JOC*Note*

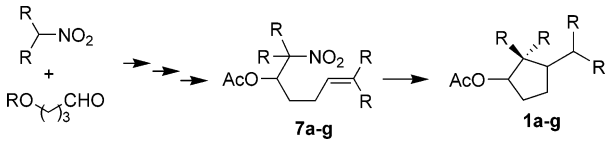
Radical-Induced Cyclopentannulation of Henry (Nitroaldol)-Derived Intermediates[1]

Frederick A. Luzzio,* Joel P. Ott, and Damien Y. Duveau

Department of Chemistry, University of Louisville, 2320 South Brook Street, Louisville, Kentucky 40292

faluzz01@gwise.louisville.edu

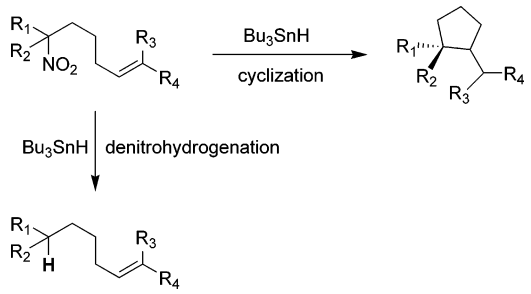
Received March 13, 2006



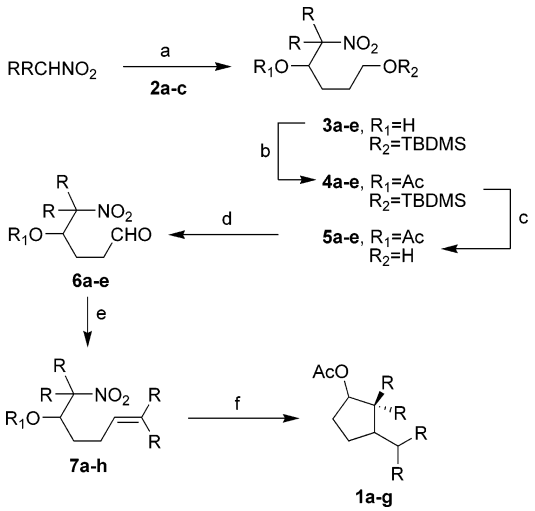
Tributyltin hydride-mediated cyclizations of 1-nitro-2-acetoxy-5-hexenes **7a**−**g** having multiple substitutions on carbons 1 and 6 result in 2,3-substituted-1-acetoxycyclopentanes **1a**−**g**. The substrates were prepared by nitroaldol reactions of silyloxyaldehydes followed by acetylation, desilylation, and oxidation to the acetoxynitroaldehydes **6a**−**e**. Wittig olefination of aldehydes **6a**−**e** then afforded substrates for the radical cyclizations. The overall scheme gave a diverse array of cyclopentanes, including *gem*-disubstituted cyclopentanes having substitution on three contiguous carbons.

