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Kinetic Resolution of Racemic Aldehydes through Asymmetric Allenoate γ-Addition: Synthesis of (+)-Xylogiblactone A

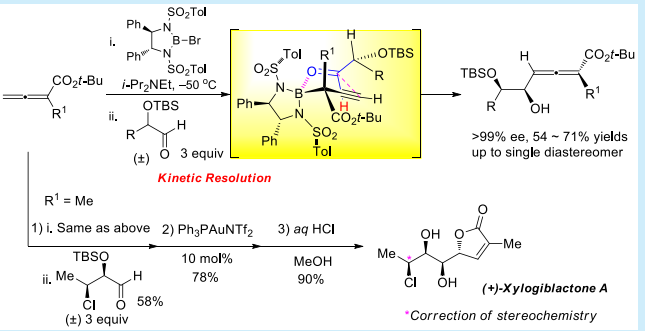
Saehansaem Park,[‡] Gyungah Pak,[‡] Changhwa Oh,[‡] Jieun Lee,[†] Jimin Kim,*[,‡] and Chan-Mo Yu*[,†]

[†]Department of Chemistry, Sungkyunkwan University, Suwon 16419, Republic of Korea

[‡]Department of Chemistry, Chonnam National University, Gwangju 61186, Republic of Korea

Supporting Information

ABSTRACT: A synthesis of (+)-xylogiblactone A has been achieved from *t*-butyl 2-methylbuta-2,3-dienoate in a linear three-step sequence. The key elements of the synthesis include a kinetic resolution of racemic 2-silyoxyaldehyde through the allenoate γ-addition to yield the γ-adduct as a single isomer and the subsequent gold catalysis to form the butenolide core. For a general method, the kinetic resolution of several racemic 2-silyloxyaldehydes is also performed to provide products in high levels of stereoselectivity with unusual *anti*-Felkin−Anh addition fashion.

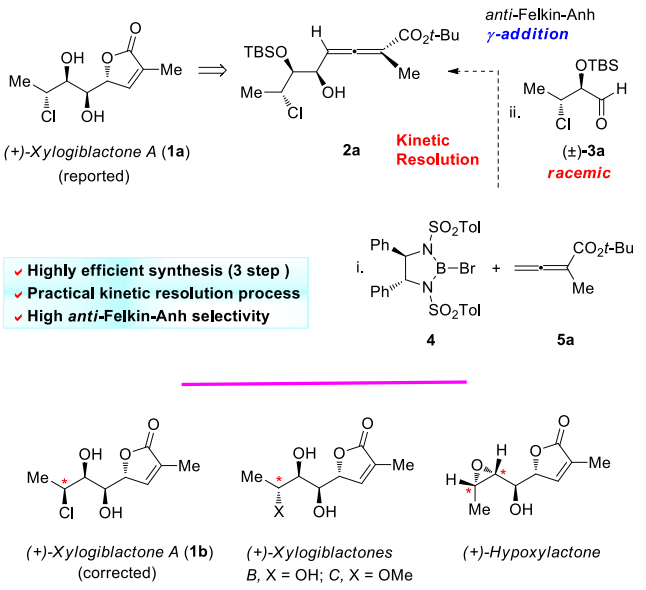


The reliable design of chemical transformations to access useful structures for target substances is an important task of current organic chemistry.[1] In this regard, control of the regio- and stereochemical pathways is one of the most essential elements of their synthetic values.[2] Accordingly, monumental discoveries of new methods with important concepts have been made in the chemical community.[3]

In the course of our research program aimed at finding new synthetic methods, we disclosed our investigations on the unprecedented γ-addition of 2-alkylallenoates to normal aldehydes to construct a unique structure with axial and central chirality.[4] The reaction usually produced a γ-adduct as a single isomer in regio- and stereochemically pure form.[5] With these observations in hand, we became quite interested in designing a synthetic route for the synthesis of naturally occurring bioactive butenolides[6] including (+)-xylogiblactone A (**1a**),[7] as shown in Scheme 1. It was envisaged that the enantioselective synthesis of **1a** can be achieved from 2-methyl allenoate **5a** within an only three-step sequence through an allenoate aldol γ-addition and gold catalysis, as depicted in Scheme 1.

