Notes

A New Approach to the Synthesis of Piperazinomycin and Bouvardin: Facile Access to Cycloisodityrosine *via* an Intramolecular S_NAr Reaction

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Cycloisodityrosine (**1**) is a key subunit in a number of bioactive natural products, such as piperazinomycin (**3**),[1] bouvardin (**4**), deoxybouvardin (**5**), and structurally related bicyclic hexapeptides RA I−XIV (Figure 1).[2] Recently, in a series of elegant papers, Boger *et al.*[3] have demonstrated that cycloisodityrosine derivatives constitute the pharmacophore of natural products in contrast to earlier considerations[2] and, thus, have stimulated interest in this class of compounds.

Until recently, efforts to critically examine the biological role of cycloisodityrosine derivatives have been limited by their synthetic inaccessibility. Cyclization *via* macrolactamization[4] under different activating conditions including polymer-supported agents, ring closure *via* C3−O2 bond formation based on Ullmann ether synthesis,[5] and intramolecular oxidative phenol coupling[6] have all failed to give the elusive 14-membered ring. An indirect thallium trinitrate (TTN)-promoted intramolecular phenol coupling has been developed by Yamamura *et al.* and used in the total synthesis of piperazinomycin[7] and deoxybouvardin,[8] but the key cyclization step proceeded in only 5% yield (Scheme 1). Alternatively, ring closure *via* C1−O2 bond formation based on intramolecular Ullmann ether synthesis has been developed by Boger's group[9] and successfully applied in the total synthsis of bouvardin,[10] deoxybouvardin,[5] and piperazinomycin.[11] However, the yield was still low to moderate. As shown in Scheme 1, cyclization of dipeptide **8** under optimal conditions gave the desired macrocycle **9** in only 5−10% yield;[11] intramolecular N-acylation resulting in the formation of **10** (5−15%) and **11** (4−25%) was inevitable under all attempted conditions.[11]

Our interest in the synthesis of vancomycin-type antibiotics has unveiled an efficient synthesis of 16-membered polypeptidic macrocycles[12] *via* biaryl ether formation based on intramolecular aromatic nucleophilic (S_NAr) substitution. This useful methodology was then-expanded to the synthesis of 17-membered natural product K-13[13] and 14-membered *m,m*-cyclophane,[14] a subunit found in teicoplanin. The very recent com-

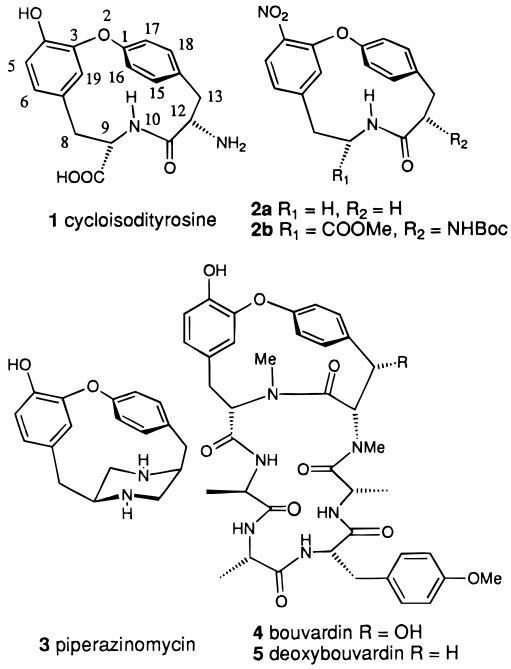
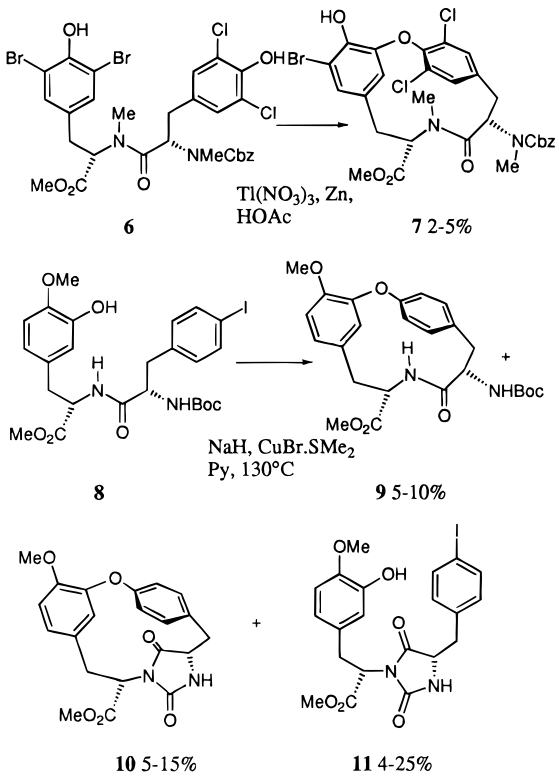


Figure 1.