The versatility of the Henry reaction in joining sensitive molecular fragments together is multifold as exemplified by the concomitant creation of a new multiply reactive center, the β-nitroalkanol group.[2a−e] In turn, the nitroalkanol group may then serve as a convenient starting point for further conversion to a number of diverse functional groups. The most frequently employed nitro alcohol conversions include in situ dehydration to the corresponding nitroolefin, reduction to the corresponding amino alcohol, or oxidation to the corresponding nitro ketone. In addition, the complete replacement or removal of the nitro group by the many variants of the Nef reaction has been utilized extensively in organic synthesis.[3] The less commonly employed transformations include removal of the nitro group by radical reduction and includes replacement with hydrogen (radical denitrohydrogenation)[4a,b] or concomitant inter- or intramolecular carbon−carbon bond formation depending on suitably disposed unsaturation (Scheme 1).[4c−f] The radical 5-hexenyl cyclizations have been reported in a few isolated cases and have included both the formation of tetrahydrofurans from allyl or propargyl ethers bearing nitro substituents[4a,d,e] and the preparation of a tricyclic cedrene intermediate through a radical cascade cyclization of a homoallylic β-nitro alcohol.[5a,b] To demonstrate substrate generality, we evaluated β-nitroalkanols or Henry-type intermediates as substrates for radical cyclization to highly substituted cyclopentanes. The cyclopentane ring system constitutes the structural core of numerous natural products and biologically active compounds; therefore, new and general approaches to diverse cyclopentanoids continue to prove valuable in total synthesis.[6] Our approach to five-membered rings employs a radical cyclization of substrates which possess both a nitro group and a suitably disposed olefinic unit (Scheme 2). The nitro group, which is susceptible to radical replacement, is introduced through a Henry reaction giving a nitro alcohol, while the olefinic unit is introduced at a later stage through a Wittig reaction. Generation of the double bond at the later stage, or after the Henry reaction, is preferable since many nitroaldols on intermediate aldehydes having conjugated olefinic units will suffer competing nitronate Michael addition. Although the individual reactions are commonplace, the overall scheme represents a novel sequence utilizing Henry intermediates and thereby tests the tolerances of the derivatized nitro alcohol function.

SCHEME 1. Tin Hydride-Mediated Pathways for Radical Reduction or 5-Hexenyl Cyclization



SCHEME 2. Multistep Synthesis of Cyclization Precursors and Cyclized Products[a]



[a] Reagents and conditions: (a) *N*,*N*,*N*′,*N*′-tetramethylguanidine/THF/rt; (b) Ac_2O/pyr/rt; (c) TFA/$H_2OCH_2Cl_2$/rt; (d) PCC/SiO_2/CH_2Cl_2; (e) R,RC═PPh_3; (f) $HSnBu_3$/AIBN/toluene/110 °C.

The scheme commences with the 4-*tert*-butylsilyloxy (TBDMS) aldehydes **2a**−**c** (Figure 1). The aldehydes are then

* Corresponding author. Tel: (502) 852-7323. Fax: (502) 852-8149.

(1) Presented at the 226th National Meeting of the American Chemical Society, New York, Sep 7 and 8, 2003; ORGN 131.

(2) (a) Seebach, D.; Colvin, E. W.; Leher, F.; Weller, T. *Chimia* **1979**, *331*; (b) Rosini, G. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 2. (c) Rosini, G.; Ballini, R. *Synthesis* **1988**, 833−847. (d) Luzzio, F. A. *Tetrahedron* **2001**, *57*, 915−945. (e) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley: New York, 2001.

(3) Ballini, R.; Petrini, M. *Tetrahedron* **2004**, *60*, 1017−1047.

(4) (a) Ono, N.; Miyake, H.; Kamimiura, A.; Hamamoto, I.; Tamura, R.; Kaji, A. *Tetrahedron* **1985**, *41*, 4013−4023. (b) Tanner, D. D.; Blackburn, B. B.; Diaz, G. E. *J. Am. Chem. Soc.* **1981**, *103*, 1557−1559. (c) DuPuis, J.; Giese, B.; Hartung, J.; Leising, M. *J. Am. Chem. Soc.* **1985**, *107*, 4332−4333. (d) Vankar, Y. D.; Bawa, A.; Kumaravel, G. *Tetrahedron* **1991**, *47*, 2027−2040. (e) Vankar, Y. D.; Chauduri, N. C. *Synth. Commun.* **1991**, 21, 885−899. (f) Crich, D.; Shirai, M.; Rumthao, S. *Org. Lett.* **2003**, *5*, 3767−3769.

(5) (a) Chen, Y.-J.; Lin, W. Y. *Tetrahedron Lett.* **1992**, *33*, 1749−1750. (b) Chen, Y.-J.; Chang, W.-H.; Lin, W.-Y. *Tetrahedron Lett.* **1993**, *34*, 2961−2962. (c) Chen, Y.-J.; Chang, W.-H. *J. Org. Chem.* **1996**, *61*, 2536−2539. (d) Chen, Y.-J.; Chang, W.-H.; Lin, W.-Y. *Tetrahedron* **1996**, *52*, 13181−13188.

