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Stereocontrolled Construction of Tetrahydrofurans and γ-Butyrolactones Using Organomolybdenum Chemistry

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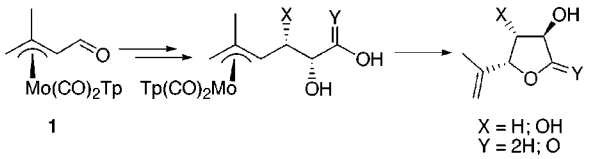
ABSTRACT



Diastereoselective conversion of π-allylmolybdenum complex aldehyde 1 to organometallic triol 4 and diols 5, 10, and 13 is described. Stereocontrolled demetalation of 4, 5, and 13 was accomplished, leading to hydroxylated tetrahydrofurans and γ-butyrolactones, as single diastereoisomers.

Substituted tetrahydrofurans and γ-butyrolactones are present in the structures of a wide variety of natural products[1] with biological importance,[2] so that their stereocontrolled synthesis represents a current objective for synthetic organic chemists.[3,4] Here we report a novel methodology for the construction of hydroxylated tetrahydrofurans and γ-butyrolactones, via a diastereoselective osmylation or hydroboration reaction of organometallic species having an allylic alcohol or, respectively, an α,β-unsaturated ester lateral to a π-allyl molybdenum system. Our work started by subjecting the previously reported[5] aldehyde **1** to a Horner−Wadsworth−Emmons reaction,[6] which afforded the α,β-unsaturated ester **2** as a single isomer, with the C−C double bond in *E*

(1) Tetrahydrofurans: Sasaki, K.; Wright, J. L. C.; Yasumoto, T. *J. Org. Chem.* **1998**, *63*, 2475−2480. Alali, F. Q.; Rogers, L.; Zhang, Y.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 31−34. Takada, N.; Sato, H.; Suenaga, K.; Arimoto, H.; Yamada, K.; Ueda, K.; Uemura, D. *Tetrahedron Lett.* **1999**, *40*, 6309−6312. Ueda, K.; Hu, Y. *Tetrahedron Lett.* **1999**, *40*, 6305−6308. Kim, E.-J.; Tian, F.; Woo, M.-H. *J. Nat. Prod.* **2000**, *63*, 1503−1506. Kubota, T.; Tsuda, M.; Takahashi, M.; Ishibashi, M.; Naoki, H.; Kobayashi, J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3483−3487. Kobayashi, J.; Kubota, T.; Endo, T.; Tsuda, M. *J. Org. Chem.* **2001**, *66*, 134−142. Satake, M.; Ofuji, K.; Naoki, H.; James, K. J.; Furey, A.; McMahon, T.; Silke, J.; Yasumoto, T. *J. Am. Chem. Soc.* **1998**, *120*, 9967−9968. Litaudon, M.; Hickford, S. J. H.; Lill, R. E.; Lake, R. J.; Blunt, J. W.; Munro, M. H. G. *J. Org. Chem.* **1997**, *62*, 1868−1871. Capon, R. J.; Barrow, R. A.; Rochfort, S.; Jobling, M.; Skene, C.; Lacey, E.; Gill, J. H.; Friedel, T.; Wadsworth, D. *Tetrahedron* **1998**, *54*, 2227−2242. γ-Butyrolactones: Maier, M. S.; Marimon, D. I. G.; Stortz, C. A.; Adler, M. T. *J. Nat. Prod.* **1999**, *62*, 1565−1567. Lee, S.-C.; Brown, G. D. *J. Nat. Prod.* **1998**, *61*, 29−33.

(2) Oberlies, N. H.; Jones, J. L.; Corbett, T. H.; Fotopoulos, S. S.; McLaughlin, J. L. *Cancer Lett.* **1995**, *96*, 55−62.