Scheme 1



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(2) Itokwa, H.; Takeya, K. *Heterocycles* **1993**, *35*, 1467−1501.
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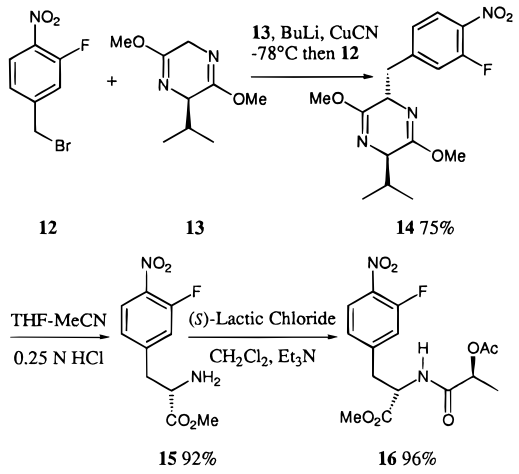
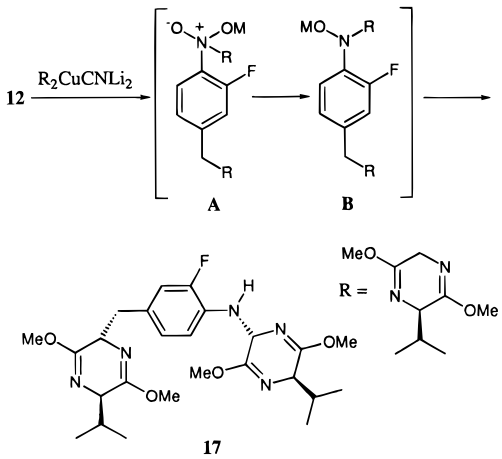
Scheme 2



Scheme 3



munication from Boger's group[15] dealing with the synthesis of simplified cycloisodityrosine (**2a**) based on our method prompts us to detail our own results concerning the synthesis of the fully functionalized cycloisodityrosine derivative (**2b**), a *m*,*p*-cyclophane, which is a key intermediate in our projected total syntheses of piperazinomycin and deoxybouvardin.

The synthesis of the nonproteinogenic amino acid methyl L-(*S*)-3-fluoro-4-nitrophenylalanate (**15**) is shown in Scheme 2.[13] A diastereoselective alkylation of Schöllkopf's bislactim ether[16] was a key step. The reaction of 3-fluoro-4-nitrobenzyl bromide **12** with the lithium azaenolate of **13** gave only a poor yield (<10%) of alkylated product, presumably due to the high acidity of benzylic protons[17] and, more importantly, the presence of multielectrophilic centers in **12**. Blank and Seebach[18] also obtained a moderate yield (30%) in the alkylation of *p*-nitrobenzyl halides with their glycine template under S_N2 conditions. An attempt to switch the reaction course from S_N2 to a radical anion mechanism[19] failed to give the coupled product **14**. However, when the lithium salt of **13** was transmetalated into a higher order (HO) organocuprate,[20] **14** could be reproducibly isolated in 75% yield, provided that the reaction was run at −78 °C. That S_N2 (displacement of bromide) prevails over S_NAr (displacement of fluoride) under these conditions may be explained by the HSAB principle if one considers the organocuprate as a soft nucleophile. Hydrolysis of **14** under acidic conditions afforded the desired amino ester **15** in 92% yield. The *S* configuration of **15** was assumed from the known alkylation mechanism.[16] The optical purity of **15** was probed by conversion to the corresponding (*S*)-lactate **16**. The ^{1}H NMR and GC/MS spectra of **16** showed that the optical purity of **15** was higher than 95%.

