De Novo Syntheses of Racemic Deoxy-C-nucleosides

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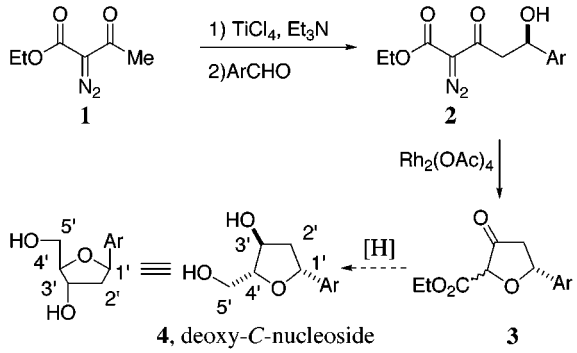
Received September 16, 1998

Introduction

C-Nucleosides have demonstrated potential as anticancer and anti-HIV agents.[1] These compounds mimic the action of regular nucleosides; however, the replacement of a C−N with a C−C linkage in C-nucleosides provides these compounds with impressive oral bioavailablities and therapeutic lifetimes. Despite the activity focused on the synthesis and testing of C-nucleosides, relatively little work has been done on their deoxy analogues, deoxy-C-nucleosides. Several groups have synthesized deoxy-C-nucleosides by C−C bond formation between an existing deoxyribose moiety and an appropriate aryl nucleophile.[2] However, these syntheses suffer from low stereoselectivity and lack of tolerance for functionality in the aryl nucleophile. To correct these deficiencies, we have developed a short, diastereoselective synthesis of deoxy-C-nucleosides from nonribosyl precursors (Scheme 1). This synthesis is also tolerant of a variety of hydrogen-bond-donating and -accepting functional groups in the aryl substituent.

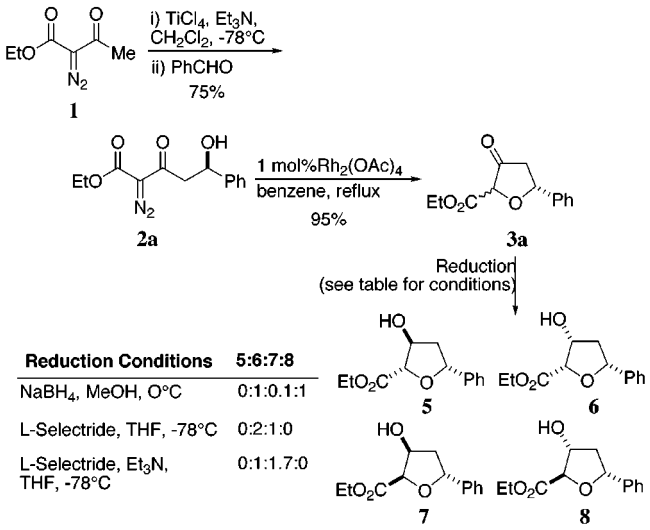
Scheme 1



Results and Discussion

The current synthesis uses our recently developed diazoketone aldol/O−H insertion reaction sequence to both construct the tetrahydrofuran ring of the product and couple the aryl group to this ring.[3] We used the sequence to produce **3a** (Ar = Ph), which we employed in model studies to determine the optimal route for conversion of **2** to **4** (Scheme 2). Compound **3a** exists as rapidly equilibrating, ∼1:1 mixture of cis and trans isomers. Thus, reduction of the ketone moiety of **3a** determines the stereochemistry at both $C_{3'}$ and $C_{4'}$. Our attempts at controlling the stereoselectivity of such a reduction met with limited success.[4] Under no conditions did we observe selectivity for any particular isomer, and furthermore, no conditions afforded detectable amounts of the desired diastereomer, **5**.

Scheme 2



The results from the direct reduction of **3a** indicated that we might want to separate the steps in which we formed the $C_{3'}$ and $C_{4'}$ stereocenters. Our strategy to accomplish this separation involved *tert*-butyldimethylsilyl (TBS) enol ether formation, ester reduction, stereoselective enol ether protonation, and stereoselective ketone reduction (Scheme 3). The silyl enol ether intermediates in this reaction sequence were both prone to hydrolysis, so we did not attempt to purify them. The enol ether and ester reduction steps were trivial; however, achieving decent levels of stereoselectivity in the protonation of the silyl enol ether required much experimentation. We found $Et_3N{\cdot}HF$ to be the optimal reagent for this conversion (vide infra). Directed reduction of the resulting hydroxy ketone to give **4a** proceeded with essentially complete stereocontrol.[2a,5] The NMR spectral data for racemic **4a** produced in this fashion exactly

(1) (a) Hacksell, U.; Daves, G. D. The Chemistry and Biochemistry of *C*-Nucleosides and *C*-Arylglycosides. In *Progress in Medicinal Chemistry*; Ellis, G. P., West, G. B., Eds.; Elservier Science Publishers: London, 1985; Vol. 22, pp 1−65. (b) Watanabe, K. A. The Chemistry of *C*-Nucleosides. In *Chemistry of Nucleosides and Nucleotides*; Townsend, L. B., Ed.; Plenum Press: New York, 1994; Vol. 3, pp 421−535.

(2) (a) Chen, J. J.; Walker, J. A., III; Liu, W.; Wise, D. S.; Townsend, L. B. *Tetrahedron Lett.* **1995**, *36*, 8363−8366. (b) Ren, R. X.-F.; Chaudhuri, N. C.; Paris, P. L.; Rumney, S.; Kool, E. T. *J. Am. Chem. Soc.* **1996**, *118*, 7671−7678.

