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Brønsted Acid Mediated Cyclization of Enaminones. Rapid and Efficient Access to the Tetracyclic Framework of the *Strychnos* Alkaloids

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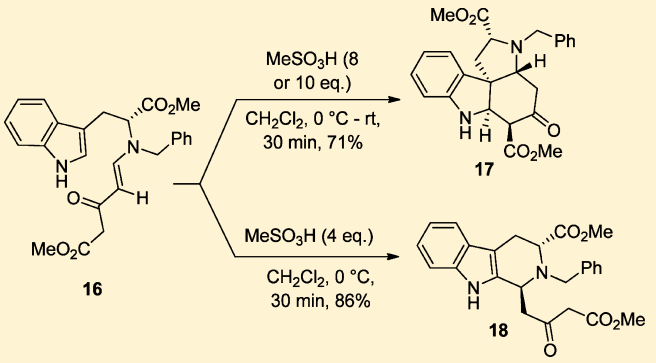
Supporting Information

ABSTRACT: The development of an efficient diastereoselective method that permits rapid construction of the tetracyclic core **17** of the *Strychnos-Aspidosperma* alkaloids is described. Enaminone **16**, synthesized in high yield, has been cyclized under the influence of a Brønsted acid to provide the core tetracyclic framework **17** of the *Strychnos* alkaloids in optically active form or alternatively to the *β*-ketoester tetrahydro-*β*-carboline (THBC) unit **18**, by varying the equivalents of acid and the molar concentration. Attempts to utilize **18** to form the C(7)−C(16) bond of the akuammiline related alkaloids represented by strictamine (**22**), using metal-carbenoid chemistry, are also described.



The pentacyclic 3,5-ethano-3*H*-pyrrolo[2,3-*d*]carbazole framework is common to a number of *Strychnos* alkaloids, of which (−)-strychnine (**1**) and (−)-akuammicine (**2**) are the most distinct members.[1] This pentacyclic unit is also found in a number of bisindoles including (−)-geissospermine (**3**),[2] (+)-geissolosimine (**4**),[3] and (+)-divaricine (**5**),[4] as illustrated in Figure 1. (+)-Geissoschizoline (**6a**),[5] which has been previously reported as a constituent of *Geissospermum vellosii* (*G. vellosii*), is the pentacyclic strychnine-related monomer of these dimeric indole alkaloids **3**−**5**.

The stem bark extracts of *G. vellosii* commonly known as *Pao periera* are used to treat malaria, poor digestion, constipation, dizziness, and as a febrifuge and tonic or stimulant.[6] In a study carried out by Lima et al.[7] this plant extract, rich in alkaloids, exhibited potent anticholinesterase activity in vitro and memory enhancing effects in vivo, in a model of cholinergic deficit that has been validated for the development of drugs for the symptomatic treatment of Alzheimer's disease. The principal alkaloid with anticholinesterase activity in the extract was identified as geissospermine (**3**), which has also been known to exhibit actions at the autonomic nervous system.[8] Because of their complex structural framework and important pharmacological activity coupled with the fact that the southern hemisphere of bisindoles **3**−**5** had been synthesized in an enantiospecific sense by us,[9] efforts have been directed toward the total synthesis of **6a,b** as part of a doubly convergent strategy.[10] To this end a concise and rapid route via the asymmetric Pictet−Spengler reaction[11] to generate the core tetracyclic framework **7**[12] which contains rings ABCE, crucial to the synthesis of the northern hemisphere of these bisindoles **3**−**5**, as well as other complex members of the *Strychnos-Aspidosperma* class of indole alkaloids was explored. Herein, a brief and rapid entry into this tetracyclic core **7** by a Brønsted acid mediated cyclization of an enaminone **16** is described.

RESULTS AND DISCUSSION

The acid-catalyzed coupling of **6a** with geissoschizine (**8**) or vellosimine (**9**), respectively, to form **3**[2d] and **4**,[3] has been documented and suggests a potential coupling of geissoschizoline N_b-oxide (**6b**) with vellosimine (**9**) to form **5**. Since the southern hemispheres **8** and **9** of the bisindoles **3**−**5** have been synthesized from D-tryptophan,[9] a doubly convergent strategy could be employed for the synthesis of both the hemispheres of the bisindoles **3**−**5**. As illustrated in Scheme 1, retrosynthetically, the northern hemisphere **6a**/**6b** might be obtained on further functionalization of the tetracyclic *Strychnos* unit **17′** which in turn might arise from an *α*-diazo *β*-ketoester tetrahydro-*β*-carboline unit **19** by making use of transition metal mediated carbenoid chemistry.[13] The nucleophilic attack of the indole double bond onto the electrophilic center of the carbene generated from **19** might lead to the tetracyclic core **17′**. Formation of such a tetracyclic framework from an *α*-ketocarbocation intermediate was originally studied by Takano et al.,[14] albeit in poor yields, in an approach toward *Aspidosperma* alkaloids.[15] In order to explore the diazonium approach via **19**, the stereoselective synthesis of the key *β*-

