) Goodwin, J. T.; Phillips, N. J.; Lynn, D. G. *J. Am. Chem. Soc.*, submitted for publication. (c) Phillips, N. J.; Fraiman, A.; Cole, R. J.; Lynn, D. G. *J. Am. Chem. Soc.*, submitted for publication.

(4) We use the numbering system of Lynn as illustrated in ref 3.

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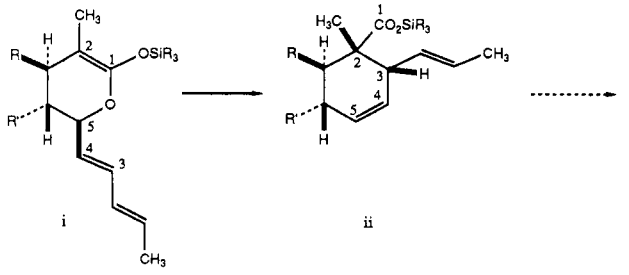
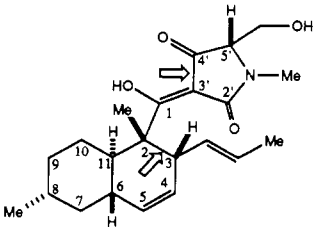
there was a particular need for independent verification. A properly designed total synthesis of the natural product would be corroboratory.

Not the least of the synthetic challenges was an accommodation for the axial *trans*-propenyl residue (at C_3) adjacent to a quaternary stereogenic center (at C_2). We anticipated this substructure to be most efficiently crafted through an intramolecular process, *in particular, via a variation of the lactonic Claisen rearrangement* (see eq 1, i → ii).

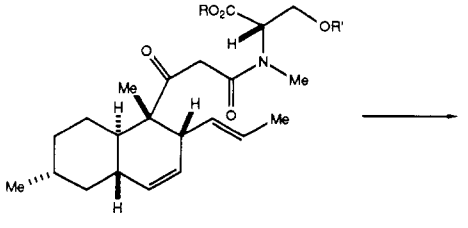


i ii

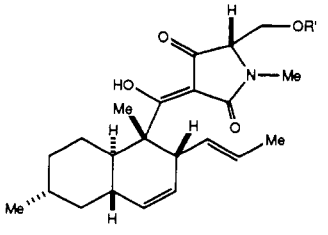


1 (1)

We also saw a need for an innovative approach for the fashioning of the 1-acyltetramate (bearing a potentially labile hydroxymethyl group at $C_{5'}$). It seemed that the quaternary nature of C_2 augured poorly for the possibility of appending a prebuilt tetramic acid derivative to the octalin-bearing C_1 center. Consequently, we contemplated a Dieckmann-type cyclization on a fully functionalized β-keto amide (iii) to produce the target system (iv) (see eq 2). Thus, the heart of the plan was to construct equisetin by establishing the C_2–C_3 and $C_{3'}$–$C_{4'}$ bond sets (see arrows in **1**) through intramolecular means.



iii

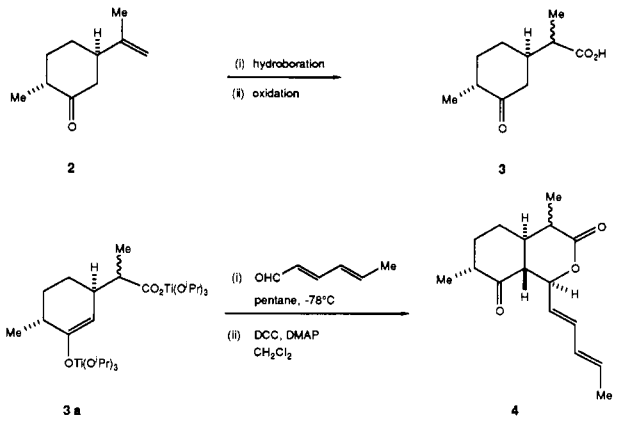


iv (2)

Accepting the *S*-configurational assignment at the $C_{5'}$ tetramate center, our design of a stereoselective synthesis called for the coupling of a "terpenoid" fragment of known stereochemistry to an L-*N*-methylserine derivative, ultimately producing either equisetin or its "ent-terpenoid" diastereomer. The absolute configuration of the "terpenoid" section would be established via synthesis from a chiral educt, namely, dihydrocarvone,[5] which is

(5) deMayo, P. In *The Chemistry of Natural Products*; Interscience: New York, 1959; Vol. 2, p 174.

Scheme I



2 3 3a 4

available in both enantiomeric forms.

Results and Discussion

(*R*)-Dihydrocarvone (**2**) was converted by hydration [(i) diisoamylborane and (ii) alkaline hydrogen peroxide] followed by Jones oxidation to a 1.1:1 mixture of carboxylic acids **3** in 87% yield as a stereoisomeric mixture at the future C_2 (Scheme I). Stereocontrolled incorporation of a hexadienyl fragment was accomplished by the aldol strategy of Reetz.[6] Thus, treatment of epimeric compounds **3** with LDA (2 equiv) followed by transmetalation with triisopropoxychlorotitanium generated a titanium carboxylate enolate (cf. **3a**). Reaction of **3a** with sorbaldehyde at low temperature followed by lactonization of the crude hydroxy acids gave lactone **4** as a 1.4:1 mixture of C_2 epimers (42% overall yield from **3**). The C_2 stereoisomerism was irrelevant to our design (vide infra). *Of great importance was the fact that only syn aldol product was obtained.* Moreover, attack of the sorbaldehyde had occurred, as expected, trans to the propionate side chain.

The key bond reorganization step was now at hand. Following the protocol previously developed in our laboratory,[7] keto lactone **4** was converted to its bissilyl derivative **5** by reaction with lithium diisopropylamide (2 equiv) and TMS-Cl[8] (excess) in THF at −78 °C (Scheme II). Compound **5** was not isolated, but instead subjected to thermolysis in toluene (ca. 105 °C). A very smooth transformation to the "Claisen" product **6** was realized. A detailed account of the factors governing the stereochemistry of this rearrangement process has already been put forth.[7] Cleavage of the silyl groups of **6** with 48% HF in THF at 0 °C provided the keto acid **7** and thence the methyl ester **8** (CH_2N_2, Et_2O), which was promptly reduced ($LiAlH_4$, Et_2O).[9] Purification was achieved at this point and a 52% overall yield (from **4**) of diol **9** was realized.

