ORGANIC LETTERS

2005
Vol. 7, No. 2
223−226

Hydrocarbon Oxidation vs C–C Bond-Forming Approaches for Efficient Syntheses of Oxygenated Molecules

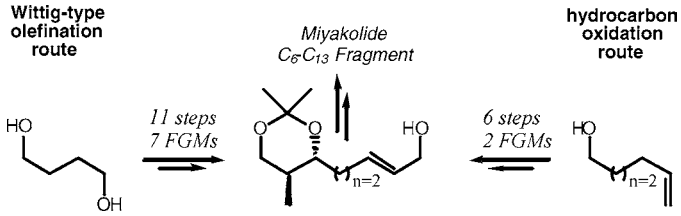
Kenneth J. Fraunhoffer, Daniel A. Bachovchin, and M. Christina White*

Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138

white@chemistry.harvard.edu

Received October 26, 2004

ABSTRACT

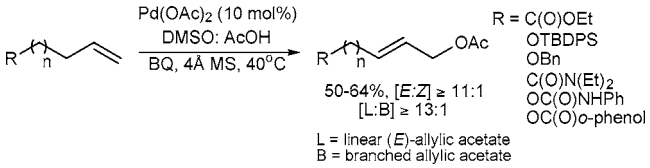


A hydrocarbon oxidation approach has been applied to the construction of several linear (*E*)-allylic alcohols that have served as intermediates in the synthesis of natural products and natural product-like molecules. In the original syntheses, these intermediates were constructed using a standard Wittig-type olefination approach. We report here that routes to these same intermediates designed around a hydrocarbon oxidation approach are more efficient both in the total number of functional group manipulations (FGMs) and overall steps, as well as in the overall yield.

A prevalent approach for introducing oxygenated functionality in complex small-molecule synthesis is the joining of preoxidized fragments via C−C bond-forming methods. Implicit in this approach is the burden of carrying oxygenated functionality throughout the synthesis, often necessitating the use of functional group manipulations (FGMs) such as alcohol protection−deprotection sequences and oxidation state changes. An attractive, alternative approach would be the direct oxidative functionalization of hydrocarbon units at late stages of a synthetic sequence. In theory, routes based on this approach would proceed with reduced FGMs, resulting in fewer steps and increased overall yields. We recently developed a method that allows us to test this hypothesis. Specifically, we reported a DMSO-promoted, $Pd(OAc)_2$-catalyzed allylic oxidation with olefin transposition method for the highly chemo-, regio-, and stereoselective synthesis of linear (*E*)-allylic acetates from monosubstituted olefins (Scheme 1).[1,2]

Linear (*E*)-allylic alcohols are very common intermediates in small-molecule synthesis. The current standard C−C bond-forming approach for their preparation involves a sequence of Horner−Wadsworth−Emmons (HWE) or stabilized Wit-

Scheme 1. Pd(II)/DMSO Allylic Oxidation



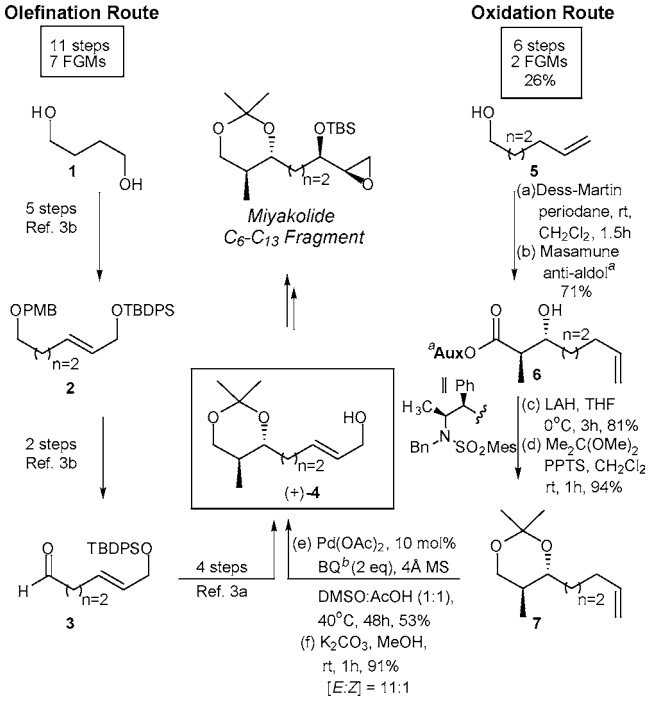
(1) (a) Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346. Other allylic oxidation systems: Pd(II)/AcOH/BQ: (b) Hansson, S.; Heumann, A.; Rein, T.; Åkermark, B. *J. Org. Chem.* **1990**, *55*, 975. (c) McMurry, J. E.; Kocovsky, P. *Tetrahedron Lett.* **1984**, *25*, 4187. (d) Macsari, I.; Szabo, K. J. *Tetrahedron Lett.* **1998**, *39*, 6345. SeO_2/*t*-BuO_2H: (e) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526. Cu(I)/*t*-Butyl Perbenzoate: (f) Andrus, M. B.; Lashley, J. C. *Tetrahedron* **2002**, *58*, 845. $Pd(OH)_2$/C/*t*-BuO_2H: (g) Yu, J.-Q.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 3232. Pd(II)/DMSO/O_2 oxidations: (h) Grennberg, H.; Gogoll, A.; Backvall, J.-E. *J. Org. Chem.* **1991**, *56*, 5808. (i) Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. *J. Org. Chem.* **1996**, *61*, 3584. Pd(II)/DMSO arene C−H functionalization: (j) Zhou, C.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 2302.