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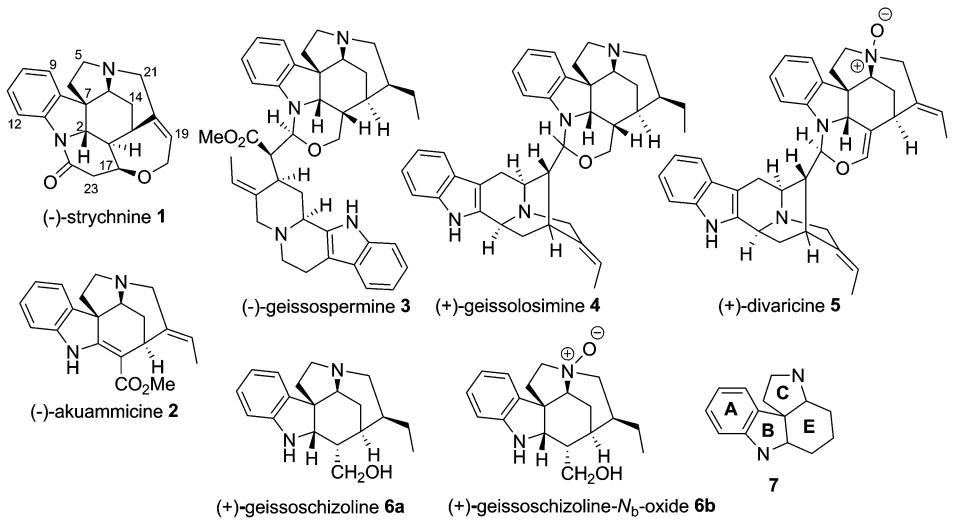
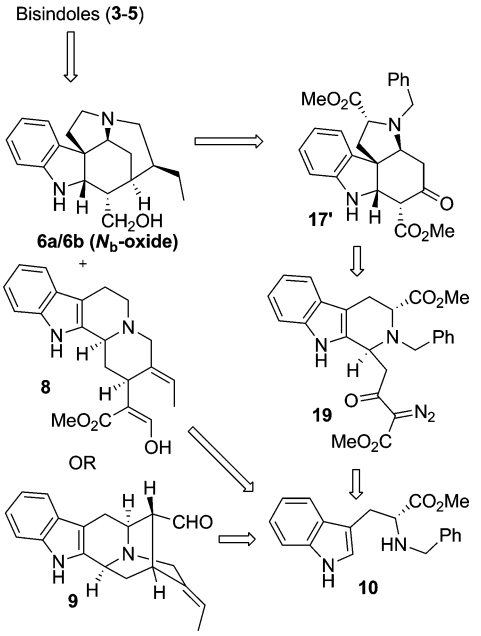
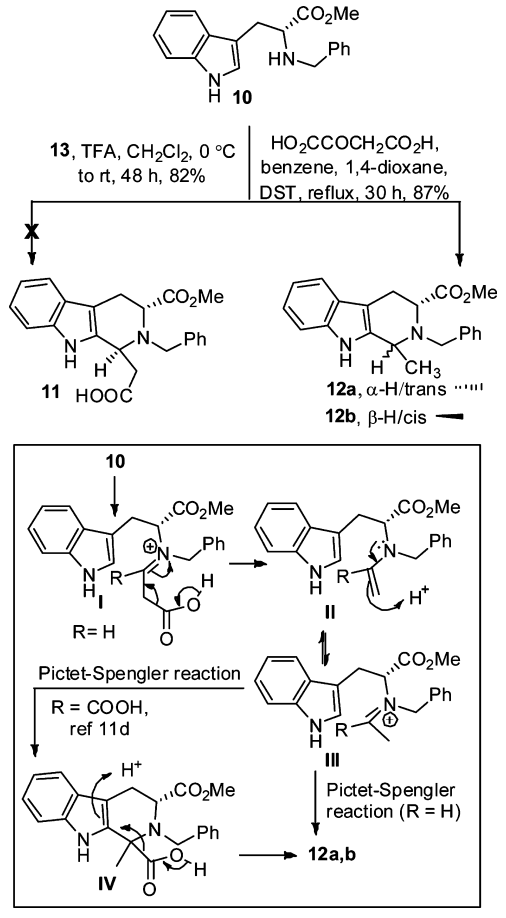


Figure 1. *Strychnos*-related indole alkaloids.

Scheme 1. Retrosynthetic Analysis



Scheme 2. Synthesis of C(1)-Substituted THBC[a]



[a]DST = Dean–Stark trap.

ketoester **18** (see Scheme 5) was required. The strategy was to generate this intermediate **18** by carrying out *C*-acylation on an acid moiety of a suitably substituted tetrahydro-*β*-carboline (THBC) such as **11** (see Scheme 2), which in turn could be synthesized from **10**[16] via the asymmetric Pictet–Spengler reaction.

The synthesis began with the D-(+)-N_b-benzyltryptophan methyl ester (**10**) which served as the starting material and the chiral transfer agent. Based on the conditions developed by Soerens et al.,[17] the asymmetric Pictet–Spengler reaction of **10** with 3,3-dimethoxypropanoic acid **13**[18] under acidic conditions or with commercially available oxaloacetic acid under thermal conditions was carried out to form the 1-hydroxycarbonyl THBC **11**. In both the cases, however, no formation of the target *β*-carboline **11** was observed. Instead, the *trans* isomer **12a** was isolated under acidic conditions, and a mixture of *cis* and *trans* diastereomers **12a,b** was formed under thermal nonacidic conditions (Scheme 2).[19] Not unexpectedly, after initial formation of the iminium ion **I**, the *β*-carboxylic acid, presumably, underwent decarboxylation to give intermediate **II**, which tautomerized to the iminium ion **III**, which cyclized to provide the 1,3-disubstituted *β*-carboline **12a**. Alternatively, oxaloacetic acid could have undergone decarboxylation under thermal conditions to generate CO_2 and pyruvic acid, which on condensation with **10** would provide **12a,b** via intermediate **IV**.

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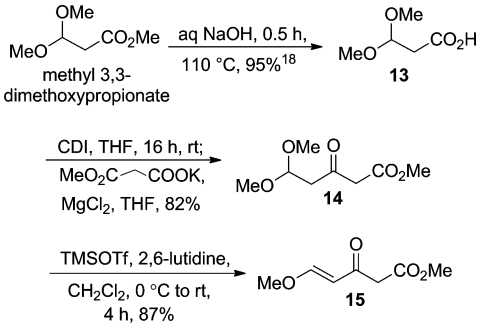
The spectroscopic data of 1-methylTHBC's **12a,b** was identical to those of racemic *cis*/*trans*-1-methylTHBC's.[20]

Based on the above results, an alternate approach was employed. The β-ketoester fragment **14** was synthesized first followed by the Pictet–Spengler reaction of β-ketoester **14** with **10** in order to form the target β-carboline **18**. The acid- and base-sensitive β-ketoester **14** was thus synthesized via *C*-acylation under the conditions developed by Brooks et al.[21] As illustrated in Scheme 3, the hydroxycarbonyl group in **13** was

