OL | Organic Letters

pubs.acs.org/OrgLett Letter

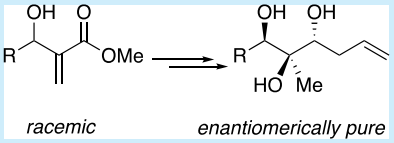
Synthesis of Enantiopure Triols from Racemic Baylis–Hillman Adducts Using a Diastereoselective Peroxidation Reaction

Dylan S. Zuckerman and K. A. Woerpel*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c03439 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Using a chiral (−)-menthone auxiliary, enantiopure cyclic derivatives of Baylis–Hillman adducts were synthesized. A diastereoselective peroxidation reaction was used to introduce an oxygen atom and establish another stereocenter. The resulting products could be elaborated by employing a one-flask reduction–acetylation protocol followed by a diastereoselective nucleophilic substitution reaction. Removal of the (−)-menthone auxiliary provided an enantiopure triol with a structure related to naturally occurring polyols.



Downloaded via UNIV OF NEW ENGLAND on November 4, 2020 at 00:36:39 (UTC).
See https://pubs.acs.org/sharingguidelines for options on how to legitimately share published articles.

The structural motif consisting of a carbon chain bearing hydroxyl groups on consecutive carbon atoms recurs in many natural products. This motif, which defines carbohydrates, is also present in a number of biologically active compounds, such as (9*S*)-dihydroerythronolide A (**1**), which is a precursor to many common antibiotics, including erythromycin,[1] azithromycin,[2] and clarithromycin (Figure 1).[3]

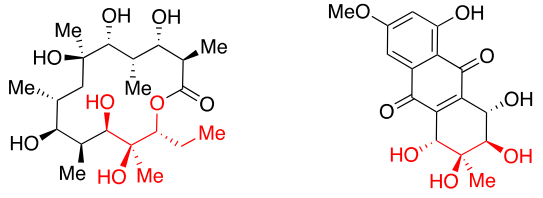
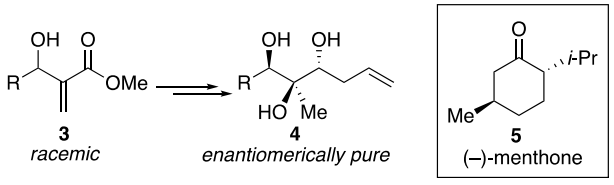


Figure 1. Biologically active compounds bearing hydroxyl groups on consecutive carbons.

Another natural product that contains this set of hydroxyl-bearing stereocenters, altersolanol A (**2**), displayed anticancer activity (Figure 1).[4] The stereoselective synthesis of a tertiary hydroxyl group positioned between two secondary hydroxyl groups, as in compounds **1** and **2**, has been particularly difficult. For example, establishing this stereochemical array in (9*S*)-dihydroerythronolide A (**1**) required lengthy synthetic routes.[5−9]

In this Letter, we report a method for the synthesis of enantiomerically pure triols with the motif highlighted in **1** and **2** using racemic Baylis–Hillman adducts as the key starting materials (Scheme 1). The enantiomers of these adducts were resolved by forming an acetal with (−)-menthone (**5**).[10−14] The configuration at the tertiary hydroxyl group was established with a diastereoselective cobalt-catalyzed peroxidation reaction[15] on the resulting acetal. A diastereoselective nucleophilic substitution reaction[16] was used to extend the chain of carbon atoms and control the configuration of the remaining stereocenter, leading to enantiopure triols[12] with the relative stereochemistry found in **1** and **2**.

Scheme 1. General Transformation from Racemic Baylis–Hillman Adducts to Enantiopure Triols



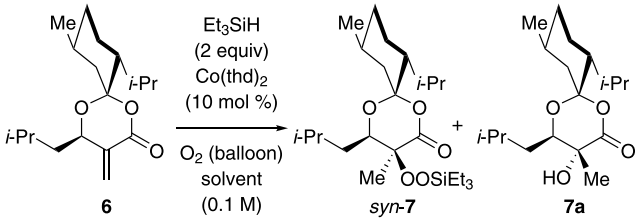
The alkene hydration reaction required optimization (Table 1). Initial studies were performed on lactone **6**, which was prepared by the route illustrated in Scheme 2 (vide infra). It was anticipated that if the stereoselective peroxidation could be developed, the resulting peroxide could be reduced to the desired alcohol. Although the cobalt-catalyzed peroxidation of alkenes is generally not diastereoselective in simple systems,[17−22] similar cyclic Baylis–Hillman adduct derivatives have been used in stereoselective radical reactions.[23] With trifluorotoluene ($PhCF_3$) as the solvent and in the presence of Et_3SiH and molecular O_2, diastereoselectivity improved as the amount of $PhSiH_3$ was increased, likely by selective decomposition of the minor diastereomer of the silyl peroxide, *anti*-**7**.[15] The yield of the major silyl peroxide *syn*-**7** also decreased, however (entries 1–3). Switching the solvent to acetonitrile (MeCN) increased the yield of the major silyl