(6) Corey, E. J.; Cheng, X. M. *The Logic of Chemical Synthesis*; Wiley: New York, 1989; pp 373, 250−307.

10.1021/jo0605546 CCC: $33.50
Published on Web 06/02/2006

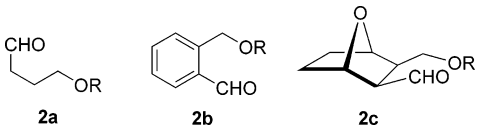
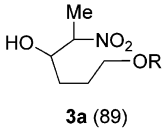
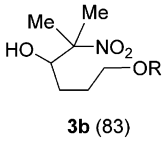
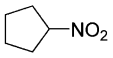
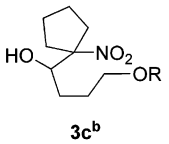
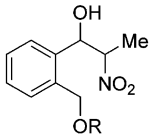
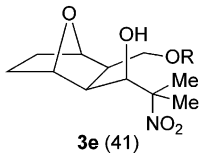


FIGURE 1. Selected aldehydes for the Henry reactions (R = *tert*-butyldimethylsilyl).

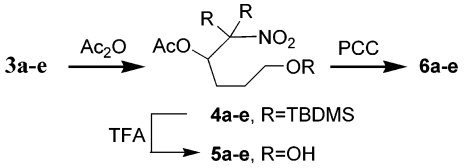
TABLE 1. Henry Reaction of Silyloxyaldehydes 2a−c with Selected Nitro Compounds

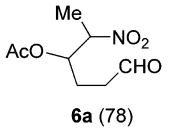
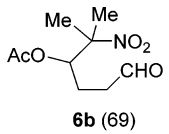
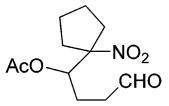
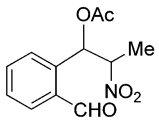
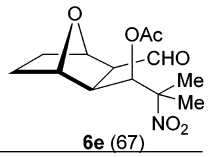
RCHO	Nitro Compound	Product[a] (Yield%)
2a	$CH_3CH_2NO_2$	 **3a** (89)
2a	$(CH_3)_2CHNO_2$	 **3b** (83)
2a		 **3c**[b]
2b	$CH_3CH_2NO_2$	 **3d** (67)
2c	$(CH_3)_2CHNO_2$	 **3e** (41)

[a] R = TBDMS. [b] Unstable to purification due to retro-Henry process and was used directly in the next step.

coupled with nitroethane, 2-nitropropane, or nitrocyclopentane in the presence of *N*,*N*,*N*′,*N*′-tetramethylguanidine (TMG) or potassium *tert*-butoxide (KO-*t*-Bu) to produce nitro alcohols **3a**−**e** in isolated yields of 89−41% (Table 1). The coupling of the 4-silyloxyaldehydes with the primary nitro compounds was easily facilitated with TMG; however, the more sluggish Henry reactions required KO-*t*-Bu. Typically, both protocols yielded chromatographically inseparable mixtures of *erythro* and *threo* isomers. Although there are methods available for gaining high *erythro* or *threo* selectivity in the nitroaldol reaction,[7] such modes of selectivity were not an issue in our multistep scheme whereby the nitro group would be lost in the cyclization step. Immediately following the isolation of the nitroalkanols **3a**−**e**, they were acetylated with acetic anhydride in pyridine to furnish the corresponding silyloxynitroacetates **4a**−**e** in yields of 75−96% (Table 2). Derivatization of the nitro alcohol function in **3a**−**e** as the nitroacetate both protects the hydroxyl group during the oxidation step and deactivates these sensitive compounds to the usual retroaldol processes that plague the use of β-nitroalkanols as synthetic intermediates. Next, the removal of the TBDMS group was accomplished with aqueous trifluoroacetic acid (TFA) to furnish the corresponding 4-acetoxy-5-nitropentanols **5a**−**e** in 71−88% yield (Table 2). We compared