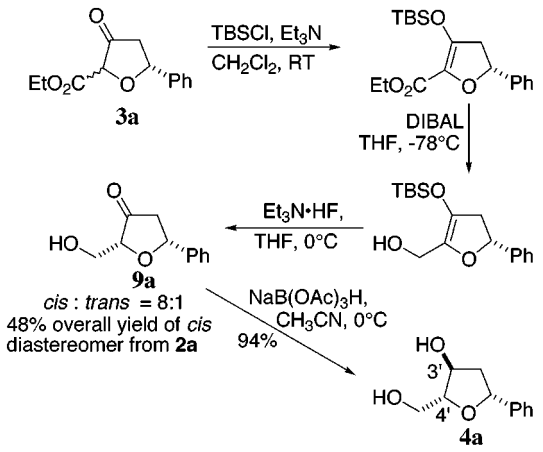
(3) Calter, M. A.; Sugathapala, P. M.; Zhu, C. *Tetrahedron Lett.* **1997**, *38*, 3837−3840.

(4) We determined the stereochemistries of **6** and **7** by reduction to the corresponding diols followed by single-crystal X-ray diffraction. We will report the X-ray structures in a separate publication. We determined the stereochemistry of **5** by reduction to the diol and comparison to the known compound (ref for **5**).

(5) (a) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560−3578. (b) Farr, R. N.; Daves, G. D., Jr. *J. Carbohydr. Chem.* **1990**, *9*, 653−660.

10.1021/jo9818834 CCC: $18.00
Published on Web 02/04/1999

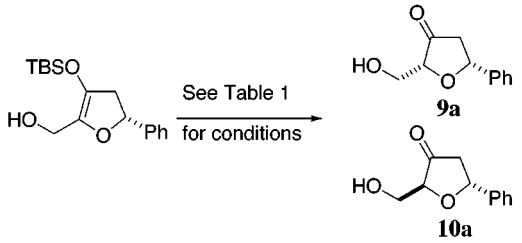
Scheme 3



matched those reported for nonracemic **4a**,[6] confirming our stereochemical assignments.

As expected, the ratio of diastereomers produced in the protonation was highly dependent on the steric bulk of the proton source (eq 1, Table 1).[7] Trialkylammonium fluoride salts gave the highest yields and diastereoselectivities. Trialkylammonium chloride salts in the absence of a fluoride source did not protonate the silyl enol ether, implying that the fluoride is necessary to activate the silyl enol ether prior to protonation.[8]

Table 1. Diastereoselectivities for the Production of 9a and 10a

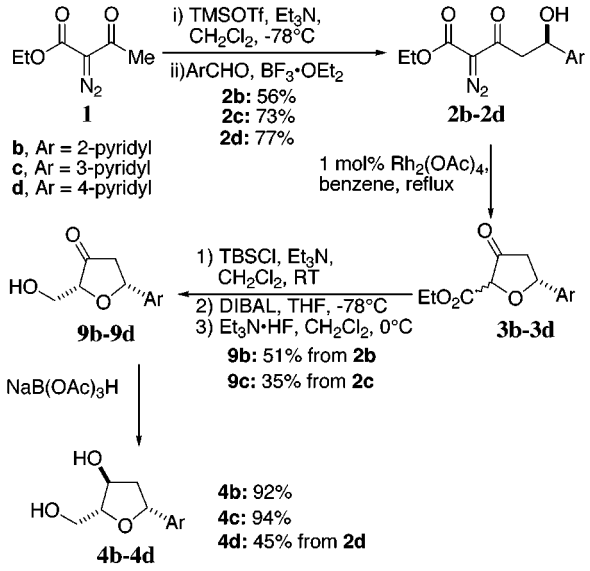


(1)

condns	**9a**:**10a**
Na_2CO_3, MeOH	2.0:1
TBAF	2.5:1
HF·pyridine	5.0:1
TBAF, Et_3N·HCl	6.6:1
Et_3N·HF	8.0:1

With a facile synthesis of **4a** in hand, we next turned to synthesizing deoxy-C-nucleosides with aromatic moieties functionalized to donate or accept hydrogen bonds. We first chose to synthesize substituted pyridines (Scheme 4). The presence of the basic pyridine nitrogen in the aldehydes necessary to construct **2b**−**d** interfered with the titanium aldol reactions required to form these intermediates. Therefore, we developed an alternative procedure for these aldol reactions, employing instead Mukaiyama's conditions.[9] The pyridine nitrogens of **2b**−**d** also slowed the insertion reactions of these compounds relative to that of **2a**, but did not lower the yields of **3b**−**d**.[10]

Scheme 4



The conversion of **3b**−**d** to **9b**−**d** using the silylation−reduction−protonation sequence proceeded in a straightforward fashion in moderate overall yields. The diastereoselectivities for the protonations to yield **9c** and **9d** were equivalent to those observed in the formation of **9a**; however, the diastereoselectivity of the protonation to yield **9b** was only 5.5:1. Fortunately, we were able to separate **9b** and **9c** from their cis isomers by chromatography. We were not able to separate **9d** from its diastereomer at this stage. Directed reduction of **9b**−**d** again proceeded in high yields and diastereoselectivities to afford **4b**−**d**. At this point, we were able to separate **4d** from its 1′−4′ trans diastereomer. Compounds **4b** and **4c** are known,[11,12] but we could find no reports on their biological activity. Therefore, we are having **4b**−**d** tested by the NCI and NIAID for anticancer and antiviral activity.

We also explored the synthesis of deoxy-C-nucleosides with hydrogen-bond-donating ability (Scheme 5). Initial attempts at carrying out the reaction scheme with unprotected anilines led to poor conversions and complicated product mixtures, so we opted to use a protected amino group as our hydrogen-bond-donating moiety. As the benzoyl-protected amino group did not contain a basic nitrogen to interfere with the titanium aldol reaction, we used these conditions to form **2e**,**f**. The insertion reactions of **2e**,**f** proceeded at the same rate as for **2a**, indicating that the protected amino group was not coordinating to the Rh(II) catalyst. The conversions of **3e**,**f** to **9e**,**f** were very diastereoselective, giving selectivities greater than 19:1.[13] This selectivity is understandable in the case of **9e**, which contains a sterically demanding, ortho-substituted aryl ring. However, we have no explanation

(6) Millican, T. A.; Mock, G. A.; Chauncey, M. A.; Patel, T. P.; Eaton, M. A. W.; Gunning, J.; Cutbush, D.; Neidle, S.; Mann, J. *Nucleic Acids Res.* **1984**, *12*, 7435−7453.