To complete the synthesis of the octalin system, deoxygenation of the secondary alcohol at C_7 was necessary. It soon became apparent, however, that this transformation would be more difficult than anticipated, undoubtedly a consequence of the sterically hindered nature of the C_7 center as well as the ease with which the C_7 axially directed homoallylic alcohol, under various activation protocols, suffers elimination.[10] After exploring a range of reduction conditions and alcohol activating groups, it was discovered that a C_7 mesylate would undergo clean dissolving-metal reduction. Following protection of the primary C_1 alcohol as its *tert*-bu-

(6) Reetz, M. T.; Peter, R. *Tetrahedron Lett.* **1981**, *22*, 4691.

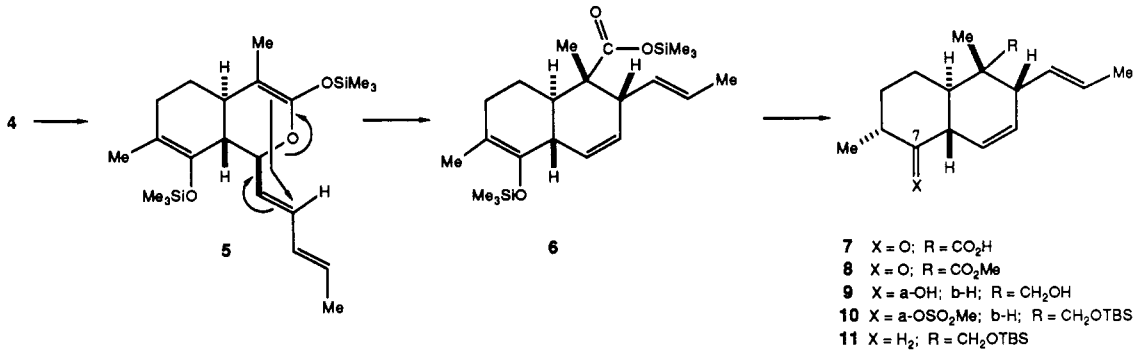
(7) (a) Danishefsky, S. J.; Audia, J. E. *Tetrahedron Lett.* **1988**, *29*, 1371. (b) Danishefsky, S. J.; Funk, R. L.; Kerwin, J. F. *J. Am. Chem. Soc.* **1980**, *102*, 6889. (c) Danishefsky, S. J.; Tsuzuki, K. *J. Am. Chem. Soc.* **1980**, *102*, 6891.

(8) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495.

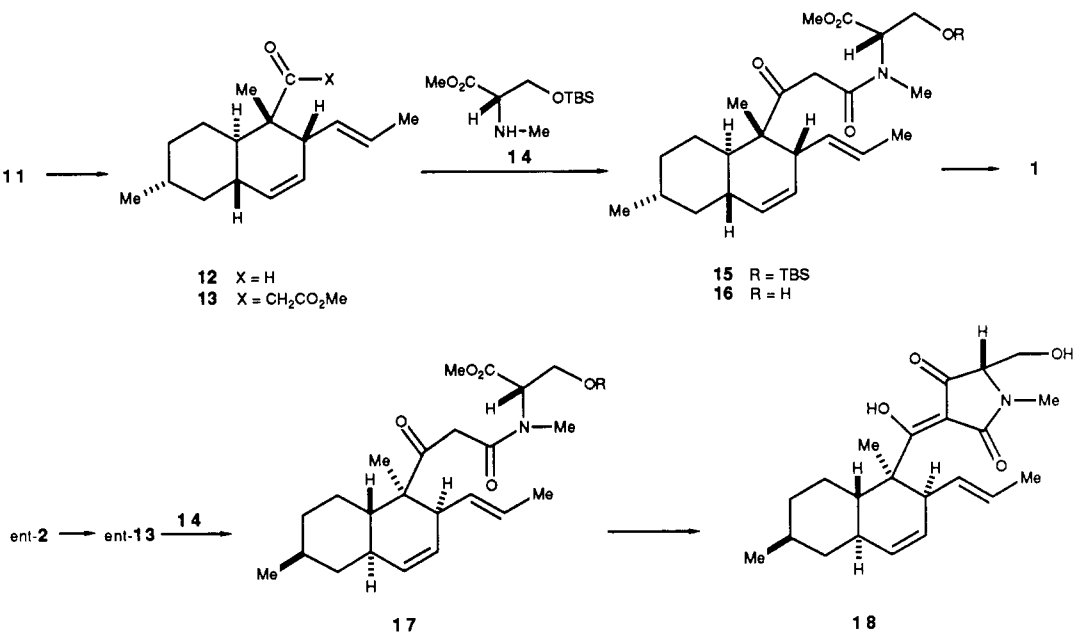
(9) Reduction of the crude keto ester to the diol **9** was typically carried out immediately due to the propensity of the β,γ-unsaturated ketone to isomerize to the α,β-unsaturated system.

(10) All other methods examined to reductively deoxygenate the C_7 center were unsuccessful. Attempts to convert the ketone moiety of either "pre-Claisen" keto lactone **4** or "post-Claisen" keto ester **8** to a more readily reducible functionality (e.g., hydrazone, dithiane, etc.) were not fruitful.

Scheme II



Scheme III



tyldimethylsilyl (TBS) derivative (TBSOTf, Et_3N, CH_2Cl_2, 0 °C) and mesylation of the secondary C_7 alcohol (MsCl, neat pyridine; 83% from **9**), compound **10** was subjected to lithium–ammonia at −78 °C to give deoxygenated product **11** in 89% yield.[11]

Having assembled the requisite octalin system, the C_1 site was readied for construction of the acyltetramic acid moiety, in a manner outlined above, by conversion to β-keto ester **13** (Scheme III). Thus, cleavage of the TBS ether of **11** (48% HF, CH_3CN), followed by Swern oxidation[12] of the resultant alcohol, afforded aldehyde **12** (99% from **11**). The latter was condensed with ethyl diazoacetate in the presence of $BF_3{\cdot}Et_2O$ in 1:1 CH_2Cl_2–diethyl ether at 0 °C to give β-keto ester **13** (51% based on recovered aldehyde).[13,14] Other attempts to prepare the β-keto ester were less efficient. *The serious steric hindrance imposed by the quaternary C_2 center was now used to good advantage.* Condensation of compound **13** with the L-*N*-methylserine derivative **14**[15] in refluxing toluene[16] occurred exclusively at the ester linkage, giving adduct **15**.