(3) For synthesis of tetrahydrofurans, see: Elliot, M. C. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1291−1318. Selected recent examples: Gasparski, C. M.; Herrinton, P. M.; Overman, L. E.; Wolfe, J. P. *Tetrahedron Lett.* **2000**, *41*, 9431−9435. Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2000**, *2*, 461−464. Garcia, C.; Soler, M. A.; Martin, V. S. *Tetrahedron Lett.* **2000**, *41*, 4127−4130. Jiang, W.; Lantrip, D. A.; Fuchs, P. L. *Org. Lett.* **2000**, *2*, 2181−2184. Pilli, R. A.; Riatto, V. B.; Vencato, I. *Org. Lett.* **2000**, *2*, 53−56. Bruns, R.; Kopf, J.; Köll, P. *Chem. Eur. J.* **2000**, *6*, 1337−1345. Loh, T.-P.; Hu, Q.-Y.; Ma, L.-T. *J. Am. Chem. Soc.* **2001**, *123*, 2450−2451. Wang, G. T.; Wang, S.; Chen, Y.; Gentles, R.; Sowin, T. *J. Org. Chem.* **2001**, *66*, 2052−2056. Vares, L.; Rein. T. *Org. Lett.* **2000**, *2*, 2611−2614. Sutterer, A.; Moeller, K. D. *J. Am. Chem. Soc.* **2000**, *122*, 5636−5637. Yang, J.; Cohn, S. T.; Romo, D. *Org. Lett.* **2000**, *2*, 763−766. Awakura, D.; Fujiwara, K.; Murai, A. *Synlett* **2000**, 1733−1736.

(4) For synthesis of γ-butyrolactones, see: Peng, Z.-H.; Woerpel, K. A. *Org. Lett.* **2001**, *3*, 675−678. Tobisu, M.; Chatani, N.; Asaumi, T.; Amako, K.; Ie, Y.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* **2000**, *122*, 12663−12674. Fernandez, A.-M.; Plaquevent, J.-C.; Duhamel, L. *J. Org. Chem.* **1997**, *62*, 4007−4014. Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **1999**, *121*, 11680−11683. Cahiez, G.; Métais, E. *Tetrahedron: Asymmetry* **1997**, *8*, 1373−1376. Miyabe, H.; Fujii, K.; Goto, T.; Naito, T. *Org. Lett.* **2000**, *2*, 4071−4074. Fukuzawa, S.; Seki, K.; Tatsuzawa, M.; Mutoh, K. *J. Am. Chem. Soc.* **1997**, *119*, 1482−1483. Martín, T.; Martín, V. S. *Tetrahedron Lett.* **2000**, *41*, 2503−2505. Zhang, Q.; Lu, X. *J. Am. Chem. Soc.* **2000**, *122*, 7604−7605. Sibi, M. P.; Lu, J.; Talbacka, C. L. *J. Org. Chem.* **1996**, *61*, 7848−7855. Forster, A.; Fitremann, J.; Renaud, P. *Tetrahedron Lett.* **1998**, *39*, 7097−7100. Chen, M.-J.; Lo, C.-Y.; Chin, C.-C.; Liu, R.-S. *J. Org. Chem.* **2000**, *65*, 6362−6367. Lin, Y.-L.; Cheng, M.-H.; Chen, W.-C.; Peng, S.-M.; Wang, S.-L.; Kuo, H.; Liu, R.-S. *J. Org. Chem.* **2001**, *66*, 1781−1786.