(7) We determined the ratio of **9a**:**10a** by integration of the signal for the C_1′-H in the ^{1}H NMR spectra of the unpurified reaction mixtures. The stereochemical assignment of **9a** was confirmed by conversion to **4a**.

(8) For another example of a diastereoselective silyl enol ether protonation, see: Takano, S.; Kudo, J.; Takahashi, M.; Ogasawara, K. *Tetrahedron Lett.* **1986**, *37*, 2405−2408.

(9) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 6. 7503−7509.

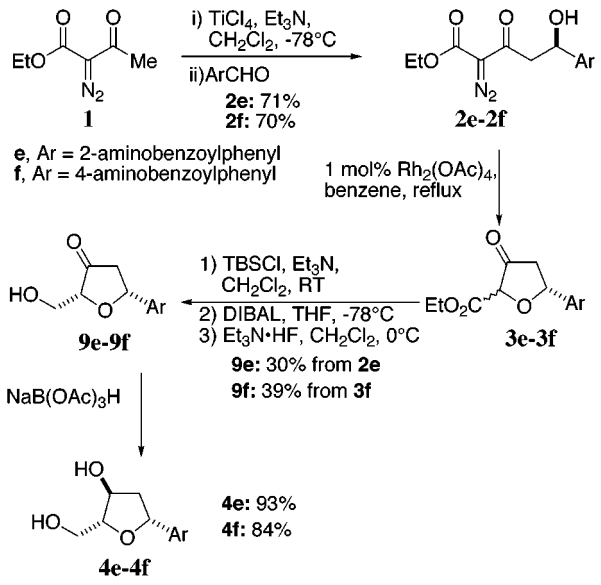
(10) Moyer, M. P.; Feldman, P. L.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 5223−5230.

(11) Yokoyama, M.; Akiba, T.; Togo, H. *Synthesis* **1995**, *6*, 638−640.

(12) Eaton, M. A. W.; Millican, T. A.; Mann, J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 545−548.

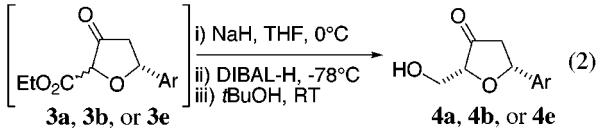
(13) We determined the ratio of **9e** and **9f** to their respective trans isomers by integration of the signal for the C_1′-H in the ^{1}H NMR spectra of the unpurified reaction mixtures.

Scheme 5



why the para-substituted aryl group of **9f** affords higher diastereoselectivity than the unsubstituted phenyl ring of **9a**, for example. In any case, reduction of **9e**,**f** yielded deoxy-C-nucleosides **4e**,**f**. These compounds have not been synthesized previously, so we have submitted them to NIAID for testing for antiviral activity.

Finally, we sought to further increase the efficiency and practicality of our deoxy-C-nucleoside synthesis. Instead of forming and later hydrolyzing a covalent metal enolate such as a silyl enol ether, we reasoned that it might be possible to form, reduce, and hydrolyze a more ionic metal enolate, all without intermediate isolation (eq 2). This sequence of reactions would allow a one-pot



(2)

compound	yield of *cis* isomer	*cis* : *trans*
4a	36% from **2a**	12:1
4b	50% from **2b**	6:1
4e	37% from **2e**	10:1

conversion of **3** to **4** and would also avoid the use of the somewhat expensive TBSCl. Preliminary experiments with **3a**,**b**,**e** indicate that such a one-pot transformation involving a sodium enolate is possible. The diastereoselectivities of these reactions are higher than those for the silyl enol ether route, although the overall yields are not yet as high.

In summary, we have developed a short, diastereoselective, and flexible synthesis of racemic deoxy-C-nucleosides that incorporate hydrogen-bonding functionality in their aryl moieties. These compounds are being tested for their biological activity. Further efforts will focus on incorporating more highly functionalized aryl groups into these compounds and on developing an asymmetric variant of this reaction sequence.

Experimental Section

General Methods. Unless otherwise mentioned, all reagents were purchased from Aldrich Chemical Co. and used without purification. Trimethylsilyltrifluoromethanesulfonate (TMSOTf) was purchased from United Chemical Technologies, Inc., and distilled at reduced pressure prior to use. $Rh_2(OAc)_4$ was purchased from Engelhard Corp. Titanium tetrachloride was purchased from Aldrich and distilled prior to use. All 2-diazo-3-oxobutanoate esters were prepared by the general procedure of Regitz et al.[14] Benzene, Et_3N, and CH_2Cl_2 were distilled over CaH_2. Flash chromatography was performed using E. Merck silica gel 60 (230−400 mesh). *N*-(2-Formyl)phenylbenzamide and *N*-(4-formyl)phenylbenzamide were prepared by reaction of the corresponding aminobenzaldehyde with benzoyl chloride.