With the fully elaborated β-keto amide ester in hand, Dieckmann condensation and removal of the silyl protecting group would complete the total synthesis of **1**. Due to both the lability of the siloxy group toward elimination as well as the instability of the resulting tetramic acid during attempted purification, the Dieckmann cyclization was most efficiently performed on the alcohol **16**, prepared from silyl ether **15** by the action of aqueous HF in acetonitrile (53% overall from **13**). Thus, upon treatment of intermediate **16** with sodium hydride in methylene chloride at 0 °C, there was obtained a foamy substance (**1**, 100%) whose ^1H NMR spectra (490 MHz, several solvents), IR spectra, and TLC characteristics were indistinguishable from those of a specimen sample of natural equisetin supplied to us by Professor David Lynn.[17]

To rigorously establish the structure of equisetin to be **1**, we needed to demonstrate unequivocably that compound **1** and its ent-terpenoid diastereomer **18** can be distinguished by ^1H NMR spectroscopy. It was thus imperative that we synthesize compound **18**. Consequently, the same synthesis as was used to reach β-keto ester **13** was used to prepare ent-**13** from (*S*)-dihydrocarvone (ent-**2**). When ent-**13**, thus produced, was condensed with L-amino ester **14** and the sequence carried to the end, the diastereomer **18** was obtained. The ^1H NMR spectra (490 MHz) of this compound showed small but clear differences in detail from those of natural and synthetic equisetin.[17,18]

(11) A small amount (6%) of the alcohol, resulting from cleavage of the O–S bond, was also obtained. A large excess of lithium metal and slow addition of mesylate **10** were required to favor cleavage of the C–O bond.

(12) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(13) Gutsche, C. D. *Org. React. (N.Y.)* **1954**, *8*, 364.

(14) For another method of converting aldehydes to β-keto esters, see: (a) Pellicciari, R.; Fringuelli, R.; Ceccherelli, P.; Sisani, E. *J. Chem. Soc., Chem. Commun.* **1979**, 959. (b) Singh, A. K.; Bakshi, R. K.; Corey, E. J. *J. Am. Chem. Soc.* **1987**, *109*, 6187.

(15) Preparation of **14** from L-*N*-(*tert*-butoxycarbonyl)-*N*-methylserine (recrystallized as its cyclohexylammonium salt) was achieved by esterification (CH_2N_2) and treatment with TBSOTf (2 equiv) and 2,6-lutidine in CH_2Cl_2, followed by hydrolysis (K_2CO_3, MeOH, H_2O, THF, 0 °C). We thank Dr. Daniel Veber at the Merck Co. for a gift of L-*N*-(*tert*-butoxycarbonyl)-*N*-methylserine.

(16) Labelle, M.; Gravel, D. *J. Chem. Soc., Chem. Commun.* **1985**, 105.

(17) Although the diastereomeric purity of synthetic **1** and **18** was not rigorously determined, the ^1H NMR (490-MHz) analysis in several solvents indicates a minimum level of 90%.

In summary, the total synthesis of equisetin has been accomplished in a manner that establishes its relative stereochemistry to be that shown in **1**.[19] The synthesis demonstrates again the value of strategies that rely on intramolecularity for achieving difficult bond constructions. Synthetic equisetin (**1**) and its diastereomer **18** are currently being examined for mutagenic and tumorogenic behavior. Details of these studies will be reported in due course.

Experimental Section

General Procedure. Melting points were measured on a Thomas Hoover capillary melting point apparatus and are uncorrected. Combustion analyses were performed by Galbraith Laboratories, Inc. Infrared spectra were recorded on a Perkin-Elmer 1420 Ratio recording infrared spectrophotometer. Low-resolution and high-resolution mass spectra were determined on a Hewlett-Packard 5985 quadrapole mass spectrometer and a Kratos MS80RFA spectrometer, respectively. High-field NMR spectra were recorded on either Bruker WM-250 or Yale-490 NMR instruments. Flash chromatography was performed on EM Science Kieselgel 60 (230–400 mesh), eluting with the indicated solvent systems. Tetrahydrofuran (THF) and diethyl ether were freshly distilled from sodium wire–benzophenone ketyl. Methylene chloride was dried over phosphorus pentoxide then distilled immediately prior to use. Toluene and benzene were distilled from CaH_2. Triethylamine, diisopropylamine, and pyridine were distilled from CaH_2 and stored under N_2 over solid KOH. Unless otherwise specified, reagents were used as received.

Keto Acids 3. To an ice-cold stirred solution of 2-methyl-2-butene (57.1 mL, 538 mmol) in THF (250 mL) was added dropwise a solution of borane–THF (1.0 M, 269 mL, 269 mmol). After 2 h a solution of (*R*)-dihydrocarvone (**2**; 16.4 g, 108 mmol) in THF (100 mL) was added, and the mixture was stirred at 5 °C for 18 h. Excess disiamylborane was destroyed by dropwise addition of EtOH (6 mL), 15% NaOH solution (100 mL), and 30% aqueous H_2O_2 (100 mL). The mixture was stirred at 5 °C for 12 h, the layers were separated, and the aqueous layer was extracted three times with Et_2O (200 mL). The combined organic layers were washed with brine (200 mL) and dried over $MgSO_4$, filtered, and evaporated.