TABLE 2. Acetylation/Desilylation/Oxidation of Nitroalkanols 3a−e to Aldehydes 6a−e through Nitroacetoxysilyl Ethers 4a−e and Nitroacetoxy Alcohols 5a−e



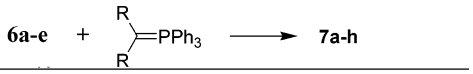
Nitro-alkanol	**4a-e** (Yield%)	**5a-e** (Yield%)	**6a-e** (Yield%)
3a	**4a** (88)	**5a** (80)	 **6a** (78)
3b	**4b** (96)	**5b** (81)	 **6b** (69)
3c	**4c** (98)	**5c** (74)	 **6c** (71)
3d	**4d** (78)	**5d** (88)	 **6d** (98)
3e	**4e** (91)	**5e** (71)	 **6e** (67)

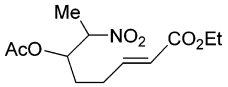
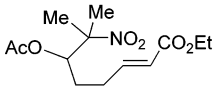
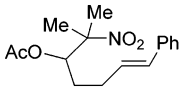
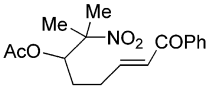
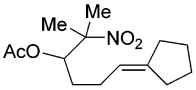
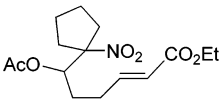
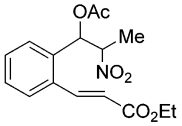
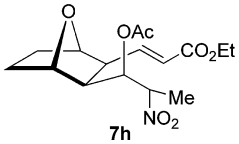
tetra-*N*-butylammonium fluoride (TBAF)/THF, which we selected for the initial attempts, with TFA for removal of the TBDMS group and noted that unwanted elimination of the acetate in **5a**, **5d**, and **5e** was facilitated by TBAF under all conditions. After removal of the TBDMS group, the alcohols **5a**−**e** were then oxidized to the corresponding aldehydes **6a**−**e** with pyridinium chlorochromate (PCC)/silical gel. To our satisfaction, the relatively polar acetoxynitroaldehydes were easily removed from the granular reduced chromium byproducts during the purification process, an operation which has been problematic when using PCC to oxidize other substrates bearing both nitro and nitroalkanol groups.

Although the 4-acetoxy-5-nitropentanals **6a**−**e** easily survived the protocol of the PCC oxidation, they proved to be unstable on storage, and the best results were obtained when they were used immediately in the olefination step. The isolated yields of aldehyde products **6a**−**e** ranged from 67 to 98% (Table 2). The 4-acetoxy-5-nitropentanals **6a**−**e** were then directly treated with several types of Wittig reagents of varying structure and reactivity (Table 3). The Wittig reagent employed for the preparation

(7) Barrett, A. G. M.; Robyr, C.; Spilling, C. D. *J. Org. Chem.* **1989**, *54*, 1233−1234. (b) Eyer, M.; Seebach, D. *J. Am. Chem. Soc.* **1985**, *107*, 3601−3606.

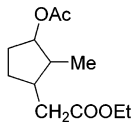
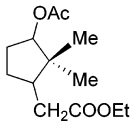
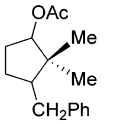
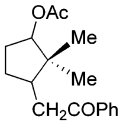
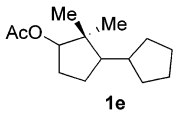
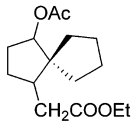
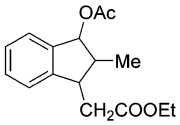
TABLE 3. Wittig Olefination of Acetoxynitroaldehydes 6a−e