General Procedure for the Formation of 2 by Titanium Aldol Reaction. To a solution of 0.856 g (5.48 mmol) **1** in 30 mL of CH_2Cl_2 at −78 °C was added dropwise 0.65 mL (1.1 g, 5.9 mmol) of $TiCl_4$ followed by 0.83 mL (0.60 g, 5.9 mmol) of Et_3N. The resulting red solution was stirred at −78 °C for 1 h, after which time it was cannulated to a −78 °C solution of 1.03 g (4.57 mmol) of *N*-(2-formyl)phenylbenzamide in 20 mL of CH_2Cl_2. The reaction mixture was stirred at −78 °C for 2 h and then the reaction quenched with 40 mL of saturated aqueous NH_4Cl and warmed to room temperature. The organic layer was separated and then washed with saturated aqueous $NaHCO_3$ (1 × 40 mL). The aqueous layers were extracted with 20 mL of CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The product was purified by flash chromatography (20% and 30% EtOAc in hexane) to yield 1.24 g (71%) of **2e** as pale yellow needles: mp 120−122 °C; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 10.19 (br s, 1H), 8.37 (d, 1H, J = 8.1 Hz), 7.94−7.97 (m, 2H), 7.54−7.46 (m, 3H), 7.36 (td, 1H, J = 7.8, 1.6 Hz), 7.19 (dd, 1H, J = 7.7, 1.6 Hz), 7.10 (td, 1H, J = 7.5, 1.2 Hz), 5.35−5.40 (m, 1H), 4.23 (q, 2H, J = 7.1 Hz), 4.14 (d, J = 2.8 Hz), 3.45 (dd, 1H, J = 18.2, 4.2 Hz), 3.38 (dd, 1H, J = 18.2, 8.9 Hz), 1.26 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 192.9, 165.4, 160.9, 137.4, 135.1, 131.8, 130.5, 129.0, 128.9, 127.4, 124.4, 122.9, 71.1, 62.0, 46.2, 14.4; IR ($CDCl_3$) 3341, 2142, 1716, 1660 cm^{-1}. Anal. Calcd for $C_{20}H_{19}N_3O_5$: C, 62.99; H, 5.02; N, 11.02. Found: C, 62.86; H, 5.08; N, 10.89.

2a: yield = 80%; yellow oil; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.38−7.22 (m, 5H), 5.20−5.15 (m, 1H), 4.26 (q, 2H, J = 7.1 Hz), 3.42 (d, 1H, J = 3.9 Hz), 3.33−3.20 (m, 2H), 1.29 (t, 3H, J = 7.1 Hz);^{13}C NMR ($CDCl_3$, 90 MHz) δ 192.2, 161.1, 142.7, 128.4, 127.5, 125.7, 70.2, 61.6, 48.5, 14.2; IR (neat) 3505, 2138, 1716, 1649 cm^{-1}. Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.52; H, 5.38; N, 10.69. Found: C, 59.52; H, 5.43; N, 10.66.

2f: yield = 70%; yellow needles; mp 125−127 °C; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.88−7.85 (m, 2H), 7.80 (br s, 1H), 7.63−7.39 (m, 7H), 5.20 (td, 1H, J = 6.2, 3.9 Hz), 4.29 (q, 2H, J = 7.1 Hz), 3.38 (d, 1H, J = 3.9 Hz), 3.28 (d, 2H, J = 6.2 Hz), 1.31 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 192.4, 166.0, 161.3, 139.2, 137.5, 135.1, 132.0, 128.9, 127.3, 126.7, 120.6, 70.1, 61.9, 48.6, 14.5; IR ($CDCl_3$) 3433, 2141, 1713, 1664 cm^{-1}. HRMS(FAB) calcd for $C_{20}H_{19}N_3O_5Na$ (MNa^+) 404.1212, found 404.1208.

General Procedure for the Formation of 2 by Mukaiyama Aldol Reaction. To a solution of 0.408 g (2.61 mmol) of **1** and 0.41 mL (0.30 g, 2.9 mmol) of Et_3N in 10 mL of CH_2Cl_2 at 0 °C was added 0.55 mL (0.63 g, 2.8 mmol) of TMSOTf dropwise. The resulting yellow solution was stirred at 0 °C for 1 h. In a separate flask, 0.55 mL (0.62 g, 4.4 mmol) of BF_3·OEt_2 was added dropwise to a solution of 0.207 mL (0.233 g, 2.18 mmol) of 2-pyridinecarboxaldehyde in 10 mL of CH_2Cl_2 at −78 °C. To this heterogeneous mixture was cannulated the above silyl enol ether solution over 5 min. The combined reaction mixture was stirred at −78 °C for 1 h and then the reaction quenched by the addition of 5 mL of concentrated pH 7 buffer solution and warmed to room temperature. The mixture was stirred vigorously at room temperature overnight and then diluted with 15 mL of water. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The product was purified by flash chromatography (25% and 33% EtOAc in hexane) to yield 0.320 g (56%) of **2b** as yellow crystals: mp 74−76 °C; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 8.51 (d, 1H, J = 4.9 Hz), 7.67 (td, 1H, J = 7.7, 1.7 Hz), 7.43 (d, 1H, J = 7.9 Hz), 7.18−7.15 (m, 1H), 5.24 (dd, 1H, J = 8.7, 3.4

(14) Regitz, M.; Hocker, J.; Liedhegener, A. *Organic Syntheses*; John Wiley: New York, 1973; Collect. Vol. V, pp 179−183.

Hz), 4.26 (q, 2H, J = 7.1 Hz), 3.39 (dd, 1H, J = 16.7, 3.5 Hz), 3.27 (dd, 1H, J = 16.7, 8.8 Hz), 1.28 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 191.7, 161.4, 161.2, 148.7, 137.0, 122.6, 120.5, 70.2, 61.7, 48.3, 14.5; IR ($CDCl_3$) 3492, 2140, 1715, 1650 cm^{-1}. Anal. Calcd for $C_{12}H_{13}N_3O_4$: C, 54.75; H, 4.98; N, 15.96. Found: C, 54.69; H, 5.05; N, 15.87.

2c: yield = 73%; yellow oil; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 8.61 (d, 1H, J = 2.2 Hz), 8.52 (dd, 1H, J = 4.8, 1.6 Hz), 7.76−7.73 (m, 1H), 7.28 (ddd, 1H, J = 7.9, 4.8, 0.6 Hz), 5.25 (dd, 1H, J = 8.4, 3.8 Hz), 4.28 (q, 2H, J = 7.1 Hz), 3.66 (br s, 1H), 3.32 (dd, 1H, J = 17.5, 3.9 Hz), 3.25 (dd, 1H, J = 17.5, 8.4 Hz), 1.31 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 192.0, 161.2, 149.1, 147.8, 138.5, 133.9, 123.7, 68.3, 61.9, 48.5, 14.5; IR (neat) 3194, 2139, 1716, 1652 cm^{-1}. Anal. Calcd for $C_{12}H_{13}N_3O_4$: C, 54.75; H, 4.98; N, 15.96. Found: C, 54.63; H, 5.02; N, 15.81.

