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Asymmetric Approaches to 1,2-Disubstituted Mitosenes Based on the Intramolecular Cyclization of Diazoesters

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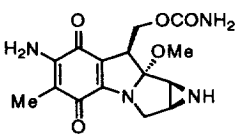
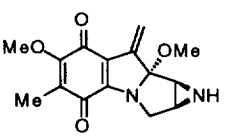
Abstract: A strategy for the asymmetric synthesis of 1,2-disubstituted mitosenes is described. The key reaction is the decomposition of a meso diazoester in the presence of chiral copper(I) catalysts. Cyclization of diazoesters derived from (1*R*, 2*S*, 5*R*)-menthol and (*R*)-pantolactone provide optically pure 1,2-disubstituted mitosenes following oxidation and purification by flash chromatography.

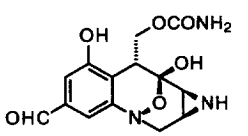
Introduction The mitomycins are among the most extensively studied group of natural products.[1] The long standing interest in this family of antitumor antibiotics results from their proven clinical utility and complex molecular structure.[2] The latter is reflected in the number of successful total syntheses of members of this group of natural products. Within the mitomycin family, syntheses of mitomycin C and mitomycin K have been reported,[3] while three syntheses of the closely related antitumor agent FR-900482 (**3**) have been described.[4] Except for one report,[4d-f] these investigations have led to the production of racemic materials. In view of the differing biological profiles of the enantiomers of **1** (for instance), the development of an enantioselective construction of the mitomycin ring system may prove beneficial.[5]



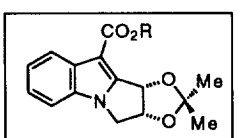
mitomycin C (**1**)



mitomycin K (**2**)



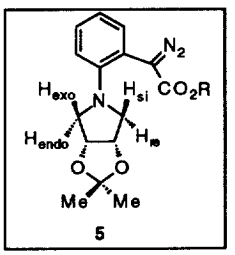
FR-900482 (**3**)



common ring system (**4**)

The 1,2-disubstituted mitosene, or pyrrolo[1,2-a]indole, ring system (cf. **4**) has proven to be a useful intermediate in synthetic approaches to **2** and **3**.[3f,6] Furthermore, bioreductive activation of the mitomycins and FR-900482 (**3**) lead to the generation of 1,2-aziridino mitosenes which induce DNA-DNA interstrand cross-links, which presumably are responsible for the observed cytotoxicity.[5,7] While various asymmetric oxidative approaches to **4** may be envisioned, we chose to examine the formation of a carbon-carbon bond through an enantioselective intramolecular C-H insertion reaction of meso diazoester **5**.[8] Notably, starting from meso **5**, either **4** or ent-**4** should be available depending on the choice of chiral catalyst or auxiliary (vide infra).

The four C-H bonds adjacent to the nitrogen atom in diazo ester **5** comprise two sets of diastereotopic hydrogens oriented endo and exo (only one set is indicated) relative to the neighboring acetonide group. A second classification divides the two exo hydrogens and two endo hydrogens into enantiotopic sets (only pro-S exo and pro-R endo hydrogens are indicated). Insertion into the pro-S exo C-H bond leads to the anti-isomer **6**, while insertion into the diastereotopic pro-R endo C-H bond will provide the syn-isomer **7**.



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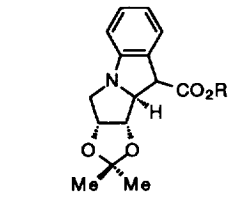
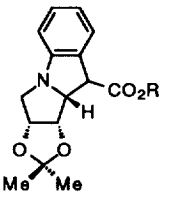
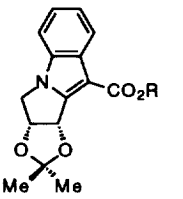


6a α-CO_2R
6b β-CO_2R



7a β-CO_2R
7b α-CO_2R



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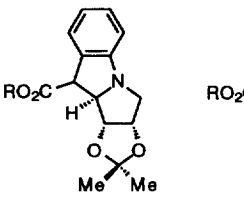
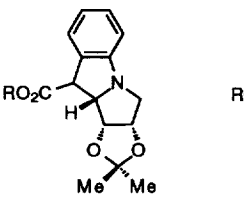
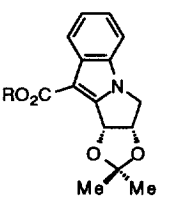