Received: October 16, 2020

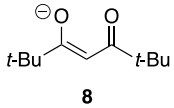
© XXXX American Chemical Society

https://dx.doi.org/10.1021/acs.orglett.0c03439
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Optimization of the Diastereoselective Peroxidation Reaction



entry	solvent	$PhSiH_3$ (mol %)	dr 7	yield *syn*-7 (%)[a]	yield **7a** (%)[a]
1	$PhCF_3$	0	94 : 6	63	10
2	$PhCF_3$	5	97 : 3	66	11
3	$PhCF_3$	10	98 : 2	57	12
4	MeCN	0	98 : 2	73	8
5	MeCN	5	99 : 1	68	7



8
thd

[a]Yields were obtained by ^1H NMR spectroscopy with mesitylene as the internal standard.

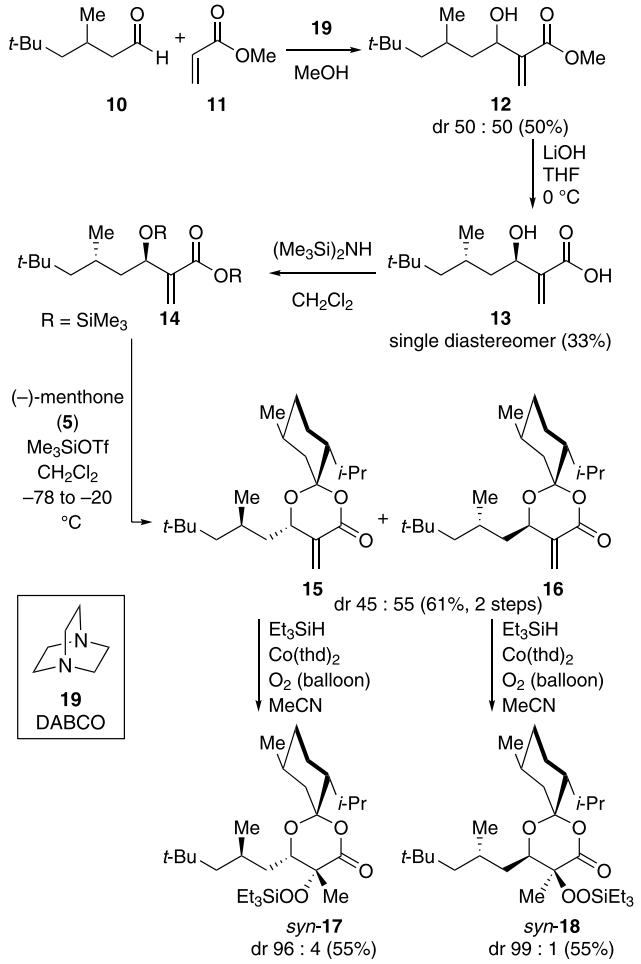
peroxide *syn*-**7** while maintaining high diastereoselectivity, even without $PhSiH_3$. Because the addition of 5 mol % of $PhSiH_3$ resulted in lower yields (entry 5), this additive was excluded from the optimal conditions (entry 4).

The purification method also required optimization. The use of $Co(thd)_2$ in cobalt-mediated peroxidation reactions results in the formation of significant quantities of cobalt-containing impurities that are difficult to separate from the desired product.[24] The use of high surface-area silica (Davisil-grade) was critical for the separation of the major silyl peroxide from the cobalt-containing impurities. After one purification, the product was isolated without residual cobalt-containing impurities, as evidenced by ^1H NMR spectroscopy and visual inspection of the resulting white solid. Purification using standard-grade silica gel caused significant decomposition of the product,[15] likely due to an acid-catalyzed[25] degradation pathway that formed methyl ketone **9** (Figure 2).[26]

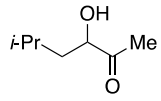
The overall sequence employed for the preparation of enantiomerically pure products from racemic Baylis–Hillman adducts is demonstrated in Scheme 2 for a substrate that bears a side chain similar to those found in peroxide-containing natural products.[27] Ester **12**, which was prepared from 3,5,5-trimethylhexanal (**10**) and methyl acrylate (**11**), was hydrolyzed to give the corresponding hydroxyacid **13** (dr 50:50). After recrystallization, a single diastereomer of hydroxyacid **13** was obtained in 33% yield. Silylation of hydroxyacid **13** with $(Me_3Si)_2NH$ provided compound **14**, which was immediately coupled to (−)-menthone (**5**) with catalytic quantities of trimethylsilyl trifluoromethanesulfonate (Me_3SiOTf).[10−13,28] The resulting diastereomeric lactones **15** and **16** were separated by flash chromatography.