2d: yield = 77%; yellow oil; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 8.53 (dd, 2H, J = 4.5, 1.6 Hz), 7.31 (ddd, 2H, J = 4.5, 1.6, 0.6 Hz), 5.18 (dd, 1H, J = 8.8, 3.4 Hz), 4.27 (q, 2H, J = 7.1 Hz), 3.98 (br s, 1H), 3.29 (dd, 1H, J = 17.3, 3.4 Hz), 3.21 (dd, 1H, J = 17.3, 8.8 Hz), 1.30 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 191.9, 161.2, 152.1, 150.0, 120.9, 69.0, 62.0, 48.1, 14.5; IR (neat) 3170, 2141, 1708, 1654 cm^{-1}. Anal. Calcd for $C_{12}H_{13}N_3O_4$: C, 54.75; H, 4.98; N, 15.96. Found: C, 54.65; H, 5.00; N, 15.88.

General Procedure for the Formation of 3 by an Insertion Reaction. To a suspension of 0.0042 g (0.0095 mmol) of $Rh_2(OAc)_4$ in 20 mL of refluxing benzene was added 0.248 g (0.945 mmol) of **2a** in 5 mL of benzene over 15 min. After an additional 15 min at reflux, the mixture was cooled to room temperature and filtered through Celite, which was then rinsed with CH_2Cl_2 (3 × 10 mL). Concentration yielded 0.217 g (98%) of **3a** as yellow oil. Data for the major diastereomer: ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.53−7.35 (m, 5H), 5.68 (dd, 0.4H, J = 9.6, 6.5 Hz), 5.28 (dd, 0.6H, J = 10.7, 6.0 Hz), 4.76 (s, 0.4H), 4.58 (s, 0.6H), 4.33−4.25 (m, 2H), 2.99−2.90 (m, 1H), 2.69−2.58 (m, 1H), 1.33 (t, 3H, J = 7.1 Hz).

3b: reaction time 1.5 h; yield 100%; yellow oil. Data for the major diastereomer: ^{1}H NMR ($CDCl_3$, 360 MHz) δ 8.59−8.58 (m, 1H), 7.73 (td, 1H, J = 7.7, 1.8 Hz), 7.50 (d, 1H, J = 7.8 Hz), 7.27−7.24 (m, 1H), 5.73(t, 1H, J = 7.3 Hz), 4.76 (s, 1H), 4.35−4.17 (m, 2H), 3.01 (dd, 1H, J = 18.2, 7.3 Hz), 2.96 (dd, 1H, J = 18.2, 7.3 Hz), 1.32 (t, 3H, J = 7.1 Hz).

3c: reaction time 24 h; yield = 96%; orange solid. Data for the major diastereomer: ^{1}H NMR ($CDCl_3$, 360 MHz) δ 8.68 (br s, 1H), 8.62 (br s, 1H), 7.79 (d, 1H, J = 7.4 Hz), 7.38−7.36 (m, 1H), 5.73 (dd, 1H, J = 9.9, 6.5 Hz), 4.78 (s, 1H), 4.34−4.25 (m, 2H), 3.01 (dd, 1H, J = 18.0, 6.4 Hz), 2.59 (dd, 1H, J = 18.0, 9.9 Hz), 1.34 (t, 3H, J = 7.2 Hz).

3d: reaction time 24 h; yield = 97%; yellow oil. Data for the major diastereomer: ^{1}H NMR ($CDCl_3$, 360 MHz) δ 8.65 (br s, 1H), 7.47 (d, 0.4H, J = 5.5 Hz), 7.33 (d, 0.6H, J = 5.4 Hz), 5.69 (dd, 0.6H, J = 9.8, 6.7 Hz), 5.31 (dd, 0.4H, J = 10.4, 6.4 Hz), 4.77 (s, 0.6H), 4.61 (s, 0.4H), 4.33−4.26 (m, 2H), 3.05−2.98 (m, 1H), 2.61−2.49 (m, 1H), 1.34 (t, 3H, J = 7.1 Hz).

3e: yield = 100%; white foam. Data for the major diastereomer: ^{1}H NMR ($CDCl_3$, 360 MHz) δ 9.46 (br s, 1H), 8.40 (dd, 1H, J = 8.1, 0.8 Hz), 8.00−7.98 (m, 2H), 7.55−7.18 (m, 6H), 5.83 (dd, 1H, J = 11.3, 5.8 Hz), 4.77 (s, 1H), 4.27 (dq, 1H, J = 10.7, 7.1 Hz), 4.14 (dq, 1H, J = 10.7, 7.1 Hz), 3.04 (ddd, 1H, J = 17.4, 11.3, 0.8 Hz), 2.91 (ddd, 1H, J = 17.4, 5.8, 0.6 Hz), 1.22 (t, 3H, J = 7.1 Hz).

3f: yield = 100%; orange-yellow solid. Data for the major diastereomer: ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.89−7.42 (m, 10H), 5.67 (dd, 0.75H, J = 9.7, 6.5 Hz), 5.29 (dd, 0.25H, J = 10.5, 6.3 Hz), 4.76 (s, 0.75H), 4.58 (s, 0.25H), 4.33−4.27 (m, 2H), 2.99−2.92 (m, 1H), 2.66−2.60 (m, 1H), 1.33 (t, 3H, J = 7.1 Hz).

General Procedure for the Formation of 9 from 3 via Silylation. To 0.447 g (1.90 mmol) of **3b** in 6 mL of CH_2Cl_2 at ambient temperature was added 0.80 mL (0.58 g, 5.7 mmol) of Et_3N followed by a solution of 0.57 g (3.8 mmol) of TBSCl in 3 mL of CH_2Cl_2 via cannula. The reaction mixture was stirred at room temperature overnight and then concentrated. A solution of 0.3 mL of Et_3N in 10 mL of anhydrous Et_2O was added to this viscous yellow oil, and then the resulting salt was removed by filtration through a fritted glass filter. The filter was then rinsed with dry ether (3 × 3 mL). Concentration of the combined filtered solution yielded 0.660 g (99%) of the silyl enol ether ester as a brown yellow oil.