A significant amount of disubstituted compound **17** was formed when the coupling of **12** and HO organocuprate of bislactim ether **13** was run at −20 °C. The structure of **17** was determined based on spectroscopic data (^{1}H and ^{13}C NMR, HRMS). While no detailed mechanistic study has yet been carried out, the formation of **17** may be tentatively explained by 1,2-addition of organocuprate onto the nitro group leading to intermediate **A**, followed by complete reduction to secondary amine **17** *via* hydroxyamino intermediate **B** (Scheme 3). Cu^+ may have a rate-accelerating effect on the last reduction step (**B** to **17**).[21] A closely related reaction of a nitroarene with an arylmagnesium halide was reported by Gilman *et al.* to afford a complex mixture including nitroso, azoxy, azo, and secondary amine.[22] However, to the best of our knowledge, the corresponding reaction with a HO organocuprate has not yet been described. The high reactivity of the nitro group toward organometallic reagents may explain the low to moderate yields obtained in the alkylation of *p*-nitrobenzyl halides.[18]

Completion of the synthesis of **2b** was as follows. Reaction of **15** with *N*-Boc-L-Tyr using EDC as coupling reagent in the presence of HOBt gave the dipeptide **18** in 97% yield. Without optimization, treatment of **18** with K_2CO_3 in DMF (0.01 M) *at room temperature for 3 h* cleanly afforded equal amounts of atropisomers[12b] **19** and **20** in 62% total yield. Apparently, the S_NAr reaction proceeded much faster than the intramolecular N-acylation[11] as no products resulting from this latter process were observed (vide supra).

The mass spectra and the elemental analysis of **19** and **20** reveal that they are constitutional isomers calculated for $C_{24}H_{27}N_3O_8$. Both compounds exibited a characteristic, strongly shielded H-19 at 5.37 and 5.34 ppm due to the anisotropic effect of the tyrosine aromatic ring, indicative of a cyclized structure. Attempted thermoatropoisomerization in DMSO-d_6 at 110 °C failed to give any equilibrium, probably due to the high energy re-

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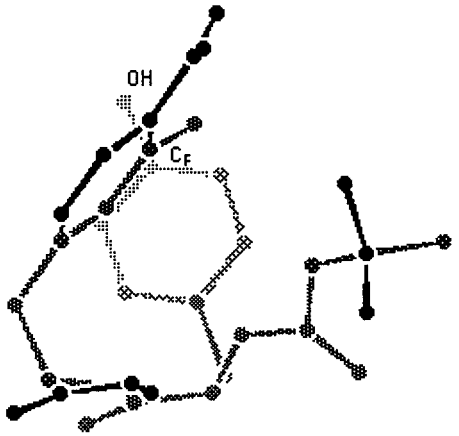


18

E = -443.91 KJ/MOL, C_F-OH = 5.129 Å

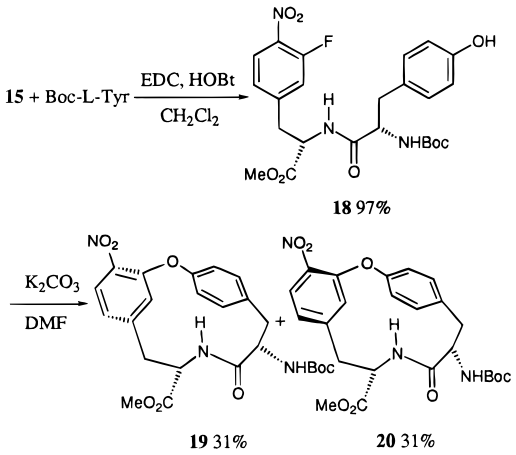
Figure 2.

quired for this process. A control experiment showed that no interchange of these two cyclic compounds occurred under the above S_NAr reaction and that both **16** and *N*-Boc-L-Tyr-Tyr OMe were configurationally stable under the cyclization conditions. These results gave indirect evidence that the two cyclization products did not result from the epimerization of two stereogenic centers and hence are atropisomers.[12b,23]

Considering the difficulty encountered in the previous syntheses of cycloisodityrosine, the facile cyclization reported here is remarkable. High dilution technique was not needed, so the solution conformation of the cyclization precursor **18** may be such that the two reactive sites are close.[24] To gain information regarding the solution conformation, we carried out a computational simulation (Macromodel, Batchmin Version 3.5 a, Oplsa force field, water set).[25] As shown in Figure 2, the lowest energy conformer has a bent orientation in which an edge-to-face geometry between two aromatic rings is evident. The two reactive sites (OH and C_F) are within 5.129 Å, resulting in a low activation energy and favorable entropy for cyclization. The atomic charge model or charge transfer (CT) model[26] may be responsible for such conformational preference.