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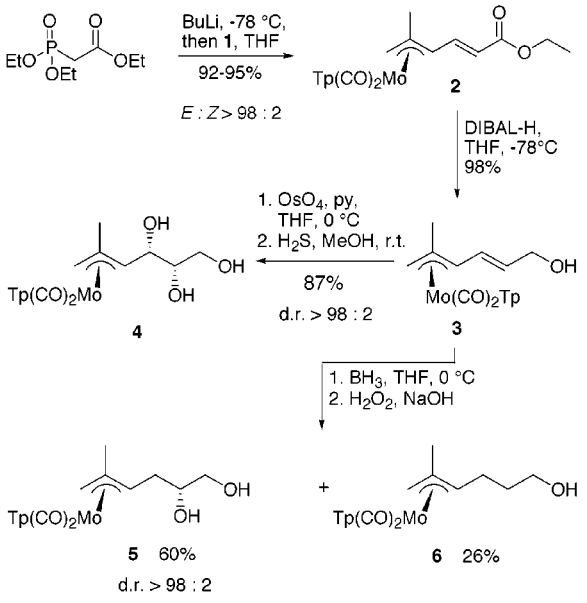
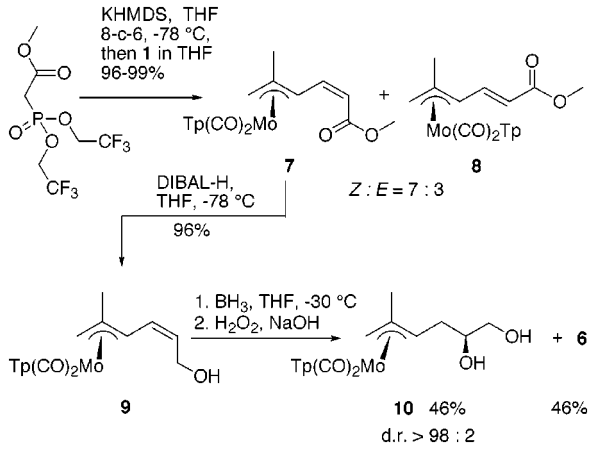
configuration. DIBAL-H reduction[7] of ester **2** provided allylic alcohol **3** in 98% yield (Scheme 1).[8]

Scheme 1



Triol **4** was obtained as a single diastereoisomer[9] (by NMR) by treating **3** with osmium tetroxide, followed by reaction of the osmate intermediate with H_2S in methanol.[10] Treatment of intermediate **3** with borane, followed by oxidative workup, resulted in a separable mixture of 1,2-diol **5** (major) and primary alcohol **6**, in a combined yield of 86%. The reaction was regioselective, with no 1,3-diol being detected in the reaction mixture. This result is probably a consequence of the well-documented[11] directing effect of the allylic hydroxy group in hydroborations, together with the bulkiness of the π-allyl molybdenum moiety. A single set of signals was observed in the ^{1}H NMR spectrum of **5**, recorded either in $CDCl_3$ or C_6D_6, indicating that the borane addition to **3** was completely diastereoselective. An accidental magnetic isochronism of all NMR signals of the two possible epimers of **5** is very unlikely but theoretically still possible, so that we considered it important to synthesize the epimer of **5** that *could* be formed as a minor product during the hydroboration of **3**. Pursuing this idea, we attempted to perform a *cis* olefination of **1** with bis(2,2,2-trifluoroethyl)(methoxy-carbonylmethyl)phosphonate, by the method that was earlier developed by Still[12] for the diastereoselective synthesis of *Z* α,β-unsaturated esters. Unfortunately, applying this protocol to our organometallic aldehyde, **1**, resulted in a *Z/E* mixture of esters in a 7:3 ratio, at best. The ester products **7** and **8** were separated by preparative thin-layer chromatography, and *Z* isomer **7** was reduced with DIBAL-H to the corresponding allylic alcohol **9**. The hydroboration of **9** under the same conditions as for **3** led to 1,2-diol **10** as a single regio- and diastereoisomer in only 24% yield, together with 55% of **6** (Scheme 2).

Scheme 2



The molar ratio of **10** to **6** was improved to 1:1 when the addition of borane was performed at −30 °C.[13] The NMR signals of **10** (both ^{1}H and ^{13}C) were different from those of its diastereoisomer, so that the single set of resonances observed for **5** (or epimer **10**) represents indeed a single diastereoisomer; hence the hydroboration of **3** (or **9**) is a highly stereocontrolled reaction.[14]

The origin of diastereoselectivity during the reactions performed on allylic alcohols **3** and **9** deserves further comment. The conformational equilibrium associated with the rotation around the single bond C(3)−C(4) is strongly shifted toward the *s-trans* conformer, as a result of the severe nonbonding interactions present in the *s-cis* conformer (Figure 1). We have previously shown[5] that the C(2)-methyl substituent plays a dominant role in controlling the conformation of these compounds.