To a solution of 0.654 g (1.87 mmol) of the silyl enol ether ester in 19 mL CH_2Cl_2 at −78 °C was added 1.0 mL (0.80 g, 5.6 mmol, an additional 1 equiv was used for **3e** and **3f**) of DIBAL dropwise. After being maintained at −78 °C for 2 h, the reaction mixture was warmed to 0 °C for 15 min and then the reaction quenched by the addition of 0.8 mL of MeOH dropwise. After this addition, 15 mL of a 20% aqueous solution of potassium tartrate was added in one portion, and the reaction mixture was vigorously stirred at room temperature for 3 h. After filtration through Celite, the organic layer was separated. The Celite and the aqueous layer were washed with CH_2Cl_2 (3 × 10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated to yield 0.539 g (94%) of the silyl enol ether alcohol as yellow oil.

To a solution of 0.533 g (1.73 mmol) of the silyl enol ether alcohol in 8 mL of THF at 0 °C was added 0.73 mL (0.53 g, 5.2 mmol) of Et_3N followed by 0.28 mL (0.28 g, 1.7 mmol) of Et_3N·3HF. The reaction mixture was stirred at 0 °C for 3 h, at which time it was diluted with 50 mL of CH_2Cl_2 and then washed with 10 mL of saturated aqueous $NaHCO_3$ (1 × 10 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (4 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The product was purified by column chromatography (2%, 3%, and 4% MeOH in CH_2Cl_2) to afford 0.183 g of **9b** as one diastereomer (55%, 51% overall from **2b**) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 360 MHz) δ 8.60 (ddd, 1H, J = 4.8, 1.7, 0.9 Hz), 7.72 (td, 1H, J = 7.7, 1.8 Hz), 7.33 (dt, 1H, J = 7.7, 0.8 Hz), 7.29−7.25 (m, 1H), 5.54 (br s, 1H), 5.41 (t, 1H, J = 8.4 Hz), 4.15 (t, 1H, J = 2.4 Hz), 3.97 (dd, 1H, J = 12.1, 2.6 Hz), 3.90 (dd, 1H, J = 12.1, 2.1 Hz), 2.96 (ddd, 1H, J = 18.7, 7.8, 0.7 Hz), 2.73 (dd, 1H, J = 18.7, 8.5 Hz); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 213.9, 160.3, 150.1, 137.6, 123.9, 122.1, 82.5, 77.4, 63.4, 43.8; IR (neat) 3222, 1759 cm^{-1}. Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.09; H, 5.79; N, 7.32.

9a: diastereomers were separated by column chromatography (2%, 4% EtOAc in CH_2Cl_2): yield of cis diastereomer = 48%; viscous colorless oil; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.45−7.35 (m, 5H), 5.23 (dd, 1H, J = 11.0, 5.8 Hz), 4.05 (t, 1H, J = 3.4 Hz), 3.97−3.94 (m, 2H), 2.89 (dd, 1H, J = 18.1, 5.8 Hz), 2.56 (dd, 1H, J = 18.1, 11.0 Hz), 1.98 (dd, 1H, J = 7.1, 6.1 Hz); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 214.1, 139.8, 129.0, 128.8, 126.4, 82.5, 77.9, 61.7, 45.5; IR (neat) 3468, 1756 cm^{-1}. HRMS(FAB) calcd for $C_{11}H_{13}O_3$ (MH^+) 193.0865, found 193.0860.

9c: diastereomers were separated by column chromatography (2%, 5% MeOH in CH_2Cl_2) followed by crystallization (EtOAc): yield of cis diastereomer = 35%; colorless crystals; mp 100−101 °C; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 8.68 (d, 1H, J = 1.9 Hz), 8.57 (dd, 1H, J = 4.8, 1.5 Hz), 7.80−7.78 (m, 1H), 7.32 (ddd, 1H, J = 7.9, 4.8, 0.6 Hz), 5.24 (dd, 1H, J = 11.0, 5.9 Hz), 4.06 (t, 1H, J = 3.2 Hz), 3.96 (d, 2H, J = 3.2 Hz), 3.03 (br s, 1H), 2.91 (dd, 1H, J = 17.9, 5.9 Hz), 2.51 (dd, 1H, J = 17.9, 11.0 Hz); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 213.2, 149.9, 148.1, 135.9, 134.2, 123.9, 82.7, 75.6, 61.6, 45.3; IR (KBr) 3199, 1762 cm^{-1}. Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.19; H, 5.77; N, 7.19.

9d: an analytical sample was prepared by crystallization (EtOAc/hexanes): colorless needles; mp 89−92 °C; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 8.54 (dd, 2H, J = 4.6, 1.6 Hz), 7.33−7.31 (m, 2H), 5.19 (dd, 1H, J = 11.0, 6.0 Hz), 4.06 (t, 1H, J = 3.2 Hz), 3.98 (dd, 1H, J = 12.2, 3.0 Hz), 3.94 (dd, 1H, J = 12.2, 3.5 Hz), 3.49 (br s, 1H), 2.90 (dd, 1H, J = 17.8, 6.0 Hz), 2.43 (dd, 1H, J = 17.8, 11.0 Hz); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 212.8, 150.1, 149.4, 121.1, 82.8, 76.1, 61.5, 45.0; IR ($CDCl_3$) 3187, 1763 cm^{-1}. Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.07; H, 5.77; N, 7.20.

9e. The diastereomers were separated by column chromatography (30% EtOAc in hexane): yield of cis diastereomer = 30%; colorless needles; mp 133−134 °C; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 9.50 (br s, 1H), 8.22 (d, 1H, J = 7.5 Hz), 7.88−7.86 (m, 2H), 7.54−7.42 (m, 4H), 7.25 (dd, 1H, J = 7.7, 1.7 Hz), 7.18 (td, 1H, J = 7.5, 1.2 Hz), 5.37 (t, 1H, J = 8.6 Hz), 4.10 (t, 1H, J = 3.3 Hz), 3.91 (br s, 2H), 2.83−2.74 (m, 2H), 1.55 (br s, 1H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 212.2, 166.4, 137.3, 135.2, 132.1, 129.8, 128.8, 128.2, 127.5, 127.4, 124.9, 124.1, 82.7, 77.7, 61.2, 42.6; IR ($CDCl_3$) 3357, 1762, 1663 cm^{-1}. HRMS(FAB) calcd for $C_{18}H_{18}NO_4$ (MH^+)

312.1236, found 312.1233. Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.34; H, 5.51; N, 4.37.