10.1021/ol047800p CCC: $30.25
Published on Web 12/30/2004

tig olefination followed by reduction.[2] Herein we report that alternative routes to the same synthetic intermediates designed around a hydrocarbon oxidation approach involving DMSO/Pd(OAc)$_2$/BQ allylic oxidation are uniformly more efficient on the basis of number of FGMs, overall number of steps, and overall yield (when available).

A representative example of the general strategy used to access functionalized linear (*E*)-allylic alcohols is the reported synthesis of key (*E*)-allylic alcohol intermediate (+)-**4** of the miyakolide C_6-C_{13} fragment (Scheme 2).[3a] The

Scheme 2. Hydrocarbon Oxidation Route vs C−C Bond-Forming Route to (*E*)-Allylic Alcohol Intermediate (+)-**4** of Miyakolide C_6-C_{13} Fragment

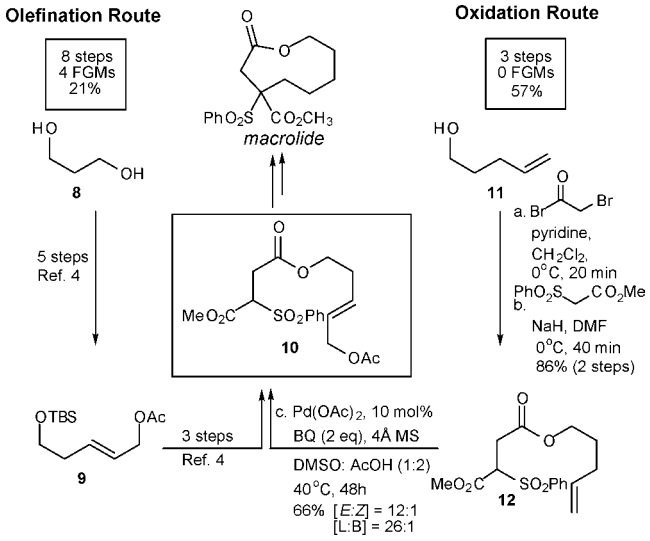


[a] Conditions: Propionic acid (1*R*,2*S*)-2-[*N*-benzyl-*N*-(mesitylenesulfonyl)-amino]-1-phenyl-1-propyl ester (1.2 equiv), Cy_2BOTf (2.3 equiv), NEt_3 (2.8 equiv), −78 °C, 3 h; 5-hexenal, −78 °C for 3 h → 0 °C for 1 h, 71% (two steps). [b]BQ = Benzoquinone.