ent-**6a** α-CO_2R
ent-**6b** β-CO_2R

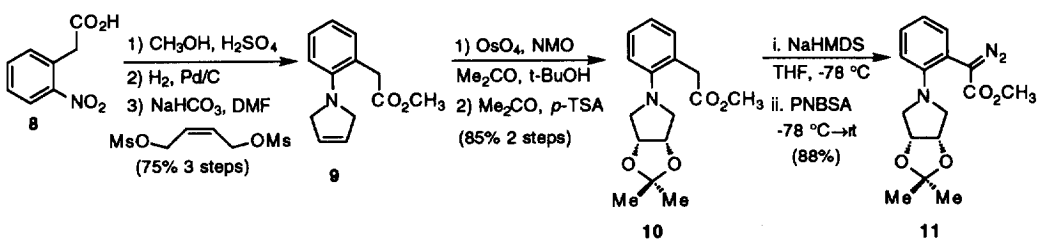


ent-**7a** β-CO_2R
ent-**7b** α-CO_2R



ent-**4**

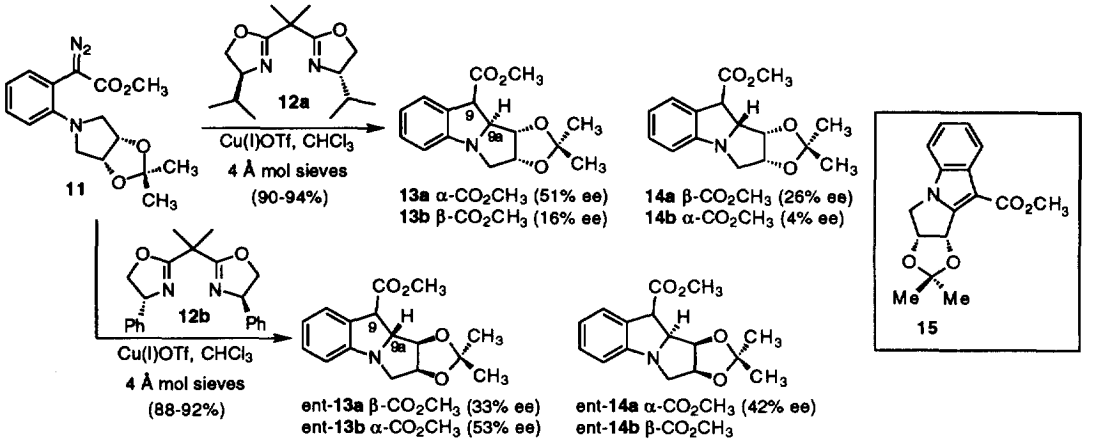
In each case the carboxylate group can emerge in the product in an exo (**6a** and **7a**) or endo (**6b** and **7b**) orientation. Alternatively, carbenoid insertion into the other set of diastereotopic methylene hydrogens will afford ent-**6** and ent-**7**. Consequently, the intramolecular carbon-hydrogen insertion reaction of diazo ester **5** could give rise to eight stereoisomers, or two enanatiomeric sets of four diastereomers. Upon oxidation, diastereomers **6** and **7** converge to a common 1,2-disubstituted mitosene enantiomer **4**, while oxidation of ent-**6** and ent-**7** would produce ent-**4**. We have examined reagent controlled (enantioselective catalysis) and substrate controlled (R = chiral auxiliary) approaches to influence the distribution of **4** and ent-**4** starting from diazoesters of the general structure **5**. A full account of these investigations is the subject of this paper.



8 **9** **10** **11**

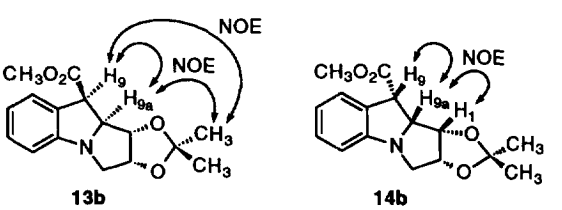
Results and Discussion Methyl ester **11** was prepared starting from 2-nitrophenylacetic acid (**8**) as outlined above. Following esterification and reduction of the nitro group, alkylation with cis-butene-1,4-dimesylate[9] afforded δ_3-pyrroline **9** in high yield (75% overall yield, three steps). Dihydroxylation of **9**, followed by acetonide formation provided acetonide **10** in 85% yield. Diazo transfer to **10** was accomplished

by generation of the sodium enolate of **10** and quenching with *p*-nitrobenzenesulfonyl azide (PNBSA).[10] Under these conditions yields of diazoester **11** up to 88% were realized.



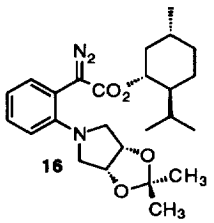
Initially, we examined the use of chiral rhodium(II) catalysts to cyclize diazoester **11**. The results, however, were discouraging.[11] We next examined the use of bis(oxazoline) copper(I) complexes made from the addition of the indicated ligand (**12**) to a suspension of copper(I) triflate in chloroform.[8,12] Addition of a chloroform solution of diazo ester **11** to a mixture of Cu(I)•**12a** afforded **13** and **14** in a 3:1 ratio and a combined yield of 90-94%. The anti isomer **13** was produced as a 1.7:1 mixture of isomers (**13a** and **13b**), while the corresponding syn diastereomers were generated as a 1.3:1 (**14a** and **14b**) mixture. The individual isomers were subjected to oxidation (DDQ, CH_2Cl_2) to afford mitosene **15** (>90% yield) and the enantiomeric excess was determined by ^1H NMR using the chiral lanthanides shift reagent Eu(hfc)$_3$.[13] All four isomers converged to **15** which was assigned the indicated absolute stereochemistry by chemical correlation (vide infra). The exo-anti isomer **13a** was produced in the highest enantiomeric excess (51% ee). In a similar fashion, the antipodal set of isomers (ent-**13** to ent-**14**) were generated from Cu(I)•**12b**. In this instance a 3:1 ratio of ent-**13** and ent-**14** was produced as a 1:3 (ent-**13a** and ent-**13b**) and 10:1 (ent-**14a** and ent-**14b**) mixture of epimeric esters, respectively. In this series the endo-anti isomer (ent-**13b**) and exo-syn isomer (ent-**14a**) were produced in 53 and 42% ee, respectively.

Structural assignments of each diastereomer (**13a/13b** and **14a/14b**) were based on differences in chemical shifts of the acetonide methyl groups and observed nOe enhancements. For instance, in the ^1H NMR spectrum of the anti isomer **13b**, the acetonide methyl groups resonated at 1.29 and 1.56 ppm, while the corresponding methyl groups of syn isomer **14b** resonated at 0.49 and 1.09 ppm. The upfield shift of methyl groups in syn isomer **14b** can be explained by a shielding effect of the neighboring aromatic ring. In nOe experiments, enhancements were observed between H_9 and H_{9a}, H_9 and CH_3, and H_{9a} and CH_3 in anti isomer **13b**. In the case of syn isomer **14b**, enhancements between H_9 and H_{9a} and between H_{9a} and H_1 were observed.



Selectivities of C-H insertion reactions and cyclopropanations of olefins using diazo esters have

been enhanced by alteration of the alkoxy group.[14] In the present study, diazo menthyl ester **16** was derived from 2-nitrophenylacetic acid (cf. **8** to **11**). Diazo menthyl ester **16**, in the presence of rhodium(II) acetate, gave a 1:1 mixture of diastereomers **17** and **18** which were easily separated by flash chromatography after DDQ oxidation.[14a] Next we examined the cyclization of **16** using Cu(I)•**12a** and Cu(I)•**12b** [chloroform solvent, 4Å molecular sieves]. Carbon-hydrogen insertion mediated by Cu(I)•**12a** followed by DDQ oxidation produced the chromatographically less mobile isomer **17** in 34% de (66% yield for **17** plus **18**), while decomposition of diazo ester **16** with Cu(I)•**12b** followed by oxidation afforded the other isomer **18** in 39% de (64% isolated yield). The diastereomeric excess was measured by HPLC analysis.