Aldehyde	Acetoxynitroolefin	Yield (%)
6a	 **7a**	70
6b	 **7b**	81
6b	 **7c**	75
6b	 **7d**	88
6b	 **7e**	67
6c	 **7f**	89
6d	 **7g**	79
6e	 **7h**	81

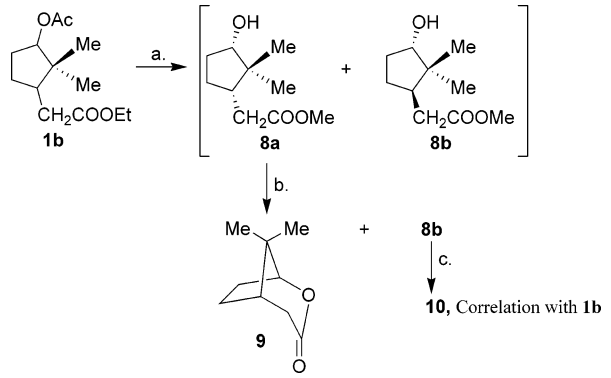
of **7a**,**b**,**f**−**h** was ethoxycarbonylmethylidenetriphenylphosphorane. Benzylidenetriphenylphosphorane was used for the preparation of **7c**, while treatment of **6b** with the more stable α-triphenylphosphoranylideneacetophenone gave olefin **7d**. Finally, treatment of aldehyde **6b** with cyclopentylidenetriphenylphosphorane afforded olefin **7e**. The aldehydes **6a**−**e** responded to the Wittig reagents quite well although the reaction conditions, particularly the mode of addition, temperature, and equivalents of reagent, were critical since the Wittig reagents possessed sufficient basicity to promote unwanted elimination in the acetoxynitroaldehydes **6a** and **6d**. In all cases except for **7c** and **7e**, the acetoxynitroolefins were obtained as the chromatographically pure *E* isomers and were used directly in the cyclization study. Olefin **7c** was used as a mixture of *E* and *Z* isomers (2:1), while *E*/*Z* stereochemistry was not an issue with the cyclopentylidene olefin **7e** (Table 3). The olefinic acetoxynitroacetates **7a**−**h** were then treated with tri-*n*-butyltin hydride (Bu_3SnH) and azobisisobutyronitrile (AIBN) in toluene at 108−110 °C.[8] The Bu_3SnH-mediated reactions resulted in smooth 5-*exo*-*trig* radical closure and thus provided the title tri- and tetrasubstituted cyclopentanes in isolated yields ranging from 43 to 82% (Table 4). Although the progress of the radical closures was conveniently monitored by analytical TLC, the cyclized products were chromatographically inseparable mixtures of *cis* and *trans* diastereoisomers as determined by ^1H and ^{13}C NMR analysis. While routine ^1H NMR was inconclusive in confirming the stereochemistry of each diastereoisomer in the mixture, a chemical expedient combined with NMR analysis led to the positive assignment of each diastereoisomer.[9] The

TABLE 4. Tri-*n*-butyltin Hydride-Mediated 5-Hexenyl Cyclizations of 7a−h to 1a−g

Substrate	Product	Yield (%)
7a	 **1a**	43
7b	 **1b**	82
7c	 **1c**	69
7d	 **1d**	70
7e	 **1e**	72
7f	 **1f**	79
7g	 **1g**	50

(8) An excess of $HSnBu_3$ (3 equiv) was required for total consumption of **7a**−**g**, although products **1a**−**g** were easily separable from the tin byproducts by chromatography. Organotin waste disposal was done in accordance with: *Prudent Practices in the Laboratory: Handling and Disposal of Chemicals*; National Academy Press: Washington D.C., 1995; pp 412−413.

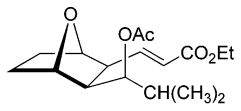
SCHEME 3. Hydrolysis and Lactonization of the *cis*-Acetoxy Ester 1b[a]



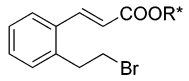
[a] Reagents and conditions: (a) LiOH/THF/MeOH/20 °C/18 h (quant); (b) $TsOH/CH_2Cl_2$/20 °C/35 h (quant); (c) Ac_2O/pyr/20 °C/23 h, 77%.