Scheme 3. Synthesis of the Michael Acceptor 15

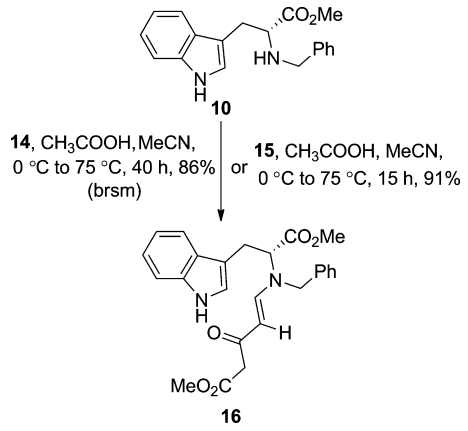


activated as an imidazolide with *N*,*N*′-carboxyldiimidazole (CDI) and condensed with the magnesium salt of methyl malonate under essentially neutral conditions. Spontaneous decarboxylation occurred during the acidic workup to afford the methyl 5,5-dimethoxy-3-oxopentanoate (**14**) in 82% yield.[22]

Attempts to generate β-carboline **18**, by condensation of **10** with **14** under the acid-mediated Pictet–Spengler reaction conditions (TFA/CH_2Cl_2), failed. Addition of excess reagent, continued stirring for extended periods at room temperature, change of solvent to MeCN, and varying the temperature from room temperature to 50 °C resulted in either no reaction or decomposition of the starting material **10**. The inability of acetal **14** to react with **10** in the presence of TFA prompted the use of a milder acid and the more reactive Michael acceptor **15**, synthesized in a single step from **14**. The ability of trimethylsilyl trifluoromethanesulfonate (TMSOTf), presumably, to bind to a single heterofunctional group and to form a supercationic species[23a] was utilized to synthesize β-ketoester **15** from the dimethoxy-β-ketoester **14** in 87% yield.[23b] This represents an important route to synthesize methyl (*E*)-5-methoxy-3-oxopent-4-enoate (**15**) in an overall yield of 88% from methyl 3,3-dimethoxypropionate (Scheme 3).

When the β-ketoester **15** was stirred with **10** in the presence of 20 equiv of HOAc in refluxing MeCN (Scheme 4), cyclization to the β-carboline **18** was not observed; however, the enaminone **16**,[24] present as the carbonyl tautomer, was formed in 91% yield. Enaminones[25] such as **16** have been previously synthesized albeit in lower yield (34%) from L-tryptophan methyl ester by Pandit et al.[26] by using an aziridine-based folate model and by Singh et al.[24] in a moderate yield (60%) by using oxazolidine-based folate models. The route toward the synthesis of the synthetically useful enaminone[26−28] **16** utilized the readily accessible Michael acceptor **15** and is an important improvement over the previous methods,[24,26] especially in yield and scale-up. The reaction between **10** and the β-ketoester **14** also furnished the enaminone **16** but required longer reaction times with a considerable amount of starting material **10** remaining.

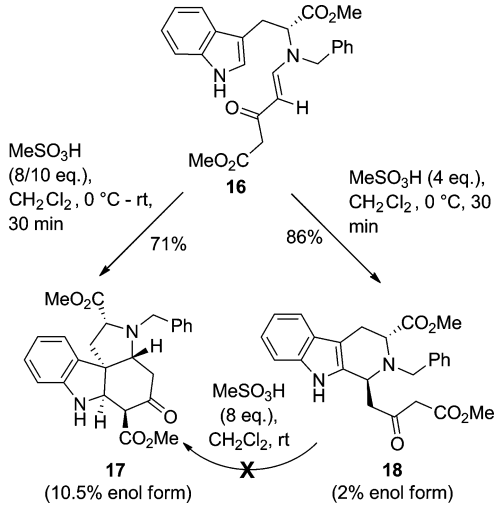
Scheme 4. Synthesis of Enaminone 16[a]



[a]brsm: based on recovered starting material **10**.

With the enaminone **16** in hand, the acid-mediated cyclization of **16** to the THBC framework in **18** was attempted (Scheme 5). Stirring the enaminone **16** in TFA/CH_2Cl_2

Scheme 5. Acid-Mediated Cyclization of Enaminone 16



resulted in no reaction, whereas treatment in HCl/MeOH[28] gave a mixture of compounds. Analysis of this crude mixture by NMR spectroscopy revealed the presence of a tetracyclic core structure of the *Strychnos* alkaloids (**17** or **17**′), accompanied by the THBC **18**. Since both the cyclized products, **17**/**17**′ and **18**, are potentially important intermediates in the doubly convergent strategy to the total synthesis of indole alkaloids,[29,30] it was decided to pursue selectivity in this process in order to obtain each exclusively. Methanesulfonic acid ($MeSO_3H$, pK_a: 1.6 in DMSO),[31] which was a stronger acid than TFA but equivalent in strength to HCl (pK_a: 1.8 in DMSO)[31] in an aprotic medium, presented an attractive option to HCl/MeOH, the acidity of which was difficult to control. The use of $MeSO_3H$ would permit one to achieve the exact concentration of the acid in the reaction mixture unlike HCl (g) whose solutions in aprotic media are less accurate and cumbersome to generate.