two ends of a symmetric, bis-oxygenated starting material, 1,4-butanediol **1**, were differentially functionalized via a series of reactions involving monoprotection, oxidation, HWE olefination, reduction, and orthogonal protection to generate the requisite (*E*)-allylic alcohol unit. The initially protected hydroxyl was unmasked and oxidized to aldehyde **3**, enabling the implementation of Masamune's anti-selective aldol methodology (Scheme 2).[3b] After reductive auxiliary cleavage and acetonide formation, the (*E*)-allylic alcohol unit was deprotected to yield the targeted intermediate (+)-**4**. This route required a total of 11 steps, 7 of which can be attributed to FGMs. An alternative approach to (+)-**4** was made possible by our allylic oxidation methodology. Monooxygenated substrate **5** was converted into the corresponding aldehyde and then transformed into the desired acetonide **7** using the aforementioned aldol sequence. The hydrocarbon appendage of **7** was directly transformed into the requisite linear (*E*)-allylic alcohol unit via DMSO/Pd(OAc)$_2$/BQ allylic oxidation (Scheme 2). Deacetylation generated (+)-**4** in a total of six steps, only two of which are FGMs, and 26% overall yield. Notably, the acid-labile acetonide functionality was tolerant of our mildly acidic allylic oxidation conditions. Key to the relative brevity of our route was the *ability to use a hydrocarbon appendage, as opposed to an oxygenated one, as a direct precursor to the target oxygenated functionality*.

In a similar vein, the reported synthesis of macrocyclization substrate **10**[4] began with bis-oxygenated precursor 1,3-propanediol **8**. Multiple protective group and oxidation state manipulations were used to enable installation of the (*E*)-allylic acetate via a HWE/reduction sequence followed by the sensitive β-sulfonyl acetate functionality via esterification. This route proceeds in eight steps and 21% overall yield. Four of these steps involve FGMs. By way of contrast, starting from a monooxygenated precursor, 4-penten-1-ol **11**, we installed the β-sulfonyl acetate ester first and directly converted the hydrocarbon appendage to the requisite (*E*)-allylic acetate in three steps with *no FGMs* and in 57% overall yield (Scheme 3). It is significant to note the

Scheme 3. Hydrocarbon Oxidation Route vs C−C Bond-Forming Route to (*E*)-Allylic Acetate Intermediate **10** of a Macrolide Precursor



compatibility of the sensitive β-sulfonyl acetate ester functionality with our allylic oxidation methodology in contrast

(2) (a) The Wittig-type reactions of aliphatic aldehydes proceed with similar *E/Z* selectivities: Kelly, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 1, p 729. (b) Cross-metathesis reactions of α-olefins with allylic alcohol equivalents proceed with moderate stereoselectivities (~4.5:1 *E/Z*). Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

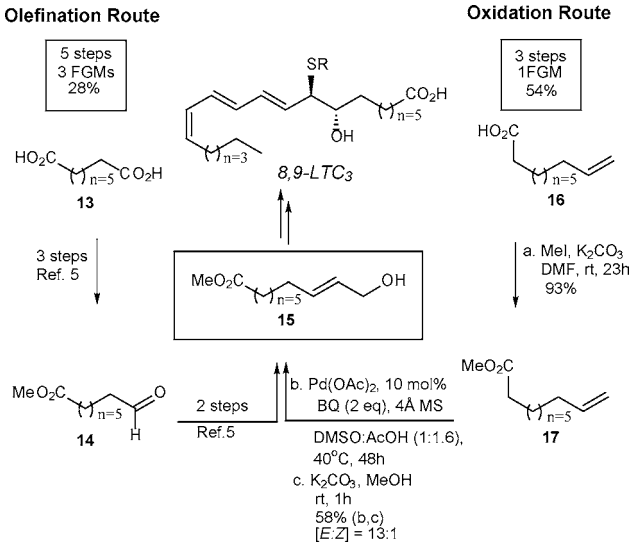
(3) (a) Yoshimitsu, T.; Song, J. J.; Wang, G.-Q.; Masamune, S. *J. Org. Chem.* **1997**, *62*, 8978. (b) Personal communication with Professor Takehiko Yoshimitsu.

(4) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4743.

to its incompatibility with the carbanion addition and reduction steps of the HWE sequence.