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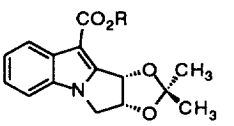
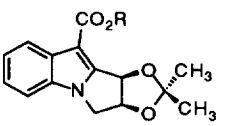
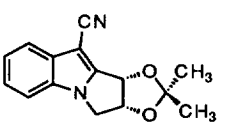


15 R = CO_2Me, $[\alpha]^D$ -209
17 R = (1*R*,2*S*,5*R*)-menthyl

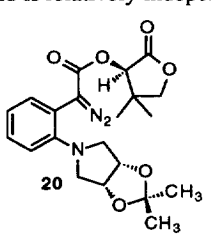


ent-**15** R = CO_2Me, $[\alpha]^D$ +212
18 R = (1*R*,2*S*,5*R*)-menthyl



19 $[\alpha]^D$ -150

Isomers **17** and **18** were individually correlated with methyl esters **15** and ent-**15** by saponification followed by esterification with diazomethane, while the relative stereochemistries of **17** and **18**, and thus the absolute stereochemistry of methyl ester **15**, were established by conversion of **17** to nitrile **19**. The enantiomer of **19** has been previously prepared by Ziegler starting from L-tartaric acid; comparison of the optical rotation with that reported by Ziegler for ent-**19** ($[\alpha]^D_{20}$ +204) led to the stereochemical assignment of **19** shown.[15] The observation that cyclization of **16** using Cu(I)•**12a** produced an excess of **17** while an excess of **18** was produced using Cu(I)•**12b** suggests the cyclization of **16** is dependent solely on the catalyst stereochemistry and is relatively independent of the menthyl group.



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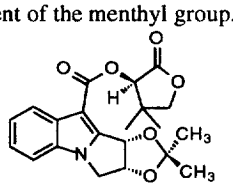

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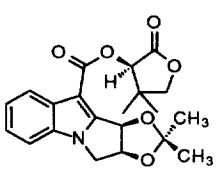

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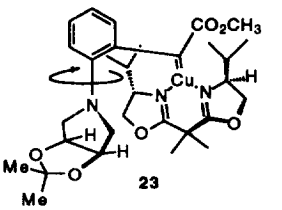
These results suggest that the incorporation of a menthyl ester within **16** does not provide any inherent substrate control in the conversion of **16** to **17/18**. In an effort to identify an auxiliary which would lead to substrate controlled cyclization we prepared pantalactone ester **20**.[14c] In contrast to reactions of menthyl diazoester **16**, cylization of **20** using rhodium(II) acetate (CH_2Cl_2, 23 °C) followed by DDQ oxidation provided a 37% de (82% yield) of mitosene **22**. In an effort to amplify the overall diastereoselectivity we examined the cyclization of **20** using Cu(I)•**12a** and Cu(I)•**12b** [chloroform solvent, 4Å molecular sieves].[14] We were disappointed to discover that decomposition of **20** followed by oxidation produced **21** (45% yield) and **22** (35% yield) in 13% and 11% de, respectively. Finally, we examined the effect of the electronic character of the rhodium(II) catalyst on the cyclization of diazoester **20**.[16-18] First we tested the cyclization-oxidation using rhodium(II) perfluorobutyrate, which afforded **21** in 13% de (94% yield) following DDQ oxidation.[17] The corresponding rhodium(II)caprolactamate produced **21** in 6% de (88% yield).[18]

Initially, we proposed the copper(I)-bis(oxazoline) catalyzed cyclization of diazoesters **11** and **16** proceeds by way of an intramolecular C-H insertion reaction. Assuming this reaction pathway, the enantioselectivity of methyl ester **11** can be rationalized by intermediate **23** (similar models have been proposed by Pfaltz for the asymmetric cyclopropanation of olefins).[14b] In this cyclization, carbenoid insertion occurs selectively at one set of diastereotopic hydrogens in the direction illustrated due to steric considerations. Based on this reaction mechanism, different enantioselectivities for the various ring C-H insertion pathways leading to isomers **13** and **14** would not be unexpected.



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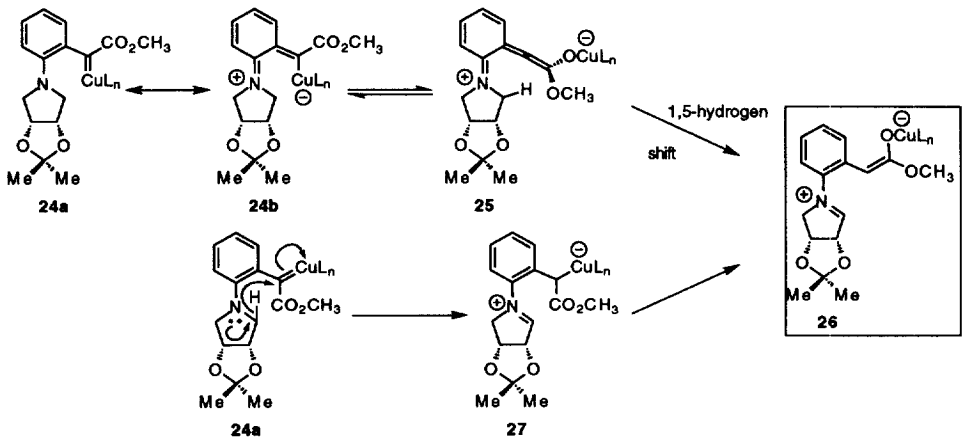
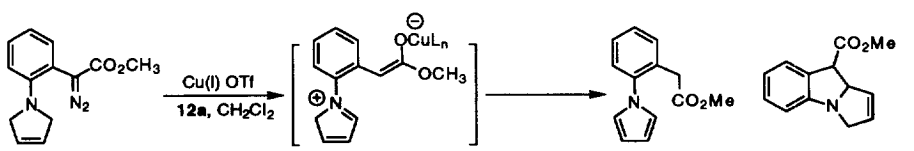
An alternative reaction mechanism for the observed cyclization could proceed through iminium ion **26**, generated by one of two pathways as outlined below.[19] In the first pathway, carbon to oxygen tautomerization of copper enolate **24b** leads to **25**, which following a 1,5-hydrogen shift generates a mixture of diastereomeric iminium ions (only one diasteromer (**26**) is shown). A second pathway to **26** proceeds by way of direct



intramolecular hydride transfer to the electron deficient carbenoid center (**24a** to **27**). Cyclization of intermediate **26** could then account for the production of **13** and **14**. Support for an iminium intermediate (**26**) is found in the copper(I) promoted decomposition of diazoester **28**, leading to pyrrole **29** as the major product and **30** as a minor product. Formation of **29** can be accounted for by proton loss from intermediate **28a**.



In conclusion, we have developed an asymmetric approach to the construction of the ring system common to various mitomycins. Currently, we are considering two possible reaction pathways (C-H insertion and ionic closure) to account for the observed cyclization. Efforts to discriminate between these pathways, as well as their extension to other nitrogen heterocyles have been initiated.