Treatment of enaminone **16** with 8 or 10 equiv of $MeSO_3H$ in CH_2Cl_2 (0.1 M) at 0 °C, followed by removal of the ice bath immediately after the addition of the acid, gave a single spot at a

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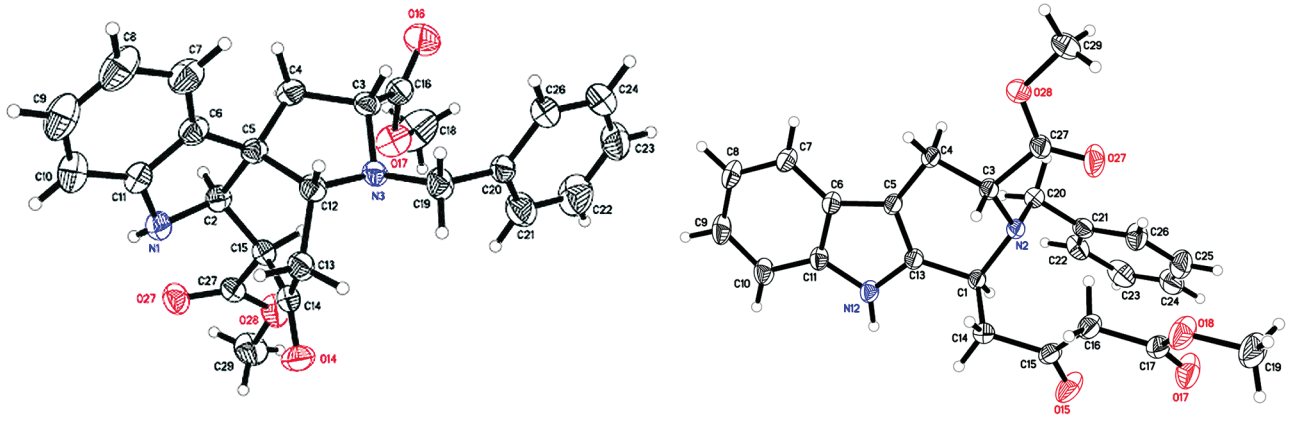


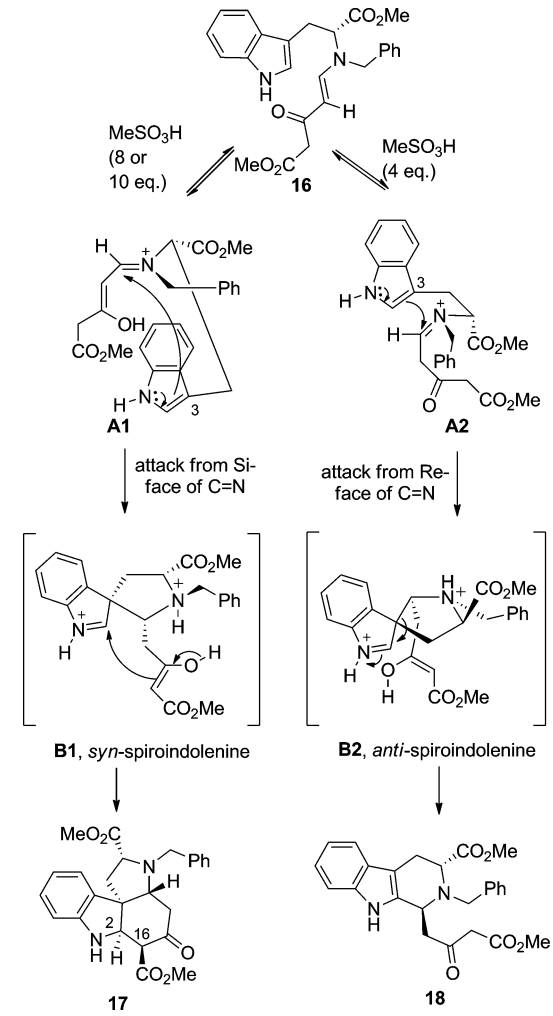
17 18

Figure 2. ORTEP view of the crystal structures of **17** and **18**.

higher R_f in 0.5 h. This indoline was isolated and identified as the dihydroindole derivative **17**. Encouraged by this result, the amount of acid was altered in order to obtain the β-ketoester THBC **18** as the sole product. It was found that addition of 4 equiv of $MeSO_3H$ and performing the reaction under more dilute conditions (0.05 M) at 0 °C (0.5 h) gave the THBC **18**, exclusively in 86% yield, as shown in Scheme 5. Separate recrystallization of analytical samples of tetracyclic **17** and the THBC **18** from a mixture of CH_2Cl_2/hexanes afforded crystalline material for single crystal X-ray analysis, as illustrated in Figure 2. The X-ray analysis confirmed the structural assignment and chirality of the ABCE *Strychnos* tetracyclic structure as **17**, which is opposite to the tetracyclic *Strychnos* template **17′** (see Scheme 1).

The stereochemistry of **17** and **18** obtained during the acid-mediated cyclization of **16** suggested[11a−c] the formation of two different spiroindolenine intermediates resulting from attack of the indole double bond at C-3 from the Si-face to give the *syn*-spiroindolenine **B1** (*syn* to the ester function) and from the Re-face to give the *anti*-spiroindolenine **B2** (*anti* to the ester function) of the iminium ion double bond (Scheme 6). It is well-known that, in acidic medium wherein the enaminone is protonated, the nucleophilic addition occurred preferentially at the iminic sp^2 carbon atom, thereby decreasing the possibility of a direct Michael addition.[32] Enaminones form stable salts with strong acids, and these salts have been found to be protonated at the oxygen atom, with only a few examples suggesting *C*-protonation.[33] Nevertheless, the five-atom π-electron system of enaminone **16**, in the presence of excess acid, presumably results in a push−pull system wherein the higher concentration of acid, higher temperature, and running the reaction more concentrated results in *O*-protonation (see **A1**) to generate the enol **B1**. In the presence of less acid (4 equiv), higher dilution, and lower temperature, the inherent reactivity of the enamine was sufficient to give an intermediate with *C*-protonation (see **A2**). The *O*-protonated intermediate **A1**, presumably, facilitated the intramolecular attack from the indole nucleus to the Si-face of the C=N double bond to give the *syn* spiroindolenine intermediate **B1** wherein the stereochemistry of the final product was irreversibly established. The C(16)−C(2) bond in **17** was formed by attack of the enolate carbon atom on the iminium ion bond, which resulted in the formation of the tetracyclic *Strychnos* template **17** with rings C and E fused in a *cis*-fashion.[30] It is possible that hydrogen