In summary, we describe a new and efficient method for the synthesis of cycloisodityrosine derivatives using an intramolecular S_NAr reaction. The conditions are much milder and the yield is much higher than those previously reported. The NO_2 function in **2b** provides an opportunity to introduce not only the hydroxyl group found in the natural products[13] but also others such as amino and amide for bioactivity evaluation. Further studies in this direction as well as toward the total synthesis of natural products based on these results will be reported in due course.

Scheme 4



Experimental Section

General procedures and methods for characterization have been described previously.[12b] Melting points are uncorrected.

(2*S*,5*R*)-2-(3′-Fluoro-4′-nitrobenzyl)-5-isopropyl-3,6-dimethoxy-2,5-dihydropyrazine (14). Copper cyanide (208 mg, 2.32 mmol) was placed in a flame-dried, two-necked round-bottomed flask (50 mL), evacuated with a vacuum pump, and purged with argon. The procedure was repeated three times, and dry THF (25 mL) was injected. In another flame-dried, two-necked flask (25 mL) were introduced (2*R*)-(−)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (**13**) (831 μL, 4.64 mmol) and dry THF (6 mL). The solution was cooled to −78 °C, and *n*-butyllithium (1.6 M, 2.9 mL, 4.64 mmol) was added dropwise. After being stirred for 10 min, it was transferred *via* cannula to the flask containing the copper cyanide slurry, precooled to 0 °C. The reaction mixture was further stirred for 5 min after addition, the resulting tan solution was recooled to −78 °C, and the THF solution (3 mL) of 3-fluoro-4-nitrobenzyl bromide (**12**, 543 mg, 2.32 mmol) was introduced dropwise *via* syringe. The reaction mixture was stirred at this temperature for 1 h and quenched by addition of 10 mL of aqueous NH_4Cl:NH_4OH (9:1). The aqueous solution was extracted with EtOAc. The combined organic phase was washed with water, dried (Na_2SO_4), and evaporated in vacuo. Purification by flash chromatography (SiO_2, heptane:ether = 10:1) afforded starting material **12** (109 mg, 20%) and product **14** as a colorless oil (586 mg, 75%): $[\alpha]_D$ = +23.2° ($CHCl_3$, *c* = 0.97); IR ($CHCl_3$) 2987, 1700, 1606, 1525, 1437, 1350, 1025 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.64 (d, *J* = 6.9 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 2.19 (d of septet, *J* = 3.4, 6.9 Hz, 1H), 3.13 (dd, *J* = 6.0, 13.2 Hz, 1H), 3.21 (dd, *J* = 4.5, 13.2 Hz, 1H), 3.63 (t, *J* = 3.4 Hz, 1H), 3.67 (s, 3H), 3.73 (s, 3H), 4.30 (dt, *J* = 4.1, 6.0 Hz, 1H), 7.09 (m, 2H), 7.95 (t, *J* = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 16.7, 19.0, 31.9, 39.8, 52.5, 55.9, 60.9, 119.7 (d, *J* = 21.0 Hz), 125.5 (d, *J* = 27.1 Hz), 125.7, 126.0 (d, *J* = 3.9 Hz), 148.1, 155.0 (d, *J* = 260.0 Hz), 161.8, 164.5; MS *m*/*z* 338 (M + 1), 294, 183. Anal. Calcd for $C_{16}H_{20}FN_3O_4$: C, 56.97; H, 5.98; N, 12.45. Found: C, 57.50; H, 6.23; N, 12.18. A variable amount of **17** was also isolated: $[\alpha]_D$ = +40.5° ($CHCl_3$, *c* = 0.5); IR ($CHCl_3$) 2975, 1700, 1675 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.60 (d, *J* = 6.6 Hz, 3H), 0.68 (d, *J* = 6.6 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 1.05 (d, *J* = 6.9 Hz, 3H), 2.12 (m, 1H), 2.25 (m, 1H), 2.98 (dd, *J* = 4.4, 13.5 Hz, 1H), 3.08 (dd, *J* = 4.7, 13.5 Hz, 1H), 3.25 (t, *J* = 3.3 Hz, 1H), 3.60 (s, 3H), 3.66 (s, 3H), 3.71 (s, 3H), 3.78 (s, 3H), 4.00 (t, *J* = 3.0 Hz, 1H), 4.31 (q, *J* = 4.4 Hz, 1H), 5.29 (d, *J* = 3.0 Hz, 1H), 5.75 (s, 1H), 6.8−7.2 (m, 2H), 7.29 (t, *J* = 8.4 Hz, 1H); MS *m*/*z* 489, 474; HRMS *m*/*z* 489.2742 ($C_{25}H_{36}FN_5O_4$ requires 489.2751).