9f. The diastereomers were separated by column chromatography (CH_2Cl_2, then 1%, 2%, 4% MeOH in CH_2Cl_2): yield of cis diastereomer = 39%; white crystals; mp 184−186 °C; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.89−7.44 (m, 10H), 5.22 (dd, 1H, J = 10.9, 5.8 Hz), 4.05 (t, 1H, J = 3.5 Hz), 3.97−3.95 (m, 2H), 2.88 (dd, 1H, J = 18.0, 5.8 Hz), 2.54 (dd, 1H, J = 18.0, 11.0 Hz), 1.99 (dd, 1H, J = 7.0, 6.2 Hz); ^{13}C NMR (CD_3OD, 90 MHz) δ 215.6, 169.1, 140.0, 138.3, 136.4, 133.1, 129.8, 128.8, 128.2, 122.3, 84.5, 78.7, 62.1, 47.0; IR (KBr) 3482, 3292, 1757, 1649 cm^{-1}. Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.43; H, 5.58; N, 4.43.

General Procedure for the Formation of 9 from 3 via Sodium Enolate. To a suspension of 0.064 g of 60% NaH (1.6 mmol, prewashed with 1 mL of hexane) in 3.5 mL of THF at 0 °C was cannulated a solution of 0.315 g (1.34 mmol) of **3b** in 3.5 mL of THF. The reaction mixture was stirred at 0 °C for 0.5 h, over which time it turned to an orange-red, almost transparent solution (enolization time varied from 0.5 to 2 h for the other substrates). After the solution was cooled to −78 °C, 0.60 mL (0.48 g, 3.3 mmol, an additional 1 equiv was used for **3e** and **3f**) of DIBAL was added, and the reaction mixture was stirred at −78 °C for 3 h. After being warmed to 0 °C for 10 min, the reaction mixture was cooled to −78 °C and then cannulated to a solution of 2.52 mL (1.98 g, 26.8 mmol) of t-BuOH in 7 mL of THF at −78 °C over 5 min. This combined reaction mixture was stirred at 78 °C for 0.5 h and then quenched with 10 mL of concentrated pH7 buffer solution and diluted with 70 mL of CH_2Cl_2. The heterogeneous mixture was warmed to room temperature and vigorously stirred overnight. The portion of the organic layer not contaminated with solids was separated, and the aqueous layer and the rest of the organic layer were filtered through Celite, which was then rinsed with water (2 × 5 mL) and CH_2Cl_2 (2 × 10 mL). The organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The product was purified by column chromatography (2%, 3%, and 4% MeOH in CH_2Cl_2) to afford 0.128 g of **9b** (50%).

General Procedure for the Formation of 4 by Diastereoselective Reduction of 9. To a mixture of 0.83 g (3.9 mmol) of $NaBH(OAc)_3$ in 4 mL of CH_3CN at 0 °C was added 0.45 mL (0.47 g, 7.9 mmol) of CH_3CO_2H, followed by a solution of 0.152 g (0.787 mmol) of **3b** in 3 mL of CH_3CN via cannula. The reaction mixture was stirred at 0 °C for 1 h and then quenched by the addition of 8 mL of CH_3OH. After concentration, CH_3OH (2 × 8 mL) was added, and the mixture was concentrated again. The product was purified by chromatography (2%, 5% CH_3OH in CH_2Cl_2) to yield 0.141 g (92%) of **4b** as a colorless oil:[15] ^{1}H NMR ($CDCl_3$, 360 MHz) δ 8.56−8.54 (m, 1H), 7.66 (td, 1H, J = 7.7, 1.8 Hz), 7.25−7.20 (m, 2H), 5.28 (dd, 1H, J = 8.9, 6.9 Hz), 4.65−4.63 (m, 1H), 4.19−4.17 (m, 1H), 3.95 (dd, 1H, J = 12.3, 2.7 Hz), 3.71 (dd, 1H, J = 12.3, 2.1 Hz), 3.10−2.50 (br s, 2H), 2.43 (ddd, 1H, J = 13.3, 9.0, 5.4 Hz), 2.33 (ddd, 1H, J = 13.3, 6.8, 1.9 Hz); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 161.6, 149.7, 137.4, 123.4, 122.3, 89.2, 80.6, 75.2, 64.2, 43.9; IR (neat) 3383, 1597 cm^{-1}. Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.17. Found: C, 61.32; H, 6.75; N, 7.04.

4a:[8] yield = 94%; colorless needles; mp 82−83 °C; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.35−7.27 (m, 5H), 5.16 (dd, 1H, J = 10.2, 5.7 Hz), 4.41−4.38 (m, 1H), 4.01−3.98 (m, 1H), 3.79 (dd, 1H, J = 11.6, 4.3 Hz), 3.72 (dd, 1H, J = 11.6, 5.0 Hz), 2.34 (br s, 2H), 2.24 (ddd, 1H, J = 13.3, 5.7, 2.0 Hz), 2.02 (ddd, 1H, J = 13.2, 10.2, 6.3 Hz).

(15) Although **4b** is a known compound, no analytical data were reported in ref 11 for this compound.