Scheme 6. Possible Mechanism of the Acid-Mediated Cyclization of the Enaminone 16



bonding between the enolate double bond and the indole N_a-H group might have resulted in some stabilization of **A1** in contrast to that observed in intermediate **A2**. On the other hand, the *C*-protonated intermediate **A2** gave the classical Pictet−Spengler product **18** with the targeted *trans*-stereoselectivity. Based on this hypothesis, the use of N_b-benzyl-L-

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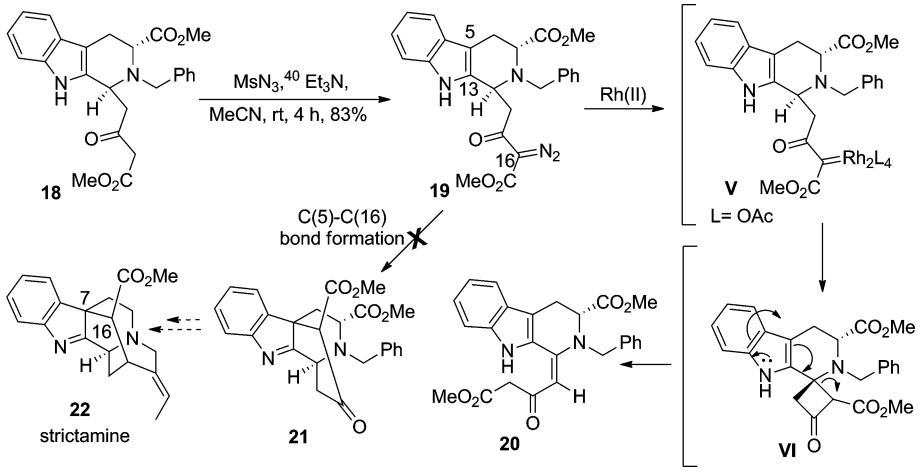
Table 1. Diazo Decomposition of 19



entry	catalyst/reagent	solvent	temp (°C)	time (h)	product	%yield
1	$Rh_2(OAc)_4$ (10 mol %)	benzene	rt	4	**20**	67%
2	$Rh_2(OAc)_4$ (10 mol %)	benzene	40	1.5	**20**	67%
3	$Rh_2(OAc)_4$ (10 mol %)	benzene	75	2	**20**	75%
4	CuOTf (80 mol %)	CH_2Cl_2	rt	1	**18**	51%
5	CuOTf (40 mol %)	CH_2Cl_2	reflux	1	**18**	47%
6	CuOTf (60−80 mol %)	benzene	rt	2	**18**	51%
7	HBF_4 (4−8 equiv)	CH_2Cl_2	rt	>24	decomposition	−
8	HBF_4 (4−8 equiv)	CH_2Cl_2	reflux	4	decomposition	−
9	$h\nu$ ($\lambda \geq 254$ nm)	CCl_4	rt	12	**19** + baseline	−

tryptophan methyl ester in the same process should provide the framework (**17′**) with all the stereogenic centers in the correct disposition. To confirm, whether the formation of **17** was not via an acid-catalyzed rearrangement of **18**, the *β*-carboline **18** was stirred at room temperature with 8 equiv of $MeSO_3H$ for 24 h. Analysis of the crude reaction mixture by ^{1}H NMR spectroscopy after workup indicated the presence of only starting **18**. Any attempt to heat the reaction mixture resulted in decomposition of the material.

With the important tetracyclic *Strychnos* template **17** and the THBC unit **18** synthesized in just two steps from **10**, the diazonium approach via **18**, to form the C(7)−C(16) bond present in the akuammiline series, represented by strictamine **22**,[34] was attempted. The required diazo compound **19** was readily obtained using standard diazo transfer conditions from **18**. With the *α*-diazo *β*-keto ester **19** in hand, the efficiency of transition metal salts as catalysts in diazo decompositions, to effect the formation of the C(5)−C(16) bond in **19**, was explored (Table 1). Diazo decomposition[13] of **19** in benzene in the presence of 5−10 mol % of $Rh_2(OAc)_4$ at room temperature, 40 °C, or 75 °C (Table 1, entries 1−3) gave compound **20** (lower R_f) with complete consumption of the starting material **19**. Based on 2D NMR experiments on **20**, it appeared that the electrophilic Rh(II) carbene[35] **V**, formed by extrusion of nitrogen,[36] had inserted into the electron-rich tertiary C−H bond at the benzylic position[35] via a single three-centered transition state[37] to form the cyclobutanone[38] **VI**. This was, presumably, followed by opening of the cyclobutanone ring and intramolecular proton transfer to provide the olefinic THBC **20** as an *E*-isomer. This was confirmed by analysis of the ^{1}H NMR spectrum which showed the indole N_a-H proton at δ 13.8 because of hydrogen bonding with the C-15 carbonyl group. The effect of a CuOTf-mediated diazo decomposition of **19** to provide the C(5)−C(16) bond was next attempted. Initial trials (not shown) using catalytic amounts (5−10 mol %) of CuOTf at room temperature or under refluxing conditions gave only starting material **19**. A new product was obtained only after increasing the amount of CuOTf[39] to 40 mol % (at reflux) and 80 mol % at room temperature to furnish the *β*-keto ester THBC **18** (Table 1, entries 4 and 5). With the failure of the transition metal mediated process to give the product with C(5)−C(16) bond formation in **21**, attention turned to the use of Brønsted acid catalysis (Table 1, entries 7 and 8). Diazocarbonyl compounds with suitably positioned internal nucleophilic sites permit cyclizations to occur with new bond formation. Treatment of the *α*-diazo *β*-keto ester **19** with 4 or 8 equiv of tetrafluoroboric acid at room temperature provided only starting material **19** (TLC, silica gel) after 4 h. Continued stirring for prolonged periods of time resulted in decomposition of **19** with no new components observed by TLC. All attempts to heat the solution also resulted in decomposition of **19**. Photolysis experiments on the diazo compound **19** also failed (Table 1, entry 9). Based on these results it is apparent that the inability to achieve the formation of the C(5)−C(16) bond in indole **21** presumably via a highly strained cyclopropane ring intermediate followed by ring opening is less favorable, as a result of the electrophilic carbene being inserted into the readily accessible benzylic C−H bond thereby forming **20**. In addition, formation of a *Strychnos* tetracycle like **17′** presumably via the nucleophilic attack of C-13 of the indole nucleus on the electrophilic carbene followed by rearrangement was also not observed. This suggests that the formed electrophilic carbenoid orients itself relatively far from the indole double bond in the *β*-carboline system **19**.