Although the sequence was generally continued with the major diastereomer of each lactone, the minor diastereomeric lactone can also be used to prepare enantiomerically pure products. When lactones **15** and **16** were subjected separately to the optimized peroxidation conditions, the corresponding silyl peroxide products *syn*-**17** and *syn*-**18** were formed in similar diastereomeric ratios (Scheme 2). X-ray crystallographic analysis was used to establish the configuration of the major silyl peroxide product *syn*-**18**.[29] Comparison of the ^1H NMR spectra of the silyl peroxide products *syn*-**17** and *syn*-**18** showed that they shared the same relative configuration.[29] These experiments demonstrate that the configuration at the allylic stereocenter, not the menthone auxiliary, controlled the stereochemical outcome of the reaction. Torsional effects[30] during the addition of molecular O_2 to the planar, stabilized radical[31,32] likely dictate the stereochemical outcome.[15]

Scheme 2. Representative Synthesis and Peroxidation of Enantiopure Lactones[a]



[a]Peroxidation reaction conditions: alkene (**15** or **16**, 1 equiv), Et_3SiH (2 equiv), and $Co(thd)_2$ (10 mol %) in MeCN (0.3 M) under a balloon of O_2, 3 h.



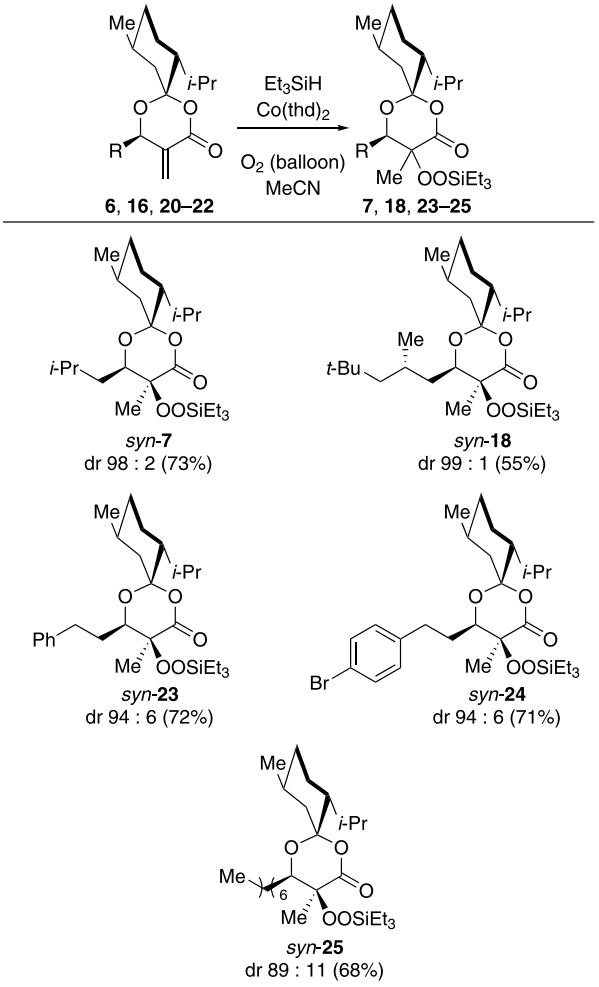
9

Figure 2. Methyl ketone decomposition product.

A range of Baylis–Hillman adduct-derived alkenes underwent this peroxidation reaction with high diastereoselectivity (Scheme 3). The diastereoselectivity of the peroxidation depended upon the size of the alkyl side chain. The peroxidations of β-branched substrates, such as **6** and **16**, occurred with the highest diastereomeric ratios (silyl peroxides **7** and **18**, dr ≥ 98:2). The reactions of lactones with less

https://dx.doi.org/10.1021/acs.orglett.0c03439
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Substrate Scope of the Diastereoselective Peroxidation Reaction[a]

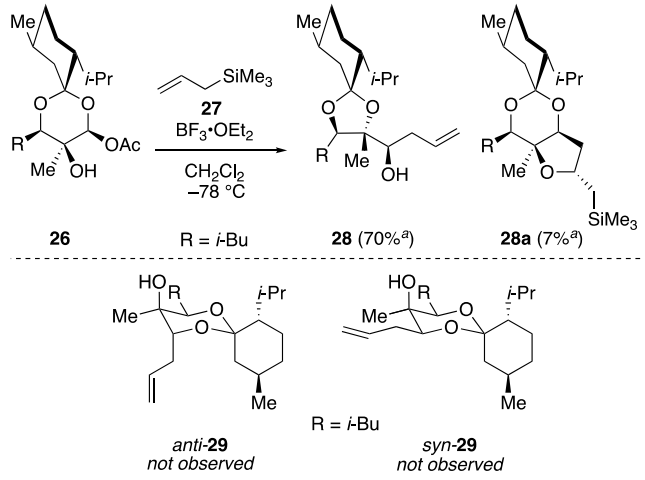


[a]Reaction conditions: alkene (**6**, **16**, **20**–**22**, 1 equiv), Et_3SiH (2 equiv), and $Co(thd)_2$ (10 mol %) in MeCN (0.3 M) under a balloon of O_2, 3 h.