50/50 *cis*/*trans* mixture of acetoxy esters **1b** was hydrolyzed (0.5 M LiOH in THF/MeOH, 1:1; rt, 18 h) giving the *cis*- and *trans*-hydroxy esters **8a** and **8b** (Scheme 3). The mixture was then treated with *p*-toluenesulfonic acid monohydrate in CH_2Cl_2 (rt/18 h), which led to both quantitative conversion of the *cis*-diastereoisomer **8a** to apocamphor lactone **9** and leaving the chromatographically separable *trans*-hydroxy ester **8b** unreacted. The unreacted hydroxy ester **8b** was separated and then acetylated with acetic anhydride/pyridine (rt/24h) to afford ester **10**. An ^{1}H NMR correlation with the acetoxy CH (dd, 4.82 ppm) was then made, thereby establishing the more downfield absorptions as those representing the *trans* diastereoisomers in products **1b**−**f** (Scheme 3). Acetoxy ester **1a** and indan **1g** were also obtained as chromatograpically inseparable mixtures of diastereoisomers.

However, the stereochemical correlation described above together with that made by Normant[10] for *cis*- and *trans*-1-acetoxy-2-methylcyclopentanes led to the assignment of the *trans*,*cis* and the *cis*,*cis* as the most downfield pair, respectively, followed by the more upfield *cis*,*trans* and *trans*,*trans*, respectively (see the Supporting Information). Substrates **7b**−**f** gave somewhat higher yields (see **1b**−**f**, Table 4) than substrates **7a** and **7g**, presumably due to the greater ease in developing the radical derived from the tertiary nitro carbon as opposed to that formed from a secondary carbon. Substrate **7h** (Table 3) failed to cyclize but instead provided only **11**. Presumably, unfavorable



11



12, R*-chiral controller

geometry together with the competing reductive denitrohydrogenation process conspired to give **11** as the sole product. With respect to the design of substrate **7g**, which leads to the formation of indan **1g**, we noted a related radical cyclization of **12** having a carbohydrate-based chiral controller group. The cyclization was tin hydride-mediated and gave an indanyl acetic ester similar to **1g**.[11] In conclusion, 5-hexenyl radical cyclizations of substrates having both esterified nitroalkanol groups (Henry nitro esters) and suitably disposed double bonds offer an expedient to highly substituted cyclopentanes. The cyclization affords most notably esters of cyclopentanols and cyclopentylacetic esters having quaternary *spiro* or *gem*-dialkyl substitution as well as substituted indans. The diversity of the nitro compounds available for construction of the pivotal β-nitroacetoxyaldeydes together with the variation of Wittig reagents available for introducing the 5-hexenyl subunit allows for versatility in the structure of the cyclized products. Current studies include both the employment of chiral or bulky controller groups to direct stereoselectivity and the use of organocatalytic tin hydride systems.

Experimental Section

General Experimental Procedures. See the Supporting Information.