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In summary, an efficient, rapid synthesis of the highly functionalized tetracyclic core **17** of the *Strychnos* alkaloids was developed. This permits stereospecific formation of rings C and E in a single step, which also generates the all important C-7 quaternary center in a stereospecific fashion. The tetracyclic core **17** of the *Strychnos* alkaloids and the β-ketoester THBC unit **18** were synthesized exclusively by simply varying the equivalents of $MeSO_3H$, molar concentration, and the reaction temperature, from a common enaminone intermediate **16**, which in turn was obtained in high yield by making use of a novel Michael acceptor **15**. We believe that by employing L-tryptophan as the starting material, stereospecific formation of the tetracycle **17′** could be readily achieved. Further functionalization of this core should provide ready access to the northern hemispheres of bisindoles **3**–**5**, as well as other complex members of this series of alkaloids.

EXPERIMENTAL SECTION

General Experimental Procedures. Melting points were taken on a Stuart melting point apparatus SMP3 manufactured by Barloworld Scientific US Ltd. Optical rotations were measured on a JASCO Model DIP-370 digital polarimeter. IR spectra were recorded on a Thermo Nicolet Nexus 870 FT-IR or a Perkin-Elmer 1600 series FT-IR spectrometer. Proton (^{1}H NMR) and carbon high resolution nuclear magnetic resonance spectra (^{13}C NMR) were obtained on a Bruker 300-MHz or a GE 500-MHz NMR spectrometer. The low resolution mass spectra (LRMS) were obtained on electron impact (EI, 70 eV) mass spectrometer, which were recorded on a Hewlett-Packard 5985B gas chromatography–mass spectrometer, while high resolution mass spectra (HRMS) were recorded on a VG Autospec (Manchester England) mass spectrometer. HRMS recorded by electrospray ionization (ESI) methods were performed on a API QStar Pulsar model, manufactured by MDS Sciex. Flash and gravity chromatography was performed using silica gel P60A, 40–63 μm purchased from Silicycle. All reactions were carried out under an argon atmosphere with dry solvents using anhydrous conditions unless otherwise stated.

(*E*)-Ethyl-5-methoxy-3-oxo-4-pentenoate (15). To a solution of methyl 5,5-dimethoxy-3-oxopentanoate **14** (3.6 g, 19.1 mmol) in dry CH_2Cl_2 (80 mL) was added 2,6-lutidine (6.1 g, 57.11 mmol). The reaction flask was cooled to 0 °C with ice, followed by dropwise addition of TMSOTf (8.5 g, 38.1 mmol). After 10 min, the ice bath was removed and the reaction mixture was allowed to stir at rt for 3 h or until analysis by TLC indicated disappearance of the starting material **14** (silica gel, EtOAc/hexanes, 13:7; run the TLC on a longer plate). After the acetal **14** was completely consumed (TLC), H_2O was added to the reaction mixture at rt, after which it was stirred for 5 min and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure to afford the crude product **15**, which was dried *in vacuo* to remove the excess 2,6-lutidine before the crude oil was purified by flash chromatography on silica gel (EtOAc/hexanes = 1:9) to provide the enol ether **15** (2.6 g, 87%) as a pale yellow oil. IR (NaCl) ν_{max} 2954, 1743, 1684, 1438 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (1H, d, J = 12.6 Hz), 5.68 (1H, d, J = 12.6 Hz), 3.75 (6H, s), 3.52 (2H, s) (Proton NMR contains 4.8% of enol); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.7 (C), 167.9 (C), 164.2 (CH), 104.7 (CH), 57.7 (CH_3), 52.3 (CH_3), 47.8 (CH_2); EIMS m/z 158 [M$^+$] (100), 127 (17); HRESIMS m/z 159.0654 [M + H]$^+$ (calcd for $C_7H_{11}O_4$, 159.0657).

Alkylation of 10 To Provide (*R*,*E*)-Methyl-5-((3-(1*H*-indol-3-yl)-1-methoxy-1-oxo-propan-2-yl)(benzyl)amino)-3-oxopent-4-enoate (16). The N_b-benzyl-D-trypthophan methyl ester **10** (1.8 g, 5.8 mmol) and the enol ether **15** (1.6 g, 9.9 mmol) were dissolved in MeCN (65 mL). The mixture was cooled to 0 °C with ice, followed by the dropwise addition of glacial acetic acid (7.0 g, 117 mmol). After the reaction mixture was stirred for 15 min at 0 °C, the ice bath was removed after which the reaction mixture was stirred for another 15 min and then the flask was transferred to a preheated oil bath (70–75 °C). The reaction mixture was stirred at this temperature under argon for 15 h, after which analysis by TLC (silica gel) indicated the disappearance of the starting material **10** and a new component was observed at a lower R_f. The reaction mixture was concentrated under reduced pressure, diluted with CH_2Cl_2, and neutralized with ice cold 10% aqueous NH_4OH. The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine and dried (Na_2SO_4), and the solvent was concentrated under reduced pressure. The brown colored residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 1:1), which provided enaminone **16** (2.3 g, 91%) as a light brown solid. R_f 0.49 (silica gel, EtOAc/hexanes, 4:1); IR (KBr) ν_{max} 3403, 3303, 2951, 1740, 1653, 1558, 743 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (1H, s), 7.88 (1H, d, J = 10.4 Hz), 7.39 (2H, d, J = 8.3 Hz), 7.22 (4H, m), 7.09 (1H, t, J = 7.5 Hz), 7.04–6.94 (3H, m), 5.30 (1H, d, J = 12.8 Hz), 4.36–4.21 (3H, m), 3.71 (3H, s), 3.65 (3H, s), 3.51 (1H, dd, J = 14.8, 6.5 Hz), 3.39 (2H, dd, J = 17.0, 14.4 Hz), 3.26 (1H, dd, J = 14.8, 8.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.0, 170.6, 169.0, 151.2, 136.1, 134.7, 128.5, 127.6, 127.2, 126.7, 123.4, 122.2, 119.6, 118.0, 111.3, 109.6, 97.6, 65.7, 53.4, 52.4, 52.0, 48.0, 27.1; EIMS m/z 434 [M]$^+$ (14), 361 (10), 334 (12), 319 (16), 305 (31), 275 (14), 243 (11), 234 (41), 201 (30), 170 (10), 130 (100), 91 (87); anal. C 68.74, H 6.10, N 6.29%, calcd for $C_{25}H_{26}N_2O_5$, C 69.11, H 6.03, N, 6.45%.