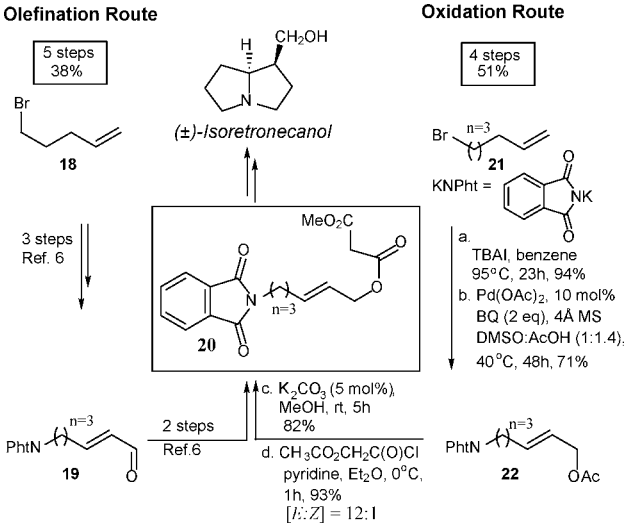
Similarly, the reported synthesis of 8,9-leukotriene intermediate **15** via a stabilized Wittig/reduction route began from bis-oxygenated precursor octanedioic acid **13**.[5a] Monoesterification followed by a two-step, selective reduction of the other carboxylate was required to install the (*E*)-allylic alcohol moiety.[5b] The route proceeded in five steps, three of which were FGMs, and 28% overall yield. In contrast, esterification of 9-decenoic acid followed by direct allylic oxidation/deacetylation afforded (*E*)-allylic alcohol **15** in three steps, with one FGM, and in 54% overall yield.

Scheme 4. Hydrocarbon Oxidation Route vs C−C Bond-Forming Route to (*E*)-Allylic Acetate Intermediate **15** of 8,9-Leukotriene C_3

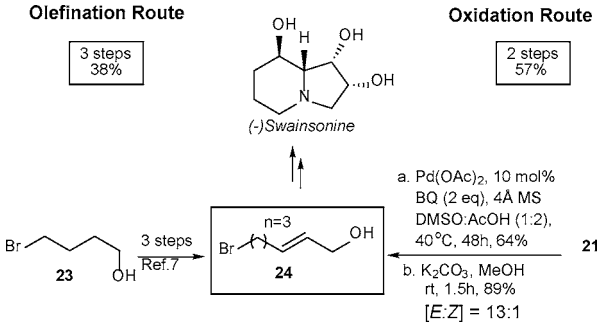


We have also observed improvements in overall yields in cases that do not differ significantly in the number of FGMs. Alternative routes to isoretronecanol intermediate **20**[6] and swainsonine intermediate **24**[7] differ only in the sequence used to install the (*E*)-allylic alcohol unit, i.e., aldehyde formation/olefination/reduction vs allylic oxidation/deacetylation (Schemes 5 and 6). We attribute the higher yields in the latter to a greater compatibility of the phthalimide and primary alkyl bromide functionalities toward the allylic oxidation sequence than to the Wittig-type olefination sequence, which exposes the substrate to a range of relatively harsh conditions. These findings directly challenge the general perception that intermolecular C−H oxidation routes would be lower yielding than standard C−C bond-forming routes to oxygenated products.

Scheme 5. Hydrocarbon Oxidation Route vs C−C Bond-Forming Route to (*E*)-Allylic Acetate Intermediate **20** of (±)-Isoretronecanol



Scheme 6. Hydrocarbon Oxidation Route vs C−C Bond-Forming Route to (*E*)-Allylic Acetate Intermediate **24** of (−)-Swainsonine



Chiral (*E*)-2-buten-1,4-diols, important intermediates in the synthesis of polyhydroxylated natural products, are usually synthesized via Wittig-type C−C bond-forming routes starting with chiral α-hydroxy aldehydes. These chiral synthons are challenging to access directly.[8] For example, the reported synthesis of key intermediate (+)-**28** en route to the C_{17}−C_{26} fragment of tautomycin proceeded via a HWE/reduction sequence from aldehyde **27** (Scheme 7).[9] The latter was prepared in multiple steps from D-valine **25** via a deamination route[9b] involving numerous FGMs of the acid moiety. We recognized that Brown's asymmetric allylation methodology[10] followed by our allylic oxidation method should provide a rapid route to chiral (*E*)-2-buten-1,4-diols.[11] The requisite homoallylic alcohol was synthesized via enantioselective allylboration of 2-methylpropionaldehyde. Conver-

(5) (a) Baker, S. R.; Boot, J. R.; Morgan, S. E.; Osborne, D. J.; Ross, W. J.; Schrubsall, P. R. *Tetrahedron Lett.* **1983**, *24*, 4469. (b) Pennington, F. C.; Celmer, W. D.; McLamore, W. M.; Bogert, V. V.; Solomons, I. A. *J. Am. Chem. Soc.* **1953**, *75*, 109.