substituted side chains, including lactones **20** and **21**, occurred with slightly lower selectivity (silyl peroxides **23** and **24**, dr = 94:6). The peroxidation of alkene **22**, which bears an *n*-alkyl group, was the least selective (silyl peroxide **25**, dr = 89:11). This trend suggests that the side chain may impede the approach of molecular O_2 to the radical intermediate.[15]

With two of the three stereogenic centers established, the next stage of the synthesis involved a nucleophilic substitution reaction. The success of this reaction was not assured because the unprotected hydroxyl group could complicate the substitution. One-flask reduction–acetylation[33] of the major silyl peroxylactone product (*syn*-**7**) with *i*-Bu_2AlH and Ac_2O resulted in the dioxane acetal **26**. This reduction also converted the silylperoxy group into the desired hydroxyl group. The resulting acetal underwent nucleophilic substitution using allyltrimethylsilane and $BF_3{\cdot}OEt_2$ to yield two products in a 91:9 ratio (Scheme 4). This result demonstrated that the acetal substitution reaction could be achieved in the presence of a free hydroxyl group.[34] The major product was initially assigned as the expected substitution product *anti*-**29**. NOE and long-range $^1H/^{13}C$ correlation spectra (heteronuclear multiple bond correlation, HMBC), however, were not

Scheme 4. Allylation of Reduced and Acetylated Acetal 26 and Expected Dioxanes 29

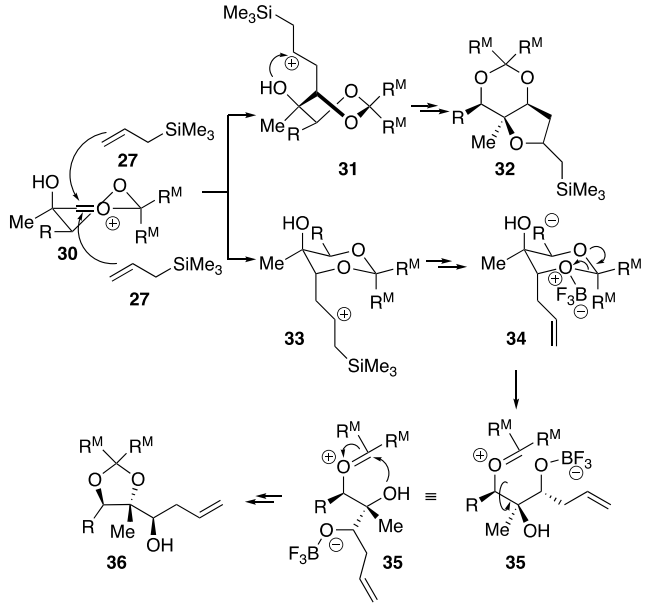


[a]Yields were obtained by ^1H NMR spectroscopy with mesitylene as the internal standard.

consistent with this connectivity. Instead, the ring-contracted product **28** was more consistent with the spectroscopic data. The minor component of the reaction mixture was not the diastereomer of **28**. Its spectra indicate that it is the product of an annulation reaction, *cis*-fused tetrahydrofuran **28a**.[35−40]

The formation of the observed products can be explained by considering the reaction mechanism (Scheme 5).[41] Upon

Scheme 5. Proposed Reaction Mechanism of the Allylation of Reduced and Acetylated Acetals[a]



[a]R^M refers to the menthone auxiliary.

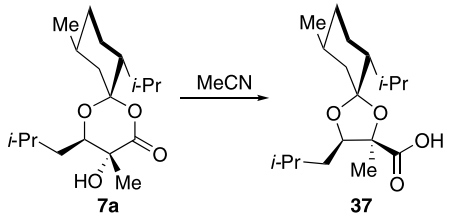
activation of the acetyl group, oxocarbenium ion **30** is formed. The nucleophile preferentially attacks from the bottom face to form the product in a chair conformer (**33**).[30,42,43] A small amount of attack from the other face of oxocarbenium ion **30** leads to the formation of an unfavorable twist-chair (**31**). The *β*-silyl carbocation **31** is trapped by the hydroxyl group, forming the *cis*-fused tetrahydrofuran **32**.

https://dx.doi.org/10.1021/acs.orglett.0c03439
Org. Lett. XXXX, XXX, XXX−XXX

The major allylation product **34**, however, is not stable to the Lewis acid because it is destabilized by a 1,3-diaxial interaction between the allyl group and the axial C−C bond of the menthone auxiliary. To alleviate the *syn*-pentane-like interaction, the Lewis acid activates the oxygen atom that is farther from the isopropyl group on the menthone auxiliary and is therefore less sterically hindered.[10,11,44] Acetal exchange leads to the favored ring-contracted product **36**. Computational studies (ωB97X-D/6-31G*) support this hypothesis: the dioxane with an axial allyl group, *anti*-**29**, was found to be 3.4 kcal/mol higher in energy than the diastereomer with an equatorial allyl group, *syn*-**29** (Scheme 4). This difference in energy is comparable to the energy inherent to a *syn*-pentane interaction, which is evident in the three-dimensional structure of dioxane *anti*-**29** (Scheme 4).[45]