The crude oil was dissolved in acetone (250 mL) and cooled to 0 °C. Celite (100 g) was added to the mechanically stirred solution, and Jones reagent (8 N, approximately 300 mL) was added dropwise until a red-brown color persisted. After 10 min, iPrOH (10 mL) was added to destroy excess Jones reagent, and the mixture was filtered and evaporated. The crude oil was partitioned between brine (250 mL) and Et_2O (500 mL), the layers were separated, and the aqueous layer was extracted twice with Et_2O (250 mL). The combined ethereal layers were dried over $MgSO_4$ and evaporated. Flash chromatography (1:10:0.1 EtOAc–hexane–glacial HOAc), with azeotropic removal of residual HOAc with benzene, gave 17.3 g (87%) of keto acids **3** as a 1.1:1 oily mixture of diastereomers: IR ($CDCl_3$) 3300–2400 (br), 2960, 2920, 1705 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) mixture of diastereomers δ 12.5 (br s, 1 H), 2.50–1.87 (m, 6 H), 1.57 (app dq, J = 3.2, 13.3 Hz, 1 H), 1.35 (app ddq, J = 2.6, 3.0, 13.0 Hz, 1 H), 1.20 (t, J = 7.1 Hz, 3 H), 1.11 (dd, J = 4.5, 6.9 Hz, 1 H), 1.03 (d, J = 6.5 Hz, 3 H); mass spectrum (EI, 20 eV), m/z (relative intensity) 184 (M^+, 11), 111 (100), 110 (17), 99 (17), 83 (17), 55 (26); HRMS exact mass calcd for $C_{10}H_{16}O_3$ 184.1095, found 184.1099.

Keto Lactones 4. *n*-Butyllithium (2.5 M in hexanes, 10.9 mL, 27.3 mmol) was added dropwise to an ice-cold solution of iPr_2NH (3.83 mL, 27.3 mmol) in THF (50 mL). After being stirred for 15 min, the solution was cooled to −78 °C. A solution of keto acids **3** (2.28 g, 12.4 mmol) in THF (30 mL) was added dropwise, during which time a colorless gel formed. The mixture was swirled vigorously over a 30-min period and then a solution of $TiCl(OiPr)_3$ (14.8 mL, 62.0 mmol) in THF (20 mL) was added, with the gel eventually becoming a red-brown solution. While being warmed to room temperature, the mixture was slowly evaporated in vacuo through a 14-gauge syringe needle exit port. The residue was suspended in pentane (250 mL, previously dried over 4A molecular sieves) and cooled to −78 °C. To this mixture was added a solution of sorbaldehyde (3.04 mL, 27.3 mmol, freshly distilled at 0.02 Torr with use of a dry ice trap) in pentane (10 mL). After being stirred at −78 °C for 2 h, the reaction mixture was poured into 5% HCl solution (250 mL), and the layers were separated. The aqueous layer was extracted three times with CH_2Cl_2 (200 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was dissolved in CH_2Cl_2 (200 mL) and cooled to 0 °C. (*N,N*-Dimethylamino)pyridine (1.53 g, 12.5 mmol) and dicyclohexylcarbodiimide (3.10 g, 15.0 mmol) were added, and the mixture was stirred at room temperature for 8 h and then filtered through a Celite pad. The filtrate was washed with 5% aqueous HCl (100 mL), dried over $MgSO_4$, and evaporated. Flash chromatography (1:4 EtOAc–hexane) of the crude mixture afforded 720 mg (22%) of the less polar epimer and 640 g (20%) of the more polar epimer as oils:

Less polar epimer: $[\alpha]_D^{23}$ $[\alpha]_D^{23}$ −52° (c = 0.019, $CHCl_3$); IR ($CDCl_3$) 3000, 2960, 2920, 2850, 1730–1700 (br), 1450, 1210, 985 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.34 (ddd, J = 0.6, 10.2, 15.3 Hz, 1 H), 6.00 (app dddd, J = 1.3, 1.6, 10.3, 13.7 Hz, 1 H), 5.74 (app dt, J = 8.3, 15.0 Hz, 1 H), 5.54 (dd, J = 5.8, 15.4 Hz, 1 H), 5.14 (dd, J = 5.8, 10.4 Hz, 1 H) 2.66–2.40 (m, 2 H), 2.38–2.25 (m, 2 H), 2.22–2.10 (m, 2 H), 1.90–1.55 (obscured m, 2 H), 1.73 (d, J = 6.4 Hz, 3 H), 1.50–1.21 (obscured m, 2 H), 1.32 (d, J = 7.0 Hz, 3 H), 1.01 (d, J = 6.4 Hz, 3 H); mass spectrum (EI, 20 eV), m/z (relative intensity) 262 (M^+, 24), 166 (59), 138 (31), 137 (52), 124 (36), 121 (30), 111 (100), 98 (84), 96 (95), 95 (97), 81 (25), 68 (37); HRMS exact mass calcd for $C_{16}H_{22}O_3$ 262.1570, found 262.1556.

More polar epimer: $[\alpha]^{23}_D$ −222° (c = 0.018, $CHCl_3$); IR ($CDCl_3$) 2920, 1720 (sh), 1705, 1230 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.33 (ddd, J = 0.6, 10.6, 15.7 Hz, 1 H), 5.99 (ddd, J = 1.5, 10.4, 15.0 Hz, 1 H), 5.75 (ddd, J = 6.6, 13.1, 15.0 Hz, 1 H), 5.54 (dd, J = 6.0, 15.1 Hz, 1 H), 5.23 (dd, J = 5.9, 10.1 Hz, 1 H), 2.76 (ddd, J = 4.7, 7.5, 15.0 Hz, 1 H), 2.59–2.39 (m, 2 H), 2.29–2.12 (m, 2 H), 1.89–1.66 (obscured m, 2 H), 1.73 (dd, J = 1.2, 6.7 Hz, 3 H), 1.53–1.24 (obscured m, 2 H), 1.29 (d, J = 7.4 Hz, 3 H), 1.03 (d, J = 6.3 Hz, 3 H).

Diol 9. A 1 M stock solution of TMS–Cl in THF was prepared as follows: TMS–Cl (1.27 mL, 10.0 mmol, freshly distilled from CaH_2) was dissolved in THF (5 mL) in a dry 15-mL centrifuge tube fitted with a rubber septum. Et_3N (0.100 mL) was added and the solution was diluted to the 10-mL mark with THF. After 10 min, the mixture was centrifuged and used immediately.

n-Butyllithium (2.5 M in hexanes, 0.88 mL, 2.2 mmol) was added dropwise to an ice-cold solution of iPr_2NH (0.31 mL, 2.2 mmol) in THF (5 mL). After stirring for 20 min, the solution was cooled to −78 °C. To this was added 1 M TMS–Cl solution (6.0 mL, 6.0 mmol), followed by a solution of the 1.1:1 mixture of keto lactones **4** (259 mg, 0.99 mmol) in THF (5 mL). The reaction mixture was stirred at −78 °C for 30 min and then warmed to room temperature while evaporating in vacuo.