Brønsted Acid Mediated Cyclization of 16 To Provide (2*R*,3a*R*,6*S*,6a*R*,11b*R*)-Dimethyl-3-benzyl-5-oxo-2,3,3a,4,5,6,6a,7-octahydro-1*H*-pyrrolo[2,3-*d*]carbazole-2,6-dicarboxylate (17). To a solution of enaminone **16** (725 mg, 1.7 mmol) in dry CH_2Cl_2 (15 mL), methanesulfonic acid (0.87 mL, 13.4 mmol) was added dropwise under an atmosphere of argon at 0 °C (ice bath). After addition of the $MeSO_3H$, the ice bath was removed immediately and the reaction mixture was allowed to stir for 30 min, at which point analysis by TLC indicated the disappearance of the starting material **16** and a new spot at higher R_f. The reaction mixture was brought to pH 8 with a saturated cold aqueous solution of $NaHCO_3$. The two layers were separated. The organic layer was washed with brine and dried (Na_2SO_4), and the solvent was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc/hexanes) to furnish **17** (518 mg, 71% yield) as a light yellow solid, a portion of which was recrystallized from a mixture of CH_2Cl_2/hexanes to give **17** as white needle-shaped crystals for X-ray analysis. R_f 0.54 (silica gel, EtOAc/hexanes, 3:5); mp 142–143 °C; $[\alpha]^{26}_D$ +81.64 (c 0.73, $CHCl_3$); IR (KBr) ν_{max} 3383, 2951, 1738, 1723, 1608, 1203, 751 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.26 (3H, m), 7.23–7.20 (2H, m), 7.14–7.06 (2H, m), 6.79 (1H, t, J = 7.4 Hz), 6.65 (1H, d, J = 7.5 Hz), 5.14 (1H, d, J = 2.0 Hz), 4.92 (1H, d, J = 3.2 Hz), 4.24 (1H, t, J = 2.0 Hz), 3.91–3.86 (4H, m), 3.62–3.54 (2H, m), 3.48 (3H, s), 2.90–2.82 (2H, m), 2.55 (2H, ddd, J = 43.1, 18.6, 2.8 Hz), 2.09 (1H, dd, J = 14.4, 6.6 Hz) (Proton NMR contains 10.5% of enol); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.9 (C), 174.0 (C), 170.9 (C), 149.9 (C), 135.8 (C), 131.1 (C), 129.4 (2 × CH), 128.8 (CH), 128.2 (2 × CH), 127.5 (CH), 122.8 (CH), 118.9 (CH), 109.5 (CH), 70.1 (CH), 67.2 (CH), 65.1 (CH), 55.9 (CH_2), 54.6 (CH), 52.7 (C), 52.3 (CH_3), 51.8 (CH_3), 42.2 (CH_2), 37.5 (CH_2); EIMS m/z 434 [M$^+$] (85), 403 (17), 375 (100), 343 (62), 319 (19), 284 (12), 259 (41), 242 (19), 204 (24), 154 (24), 143 (18), 130 (44), 91 (91); anal. C 68.76, H 6.19, N 6.28%, calcd for $C_{25}H_{26}N_2O_5$, C 69.11, H 6.03, N 6.45%.

Brønsted Acid Mediated Cyclization of 16 To Provide (1*S*,3*R*)-Methyl-2-benzyl-1-(4-methoxy-2,4-dioxobutyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (18). To a solution of enaminone **16** (840 mg, 1.94 mmol) in dry CH_2Cl_2 (38 mL) was added dropwise methanesulfonic acid (0.50 mL, 7.74 mmol) under an atmosphere of argon at 0 °C (ice bath). After stirring the reaction mixture for 30 min at 0 °C, analysis by TLC indicated the disappearance of the starting material **16** and a new spot at higher R_f. The reaction mixture was neutralized with an ice cold saturated solution of $NaHCO_3$. The two layers were separated. The organic layer was washed with brine and dried (Na_2SO_4), and the solvent was

concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc/hexanes) to furnish **18** (730 mg, 86% yield) as a light yellow solid, a portion of which was recrystallized from a mixture of CH_2Cl_2/hexanes to give **18** as yellow needle-shaped crystals for X-ray analysis. For subsequent batches, the crude residue obtained after workup was directly subjected to the diazo transfer reaction without any further purification. R_f 0.55 (silica gel, EtOAc/hexanes, 2:3); mp 126−127 °C; $[\alpha]^{26}_D$ −10.71 (*c* 1.12, $CHCl_3$); IR (KBr) ν_{max} 3335, 3034, 2949, 2880, 1757, 1732, 1359, 1048 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.42 (1H, s), 7.56 (1H, d, *J* = 7.6 Hz), 7.39−7.25 (6H, m), 7.23−7.11 (2H, m), 4.38 (1H, dd, *J* = 9.4, 3.4 Hz), 4.01 (1H, dd, *J* = 9.5, 4.8 Hz), 3.94−3.77 (4H, m), 3.70 (3H, s), 3.62 (1H, d, *J* = 14.0 Hz), 3.45 (2H, s), 3.30−3.02 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.2 (C), 172.9 (C), 167.0 (C), 138.9 (C), 135.9 (C), 133.5 (C), 128.5 (2 × CH), 128.3 (2 × CH), 127.2 (CH), 126.5 (C), 121.9 (CH), 119.4 (CH), 118.0 (CH), 111.0 (CH), 106.8 (C), 57.7 (CH), 53.4 (CH_2), 52.4 (CH_3), 52.0 (CH_3), 51.4 (CH), 49.8 (CH_2), 49.2 (CH_2), 20.8 (CH_2); EIMS *m*/*z* 434 [M^+] (14), 375 (10), 343 (23), 319 (100), 257 (24), 183 (8), 169 (15), 156 (19), 91(84); anal. C 68.92, H 6.14, N 6.24%, calcd for $C_{25}H_{26}N_2O_5$, C 69.11, H 6.03, N 6.45%.