Experimental[20]

Methyl 2-nitrophenylacetate. Concentrated sulfuric acid (0.2 mL) was added to a solution of 2-nitrophenylacetic acid (9.05 g, 50 mmol) in anhydrous methanol (40 mL). The reaction mixture was then refluxed for 4 h, cooled to room temperature, concentrated *in vacuo* and the residue diluted with ethyl acetate (150 mL). The mixture was washed with cold saturated sodium bicarbonate (3 x 100 mL), water (100 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (1:2 EtOAc-hexane) afforded 9.7 g (100%) of methyl 2-nitrophenylacetate as a colorless oil: IR (CCl_4) 1749, 1549, 1349 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.65 (s, 3H), 3.99 (s, 2H), 7.30-7.60 (m, 3H), 8.06 (dd, J = 8.3, 1.5 Hz, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 39.4, 52.0, 125.1, 128.5, 129.6, 133.2, 133.5, 148.6, 170.3.

Methyl 2-aminophenylacetate. A solution of methyl 2-nitrophenylacetate (498 mg, 2.55 mmol) in methanol (15 mL) was hydrogenated over 5%Pd-C (ca. 5 mg) at 40 psi for 4 h and concentrated *in vacuo*. The residue was diluted with ethyl acetate, filtered through celite and concentrated *in vacuo*. The crude product was used in the next reaction without purification. A sample was purified by flash chromatograpy (1:7 to 1:3 EtOAc-hexane) for characterization purposes to provide a colorless oil: ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.56 (s, 2H), 3.67 (s, 3H), 4.04 (s, 2H), 6.67-6.98 (m, 2H), 7.05-7.09 (m, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 38.1, 52.0, 116.4, 118.8, 119.2, 128.4, 131.0, 145.4, 172.1.

Methyl 2-(3,4-dihydro)pyrrolidinophenylacetate (9). Solid sodium bicarbonate (1.07 g, 12.7 mmol) and cis-2-butene-1,4-di-methanesulfonate[9] (1.56 g, 6.37 mmol) was added to a solution of methyl 2-aminophenylacetate (450 mg, 2.55 mmol) in dimethylformamide (5 mL). The reaction mixture was stirred overnight at room temperature, diluted with ether (30 mL), washed with saturated sodium bicarbonate, water and brine (ca. 30 mL each). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (1:20 EtOAc-hexane) to afford 398 mg (72% from methyl 2-nitrophenylacetate) of methyl 2-(3,4-dihydro)pyrrolidinophenylacetate (**9**) as a colorless oil: IR (CCl_4) 3075, 3025, 2950, 1739, 1599 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.70 (s, 3H), 3.77 (s, 2H), 4.08 (s, 4H), 5.88 (s, 2H), 6.93-7.29 (m, 4H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 38.6, 51.8, 58.7, 119.9, 122.0, 126,6. 127.9, 128.2, 131.7, 149.4, 172.8. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.91; N, 6.45. Found: C, 71.32; H, 6.44; N, 6.33.

Methyl 2-(3,4-dihydroxy)pyrrolidinophenylacetate. Methyl 2-(3,4-dihydro)pyrrolidino-phenylacetate (**9**) (4.10 g, 18.9 mmol) was dissolved in water-acetone-*t*-butanol (35 mL, 4:2:1 ratio) and N-methylmorpholine N-oxide (2.51g, 20.7 mmol) added to the resultant solution. After 10 min, a catalytic amount of osmium tetroxide (ca. 2-3 mg) was added and the solution was maintained overnight at room temperature. The reaction mixture was quenched with 2% $Na_2S_2O_4$ (30 mL) and stirred for 10 minutes. Following neutralization with 1N HCl, the mixture was extracted with ethyl acetate (2 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (2:1 EtOAc-hexane) to afford 4.13g (90%) of methyl 2-(3,4-dihydroxy)pyrrolidinophenylacetate as a yellow oil: IR (CCl_4) 3442, 2952, 1729, 1600, 1495, 1159 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 3.09-3.28 (m, 6H), 3.66 (s, 2H), 3.68 (s, 3H), 4.29 (bs, 2H), 7.04-7.26 (m, 4H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 38.5, 51.9, 57.5, 70.8, 119.0, 122.9, 128.0, 128.6, 131.2, 148.0, 173.3; High-resolution mass spectrum (FAB) *m/z* 252.1229 [$(M+H)^+$, calcd for $C_{13}H_{18}NO_4$ 252.1236].

Acetonide 10. A catalytic amount of *p*-toluenesulfonic acid (ca. 10 mg) was added to a solution of methyl 2-(3,4-dihydroxy)pyrrolidinophenylacetate (4.05 g, 16.2 mmol) and 2,2-dimethoxypropane (2.37 mL, 19.4 mmol) in acetone (100 mL). The solution was maintained for two days, concentrated *in vacuo*, diluted with saturated sodium bicarbonate (100 mL) and extracted with ether (2 x 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue

was purified by flash column chromatography (1:2 EtOAc-hexane) to afford 4.30 g (94%) of **10** as a yellow oil: IR (CCl_4) 2991, 2935, 2805, 1741, 1494, 1209 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.35 (s, 3H), 1.55 (s, 3H), 2.83 (dd, *J* = 11.3, 1.2 Hz, 2H), 3.32 (d, *J* = 11.4 Hz, 2H), 3.67 (s, 3H), 3.82 (s, 2H), 4.74 (d, *J* = 1.2 Hz, 2H), 7.00-7.09 (m, 2H), 7.19-7.27(m, 2H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 24.7, 26.2, 36.3, 51.8, 58.6, 79.1, 111.2, 119.7, 123.8, 127.9, 129.9, 130.8, 147.3, 172.7. Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.92; H, 7.25; N, 4.79.

Diazo Ester 11. To a solution of acetonide **10** (1.34 g, 4.6 mmol) in THF (30 mL) was added NaHMDS (5.51 mL of 1 M solution in THF) at -78 °C. After 30 min a pre-cooled solution (-78 °C) of 4-nitrobenzenesulfonyl azide (1.10 g, 4.83 mmol) in dry THF (10 mL) was added via cannula. The solution was maintained for an additional 1h at -78 °C, the resulting deep brown solution was then slowly warmed to room temperature, resulting in a color change from deep brown to a yellow solution. The solution was stirred for an additional 1h and poured into pH 7 phosphate buffer solution (50 mL). The mixture was extracted with dichloromethane (3 x 50 mL). The combined organic extracts were dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:6 EtOAc-hexane) to provide 1.29 g (88%) of diazo ester **11** as a yellow oil: IR($CHCl_3$) 3012, 2940, 2104, 1691 cm^{-1}; ^{1}H-NMR (200 MHz , $CDCl_3$) δ 1.35 (s, 3H), 1.58 (s, 3H), 2.81 (ddd, *J* = 11.6, 3.1, 1.2 Hz, 2H), 3.55 (d, *J* = 11.6 Hz, 2H), 3.84 (s, 3H), 4.77 (dd, *J* = 2.8, 1.2 Hz, 2H), 6.91-7.46 (m, 4H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 24.2, 25.8, 52.0, 56.1, 78.4, 111.1, 116.7, 117.6, 122.2, 128.9, 132.4, 146.7, 166.0; High-resolution mass spectrum (FAB) *m/z* 318.1453 [$(M+H)^+$, calcd for $C_{16}H_{20}N_3O_4$ 318.1453].