The propensity to undergo rearrangement was even present in the starting lactone. Upon standing in MeCN over several weeks, alcohol **7a** rearranged to acid **37** (Scheme 6). This

Scheme 6. Rearrangement of Alcohol Side Product 7a



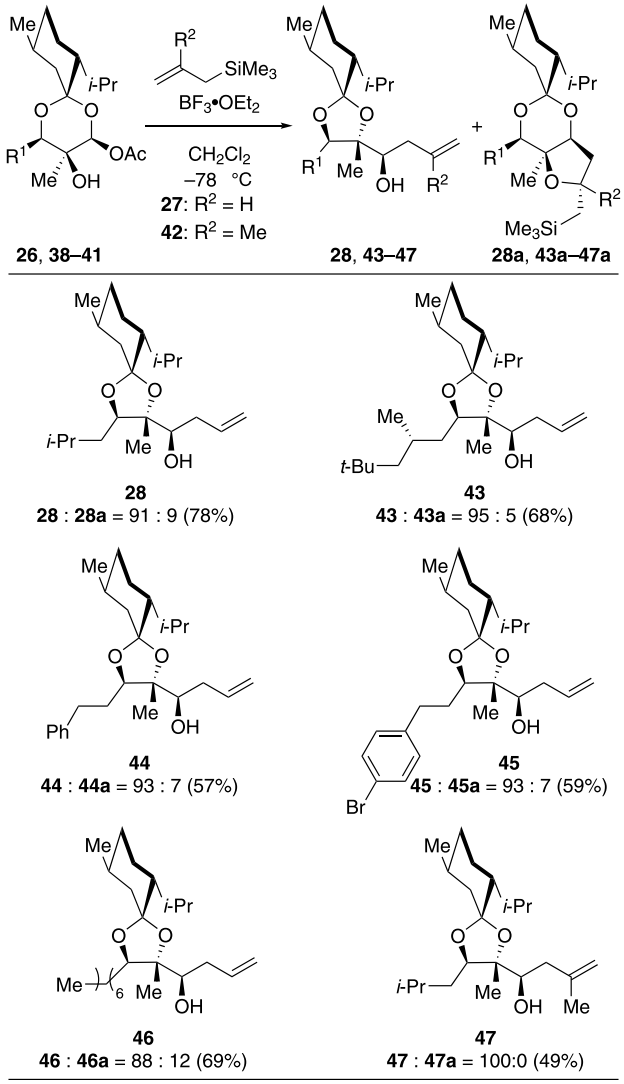
rearrangement revealed that not only 1,3-diaxial interactions contribute to the tendency for these substrates to undergo ring contraction. This destabilizing effect may be stereoelectronic in origin, considering that the hydrolysis of 1,3-dioxanes has been shown to be about 40 times faster than the hydrolysis of 1,3-dioxolanes due to improved orbital alignment during the protonation/elimination step.[46]

The stereoselective addition and rearrangement reaction was general for the other substrates. In each case, the major product of the allylations of dioxanes **26** and **38**−**41** shared the same overall structure as the product shown in Scheme 4 (**28** and **43**−**46**, Scheme 7). Methallyltrimethylsilane (**42**) also reacted with the acetylated acetal **26** to form a single diastereomer of 1,3-dioxolane **47** without formation of a side product.

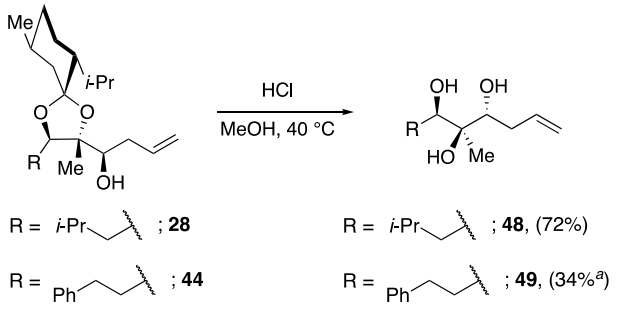
The final step of the overall synthesis of triols involves a hydrolysis reaction, which was demonstrated on allylated dioxolanes **28** and **44**.[11] Removal of the menthone auxiliary in acidic methanol yielded single stereoisomers of the triols **48** and **49** (Scheme 8).