Methyl (*S*)-3-Fluoro-4-nitrophenylalanate (15). To a solution of **14** (230 mg, 0.68 mmol) in THF−acetonitrile (3/1) was added 0.25 N HCl. After the solution was stirred for 30 min at room temperature, the volatiles were removed under reduced pressure, the residue was extracted with CH_2Cl_2 to remove the neutral species, and the aqueous phase was then

(23) Inoue *et al.* have recently detailed their total synthesis of deoxybouvardin: Inoue, T.; Inaba, T.; Umezawa, I.; Yuasa, M.; Itokawa, H.; Ogura, K.; Komatsu, K.; Hara, H.; Hoshino, O. *Chem. Pharm. Bull.* **1995**, *43*, 1325−1335. They noted that the 14-membered cycloisodityrosine, obtained *via* Yamamura's method, is an equilibrium mixture of two compounds. We think that these two *separable* compounds could be the two atropisomers instead of the two conformers as mentioned in ref 8.

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(26) Hunter, C. A.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1990**, *112*, 5525−5534.

basified with aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried (Na_2SO_4), and evaporated to afford **15** (150 mg, 92%): $[\alpha]_D = +15°$ ($c = 1$, $CHCl_3$); IR ($CHCl_3$) 3450, 2988, 1738, 1613, 1531, 1269, 1063 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.62 (brs, 2H), 2.93 (dd, J = 7.9, 13.7 Hz, 1H), 3.15 (dd, J = 5.3, 13.7 Hz, 1H), 3.73 (m, 1H), 3.74 (s, 3H), 7.17 (m, 2H), 8.02 (t, J = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 40.6, 55.3, 68.1, 119.2 (d, J = 17.0 Hz), 125.5 (d, J = 30.5 Hz), 126.1, 147.3, 155.5 (d, J = 211.0 Hz), 174.8; MS m/z 243 ($M^+ + 1$), 242 (M^+), 189. **15** contained a small amount of methyl L-valinate, so no microanalysis was done.

16. To a solution of **15** (50 mg, 0.21 mmol) in CH_2Cl_2 was added (*S*)-Me(MeCOO)CHCOCl (29 mL, 0.25 mmol), Et_3N (35 mL, 0.25 mmol), and DMAP (3 mg, 0.025 mmol). After being stirred at room temperature for 1 h, the reaction was quenched by addition of aqueous NH_4Cl and extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried (Na_2SO_4), and evaporated. Purification by flash chromatography (SiO_2, heptane:EtOAc = 1:2) afforded product **16** as a yellow solid (72 mg, 96%): mp 80−81°C; $[\alpha]_D = +41.7°$ ($CHCl_3$, c = 0.23); IR ($CHCl_3$) 3419, 2985, 1744, 1688, 1606, 1531, 1375 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.45 (d, J = 6.8 Hz, 3H), 2.14 (s, 3H), 3.17 (dd, J = 5.6, 13.8 Hz, 1H), 3.36 (dd, J = 5.8, 13.8 Hz, 1H), 3.80 (s, 3H), 4.88 (m, 1H), 5.13 (q, J = 6.8 Hz, 1H), 6.64 (d, J = 6.9 Hz, 1H), 7.0−7.1 (m, 2H), 8.02 (t, J = 8.0 Hz, 1H); MS m/z 356 (M^+), 241; HRMS m/z 356.1124 ($C_{15}H_{17}FN_2O_7$ requires 356.1020).