The residue was suspended in toluene (25 mL) and heated to reflux for 10 h. After being cooled to room temperature, the mixture was poured into 5% HCl solution (25 mL), the layers were separated, and the aqueous layer was extracted three times with CH_2Cl_2 (25 mL). The combined organic layers were dried over $MgSO_4$ and evaporated. The residue was dissolved in THF (5 mL) and cooled to 0 °C. Aqueous HF solution (48%, 10 drops) was added, and the mixture was stirred at 0 °C for 1.5 h. Et_2O (15 mL) was added and the mixture was poured into brine (15 mL). The layers were separated, the aqueous layer was extracted three times with Et_2O (15 mL), and the combined ethereal layers were dried over $MgSO_4$ and concentrated to approximately half-volume. Ethereal CH_2N_2 was added at 0 °C until a yellow color persisted and N_2 evolution ceased. The solution was concentrated to half-volume under a stream on N_2; the solution was poured into brine (25 mL) and extracted three times with Et_2O. The combined ethereal layers were dried over $MgSO_4$ and evaporated.

The crude oil was dissolved in Et_2O (10 mL) and added to an ice-cold suspension of $LiAlH_4$ (89 mg, 2.3 mmol) in Et_2O (20 mL). The reaction was stirred for 3 h and then quenched by sequential dropwise additions of H_2O (0.1 mL), 15% aqueous NaOH (0.2 mL), and saturated NH_4Cl solution (0.3 mL). The mixture was stirred for 30 min and filtered through a Celite pad, and the salts were washed with Et_2O (100 mL). The filtrate was washed with brine (100 mL), dried over $MgSO_4$, and evaporated. Flash chromatography (1:4 EtOAc–hexane) of the crude product provided 128 mg (52%) of diol **9** as a white crystalline solid: mp 107–108 °C (EtOAc); $[\alpha]^{23}_D$ −290° (c = 0.015, $CHCl_3$); IR ($CDCl_3$) 3580 (OH), 2965, 2935, 2880, 975 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$)

(18) Lynn and co-workers demonstrated that equisetin slowly epimerizes in pyridine. The high-field ^1H NMR spectrum of this mixture showed the presence of two sets of signals, indicating that as a mixture the two epimers could be distinguished spectroscopically. We confirmed this observation by equilibrating compound **1** to a mixture of **1** and ent-**18**, and compound **18** to a mixture of **18** and ent-**1**. In both cases, the ^1H NMR spectrum of the resulting epimeric mixture was similar to that of Lynn's equilibrated mixture.

(19) Although the specimen sample of natural equisetin from Professor Lynn was sufficiently homogeneous for correlation purposes by ^1H NMR spectroscopy, it appeared to be contaminated with hydrocarbon residuals. Thus, the magnitude of its optical rotation ($[\alpha]^{23}_D$ = −146°) was less than that of a purified sample of our synthetic equisetin ($[\alpha]^{23}_D$ = −253°) (see Experimental Section). Nevertheless, since the rotations of both natural and synthetic equisetin are of the same sign, our findings support Lynn's assignment of the absolute stereochemistry of the natural product to be that shown in **1**.

δ 5.67–5.48 (m, 4 H), 3.81 (app s, 1 H), 3.45 (app s, 2 H), 2.45 (app t, J = 5.8 Hz, 1 H), 1.95 (tdd, J = 2.1, 4.2, 11.2 Hz, 1 H), 1.81–1.25 (obscured m, 6 H), 1.70 (d, J = 4.9 Hz, 3 H), 1.13–0.97 (partially obscured m, 2 H), 0.99 (d, J = 6.6 Hz, 3 H), 0.85 (s, 3 H); mass spectrum (EI, 20 eV), m/z (relative intensity) 250 (M^+, 12), 232 (34), 201 (100), 159 (59), 145 (83), 123 (90); HRMS exact mass calcd for $C_{16}H_{26}O_2$ 250.1934, found 250.1926. Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.24; H, 10.46.

Mesylate 10. A solution of diol **9** (754 mg, 3.02 mmol) in CH_2Cl_2 (30 mL) was cooled to 0 °C and pyridine (0.50 mL, 6.2 mmol) was added. To this was added dropwise *tert*-butyldimethylsilyl triflate (0.70 mL, 3.05 mmol). The mixture was stirred for 30 min then poured into 5% HCl solution (30 mL). The layers were separated, the aqueous layer was extracted three times with CH_2Cl_2 (30 mL), and the combined extracts were dried over $MgSO_4$ and evaporated. Flash chromatography (1:9 EtOAc–hexane) of the crude product afforded 1.00 g (91%) of the monosilyl ether as a colorless oil: $[\alpha]^{23}_D$ −161° (c = 0.026, $CHCl_3$); IR ($CDCl_3$) 3580 (small OH), 2960, 2935, 2860, 1095, 845 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.64 (ddd, J = 2.7, 5.1, 9.8 Hz, 1 H), 5.55–5.35 (m, 3 H), 3.79 (app s, 1 H), 3.35 (app s, 2 H), 2.52 (app t, J = 5.2 Hz, 1 H), 1.93 (tdd, J = 2.2, 4.5, 11.1 Hz, 1 H), 1.71–1.25 (m, 5 H), 1.66 (d, J = 6.3 Hz, 3 H), 1.21 (m, 1 H), 1.15–0.90 (obscured m, 1 H), 0.99 (d, J = 6.6 Hz, 3 H), 0.90 (s, 9 H), 0.86 (s, 3 H), 0.02 (s, 6 H); mass spectrum (EI, 20 eV), m/z (relative intensity) 307 (M − tBu, 29), 289 (11), 215 (37), 173 (45), 159 (62), 145 (52), 105 (100), 84 (96); CI HRMS (M + 1) exact mass calcd for $C_{22}H_{40}O_2Si$ 365.2877, found 365.2869. Anal. Calcd for $C_{22}H_{40}O_2Si$: C, 72.47; H, 11.06. Found: C, 72.34; H, 10.60.