In summary, racemic Baylis−Hillman adducts were converted to enantiopure spirolactones using a (−)-menthone (**5**) auxiliary. These lactones were peroxidized diastereoselectively. The resulting silyl peroxides were subjected to a one-flask reduction−acetylation reaction. Diastereoselective nucleophilic substitution on the resulting acetylated spiroacetals, followed by removal of the (−)-menthone (**5**) auxiliary, yielded enantiopure triols that mirror substructures present in biologically active compounds.

Scheme 7. Substrate Scope of Nucleophilic Additions



Scheme 8. Hydrolysis of the Menthone Auxiliary



[a]The low yield resulted from difficulty with purification. Details are provided as Supporting Information.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03439.

Experimental procedures, NMR spectra, and analytical data for all new compounds (PDF)

https://dx.doi.org/10.1021/acs.orglett.0c03439
Org. Lett. XXXX, XXX, XXX−XXX

Accession Codes

CCDC 2026783−2026784 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author

K. A. Woerpel − *Department of Chemistry, New York University, New York, New York 10003, United States;* orcid.org/0000-0002-8515-0301; Email: kwoerpel@nyu.edu

Author

Dylan S. Zuckerman − *Department of Chemistry, New York University, New York, New York 10003, United States;* orcid.org/0000-0002-2269-9372

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c03439

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This research was supported by the National Institute of General Medical Sciences of the National Institutes of Health (1R01GM118730). D.S.Z. thanks the NYU Department of Chemistry for support in the form of a Margaret Strauss Kramer Fellowship. NMR spectra acquired with the TCI cryoprobe, Bruker Avance 400, and 500 NMR spectrometers were supported by the National Institutes of Health (OD016343) and the National Science Foundation (CHE-01162222). The authors thank Dr. Chin Lin (NYU) for his assistance with NMR spectroscopy and mass spectrometry. The authors also thank the Molecular Design Institute of NYU for purchasing a single-crystal diffractometer and Dr. Chunhua Hu (NYU) for his assistance with data collection and structure determination.

REFERENCES

(1) Toshima, K.; Nozaki, Y.; Mukaiyama, S.; Tamai, T.; Nakata, M.; Tatsuta, K.; Kinoshita, M. Application of Highly Stereocontrolled Glycosidations Employing 2,6-Anhydro-2-thio Sugars to the Syntheses of Erythromycin A and Olivomycin A Trisaccharide. *J. Am. Chem. Soc.* **1995**, *117*, 3717.

(2) Yang, B. V.; Goldsmith, M.; Rizzi, J. P. A Novel Product from Beckmann Rearrangement of Erythromycin A 9(*E*)-oxime. *Tetrahedron Lett.* **1994**, *35*, 3025.

(3) Watanabe, Y.; Adachi, T.; Asaka, T.; Kashimura, M.; Matsunaga, T.; Morimoto, S. Chemical Modification of Erythromycins − A Facile Synthesis of Clarithromycin (6-*O*-methylerythromycin A) *via* 2'-Silylethers of Erythromycin A Derivatives. *J. Antibiot.* **1993**, *46*, 1163.

(4) Teiten, M.-H.; Mack, F.; Debbab, A.; Aly, A. H.; Dicato, M.; Proksch, P.; Diederich, M. Anticancer Effect of Altersolanol A, a Metabolite Produced by the Endophytic Fungus *Stemphylium globuliferum*, Mediated by Its Pro-Apoptotic and Anti-Invasive Potential *via* the Inhibition of NF-κB Activity. *Bioorg. Med. Chem.* **2013**, *21*, 3850.

(5) Peng, Z.-H.; Woerpel, K. A. [3 + 2] Annulation of Allylic Silanes in Acyclic Stereocontrol: Total Synthesis of (9*S*)-Dihydroerythronolide A. *J. Am. Chem. Soc.* **2003**, *125*, 6018.

(6) Peng, Z.-H.; Woerpel, K. A. Synthesis of (±)-5-*epi*-Citreoviral and (±)-Citreoviral and the Kinetic Resolution of an Allylic Silane by a [3 + 2] Annulation. *Org. Lett.* **2002**, *4*, 2945.

(7) Stork, G.; Rychnovsky, S. D. Concise Total Synthesis of (+)-(9*S*)-Dihydroerythronolide A. *J. Am. Chem. Soc.* **1987**, *109*, 1565.

(8) Stork, G.; Kahn, M. A Highly Stereoselective Osmium Tetroxide-Catalyzed Hydroxylation of γ-Hydroxy α,β-Unsaturated Esters. *Tetrahedron Lett.* **1983**, *24*, 3951.

(9) Stork, G.; Rychnovsky, S. D. Iterative Butenolide Construction of Polypropionate Chains. *J. Am. Chem. Soc.* **1987**, *109*, 1564.

(10) Harada, T.; Ikemura, Y.; Nakajima, H.; Ohnishi, J.; Oku, A. Enantiodifferentiating Functionalization of Prochiral Diols by Highly Stereoselective Ring-Cleavage Reaction of Spiroacetals Derived from *l*-Menthone with Allyltrimethylsilane-Titanium Tetrachloride. *Chem. Lett.* **1990**, *19*, 1441.