Representative Experimental: Copper-catalyzed Cyclization of Diazo Ester 11. To a suspension of Cu(I)OTf (~60 mg, 0.240 mmol) in dry chloroform (20 mL) was added a solution of **12a** (67 mg, 0.250 mmol) in chloroform (10 mL). After 2h, the resultant blue-green solution was transfered via canula to a dry flask containg activated 4 Å molecular sieves (powder, 1 g). To this was added a solution of diazo ester **11** (760 mg, 2.39 mmol) in dry chloroform (10 mL) dropwise over 12 h. After 5 days, the mixture was filtered through neutral alumina and concentrated *in vacuo* to a green oil. This was purified by flash column chromatography (1:6 EtOAc-hexane). The products were isolated as a mixture of two anti (**13a** and **13b**) and two syn isomer (**14a** and **14b**). The first product to elute was a 1.7:1 mixture of **13a** and **13b** (489 mg, 71%) [TLC, R_f 0.35 (1:4 EtOAc-hexane)]. The second product to elute was a 1.3:1 mixture of syn isomers **14a** and **14b** (160 mg, 23%) [TLC, R_f 0.14 (1:4 EtOAc-hexane)].

The isomers were separated by flash chromatography (3 x 24 cm silica, 1:10 to 1:6 EtOAc-hexane as eluant, analysis of fractions by capillary gas chromatography at 210 °C) and identified.

Exo-anti (13a): GC, R_t 8.39; $[\alpha]_D$ +42.7° (*c* 0.8, CH_2Cl_2); IR(CH_2Cl_2) 3010, 1737, 1601, 1479, 1211 cm^{-1}; ^{1}H-NMR (200 MHz , $CDCl_3$) δ 1.32 (s, 3H), 1.59 (s, 3H), 3.50 (dd, *J* = 13.0, 4.3, 1H), 3.75 (m, 1H), 3.74 (s, 3H), 4.22-4.42 (m, 3H), 4.67 (m, 1H), 6.59 (d, *J* = 7.8 Hz, 1H), 6.79 (td, *J* = 7.5, 1.0 Hz, 1H), 7.16 (td, *J* = 7.5, 1.3 Hz, 1H), 7.26 (d, *J* = 6.9 Hz, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 25.4, 27.6, 51.3, 52.6, 56.6, 72.6, 80.0, 85.2, 110.3, 114.1, 120.0, 125.6, 125.8, 129.4, 152.9, 172.0.

Endo-anti (13b): GC, R_t 7.66; $[\alpha]_D$ -+9.2° (*c* 4.2, CH_2Cl_2); IR(CCl_4) 2991, 2952, 1737, 1602, 1479, 1374 cm^{-1}; ^{1}H-NMR (200 MHz , $CDCl_3$) δ 1.29 (s, 3H), 1.56 (s, 3H), 3.43 (dd, *J* = 12.7, 3.9, 1H), 3.75 (dd, *J* = 12.7, 6.2 Hz, 1H), 3.83 (s, 3H), 4.14 (dd, *J* = 9.2, 5.1 Hz, 1H), 4.34 (d, *J* = 9.2 Hz, 1H), 4.55 (dd, *J* = 6.9, 5.1 Hz, 1H), 4.61-4.69 (m, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 6.83 (t, *J* = 7.4 Hz, 1H), 7.15 (t, *J* = 7.8 Hz, 1H), 7.24 (d, *J* = 7.4 Hz, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 25.2, 27.4, 48.4, 52.1, 56.8, 72.7, 80.3, 81.3, 110.3, 113.7, 120.3, 125.6, 126.2, 128.7, 153.2, 171.0; High-resolution mass spectrum (FAB) *m/z* 290.1394 [$(M+H)^+$, calcd for $C_{16}H_{20}NO_4$ 290.1392].

Exo-syn (14a): GC, R_t 7.43; mp 59-62 °C; $[\alpha]_D$ -51.9° (*c* 1.8, CH_2Cl_2); IR(CH_2Cl_2) 2952, 1736, 1603, 1480, 1211 cm^{-1}; ^{1}H-NMR (200 MHz , $CDCl_3$) δ 0.65 (s, 3H), 1.18 (s, 3H), 3.21 (dd, *J* = 13.9, 3.7 Hz, 1H), 3.73 (s, 3H), 3.82 (d, *J* = 13.7 Hz, 1H), 4.21 (dd, *J* = 5.0, 1.9 Hz, 1H), 4.46 (br s, 1H), 4.67 (t, *J* = 5.4 Hz, 1H), 4.80 (dd, *J* = 5.5, 3.9 Hz, 1H), 6.62 (d, *J* = 7.6 Hz, 1H),

6.72 (t, J = 7.3 Hz, 1H), 7.10 (t, J = 7.5 Hz, 1H), 7.22 (d, J = 7.6 Hz, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 24.0, 25.0, 47.1, 52.4, 54.5, 70.4, 81.0, 81.8, 109.4, 111.7, 119.0, 124.9, 127.4, 128.5, 153.1, 172.8.

Endo-syn (14b): GC, R_t 7.12; $[\alpha]_D$ -8.4° (*c* 1.8, CH_2Cl_2); IR(CCl_4) 2991, 2938, 1731, 1698, 1604, 1479 cm^{-1}; ^{1}H-NMR (200 MHz , $CDCl_3$) δ 0.49 (s, 3H), 1.09 (s, 3H), 3.14 (dd, J = 14.0, 3.6 Hz, 1H), 3.79 (s, 3H), 3.89 (d, J = 14.0 Hz, 1H), 4.06 (dd, J = 9.1, 4.3 Hz, 1H), 4.36 (d, J = 8.9 Hz, 1H), 4.69-4.80 (m, 2H), 6.62 (d, J = 7.8 Hz, 1H), 6.72 (t, J = 9.1 Hz, 1H), 7.09 (t, J = 7.4 Hz, 1H), 7.21 (d, J = 7.4 Hz, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 24.0, 24.4, 46.3, 51.6, 55.0, 70.7, 81.2, 81.9, 109.2, 111.5, 119.1, 125.2, 126.8, 127.6, 153.1, 171.4.