NOESY experiments performed on **3** and **9** support this conclusion. Thus, a NOESY cross-peak was observed for the methyl↔H(4) signals of **3**, but not for the methyl↔H(5) signals. Similarly, NOESY cross-peaks were observed for methyl↔H(4) and H(3)↔H(6) signals of **9**, but not for methyl↔H(6) signals. These observations clearly suggest that

(5) Pearson, A. J.; Neagu, I. B.; Pinkerton, A. A.; Kirschbaum, K.; Hardie, M. J. *Organometallics* **1997**, *16*, 4346−4354. Pearson, A. J.; Neagu, I. B. *J. Org. Chem.* **1999**, *64*, 2890−2896.

(6) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863−927. Coutrot, P.; Snoussi, M.; Savignan, P. *Synthesis* **1978**, 133−134.

(7) Tadano, K.; Idogaki, Y.; Yamada, H.; Suami, T. *J. Org. Chem.* **1987**, *52*, 1201−1210.

(8) Tp = hydridotris(1-pyrazolyl)borate

(9) By diastereomeric ratios of >98:2 we mean that only one isomer was detected in both ^{1}H NMR and ^{13}C NMR spectra of a given product.

(10) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943−3946. Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1984**, *40*, 2247−2255.

(11) Brown, H. C.; Gallivan, R. M., Jr. *J. Am. Chem. Soc.* **1968**, *90*, 2906−2915. Brown, H. C.; Cope, O. J. *J. Org. Chem.* **1964**, *29*, 1801−1807.

(12) Still, W. C.; Gennari, C. *Tetrahedron. Lett.* **1983**, *24*, 4405−4408.

(13) Side products analogous to **6** have previously been observed during hydroboration of allylic alcohols and have been solved by using the corresponding benzyl ether as starting material (ref 10). In our work, no difference was observed between alcohol and ether.

(14) ^{1}H and ^{13}C NMR spectra of **5** and **10**, as well as of a mixture of the two are available within the Supporting Information.

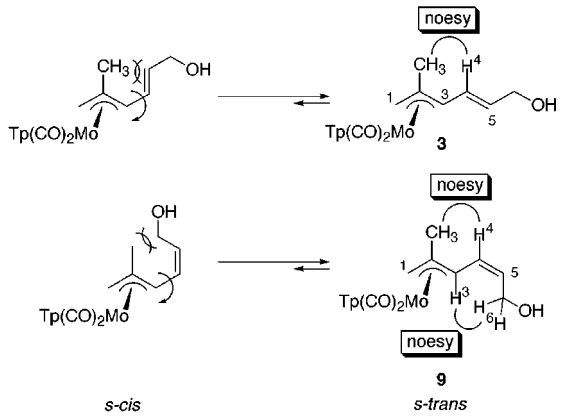


Figure 1. Conformational equilibrium associated with the rotation around the C(3)−C(4) single bond of **3** and **9**, shown by NOESY correlations to be strongly shifted toward *s-trans* conformers (arbitrary numbering).

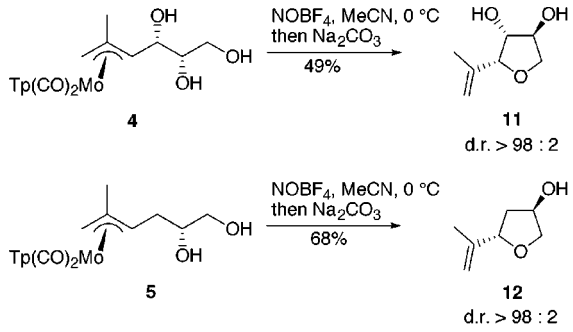
s-trans conformers of **3** and **9** are dominant in solution. Semiempirical calculations (Spartan PM3)[15] also showed that *s-trans* conformers are more stable than *s-cis* ones by 4.7 kcal/mol for **3** and 3.3 kcal/mol for **9**. This conformational homogeneity,[16] together with the ability of $[Tp(CO)_2Mo]$ moiety to direct attack of the reagents on the double bond *anti* to the metal, renders the reaction diastereoselective.[17] The relative stereochemistry of the newly formed stereogenic centers in **4**, **5**, and **10** with respect to the metal was assigned on the basis of these arguments, as well as on previously reported X-ray diffraction data.[5] A similar stereochemical outcome was previously observed by Liu and co-workers for the C-alkylation of lithium enolates attached to an acyclic $[(\pi\text{-allyl})Cp(CO)_2Mo]$[18] system with aldehydes, as well as for the reduction of ketone groups attached to the same organometallic system.[19]