Dipeptide 18. To a solution of compound **16** (162 mg, 0.67 mmol) in 20 mL of CH_2Cl_2 were added *N*-Boc-L-(*S*)-tyrosine (188 mg, 0.67 mmol), HOBt (135 mg, 0.67 mmol), and EDC (141 mg, 0.74 mmol). After being stirred at room temperature for 12 h, the reaction mixture was diluted with aqueous HCl (0.1 N), and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried (Na_2SO_4), and evaporated. Recrystallization from CH_2Cl_2 and heptane afforded product **18** as a yellow solid (320 mg, 97%): mp 96−97 °C; $[\alpha]_D = +12.3°$ ($CHCl_3$, c = 0.13); IR ($CHCl_3$) 3429, 3329, 2977, 1749, 1696, 1683, 1616 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.43 (s, 9H), 2.92 (dd, J = 7.1, 13.8 Hz, 1H), 3.02 (dd, J = 6.5, 13.8 Hz, 1H), 3.09 (dd, J = 5.8, 13.9 Hz, 1H), 3.21 (dd, J = 5.8, 13.9 Hz, 1H), 3.72 (s, 3H), 4.26 (q, J = 7.1 Hz, 1H), 4.80 (q, J = 6.0 Hz, 1H), 4.92 (brs, 1H), 5.09 (brs, 1H), 6.42 (d, J = 7.1 Hz, 1H), 6.75 (d, J = 8.5 Hz, 2H), 6.9−7.0 (m, 2H), 7.05 (d, J = 8.5 Hz, 2H), 7.96 (t, J = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, a drop of CD_3OD) δ 28.2, 37.5, 37.6, 52.6, 52.7, 56.1, 80.6, 115.5, 119.2 (d, J = 20.3 Hz), 125.6 (d, J = 27.5 Hz), 126.1 (d, J = 2.6 Hz), 127.3, 130.3, 145.8, 155.4 (d, J = 264.0 Hz), 155.8, 170.7, 171.9; MS m/z 506, 505. Anal. Calcd for $C_{24}H_{28}FN_3O_8$: C, 57.02; H, 5.58. Found: C, 57.04; H, 5.71.

Macrocyclization of 18. To a solution of **18** (20 mg, 0.04 mmol) in DMF (4 mL) was added K_2CO_3 (16 mg, 0.12 mmol). After being stirred at room temperature for 3 h, the reaction mixture was diluted with aqueous $NaHCO_3$ and extracted with EtOAc (10 × 20 mL). The combined organic phase was washed with brine, dried (Na_2SO_4), and evaporated. Purification by flash chromatography (SiO_2, heptane:EtOAc = 1:1) afforded two products, **19** (6 mg, 31%) and **20** (6 mg, 31%). Compound **19**: mp 249−250 °C; $[\alpha]_D = -9.0°$ ($CHCl_3$, c = 0.1); IR ($CHCl_3$) 3625, 3427, 3025, 1744, 1683, 1506 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.40 (s, 9H), 2.7−3.0 (m, 3H), 3.32 (dd, J = 5.3, 12.1 Hz, 1H), 3.65 (s, 3H), 4.1−4.2 (m, 2H), 5.23 (d, J = 9.3 Hz, 1H), 5.37 (br s, 1H), 6.45 (d, J = 7.4 Hz, 1H), 6.73 (dd, J = 1.6, 8.4 Hz, 1H), 7.04 (dd, J = 2.5, 8.3 Hz, 1H), 7.10 (dd, J = 2.5, 8.3 Hz, 1H), 7.27 (dd, J = 2.1, 8.3 Hz, 1H), 7.46 (dd, J = 2.1, 8.3 Hz, 1H), 7.88 (t, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.4, 34.9, 39.0, 52.7, 53.2, 58.5, 80.7, 115.8, 117.0, 121.5, 124.2, 124.6, 125.7, 130.6, 131.2, 133.1, 135.7, 137.0, 144.8, 156.3, 156.6, 171.4; MS m/z 485 (M^+), 426, 384. Anal. Calcd for $C_{24}H_{27}N_3O_8$: C, 59.37; H, 5.61. Found: C, 59.11; H, 5.65. Compound **20**: mp 130−131 °C; $[\alpha]_D = +35.4°$ ($CHCl_3$, c = 0.28); IR ($CHCl_3$) 3425, 3031, 1744, 1718, 1681, 1500 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.50 (s, 9H), 2.9−3.0 (m, 3H), 3.51 (dd, J = 5.3, 13.5 Hz, 1H), 3.68 (s, 3H), 4.25 (m, 1H), 4.57 (dt, J = 4.9, 9.0 Hz, 1H), 5.09 (d, J = 9.0 Hz, 1H), 5.34 (br s, 1H), 5.99 (brs, 1H), 6.74 (dd, J = 1.6, 8.4 Hz, 1H), 7.08 (dd, J = 2.5, 8.3 Hz, 1H), 7.17 (dd, J = 2.5, 8.3 Hz, 1H), 7.4−7.5 (m, 2H), 7.87 (t, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 28.4, 35.3, 38.8, 52.7, 53.0, 57.1, 81.6, 117.4, 121.8, 123.8, 124.9, 125.8, 130.3, 133.2, 135.0, 144.5, 156.5, 156.9, 171.2; MS m/z 485 (M^+), 426, 384; HRMS m/z 485.1816 ($C_{24}H_{27}N_3O_8$ requires 485.1798).

Supporting Information Available: ^1H NMR spectra of **15**−**19**, and **20** and GC analysis of **16** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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