The utilization of readily available racemic (±)-**3a** instead of inaccessible chiral **3a** can be more ideal to produce the key intermediate **2a** through a kinetic resolution in the allenoate γ-addition (Scheme 1). Although there are extensive studies of the relationship of chiral aldehydes in asymmetric aldol-type additions in terms of matching or mismatching cases,[8] the lack of data in the literature concerning the direct addition of a chiral enolate to racemic carbonyl units via kinetic resolution surprised us. Known methods for the kinetic resolution of racemic aldehydes in carbonyl additions are limited to specific substrates[9] despite the expected similarities of the well-established kinetic-resolution processes.[10] To achieve correct

Scheme 1. General Strategy



stereochemical relationships appearing in the structure of (+)-xylogiblactone A, it is required to obtain an addition product through an *anti*-Felkin−Anh fashion (Scheme 1).[11] On the basis of the reasonable speculation that the stereochemical model for this regio- and stereochemically specific transformation of the allenoate γ-addition is highly organized, the investigation of such an organization like a

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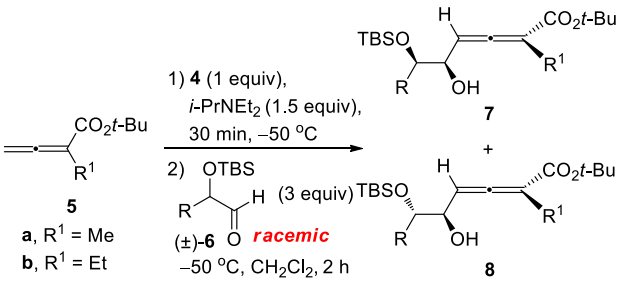
Table 1. Preliminary Investigations of Kinetic Resolution[a]



entry	R	5	dr (7:8)[b]	product	ee (%)[c]	yield (%)[d]
1	Me (**6a**)	**5a**	20:01	**7a**	>99	68
2	Me (**6a**)	**5b**	9:01	**7b**	>99	71
3	Ph (**6b**)	**5a**	5:01	**7c**	>99	54
4	$PhCH_2CH_2$ (**6c**)	**5a**	>50:1	**7d**	>99	61
5	$PhCH_2CH_2$ (**6c**)	**5b**	>50:1	**7e**	>99	58
6	Me_2CH (**6d**)	**5a**	>99:1	**7f**	>99	63
7	Me_2CH (**6d**)	**5b**	>99:1	**7g**	>99	61

[a]See the Supporting Information (SI) for the experimental details and the analysis of data. [b]Diastereomeric ratio (dr) values were determined by the analysis of ^{1}H NMR. [c]Enantiomeric excess (*ee*, %) values were determined by the analysis of the ^{1}H NMR of (R)-MTPA esters in comparison with authentic samples prepared from (*S*,*S*)-**4**. [d]Yields (%) are those of products isolated after purification by chromatography.

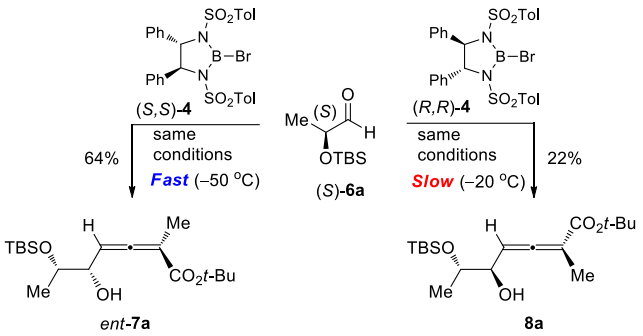
kinetic-resolution process assumes another importance. On a positive note, we envisaged that an *anti*-Felkin–Anh adduct could be a major product after the extensive analysis of cyclic stereochemical models to regulate stereoselectivity based on our previous observation.[4]

We describe herein our discovery of a conversion of 2-alkyl-allenoates **5** with racemic 2-silyoxyaldehydes (±)-**6** to afford γ-adducts with high levels of diastereoselectivity with a single enantiomer through *anti*-Felkin–Anh carbonyl π-facial selectivity. Synthetic applications to (+)-xylogiblactone A are achieved in three steps with the correction of the stereochemical relationship, which proves that chemical synthesis has an important role to play in the process of solving the molecular structure.[12] The concise synthesis of bioactive butenolides could demonstrate the utility of this synthetic tool.