(6) Danishefsky, S.; McKee, R.; Singh, R. K. *J. Am. Chem. Soc.* **1977**, *99*, 4783.

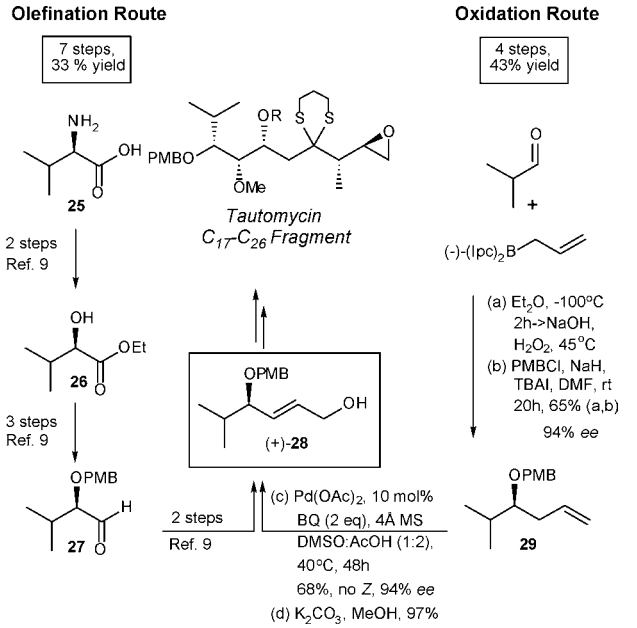
(7) Swainsonine: (a) Hunt, J. A.; Roush, W. R. *J. Org. Chem.* **1997**, *62*, 1112. Overall yield for HWE route to **5** calculated starting from commercial 4-bromobutanol: (b) Vedejs, E.; Arnost, M. J.; Hagan, J. P. *J. Org. Chem.* **1979**, *44*, 3230.

(8) Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808.

(9) (a) Tsuboi, K.; Ichikawa, Y.; Naganawa, A.; Isobe, M.; Ubukata, M.; Isono, K. *Tetrahedron* **1997**, *53*, 5083. (b) Ichikawa, Y.; Tsuboi, K.; Naganawa, A.; Isobe, M. *Synlett* **1993**, 907.

(10) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401.

Scheme 7. Hydrocarbon Oxidation vs C−C Bond-Forming Route to Chiral (*E*)-2-Buten-1,4-diol (+)-**28** Intermediate of Tautomycin C_{17}−C_{26} Fragment



sion of the alcohol to its PMB ether **29** followed by an allylic oxidation/deacetylation sequence afforded (+)-**28** in a total of four steps (Scheme 7). Remarkably, this allylic oxidation proceeded in exceptionally high stereo- and regioselectivity (no *Z* or branched isomers were detected by ^{1}H NMR) and with *no degradation of enantiomeric purity*.

In summary, this study introduces a new approach for the synthesis of linear (*E*)-allylic alcohol intermediates that entails installation of oxygenated functionality late in a synthetic sequence via direct oxidation of an inert hydrocarbon appendage. Using this strategy, we have achieved efficient syntheses of a variety of (*E*)-allylic alcohol intermediates that proceed with fewer FGMs, in fewer steps, and in higher overall yields than alternative routes involving conventional Wittig-type C−C bond-forming sequences. These results suggest that the development of selective C−H oxidation reactions with general substrate profiles can streamline synthesis.

Acknowledgment. This work was supported by Harvard University, the Camille and Henry Dreyfus Foundation (M.C.W.), an Eli Lilly Graduate Fellowship (K.J.F.), and the Undergraduate Harvard Research Program (D.A.B.). We are grateful to Merck for a generous gift of GC equipment and to Dr. G. Dudek, Mr. P. Wang, and Ms. Q. Liao for mass spectral analyses.

Supporting Information Available: Detailed experimental procedures and full spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL047800P

(11) Chiral (*E*)-2-buten-1,4-diols with good to moderate enantioselectivities via allylation with chiral (*E*)-γ-($PhMe_2Si$) allylboronate reagents followed by epoxidation/Petersen elimination: (a) Roush, W. R.; Grover, P. T. *Tetrahedron Lett.* **1990**, *31*, 7567. (b) Roush, W. R.; Pinchuk, A. N.; Micalizio, G. C. *Tetrahedron Lett.* **2000**, *41*, 9413.