A solution of the above silyl ether (0.977 g, 2.68 mmol) in pyridine (3 mL) was treated with methanesulfonyl chloride (1.0 mL, 12.9 mmol). After stirring at room temperature for 9 h, the resulting black reaction mixture was partitioned between Et_2O (20 mL) and 5% $CuSO_4$ solution (20 mL). The aqueous layer was extracted twice with Et_2O (20 mL), and the combined organic extracts were washed three times with 5% $CuSO_4$ solution (20 mL), dried over $MgSO_4$, and evaporated. Flash chromatography (1:9 EtOAc–hexane) of the crude oil gave 1.08 g (91%) of mesylate **10** as a colorless oil: $[\alpha]^{22}_D$ −97° (c = 0.026, $CHCl_3$); IR ($CDCl_3$) 2960, 2935, 2860, 1350, 1180 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.67–5.56 (AB m, 2 H), 5.44–5.41 (AB m, 2 H), 5.02 (app s, 1 H), 3.35 (app s, 2 H), 3.04 (s, 3 H), 2.53 (m, 1 H), 2.05 (br d, J = 11.0 Hz, 1 H), 1.77–1.65 (obscured m, 2 H), 1.66 (d, J = 4.6 Hz, 3 H), 1.62–1.50 (obscured m, 2 H), 1.47–1.25 (m, 1 H), 1.20–1.00 (m, 1 H), 1.06 (d, J = 6.7 Hz, 3 H), 0.91 (s, 9 H), 0.86 (s, 3 H), 0.02 (s, 6 H); mass spectrum (EI, 20 eV), m/z (relative intensity) 385 (M − tBu, 26), 289 (24), 215 (100), 173 (60), 159 (76), 153 (91); CI HRMS (M + 1) exact mass calcd for $C_{23}H_{42}O_4SSi$ 443.2653, found 443.2651. Anal. Calcd for $C_{23}H_{42}O_4SSi$: C, 62.40; H, 9.56. Found: C, 61.62; H, 9.62.

Silyl Ether 11. Li wire (530 mg, 77 mmol, cut into small pieces) was added to anhydrous ammonia (100 mL) at −78 °C and the mixture was stirred until the lithium metal was completely dissolved (approximately 30 min). A solution of mesylate **10** (1.077 g, 2.44 mmol) in THF (25 mL) was added dropwise over 30 min, the mixture was stirred at −78 °C for 30 min, and the reaction was quenched by addition of solid NH_4Cl (300 mg). Upon evaporation of the ammonia, the mixture was partitioned between H_2O (100 mL) and Et_2O (100 mL), the layers were separated, and the aqueous layer was extracted two times with Et_2O (50 mL). The combined extracts were dried over $MgSO_4$ and evaporated. Flash chromatography (1:10 Et_2O–hexane) afforded 48 mg (6%) of the alcohol and 751 mg (89%) of silyl ether **11** as a colorless oil: $[\alpha]^{22}_D$ −182° (c = 0.014, $CHCl_3$); IR ($CDCl_3$) 2960, 2935, 2860, 1095, 860, 845 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.56–5.32 (m, 4 H), 3.34 (AB m, 2 H), 2.48 (m, 1 H), 1.82–1.70 (m, 3 H), 1.67 (d, J = 6.1 Hz, 3 H), 1.53–1.35 (m, 2 H), 1.18–1.00 (m, 2 H), 0.99–0.61 (obscured m, 1 H), 0.91 (s, 9 H), 0.87 (d, J = 6.2 Hz, 3 H), 0.02 (s, 6 H); mass spectrum (EI, 20 eV), m/z (relative intensity) 348 (M^+, 0.1), 291 (56), 215 (67), 175 (70), 75 (100); CI HRMS (M + 1) exact mass calcd for $C_{22}H_{40}OSi$ 349.2928, found 349.2914. Anal. Calcd for $C_{22}H_{40}OSi$: C, 75.79; H, 11.56. Found: C, 75.59; H, 11.41.

Aldehyde 12. A suspension of silyl ether **11** (689 mg, 1.98 mmol) in CH_3CN (25 mL) was treated with 48% HF solution (20 drops). The cloudy mixture was stirred until homogeneous (approximately 1 h). Solid $NaHCO_3$ (200 mg) and then saturated $NaHCO_3$ solution (20 mL) were added carefully, and the mixture was concentrated to approximately a 40-mL volume. The mixture was diluted with H_2O (20 mL) and extracted three times with Et_2O (50 mL). The combined extracts were dried over $MgSO_4$ and evaporated. Flash chromatography (1:4 Et_2O–hexane) of the crude material provided 463 mg (100%) of the alcohol as a colorless oil: $[\alpha]^{23}_D$ −237° (c = 0.011, $CHCl_3$); IR ($CDCl_3$) 3550 (small OH), 2960, 2920, 2870 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.66–5.41 (m, 3 H), 5.35 (ddd, J = 2.3, 4.6, 10.0 Hz, 1 H), 3.46 (AB m, 2 H), 2.45 (m, 1 H), 1.85–1.70 (obscured m, 3 H), 1.71 (d, J = 6.1 Hz, 3 H), 1.65–1.55 (m, 2 H), 1.54–1.37 (m, 1 H), 1.25–0.72 (obscured m, 4 H), 0.91 (d, J = 6.5 Hz, 3 H), 0.85 (s, 3 H); mass spectrum (EI, 20 eV), m/z (relative intensity) 234 (M^+, 28), 203 (100), 161 (28), 149 (23), 147 (22); HRMS exact mass calcd for $C_{16}H_{26}O$ 234.1985, found 234.1986. Anal. Calcd for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 80.66; H, 11.11.