Representative Experimental: Oxidation of 13a to Mitosene 15. To a solution of **13a** (30.8 mg, 0.106 mmol) in CH_2Cl_2 (10 mL) was added DDQ (28 mg, 0.128 mmol). After 1h, the reaction mixture was diluted with ether (30 mL), washed with saturated sodium bicarbonate solution (3 x 20 mL), water (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (1:2 ethyl acetate-hexane) to afford 27.3 mg (96%) of **15** as a white solid: mp 166-167 °C; TLC, R_f 0.15 (4:1 hexane/EtOAc); $[\alpha]_D$ -104.6° (*c* 1.46, CH_2Cl_2); IR (CCl_4) 2992, 2950, 1710 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.29 (s, 3H), 1.48 (s, 3H), 3,94 (s,3H), 4.22-4.25 (m,2H), 5.34-5.41 (m, 1H), 5.84 (d, J = 6.0 Hz, 1H), 7.25-7.27 (m, 3H), 8.13-8.18 (m, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 25.5, 26.9, 50.8, 51.1, 76.7, 81.5, 101.5, 110.3, 113.0, 122.2, 122.8, 130.5, 132.2, 147.3, 165.0. Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.96;N,4.87. Found: C, 66.73; H, 6.01; N, 4.88.

In order to determine the optical purity **15** (ca. 15mg, 5.2 *u*mol) was dissolved in $CDCl_3$ (0.7 mL) and added tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato], europium(III) (ca. 18 mg, 1.5 *u*mol). The resultant proton NMR spectrum of this sample showed two sets of acetonide methyl singlets. Integration of these two sets of methyl groups determined the enantiomeric excess of **15**.

Menthyl 2-nitrophenylacetate To a suspension of 2-nitrophenylacetic acid (5.0 g, 27.6 mmol) in dry benzene (54 mL) was added oxalyl chloride (3.6 mL, 41.4 mmol) and a catalytic amount of DMF. After 30 min, the reaction mixture was heated to reflux for 1h and then concentrated *in vacuo* . The residue was dissolved in CH_2Cl_2 (20 mL) and added dropwise to a stirred solution of (1*R*, 2*S*, 5*R*)-menthol (3.88 g, 24.8 mmol) and triethylamine (9.6 mL, 69.0 mmol) in CH_2Cl_2 (50 mL) at 0 °C for 10 min. The solution was warmed to room temperature, maintained for 1h and diluted with CH_2Cl_2 (150 mL). The organic solution was washed with 5% HCl (2 x 50 mL), saturated sodium bicarbonate (2x50 mL), brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* . The crude product was purified by flash column chromatography (1:10 ethyl acetate-hexane) to afford 7.32 g (92%) of menthyl ester as a white solid solid: mp 80-82 °C; $[\alpha]_D$ -62.0° (*c* 5.6, CH_2Cl_2); IR (CCl_4) 2958, 1737, 1531, 1348 cm^{-1}; ^{1}H-NMR(200 MHz, $CDCl_3$) δ 0.71-1.15 (m, 12H), 1.25-2.10 (m, 6H), 3.90-4.10 (m, 2H), 4.63-4.76 (m, 1H), 7.34-7.65 (m, 3H), 8.07-8.12 (m, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 16.2, 20.6, 21.9, 23.4, 26.2, 31.3, 34.1, 40.0, 40.6, 47.0, 75.3, 125.1, 128.4, 130.0, 133.2, 133.3, 169.4. Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 7.38. Found: C, 67.76; H, 7.84; N, 7.38.

Menthyl 2-(3,4-dihydro)pyrrolidinophenylacetate A solution of menthyl 2-nitrophenylacetate (7.1g, 22.2 mmol) in methanol (110 mL) was hydrogenated over 5% Pd-C (0.47 g, 0.22 mmol) at 40 psi for 4h and concentrated *in vacuo*. The residue was diluted with ethyl acetate, filtered through celite and concentrated *in vacuo*. The crude product was used directly in the next reaction without purification.

Solid sodium bicarbonate (7.75 g, 92.25 mmol) and *cis*-2-butene-1,4-di-methanesulfonate (13.52 g, 55.34 mmol) was added to a solution of menthyl 2-aminophenylacetate (5.34 g, 18.45 mmol) in dimethylformamide (35 mL). The reaction mixture was stirred overnight at room temperature, diluted with ether (100 mL), washed with saturated sodium bicarbonate, water and brine (ca. 100 mL each). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column

chromatography (1:20 EtOAc-hexane) to afford 4.88 g (77% from menthyl 2-nitrophenylacetate) of menthyl 2-(3,4-dihydro)pyrrolidinophenylacetate as a colorless oil: $[\alpha]_D$ -47.0° (*c* 1.8, CH_2Cl_2); IR ($CDCl_3$) 3073, 2956, 2871, 1729 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.71 (d, *J* = 7.0 Hz, 3H), 0.83-2.05 (m, 15 H), 3.73 (s, 2H), 4.09 (s, 4H), 4.63-4.76 (m, 1H), 5.86 (s, 2H), 6.85-7.25 (m, 4H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 16.2, 20.8, 22.0, 23.3, 26.0, 31.3, 34.2, 39.3, 40.8, 47.0, 58.5, 74.4, 119.1, 121.4, 126.6, 127.2, 128.1, 132.1, 149.3, 172.0. Anal. Calcd for $C_{22}H_{31}NO_2$: C, 77.38; H, 9.15; N, 4.10. Found: C, 77.62; H, 8.79; N, 4.08.