Compounds **4** and **5** were demetalated by a ligand exchange reaction with $NOBF_4$ at 0 °C, followed by treatment with Na_2CO_3 and exposure to air at room temperature.[19] The π-allylmolybdenum moiety is activated toward an internal nucleophilic attack by the primary hydroxy group, by replacing a CO neutral ligand on molybdenum with the positively charged NO^+. Tetrahydrofuran products **11** and **12** were obtained as single diastereoisomers, judged from their NMR spectra.

For dihydroxylation of the unsaturated ester **2**, which is more electron-deficient than **3**, we used the procedure reported by Donohoe and co-workers[20] for the osmylation of allylic trichloroacetamides, also electron-deficient. The

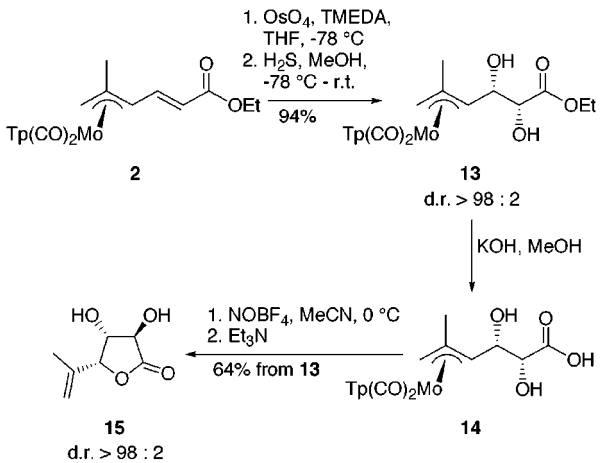
(15) Hehre, W. J.; Huang, W. W. *Chemistry with Computation: An Introduction to SPARTAN*; Wavefunction, Inc.: Irvine, CA, 1995.
(16) Harvey, D. F.; Selchau, V. B. *J. Org. Chem.* **2000**, *65*, 2282−2286.
(17) Ley, V. S.; Wright, E. A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1677−1683. Takemoto, Y.; Ishii, K.; Honda, A.; Okamoto, K.; Yanada, R.; Ibuka, T. *J. Chem. Soc., Chem. Commun.* **2000**, 1445−1446.
(18) Cp = cyclopentadienyl
(19) Lin, S.-H.; Lush, S.-F.; Cheng, W.-J.; Lee, G.-H.; Peng, S.-M.; Liao, Y.-L.; Wang, S.-L.; Liu, R.-S. *Organometallics* **1994**, *13*, 1711−1719. Lin, S.-H.; Lee, G.-H.; Peng, S.-M.; Liu, R.-S. *Organometallics* **1993**, *12*, 2591−2599.

Scheme 3



ester **2** was treated with osmium tetroxide in THF, in the presence of tetramethylethylenediamine (TMEDA), at −78 °C, leading diastereoselectively to diol **13** in 94% yield after cleavage of the osmate intermediate. The relative stereochemistry of **13** was assigned on the basis of the same rationale as discussed earlier for **4**, **5**, and **10**. Several attempts to hydrolyze diol ester **13** with LiOH or KOH failed during or after the neutralization of the resulting salt with diluted HCl. This behavior was attributed to the presence of a hydroxy group vicinal to the π-allylmolybdenum moiety in **14**, which might undergo metal-assisted elimination in acidic conditions. Eventually we resolved the problem by hydrolyzing **13** with KOH, followed by neutralization with HCl at 0 °C, extraction into EtOAc, and addition of small amounts of Et_3N to the solution of crude acid **14** to neutral pH. Removal of solvent provided the triethylammonium salt of **14**,[21] which was subjected to demetalation[22] without further purification. Treatment with $NOBF_4$ at 0 °C, followed by addition of Et_3N and subsequent exposure to air at room temperature, afforded lactone **15** (Scheme 4) as a single diastereoisomer (by NMR).