A solution of the above alcohol (436 mg, 1.8 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a stirred solution of oxalyl chloride (0.350 mL, 4.0 mmol) and DMSO (0.570 mL, 8.0 mmol) in CH_2Cl_2 (10 mL) at −78 °C. The mixture was stirred for 30 min, Et_3N (1.20 mL, 8.58 mmol) was added, and the solution was warmed to room temperature. Aqueous HCl (5%, 25 mL) was added, the layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined extracts were dried over $MgSO_4$ and concentrated. Flash chromatography (1:10 Et_2O–hexane) of the crude product afforded 427 mg (99%) of aldehyde **12** as a colorless oil, which slowly crystallized in the freezer to give a waxy solid: $[\alpha]^{23}_D$ −311 (c = 0.058, $CHCl_3$); IR ($CDCl_3$) 3000, 2940, 2910, 1710, 1450, 975 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.47 (s, 1 H), 5.60–5.34 (m, 4 H), 2.54 (m, 1 H), 1.88–1.70 (m, 3 H), 1.66 (d, J = 4.9 Hz, 3 H), 1.66–1.36 (obscured m, 3 H), 1.35–0.80 (obscured m, 4 H), 1.00 (s, 3 H), 0.94 (d, J = 6.5 Hz, 3 H); mass spectrum (EI, 20 eV), m/z (relative intensity) 232 (M^+, 97), 217 (38), 161 (47), 150 (51), 148 (58), 147 (72), 123 (42), 110 (43), 107 (49), 106 (81), 105 (100).

β-Keto Ester 13. An ice-cold solution of aldehyde **12** (35 mg, 0.15 mmol) in 1:1 Et_2O–CH_2Cl_2 (2 mL) was treated dropwise with $BF_3{\cdot}Et_2O$ (0.020 mL, 0.16 mmol) and then ethyl diazoacetate (0.030 mL, 0.29 mmol). After 2 h, the solution was diluted with CH_2Cl_2 (10 mL) and poured into 5% aqueous $NaHCO_3$ (5 mL). The layers were separated, the aqueous layer was extracted twice with CH_2Cl_2 (5 mL), and the combined extracts were dried over $MgSO_4$ and evaporated. Preparative TLC (1:8 EtOAc–hexane) of the crude mixture gave 14.6 mg of recovered aldehyde **12** and 14.4 mg (30%, 51% based on recovered aldehyde) of β-keto ester **13** as a colorless oil: $[\alpha]^{23}_D$ −213° (c = 0.065, $CHCl_3$); IR ($CDCl_3$) 2965, 2920, 1735, 1705 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.59–5.25 (m, 3 H), 5.20–5.08 (m, 1 H), 4.28–4.09 (m, 2 H), 3.53 (d, J = 15.8 Hz, 1 H), 3.35 (d, J = 15.8 Hz, 1 H), 2.61–2.54 (m, 1 H), 1.90–0.80 (m, 12 H), 1.61 (dd, J = 1.5, 6.4 Hz, 3 H), 1.18 (s, 3 H), 0.90 (d, J = 6.5 Hz, 3 H); mass spectrum (EI, 20 eV), m/z (relative intensity) 318 (M^+, 10), 300 (14), 237 (19), 203 (70), 107 (67), 105 (100); HRMS exact mass calcd for $C_{20}H_{30}O_3$ 318.2196, found 318.2190.

Coupled Adduct 15. A solution of β-keto ester **13** (17 mg, 0.053 mmol) and *N*-methylamino ester **14** (27 mg, 0.11 mmol) in toluene (2 mL) was heated to reflux for 10 h. Evaporation of the solvent and flash chromatography (1:3 EtOAc–hexane) of the crude product afforded 17.7 mg (64%) of adduct **15** as a colorless foam: IR ($CDCl_3$) 2940, 2915, 2840, 1735, 1700, 1635, 1600, 1455, 1255, 1115, 835, 775 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) mixture of amide rotamers δ 5.42–5.32 (m, 3 H), 5.32–5.08 (m, 2 H), 4.89–4.82 (m, minor), 4.13 (dd, J = 6.4, 10.8 Hz, 1 H), 4.03–3.95 (m, 1 H), 3.79–3.72 (m, 3 H), 3.46–3.34 (m, minor), 3.09–2.99 (m, 3 H), 2.59–2.54 (br dd, J = 4.3, 9.0 Hz, 1 H), 2.46–2.38 (m, minor), 1.88–1.57 (m, 5 H), 1.60 (dd, J = 1.1, 6.1 Hz, 3 H), 1.57–1.40 (m, 2 H), 1.23 (m, 3 H), 1.18–0.80 (obscured m, 4 H), 0.90 (d, J = 6.5 Hz, 3 H), 0.90 (s, minor), 0.87 (s, 9 H), 0.10 (s, minor), 0.06 (s, 6 H); mass spectrum (EI, 20 eV), m/z (relative intensity) 519 (M^+, 15), 462 (100), 387 (30), 248 (40), 184 (25); HRMS exact mass calcd for $C_{29}H_{49}O_5NSi$ 519.3382, found 519.3388.

Pretoxin 16. A suspension of silyl ether **15** (22 mg, 0.042 mmol) in CH_3CN (2 mL) was treated with 48% HF solution (5 drops). The cloudy mixture was stirred for 15 min, and solid $NaHCO_3$ (200 mg) and then H_2O (1 mL) were added carefully. After concentrating under a stream of N_2, the mixture was diluted with H_2O (5 mL) and extracted five times with EtOAc (5 mL). The combined extracts were dried over $MgSO_4$ and evaporated. Flash chromatography (1:2 EtOAc–hexane) of the residue gave 13.6 mg (79%) of pretoxin **16** as a colorless foam: $[\alpha]^{23}_D$ −183° (c = 0.014, $CHCl_3$); IR ($CDCl_3$) 3650–3300 (OH), 3020, 2960, 2925, 2870, 2850, 1740, 1710 (sh), 1650, 1460, 1295, 1055 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) mixture of amide rotamers δ 5.46–5.28 (m, 3 H), 5.26–5.12 (m, 1 H), 4.84–4.75 (m, minor), 4.11–4.00 (m, 2 H), 3.77–3.74 (m, 3 H), 3.58–3.40 (m, 1 H), 2.97–2.92 (major and minor s, 3 H), 2.57 (br dd, J = 4.4, 9.0 Hz, 1 H), 1.87–1.60 (m, 5 H), 1.59 (d, J = 6.8 Hz, 3 H), 1.59–1.38 (m, 2 H), 1.38–0.80 (obscured m, 5 H), 1.23 (s, 3 H), 0.91 (d, J = 6.5 Hz, 3 H); mass spectrum (EI, 20 eV), m/z (relative intensity) 406 (M^+, 5), 388 (9), 232 (24), 203 (42), 174 (38), 134 (100), 84 (38); HRMS exact mass calcd for $C_{23}H_{35}O_5N$ 405.2517, found 405.2530.