Diazo Transfer Reaction of 18 To Provide (1*S*,3*R*)-Methyl-2-benzyl-1-(3-diazo-4-methoxy-2,4-dioxobutyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (19). To the above keto ester **18** (390 mg, 0.90 mmol) in MeCN (12 mL), Et_3N (0.20 mL, 1.44 mmol) was added at rt. The solution which resulted was allowed to stir for 15 min, at which time mesyl azide (192 mg, 1.8 mmol) was added, and the reaction mixture was allowed to stir at rt for 4 h. The reaction mixture was quenched with H_2O, and the mixture was partitioned between ether and H_2O. The aqueous layer was extracted with ether, and the combined organic layers were washed with brine and dried ($MgSO_4$), and the solvent was concentrated under reduced pressure. The residue was subjected to flash silica gel column chromatography to afford the diazo compound **19** as a yellow solid (343 mg, 83%). R_f 0.61 (silica gel, EtOAc/hexanes, 2:3); IR (neat) ν_{max} 3369, 2952, 2136, 1718, 1641, 1436, 741 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.48 (1H, s), 7.58 (1H, d, *J* = 7.4 Hz), 7.39−7.28 (5H, m), 7.25−7.12 (3H, m), 4.34 (1H, t, *J* = 6.7 Hz), 4.15 (1H, dd, *J* = 10.1, 5.2 Hz), 3.90−3.79 (7H, m), 3.52 (1H, d, *J* = 13.6 Hz), 3.33 (2H, ddd, *J* = 22.1, 14.3, 7.5 Hz), 3.17 (1H, dd, *J* = 16.0, 10.2 Hz), 3.08 (1H, dd, *J* = 16.0, 5.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.3 (C), 173.0 (C), 161.5 (C), 139.3 (C), 135.8 (C), 133.5 (C), 128.9 (2 × CH), 127.9 (2 × CH), 127.0 (CH), 126.7 (C), 121.8 (CH), 119.3 (CH), 118.1 (CH), 110.9 (CH), 107.2 (CH), 90.5 (C), 57.4 (CH), 53.1 (CH_2), 52.2 (CH), 52.0 (2 × CH_3), 46.8 (CH_2), 20.4 (CH_2); HRESIMS *m*/*z* 461.1824 [M + H]$^+$ (calcd for $C_{25}H_{25}N_4O_5$, 461.1825); anal. C 64.93, H 5.42, N 11.90%, calcd for $C_{25}H_{24}N_4O_5$, C 65.21, H 5.25, N 12.17%.

(*R*,*E*)-Methyl-2-benzyl-1-(4-methoxy-2,4-dioxobutylidene)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (20). Procedure described for entry 1 (Table 1): To a solution of **19** (207 mg, 0.45 mmol) in dry benzene (6 mL) under nitrogen, rhodium(II) acetate (20 mg, 0.045 mmol) was added. The mixture was allowed to stir at rt for 4.0 h. The solution was then filtered through a pad of Celite and washed with ether. The filtrate was concentrated under reduced pressure, and the residue was subjected to flash silica gel column chromatography (EtOAc/hexanes) to furnish **20** (130 mg, 67% yield) as a light yellow oil. R_f 0.41 (silica gel, EtOAc/hexanes, 2:3); IR (neat) ν_{max} 2952, 1735, 1508, 1463, 733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 13.8 (1H, s), 7.58 (1H, d, *J* = 8.0 Hz), 7.50 (1H, d, *J* = 8.3 Hz), 7.44−7.31 (6H, m), 7.14 (1H, t, *J* = 7.7 Hz), 5.55 (1H, s), 5.13 (1H, d, *J* = 16.2 Hz), 4.42−4.40 (2H, m), 3.68−3.61 (7H, m), 3.50 (2H, t, *J* = 14.6 Hz), 3.39 (1H, dd, *J* = 16.5, 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.0 (C), 171.4 (C), 169.0 (C), 152.3 (C), 136.5 (C), 135.8 (C), 129.0 (2 × CH), 127.9 (CH), 127.7 (C), 126.9 (2 × CH), 125.0 (CH), 124.6 (C), 119.9 (CH), 119.2 (CH), 113.0 (CH), 112.1 (C), 94.7 (CH), 62.4 (CH), 56.7 (CH_2), 52.8 (CH_3), 52.1 (CH_3), 50.6 (CH_2), 23.8 (CH_2); EIMS *m*/*z* 432 [M^+] (17), 373 (10), 359 (58), 341 (17), 331 (100), 299 (24), 271 (84), 257 (20), 226 (22), 209 (53), 195 (19), 181 (31), 154 (12); HREIMS *m*/*z* 432.1672 (calcd for $C_{25}H_{24}N_2O_5$, 432.1685).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures for compounds **12a,b**, **13**, **14** and spectral data for all the compounds including X-ray data for **17** and **18** (CIF files). This material is available free of charge via the Internet at http://pubs.acs.org.

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NOTE ADDED AFTER ASAP PUBLICATION

This paper was published on the Web on Jan 18, 2012, with errors in compounds **18** and **19** in the Supporting Information. The corrected version was reposted on Jan 20, 2012.