(11) Harada, T.; Kurokawa, H.; Kagamihara, Y.; Tanaka, S.; Inoue, A.; Oku, A. Stereoselective Acetalization of 1,3-Alkanediols by *l*-Menthone: Application to the Resolution of Racemic 1,3-Alkanediols and to the Determination of the Absolute Configuration of Enantiomeric 1,3-Alkanediols. *J. Org. Chem.* **1992**, *57*, 1412.

(12) Harada, T.; Kurokawa, H.; Oku, A. Resolution of 1,3-Alkanediols *via* Chiral Spiroketals Derived from *l*-Menthone. *Tetrahedron Lett.* **1987**, *28*, 4843.

(13) Harada, T.; Sakamoto, K.; Ikemura, Y.; Oku, A. Enantiodifferentiating Functionalization of *meso*-1,3-Diols *via* Spiroacetals Derived from *l*-Menthone. *Tetrahedron Lett.* **1988**, *29*, 3097.

(14) Harada, T.; Yoshida, T.; Kagamihara, Y.; Oku, A. Resolution and Asymmetric Synthesis of 3-Hydroxycarboxylic Acids by using (−)-Menthone as a Chiral Template. *J. Chem. Soc., Chem. Commun.* **1993**, 1367.

(15) Zuckerman, D. S.; Woerpel, K. A. Diastereoselective Peroxidation of Derivatives of Baylis−Hillman Adducts. *Tetrahedron* **2019**, *75*, 4118.

(16) Rychnovsky, S. D.; Sinz, C. J. Diastereoselective Synthesis of Polypropionates: Cationic Couplings of 4-Acetoxy-1,3-Dioxanes with Crotyl-Metal Reagents. *Tetrahedron Lett.* **1998**, *39*, 6811.

(17) Tokuyasu, T.; Kunikawa, S.; McCullough, K. J.; Masuyama, A.; Nojima, M. Synthesis of Cyclic Peroxides by Chemo- and Regioselective Peroxidation of Dienes with Co(II)/O_2/Et_3SiH. *J. Org. Chem.* **2005**, *70*, 251.

(18) Hurlocker, B.; Miner, M. R.; Woerpel, K. A. Synthesis of Silyl Monoperoxyketals by Regioselective Cobalt-Catalyzed Peroxidation of Silyl Enol Ethers: Application to the Synthesis of 1,2-Dioxolanes. *Org. Lett.* **2014**, *16*, 4280.

(19) Hilf, J. A.; Witthoft, L. W.; Woerpel, K. A. An S_N1-type Reaction To Form the 1,2-Dioxepane Ring: Synthesis of 10,12-Peroxycalamenene. *J. Org. Chem.* **2015**, *80*, 8262.

(20) Dai, P.; Dussault, P. H. Intramolecular Reactions of Hydroperoxides and Oxetanes: Stereoselective Synthesis of 1,2-Dioxolanes and 1,2-Dioxanes. *Org. Lett.* **2005**, *7*, 4333.

(21) Tokuyasu, T.; Kunikawa, S.; Masuyama, A.; Nojima, M. Co(III)−Alkyl Complex- and Co(III)−Alkylperoxo Complex-Catalyzed Triethylsilylperoxidation of Alkenes with Molecular Oxygen and Triethylsilane. *Org. Lett.* **2002**, *4*, 3595.

(22) Crossley, S. W. M.; Obradors, C.; Martinez, R. M.; Shenvi, R. A. Mn-, Fe-, and Co-Catalyzed Radical Hydrofunctionalizations of Olefins. *Chem. Rev.* **2016**, *116*, 8912.

(23) Bulliard, M.; Zehnder, M.; Giese, B. 1,2-Stereoinduction in Radical Reactions: Stereoselective Synthesis of 2-Alkyl-3-hydroxybutanoates. *Helv. Chim. Acta* **1991**, *74*, 1600.

(24) Palmer, C.; Morra, N. A.; Stevens, A. C.; Bajtos, B.; Machin, B. P.; Pagenkopf, B. L. Increased Yields and Simplified Purification with a Second-Generation Cobalt Catalyst for the Oxidative Formation of *trans*-THF Rings. *Org. Lett.* **2009**, *11*, 5614.

(25) Dugger, D. L.; Stanton, J. H.; Irby, B. N.; McConnell, B. L.; Cummings, W. W.; Maatman, R. W. The Exchange of Twenty Metal Ions with the Weakly Acidic Silanol Group of Silica Gel. *J. Phys. Chem.* **1964**, *68*, 757.