Menthyl 2-(3,4-dihydroxy)pyrrolidinophenylacetate. To a solution of menthyl 2-(3,4-dihydro)pyrrolidinophenylacetate (4.80 g, 14.1 mmol) in water-acetone-*t*-butanol (45 mL, 2:3:6 ratio) was added N-methylmorpholine N-oxide (2.47g, 21.1 mmol). After 10 min, a catalytic amount of osmium tetroxide (ca. 2-3 mg) was added and the solution was maintained overnight at room temperature. The reaction mixture was quenched with 2% $Na_2S_2O_4$ (30 mL) and stirred for 10 minutes. Following neutralization with 1N HCl, the mixture was extracted with ethyl acetate (2x100 mL). The combined organic extracts were washed with brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:1 EtOAc-hexane) to afford 5.28 g (100%) of menthyl 2-(3,4-dihydroxy)pyrrolidinophenylacetate as a colorless oil: $[\alpha]_D$ -48.2° (*c* 1.8, CH_2Cl_2); IR($CDCl_3$) 3442, 2958, 2929, 2871, 1722, 1600 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.68 (d, *J* = 7.0 Hz, 3H), 0.80 (d, *J* = 8.0 Hz, 3H), 0.87 (d, *J* = 6.4 Hz, 3H), 0.78-1.75 (m, 9H), 3.08-3.18 (m, 2H), 3.25-3.38 (m, 2H), 3.63 (s, 2H), 3.70 (bs, 2H), 4.22 (s, 2H), 4.59-4.71 (m, 1H), 6.90-7.20 (m, 4H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 16.1, 20.5, 21.8, 23.1, 25.8, 31.1, 34.0, 38.9, 40.5, 46.7, 57.1, 57.2, 70.8, 74.6, 118.1, 122.2, 127.5, 127.8, 131.5, 148.2, 172.2; High-resolution mass spectrum (FAB) *m/z* 376.2487 [$(M+H)^+$, calcd for $C_{22}H_{33}NO_4$ 376.2487].

Acetonide menthyl ester. A catalytic amount of *p*-toluenesulfonic acid (ca. 10 mg) was added to a solution of menthyl 2-(3,4-dihydroxy)pyrrolidinophenylacetate (4.32 g, 11.5 mmol) and 2,2-dimethoxypropane (3.54 mL, 28.7 mmol) in acetone (120 mL). The solution was maintained for two days, concentrated *in vacuo,* diluted with saturated sodium bicarbonate (100 mL) and extracted with ether (2 x 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:2 EtOAc-hexane) to afford 4.04 g (85 %) of the titled compound as a white solid: mp 78-79 °C; $[\alpha]_D$ -53.4° (*c* 5.7, CH_2Cl_2); IR($CDCl_3$) 2956, 2931, 2871, 2803, 1729, 1494, 1454 cm^{-1}; ^{1}H-NMR(200 MHz, $CDCl_3$) δ 0.71 (d, *J* = 6.9 Hz, 3H), 0.84 (d, *J* = 7.1 Hz, 3H), 0.89 (s, *J* = 6.5 Hz, 3H), 0.60-1.90 (m, 9H), 1.35 (s, 3H), 1.54 (s, 3H), 2.74-2.87 (m, 2H), 3.29-3.56 (m, 2H), 3.70-3.92 (m, 2H), 4.65-4.75 (m, 3H), 7.00-7.29 (m, 4H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 16.1, 20.7, 22.0, 23.3, 24.9, 25.9, 26.4, 31.3, 34.2, 36.5, 40.7, 46.9, 58.3, 58.6, 74.4, 79.1, 79.2, 111.5, 119.1, 123.4, 127.6, 129.7, 130.7, 147.1, 171.9. Anal. Calcd for $C_{25}H_{37}NO_4$: C, 72.25; H, 8.97; N, 3.37. Found: C, 72.24; H, 8.96; N, 3.30.

Menthyl diazo ester (16). To a solution of menthyl ester (1.38 g, 3.32 mmol) in dry THF (30 mL) was added NaHMDS (3.65 mL of 1 M solution in THF) at -78 °C. After 30 min a pre-cooled solution (-78 °C) of 4-nitrobenzenesulfonyl azide (0.80 g, 3.48 mmol) in dry THF (8 mL) was added via cannula. The solution was maintained for an additional 1h at -78 °C, the resulting deep brown solution was then slowly warmed to room temperature, resulting in a color change from deep brown to a yellow solution. The solution was stirred for an additional 2h and poured into pH 7 phosphate buffer solution (50 mL). The mixture was extracted with dichloromethane (3x50 mL). The combined organic extracts were dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography (1:6 EtOAc-hexane) to provide 0.62 g (42%) of diazo ester **16** as a yellow oil: $[\alpha]_D$ -43.9° (*c* 3.2, CH_2Cl_2); IR (CCl_4) 2958, 2929, 2100, 1689, 1429, 1207 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.79 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 6.9 Hz, 3H), 0.90 (s, *J* = 6.4 Hz, 3H), 0.60-2.20 (m, 9H), 1.33 (s, 3H), 1.54 (s, 3H), 2.81 (d, *J* = 11.3 Hz, 2H), 3.50 (d, *J* = 11.5 Hz, 2H), 4.73-4.89 (m, 3H), 6.91 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.00 (td, *J* = 9.3, 1.2 Hz, 1H), 7.20 (td, *J* = 7.4,

1.6 Hz, 1H), 7.41 (dd, J = 7.9, 1.7 Hz, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 16.5, 20.6, 22.0, 23.6, 24.3, 25.9, 26.5, 31.4, 34.2, 41.3, 47.1, 55.9, 56.3, 75.0, 78.4, 78.5, 111.2, 117.1, 117.6, 122.1, 128.8, 132.7, 146.8, 166.1.

Menthyl esters 17 and 18. To a suspension of Cu(I)OTf (12.7 mg, 0.05 mmol) in dry chloroform (10 mL) was added a solution of **12a** (14 mg, 0.05 mmol) in chloroform (2 mL). To this solution was added a diazo ester **16** (220 mg, 0.499 mmol) in dry chloroform (5 mL) dropwise over 12 h. The mixture was filtered through neutral alumina and concentrated *in vacuo* to a green oil. Without purification this mixture was directly oxidized with DDQ.

To a solution of the crude product in CH_2Cl_2 (10 mL) was added DDQ (170 mg, 0.747 mmol). After 1h, the reaction mixture was diluted with ether (30 mL), washed with saturated sodium bicarbonate solution (3x20 mL), water (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. HPLC analysis of the crude products (20% EtOAc/hexane, 3 mL/min) determined the ratio of diastereomers to be 2:1, the slower eluting diastereomer predominating. The products were separated by flash column chromatography (1:6 EtOAc-hexane). The first product to elute was **17** (82 mg, 40%) obtained as a colorless solid: mp 184-186 °C; TLC, R_f 0.33 (1:4 EtOAc-hexane); R_t 13.4 min (20% EtOAc/hexane, 3 mL/min); $[\alpha]_D$ -209.5° (c 4.3, CH_2Cl_2); IR($CHCl_3$) 2958, 2870, 1688, 1563, 1453, 1210; ^{1}H-NMR (200 MHz , $CDCl_3$) δ 0.82 (d, J =6.9 Hz, 3H), 1.30 (s, 3H), 0.75-1.80 (m, 13 H), 2.05-2.20 (m, 2H), 4.23-4.27 (m, 2H), 4.88-5.00 (m, 1H), 5.38-5.40 (m, 1H), 5.88 (d, J = 6.1 Hz, 1H), 7.25-7.27 (m, 3H), 8.12-8.17 (m, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 16.5, 21.0, 22.1, 23.6, 25.5, 26.4, 26.9, 31.4, 34.4, 41.2, 47.4, 50.8, 73.7, 76.9, 81.6, 102.4, 110.2, 112.2, 113.0, 122.1, 122.3, 122.8, 130.6, 132.3, 147.0, 164.3; High-resolution mass spectrum (FAB) m/z 412.2480 [$(M+H)^+$, calcd for $C_{25}H_{33}NO_4$ 412.2488].