4c:[11] yield = 94%; colorless oil; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 8.61 (d, 1H, J = 2.2 Hz), 8.51 (dd, 1H, J = 4.9, 1.6 Hz), 7.69−7.66 (m, 1H), 7.28 (dd, 1H, J = 7.9, 4.9 Hz), 5.20 (dd, 1H, J = 10.2, 5.6 Hz), 4.49−4.46 (m, 1H), 4.06−4.03 (m, 1H), 3.82 (dd, 1H, J = 11.7, 4.2 Hz), 3.72 (dd, 1H, J = 11.7, 4.8 Hz), 2.60 (br s, 2H), 2.30 (ddd, 1H, J = 13.2, 5.6, 2.0 Hz), 2.02 (ddd, 1H, J = 13.2, 10.2, 6.2 Hz); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 149.1, 147.9, 137.5, 134.2, 123.8, 87.8, 78.1, 73.8, 63.5, 44.1.

4d. The diastereomers were separated by column chromatography (5%, 10% MeOH in CH_2Cl_2) followed by crystallization (EtOAc/hexanes): yield = 39% from **2d**; white crystals; mp 89−92 °C; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 8.55 (dd, 2H, J = 4.5, 1.6 Hz), 7.27−7.25 (m, 2H), 5.17 (dd, 1H, J = 10.2, 5.8 Hz), 4.46−4.44 (m, 1H), 4.06 (td, 1H, J = 4.5, 2.9 Hz), 3.84 (dd, 1H, J = 11.6, 4.3 Hz), 3.76 (dd, 1H, J = 11.6, 4.8 Hz), 2.33 (ddd, 1H, J = 13.2, 5.8, 2.0 Hz), 2.14 (br s, 1H), 1.95 (ddd, 1H, J = 13.2, 10.2, 6.2 Hz), 1.64 (br s, 1H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 150.9, 150.1, 120.9, 87.8, 78.7, 73.8, 63.6, 44.0; IR (KBr) 3346, 3144, 1611 cm^{-1}. Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.17. Found: C, 61.41; H, 6.69; N, 7.22.

4e: yield = 93%; white crystals; mp 132−134 °C; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 9.75 (br s, 1H), 8.32 (d, 1H, J = 8.3 Hz), 7.90−7.87 (m, 2H), 7.53−7.35 (m, 4H), 7.17 (dd, 1H, J = 7.7, 1.5 Hz), 7.10 (td, 1H, J = 7.5, 1.2 Hz), 5.29 (dd, 1H, J = 10.9, 5.2 Hz), 4.44−4.42 (m, 1H), 4.11−4.08 (m, 1H), 3.77−3.67 (m, 2H), 2.32 (ddd, 1H, J = 13.1, 10.9, 6.0 Hz), 2.23 (ddd, 1H, J = 13.1, 5.2, 1.5 Hz), 1.97 (d, 1H, J = 3.7 Hz), 1.52 (t, 1H, J = 5.9 Hz); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 166.0, 137.6, 135.3, 132.1, 129.1, 128.94, 128.85, 127.3, 126.9, 124.5, 122.8, 88.1, 79.4, 73.1, 63.2, 40.9; IR (KBr) 3346, 3245, 1648 cm^{-1}. Anal. Calcd for $C_{18}H_{19}NO_4$: C, 69.00; H, 6.11; N, 4.47. Found: C, 68.76; H, 6.11; N, 4.46.

4f: yield = 84%; white powder; mp 179−181 °C; ^{1}H NMR (CD_3OD, 360 MHz) δ 7.94−7.40 (m, 9H), 5.13 (dd, 1H, J = 10.5, 5.4 Hz), 4.34−4.33 (m, 1H), 3.95 (td, 1H, J = 5.1, 2.4 Hz), 3.72−3.64 (m, 2H), 2.19 (ddd, 1H, J = 13.1, 5.4, 1.6 Hz), 1.97 (ddd, 1H, J = 13.1, 10.6, 5.9 Hz); ^{13}C NMR (CD_3OD, 90 MHz) δ 169.0, 139.5, 139.4, 136.4, 133.0, 129.8, 128.8, 127.8, 122.3, 89.3, 81.5, 74.6, 64.2, 45.1; IR (KBr) 3289, 1648 cm^{-1}; HRMS(FAB) calcd for $C_{18}H_{20}NO_4$ (MH^+) 314.1392, found 314.1386.

6: colorless oil; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.52−7.25 (m, 5H), 5.01 (t, 1H, J = 7.5 Hz), 4.71−4.68 (m, 1H), 4.52 (d, 1H, J = 5.3 Hz), 4.32−4.25 (m, 2H), 2.66 (ddd, 1H, J = 13.3, 7.4, 6.5 Hz), 2.51 (d, 1H, J = 6.3 Hz), 2.07 (ddd, 1H, J = 13.3, 7.6, 4.6 Hz), 1.32 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 170.1, 141.7, 128.6, 127.9, 126.3, 82.2, 80.5, 73.6, 61.5, 42.8, 14.4; IR (neat) 3473, 1742 cm^{-1}. Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.19; H, 6.79.

7: pale yellow oil; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.34−7.25 (m, 5H), 5.43 (dd, 1H, J = 10.2, 5.5 Hz), 4.81−4.77 (m, 2H), 4.36−4.22 (m, 2H), 2.73 (br s, 1H), 2.47−2.41 (m, 1H), 2.07−1.99 (m, 1H), 1.32 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 170.7, 141.5, 128.6, 127.9, 125.9, 82.9, 81.0, 73.9, 61.6, 44.1, 14.5; IR (neat) 3465, 1742 cm^{-1}. Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.06; H, 6.79.

8: colorless oil; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.42−7.26 (m, 5H), 5.29 (t, 1H, J = 7.4 Hz), 4.68−4.63 (m, 1H), 4.58 (d, 1H, J = 3.8 Hz), 4.31−4.23 (m, 2H), 2.73−2.65 (m, 1H), 2.10 (d, 1H, J = 5.1 Hz), 2.08−2.01 (m, 1H), 1.32 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 68 MHz) δ 171.6, 141.9, 128.4, 127.7, 125.8, 84.5, 80.8, 75.9, 61.3, 42.5, 14.2; IR (neat) 3453, 1736 cm^{-1}. Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.14; H, 6.85.

Acknowledgment. We thank the Petroleum Research Fund and the Virginia Tech Chemistry Department for financial support of this project.

JO9818834