Synthetic Equisetin (1). β-Keto amide ester **16** (13.6 mg, 0.034 mmol) was dissolved in CH_2Cl_2 (2 mL) and cooled to 0 °C. Sodium hydride (60% in mineral oil, 7.7 mg, 0.19 mmol) was added and the reaction

mixture was warmed to room temperature. After 30 min, excess NaH was destroyed by addition of 5% aqueous HCl (2 mL). The layers were separated, the aqueous layer was extracted three times with CH_2Cl_2 (2 mL), and the combined organic layers were dried over $MgSO_4$ and evaporated. The crude product was purified by dissolving in 1 N NaOH solution (2 mL) and washing twice with 5:1 hexane–CH_2Cl_2 (2 mL). The aqueous layer was acidified to pH 1 with 5% HCl solution and extracted five times with CH_2Cl_2 (2 mL). The combined acid extracts were dried over $MgSO_4$ and evaporated to afford 12.5 mg (100%) of synthetic equisetin (**1**) as a colorless foam: $[\alpha]^{23}_D$ −253° (c = 0.038, $CHCl_3$);[18] IR ($CDCl_3$) 3600–3100 (OH), 3020, 2940, 2910, 2840, 1560, 1405, 1265 cm^{-1}; ^{1}H NMR (490 MHz, $CDCl_3$) δ 5.40 (m, 2 H), 5.30–5.10 (m, 2 H), 4.07 (dd, J = 3.5, 12.0 Hz, 1 H), 3.90 (dd, J = 5.0, 12.0 Hz, 1 H), 3.67 (app t, J = 5.0 Hz, 1 H), 3.32 (br, 1 H), 3.07 (s, 3 H), 2.00–1.70 (m, 4 H), 1.56 (d, J = 6.5 Hz, 3 H), 1.60–1.40 (m, 7 H), 1.30–0.90 (m, 3 H), 0.92 (d, J = 6.5 Hz, 3 H); mass spectrum (EI, 20 eV), m/z (relative intensity) 373 (M^+, 8), 355 (20), 210 (68), 200 (71), 199 (100), 170 (88), 149 (52), 143 (37); HRMS exact mass calcd for $C_{22}H_{31}O_4N$ 373.2254, found 373.2241.

Ent-Epimer 18: IR ($CDCl_3$) 3600–3100 (OH), 3020, 2940, 2910, 2840, 1560, 1405, 1265 cm^{-1}; ^{1}H NMR (490 MHz, $CDCl_3$) δ 5.42 (m, 2 H), 5.30–5.10 (m, 2 H), 4.06 (dd, J = 3.5, 12.0 Hz, 1 H), 3.85 (dd, J = 5.0, 12.0 Hz, 1 H), 3.66 (app t, J = 3.5 Hz, 1 H), 3.36 (br, 1 H), 3.05 (s, 3 H), 2.00–1.70 (m, 4 H), 1.56 (d, J = 6.5 Hz, 3 H), 1.60–1.40 (m, 7 H), 1.30–0.90 (m, 3 H), 0.92 (d, J = 6.5 Hz, 3 H); mass spectrum (EI, 20 eV), m/z (relative intensity) 373 (M^+, 8), 355 (20), 210 (68), 200 (71), 199 (100), 170 (88), 149 (52), 143 (37).

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Intramolecular Reductive Coupling Reactions Promoted by Samarium Diiodide

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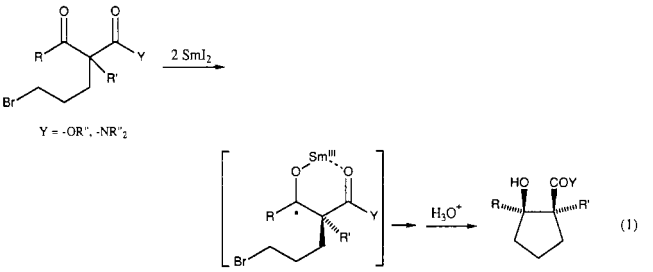
Abstract: Samarium diiodide is a useful reagent for promoting intramolecular reductive coupling reactions, generating functionalized carbocycles. Ketone–olefin coupling, pinacolic coupling, and other related reductive coupling reactions are accomplished under mild conditions with samarium diiodide. Products are accessed in high yield, and in many cases excellent stereochemical control is achieved at three contiguous stereocenters. Factors controlling the stereochemical outcome of these reactions are discussed, and mechanistic considerations are also outlined.

Samarium diiodide (SmI_2) has become an extremely useful reagent to organic chemists.[2] Recent applications, including intramolecular Barbier reactions,[3] intramolecular Reformatsky reactions,[4] and ketyl coupling reactions[5] reveal the outstanding versatility of this reagent. We have demonstrated that SmI_2 is particularly efficient and perhaps unique in promoting highly selective, stereocontrolled reductive coupling reactions. The continued development of SmI_2-mediated stereoselective reactions has thus allowed entry into highly functionalized organic molecules inaccessible by more conventional methods.

Initial studies performed by Kagan and co-workers demonstrated that SmI_2 was a useful reagent for promoting intermolecular Barbier coupling reactions.[6] Our earliest studies utilized SmI_2 to promote intramolecular Barbier coupling reactions.[3a] This route to functionalized carbocycles permits excellent stereochemical control at two adjacent stereocenters utilizing 2-(ω-haloalkyl)-β-keto esters and 2-(ω-haloalkyl)-β-keto amides as cyclization substrates. Highly functionalized five- and (in some instances) six-membered carbocycles can be generated by this method in high yield and with excellent stereochemical control. In our studies, the Sm(III) Lewis acid generated during the reduction was utilized as a template for stereochemical control during the ensuing cyclization (eq 1).[3b,4a]



(1)

Early attempts to generate carbocycles containing three contiguous stereocenters via the SmI_2-mediated intramolecular Barbier coupling reaction were thwarted by the instability of the cyclic intermediate generated from secondary haloalkyl β-keto ester substrates.[3b] Presumably, a carbocyclic intermediate is initially

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