Cyclization of Ethyl 6-Acetoxy-7-methyl-7-nitrooct-2-enoate (7b). *cis*- and *trans*-Ethyl (3-Acetoxy-2,2-dimethylcyclopentyl)-acetate (1b). To a solution of the nitroolefin **7b** (56.0 mg, 0.195 mmol) in dry toluene (1.5 mL) were added tributyltin hydride (165 μL, 0.595 mmol) and AIBN (6.4 mg, 0.039 mmol). The clear solution was stirred at 110 °C for 1.5 h and then allowed to cool to room temperature. The solvent was removed under high vacuum, and the residue was purified by flash chromatography (hexanes/ethyl acetate, 5:1) giving **1b** (38.7 mg, colorless oil) as a mixture of diastereoisomers (1:1, *cis*/*trans*) in 82% yield: R_f 0.27 (hexanes/ethyl acetate, 3:1); IR 2963, 2874, 1740, 1734; ^{1}H NMR 4.82 (dd, J = 1.8 Hz, 6.9 Hz, 0.5 × 1H, trans), 4.72 (t, J = 7.9 Hz, 0.5 × 1H, cis), 4.14 (m, 2H), 2.36−2.42 (m, 1H), 1.88−2.18 (m, 4H), 2.06 (s, 0.5 × 3H), 2.04 (s, 0.5 × 3H), 1.32−1.62 (m, 2H), 1.27 (m, 3H), 0.97 (s, 1.5H), 0.95 (s, 1.5H), 0.79 (s, 3H); ^{13}C NMR 173.5, 173.2, 170.8, 170.7, 83.7, 82.1, 60.65, 60.60, 44.26, 44.23, 42.9, 42.80, 42.75, 35.5, 35.0, 29.3, 28.1, 27.4, 26.73, 26.70, 25.4, 21.2, 21.1, 20.3, 15.5, 14.2; HRMS (CI, MNH_4^+) calcd for $C_{13}H_{26}NO_4$ 260.1861, found 260.1869.

Cyclization of Ethyl 6-Acetoxy-6-(1-nitrocyclopentyl)hex-2-enoate (7f). *cis*- and *trans*-Ethyl (4-Acetoxyspiro[4.4]non-1-yl)-acetate (1f). To a solution of the nitroolefin **7f** (15.9 mg, 0.051 mmol) in dry toluene (1.0 mL) were added tributyltin hydride (40 μL, 0.149 mmol) and AIBN (1.7 mg, 0.010 mmol). The clear solution was stirred at 110 °C for 1 h and then allowed to cool to room temperature. Following removal of the solvent under high vacuum, the residue was purified by flash chromatography (hexanes/ethyl acetate, 4:1) affording **1f** (10.8 mg, colorless oil) as a mixture of diastereoisomers (40:60, *cis*/*trans*) in 79% yield: R_f 0.52 (hexane/ethyl acetate, 3:1); IR 2963, 2874, 1741, 1733; ^{1}H NMR 4.86 (dd, J = 4.7 Hz, 6.7 Hz, 0.6 × 1H, trans), 4.82 (d, J = 5.6 Hz, 0.4 × 1H, cis), 4.14 (m, 2H), 2.23−2.48 (m, 2H), 2.04 (s, 3H), 1.90−2.20 (m, 3H), 1.33−1.74 (m, 9H), 1.26 (m, 3H); ^{13}C NMR 173.7, 173.6, 170.9, 170.8, 82.1, 81.8, 60.4, 60.3, 55.9, 55.6, 42.8, 41.3, 37.3, 36.9, 35.1, 30.4, 29.6, 29.1, 28.2, 28.1, 27.7, 25.6, 25.5, 25.3, 24.9, 21.4, 21.3, 14.3; HRMS (CI, MNH_4^+) calcd for $C_{15}H_{28}NO_4$ 286.2018, found 286.2031.

Acknowledgment. Financial support by the National Cancer Institute and the University of Louisville (Assistantships to J.P.O. and D.Y.D.) is gratefully acknowledged.

Supporting Information Available: Experimental procedures for the preparation of all new compounds and ^{1}H NMR and ^{13}C NMR spectra of **1a**,**c**−**e**,**g**, **3a**,**b**,**d**,**e**, **4a**−**e**, **5a**−**e**, **6a**−**d**, **7a**−**h**, **8a**/**b**, **8b**, and **9**−**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0605546

(9) Wu, Y.; De Clercq, P.; Vandewalle, M.; Bouillon, R.; Verstuyf, A. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1633−1636.

(10) Meyer, C.; Marek, I.; Courtemanche, G.; Normant, J.-F. *Tetrahedron* **1994**, *50*, 11665−11692.

(11) Enholm, E. J.; Cottone, J. S.; Allais, F. *Org. Lett.* **2001**, *3*, 145−147.