(26) Yaremenko, I. A.; Vil', V. A.; Demchuk, D. V.; Terent'ev, A. O. Rearrangements of Organic Peroxides and Related Processes. *Beilstein J. Org. Chem.* **2016**, *12*, 1647.
(27) Casteel, D. A. Peroxy Natural Products. *Nat. Prod. Rep.* **1992**, *9*, 289.
(28) Harada, T.; Nakajima, H.; Ohnishi, T.; Takeuchi, M.; Oku, A. A General Method for the Preparation of Enantiomerically Pure 2-Substituted Glycerol Derivatives by Utilizing *l*-Menthone as a Chiral Template. *J. Org. Chem.* **1992**, *57*, 720.
(29) Details are provided as Supporting Information.
(30) Ayala, L.; Lucero, C. G.; Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. Stereochemistry of Nucleophilic Substitution Reactions Depending upon Substituent: Evidence for Electrostatic Stabilization of Pseudoaxial Conformers of Oxocarbenium Ions by Heteroatom Substituents. *J. Am. Chem. Soc.* **2003**, *125*, 15521.
(31) Matsumoto, A.; Giese, B. Conformational Structure of Methacrylate Radicals as Studied by Electron Spin Resonance Spectroscopy: From Small Molecule Radicals to Polymer Radicals. *Macromolecules* **1996**, *29*, 3758.
(32) Lung-min, W.; Fischer, H. Electron Spin Resonance of α-(Alkoxycarbonyl)alkyl Radicals in Solution. *Helv. Chim. Acta* **1983**, *66*, 138.
(33) Dahanukar, V. H.; Rychnovsky, S. D. General Synthesis of α-Acetoxy Ethers from Esters by DIBALH Reduction and Acetylation. *J. Org. Chem.* **1996**, *61*, 8317.
(34) Hanessian, S.; Lou, B. Stereocontrolled Glycosyl Transfer Reactions with Unprotected Glycosyl Donors. *Chem. Rev.* **2000**, *100*, 4443.
(35) Knölker, H.-J.; Foitzik, N.; Graf, R.; Pannek, J.-B.; Jones, P. G. Dual Reactivity of Allyltrimethylsilane: Sakurai Reaction versus Trimethylsilylcyclopentane Annulation. *Tetrahedron* **1993**, *49*, 9955.
(36) Danheiser, R. L.; Dixon, B. R.; Gleason, R. W. Five-Membered Ring Annulation *via* Propargyl- and Allylsilanes. *J. Org. Chem.* **1992**, *57*, 6094.
(37) Organ, M. G.; Dragan, V.; Miller, M.; Froese, R. D. J.; Goddard, J. D. Sakurai Addition and Ring Annulation of Allylsilanes with α,β-Unsaturated Esters. Experimental Results and ab Initio Theoretical Predictions Examining Allylsilane Reactivity. *J. Org. Chem.* **2000**, *65*, 3666.
(38) Akiyama, T.; Yasusa, T.; Ishikawa, K.; Ozaki, S. Asymmetric Synthesis of Tetrahydrofurans by Diastereoselective [3 + 2] Cycloaddition of Allylsilanes with α-Keto Esters Bearing an Optically Active Cyclitol as a Chiral Auxiliary. *Tetrahedron Lett.* **1994**, *35*, 8401.
(39) Roberson, C. W.; Woerpel, K. A. The [3 + 2] Annulation of Allylsilanes and Chlorosulfonyl Isocyanate: Stereoselective Synthesis of 2-Pyrrolidinones. *J. Org. Chem.* **1999**, *64*, 1434.
(40) The stereochemical configuration of this product was assigned using NOE measurements. Details are provided as Supporting Information.
(41) The ring contraction observed in the nucleophilic substitution reaction is catalytic in Lewis acid. In the presence of only a single equivalent of $BF_3{\cdot}OEt_2$, 83% of the starting material **26** was consumed, and the previously observed products **28** and **28a** were observed by ^1H NMR spectroscopy.
(42) Stevens, R. V. Nucleophilic Additions to Tetrahydropyridinium Salts. Applications to Alkaloid Syntheses. *Acc. Chem. Res.* **1984**, *17*, 289.
(43) Stevens, R. V.; Lee, A. W. M. On the Stereochemistry of the Robinson-Schöpf Reaction. A Stereospecific Total Synthesis of the Ladybug Defense Alkaloids Precoccinelline and Coccinelline. *J. Am. Chem. Soc.* **1979**, *101*, 7032.
(44) The three-dimensional representations of *anti*- and *syn*-**29** in Scheme 4 illustrate the difference in steric hindrance.
(45) Wiberg, K. B.; Murcko, M. A. Energies of Alkane Rotamers. An Examination of Gauche Interactions. *J. Am. Chem. Soc.* **1988**, *110*, 8029.
(46) Li, S.; Dory, Y. L.; Deslongchamps, P. On the Relative Rate of Hydrolysis of a Series of Ketals and their Proton Affinities. *Isr. J. Chem.* **2000**, *40*, 209.

https://dx.doi.org/10.1021/acs.orglett.0c03439
Org. Lett. XXXX, XXX, XXX−XXX