The second product to elute was **18** (54 mg, 26%), as a yellow oil: TLC, R_f 0.28 (1:4 EtOAc-hexane); R_t 15.3 min (20% EtOAc/hexane, 3 mL/min); $[\alpha]_D$ +63.9° (c 1.1, CH_2Cl_2); IR($CHCl_3$) 2938, 2870, 1689, 1562, 1453, 1211; ^{1}H-NMR (200 MHz , $CDCl_3$) δ 0.78 (d, J = 6.9 Hz, 3H), 0.91 (d, J = 6.9 Hz, 3H), 0.93 (d, J = 6.4 Hz, 3H), 1.27 (s, 3H), 1.46 (s, 3H), 0.70-1.86 (m, 7H), 2.18-2.25 (m, 2H), 4.15-4.30 (m, 2H), 4.92-5.05 (m, 1H), 5.35-5.41 (m, 1H), 5.88 (d, J = 6.1 Hz, 1H), 7.25-7.28 (m, 3H), 8.17-8.22 (m, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 16.0, 21.1, 22.1, 23.1, 25.5, 25.6, 26.9, 31.4, 34.4, 41.6, 47.3, 50.8, 73.4, 77.1, 81.5, 102.0, 110.2, 112.9, 122.1, 122.3, 122.8, 130.8, 132.3, 147.0, 164.2; High-resolution mass spectrum (FAB) m/z 412.2482 [$(M+H)^+$, calcd for $C_{25}H_{33}NO_4$ 412.2488].

Nitrile 19. A solution of ester **17** (260 mg, 0.63 mmol) and 4N LiOH (20 mL) in diglyme (20 mL) was refluxed for 7 days. The solution was cooled to room temperature, neutralized with 2.4N HCl and extracted with ethyl acetate (100 mL). The organic layer was washed with water (3 x 50 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give 92.0 mg of the corresponding acid (53%), which was not purified but used directly.

To a solution of the above acid (87 mg, 0.32 mmol) in benzene (15 mL) was added 60% NaH (27 mg, 0.38 mmol) at 0°C, and the mixture was warmed to room temperature. Oxalyl chloride (34 μL, 0.38 mmol) was added to this sodium carboxylate. The solution was then refluxed for 1h and concentrated *in vacuo*. To a suspension of resulting solid in dichloromethane (10 mL) was passed anhydrous ammonia for 30 min at 0°C. The mixture was warmed to room temperature and stirred for 15h. The solution was diluted with ethyl acetate (20 mL), washed with saturated sodium bicarbonate (20 mL), and concentrated *in vacuo* to give the corresponding amide. A solution of amide and *p*-toluenesulfonyl chloride (104.0 mg, 0.54 mmol) in pyridine (6 mL) was refluxed for two days. The solution was concentrated *in vacuo*, diluted with ethyl acetate (20 mL), washed with saturated sodium bicarbonate (2 X 20 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography (1:4 ethyl acetate-hexane) to afforded 58 mg of nitrile **19** (71%) as a white solid: mp 166-167 °C; $[\alpha]_D$ -150.0° (c 0.1, $CHCl_3$); IR ($CHCl_3$) 2222 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.28 (s, 3H), 1.47 (s, 3H), 4.31-4.33 (m, 2H), 5.38-5.45 (m, 1H), 5.79 (d, J =

6.0 Hz, 1H), 7.26-7.32 (m, 3H), 7.71-7.76 (m, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 25.7, 27.0, 51.0, 75.7, 81.9, 110.9, 113.8, 115.0, 120.4, 122.5, 123.9, 131.6, 132.2, 148.4.

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(20) **Materials and Methods.** All reactions were carried out under a nitrogen atmosphere using dry glassware which had been flame-dried under a stream of nitrogen, unless otherwise noted. When necessary, solvents were purified prior to use. Tetrahydrofuran was distilled from sodium/benzophenone; dichloromethane was distilled from calcium hydride. Triethylamine was distilled from calcium hydride and stored over potassium hydroxide. Chloroform was washed with water to remove ethanol, dried over potassium carbonate, distilled from phosphorous pentoxide and stored in the dark. Copper (I) triflate was purchased (Aldrich) and handled in a drybox under a nitrogen atmosphere. Reactions were monitored by thin-layer chromatography (TLC) using 0.25-mm E. Merck precoated silica gel plates. Visualizatoin was accomplished with UV light and aqueous ceric ammonium molybdate solution or anisaldehyde stain followed by charring on a hot-plate. Flash chromatography was perfomed with the indicated solvents using silica gel 60 (particle size 0.040-0.063 mm). Gas-liquid chromatography (GLC) analyses were performed with a Hewlett-Packard 5790A chromatograph equipped with a 30-m x 0.32-mm x 0.25-μm Hewlett-Packard Ultra (cross-linked methyl silicone) column. High-performance liquid chromatography (HPLC) was performed with a Rainin sytem. The HPLC system was equipped with a Dynamax method manager, Rainin HPXL solvent delivery system, a Rheodyne injector and a Dynamax model UV-1 variable-wavelength UV detector. The column measured 10 mm X 25 cm with 8-μm, 60 Å normal-phase packing. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. Melting points are uncorrected unless otherwise noted. ^{1}H and ^{13}C NMR spectra were recorded on a Varian-200 spectrometer at ambient temperature. ^{1}H and ^{13}C NMR data are reported as δ values relative to tetramethylsilane. Infrared spectra were recorded on a Mattson Galaxy Series FT-IR 5000 spectrometer. Optical rotations were measured on a Jasco DIP-181 digital polarimeter at ambient temperature. High-resolution mass spectra were obtained at Texas A&M University Mass Spectrometry Service Center by Dr. Llyod Sumners on a VG Analytical 70S high resolution, double focusing, sectored (EB) mass spectrometer. Combustion analyses were performed by Atlantic Mircrolab, Inc. (Norcross, GA).

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