Scheme 4



The relative stereochemistry assignment for the stereogenic centers in **11**, **12**, and **15** was straightforward, based solely on the stereochemistry of their precursors and on the known

fact that during demetalation nucleophiles attack the activated allyl moiety *anti* to the metal.[23] The coupling constants of proton H(3) in **12** with pseudoaxial protons H(4) and H(2) are 5.2 and 4.1 Hz, and with pseudoequatorial protons H(4) and H(2) they are 1.3 and 1.4 Hz, respectively. These values are in agreement with a pseudoequatorial orientation for proton H(3), that is, a *trans* relationship between the 3-hydroxy group and the 5-isopropenyl group,[24] with the last one, being oriented pseudoequatorial,[25] as inferred from the vicinal coupling constants of H(5) with protons at position 4 (Figure 2).[26] The NOE experiment that we performed on compound **11** by irradiating the methyl protons of the isopropenyl group showed an enhancement only for the signals of the *Z* vinyl proton, for H(5) and for H(4), being thus unhelpful for a configuration assignment.

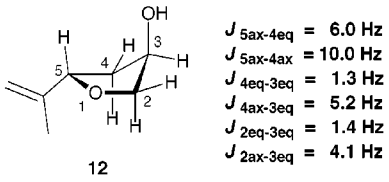


Figure 2. Diagnostic ^{1}H NMR (200 MHz) coupling constants in **12**, showing a *trans* configuration for 3-hydroxy and 5-isopropenyl groups.

In summary, we have demonstrated that osmylation and hydroboration of allylic alcohols and osmylation of α,β-unsaturated esters attached to a π-allylmolybdenum system occur with essentially complete diastereoselectivity and that the products can be demetalated to give tetrahydrofuran and γ-butyrolactone derivatives in a completely stereocontrolled manner. This research in combination with the accessibility of optically pure molybdenum complexes[27] may represent a useful entry into the field of natural product synthesis.

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Supporting Information Available: Experimental procedures, spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra for compounds **2**−**13** and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Donohoe, T. J.; Blades, K.; Helliwell, M.; Moore, P. R.; Winter, J. J. G. *J. Org. Chem.* **1999**, *64*, 2980−2981.

(21) Formation of **14** was confirmed by the absence of ethyl signals (present for ester **13**) from its ^{1}H NMR spectrum, and the upfield shift of the signal belonging to α-H with respect to carboxyl group to $\delta = 4.56$ ppm, compared to $\delta = 4.89$ ppm in precursor **13**.

(22) Pearson, A. J.; Douglas, A. R. *Organometallics* **1998**, *17*, 1446−1448.

(23) The same *anti* stereochemistry was reported by Liu and co-workers for a demetalation protocol in which aldehydes are allylated with a [(π-allyl)Cp(NO)ClMo] or a [(π-allyl)Cp(NO)IW] system: Lin, S.-H.; Chen, C.-C.; Vong, W.-J.; Liu, R.-S. *Organometallics* **1995**, *14*, 1619−1625. Chandrasekharam, M.; Liu, R.-S. *J. Org. Chem.* **1998**, *63*, 9122−9124. For a recent review, see: Li, C.-L.; Liu, R.-S. *Chem. Rev.* **2000**, *100*, 3127−3161.

(24) In a *cis* configuration, both groups would be pseudoequatorial, placing proton H(3) in a pseudoaxial position. Then it would be coupled with the protons at positions 2 and 4 with significantly larger magnitudes (9−10 Hz with the pseudoaxial ones and 5−6 Hz with the pseudoequatorial ones).

(25) Fuchs, B. In *Topics in Stereochemistry*; Eliel, E. L., Allinger, N. L., Eds.; John Wiley & Sons: New York, 1978; Vol. 10, pp 1−94.

(26) Andersson, T.; Berova, N.; Nakanishi, K.; Carter, G. T. *Org. Lett.* **2000**, *2*, 919−922.

(27) Christopher, J. A.; Kocienski, P. J.; Kuhl, A.; Bell, R. *Synlett* **2000**, 463−466.