With this issue in mind, our investigations began with **5a** and(±)-**6a** to judge and prove the efficiency of the kinetic resolution. The initial attempts of a γ-addition reaction of **5a** (R^1 = Me) with (*R*,*R*)-**4** in the presence of *i*-Pr_2NEt, followed by the addition of (±)-**6a** (R = Me, 3 equiv) at −78 °C indicated that the conversion to the desired **7** or **8** could not be satisfied mainly due to a lack of reactivity at low temperature. After surveying numerous conditions, the following observations emerged (entry 1, Table 1): (1) The reaction performed at −50 °C for 1 h in CH_2Cl_2 turned out to be most efficient in terms of chemical yield (68%). (2) The diastereoselectivity (dr) was confirmed to be a 20:1 (**7**/**8**) ratio, as judged by the analysis of 500 MHz ^{1}H NMR. (3) The enantiomeric excesses of products **7a** and **8a** were proved to be >99% *ee*, determined by the analysis of the ^{1}H NMR of corresponding (+)-MTPA esters in comparison with an authentic sample prepared from (*S*,*S*)-**4**.

To verify the stereochemistry of products **7a** and **8a**, the reactions of chiral (*S*)-**6a** carried out with (*R*,*R*)-**4** and (*S*,*S*)-**4** under similar conditions are shown in Scheme 2. The reaction of (*S*,*S*)-**4** with (*S*)-**6a** at −50 °C under the same procedure resulted in the formation of *ent*-**7a** in 64% yield. The formation of *ent*-**7a** was proved by a comparison of ^{1}H NMR with **7a** and corresponding (*R*)-MTPA esters. On the contrary, the reaction

Scheme 2. Allenoate γ-Additions of Chiral (*S*)-6a



with (*R*,*R*)-**4** tuned out to be extremely slow. Product **8a** was only obtained at −20 °C in 22% yield, whereas the reaction did not take place at −50 °C. These experiments clearly demonstrated that the kinetic resolution of (±)-**6a** in the allenoate γ-addition provided the *anti*-Felkin–Anh addition product as a predominant reaction route.

With the notion that this approach might lead to a general and efficient method for the kinetic resolution of racemic (±)-**6** to extend the reaction scope, we set out to explore different aldehydes, as shown in Table 1. Indeed, the method turned out to be successful with structurally diverse racemic 2-silyoxyaldehydes (±)-**6** in forming exclusively γ-addition products **7** in moderate to good yield with high levels of diastereoselectivity (except for the R = phenyl case of 5:1 dr, entry 3). It is worth noting that the reaction produced **7** as a single enantiomer of >99% *ee* for all cases in Table 1. Fortunately, the X-ray structure of **7f** was obtained to prove the stereochemistry unambiguously (Figure 1). To the best of our knowledge, the kinetic-resolution process of the allenoate γ-addition described herein represents the first instance of a highly diastereo- and enantioselective carbonyl addition reaction.

From the mechanistic perspective, two major functions for the stereoselectivity are immediately discernible in a kinetic resolution of the allenoate γ-addition. Although the exact mechanistic aspects of this transformation have not been

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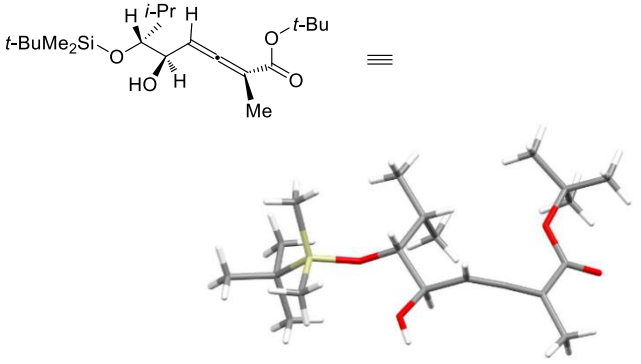
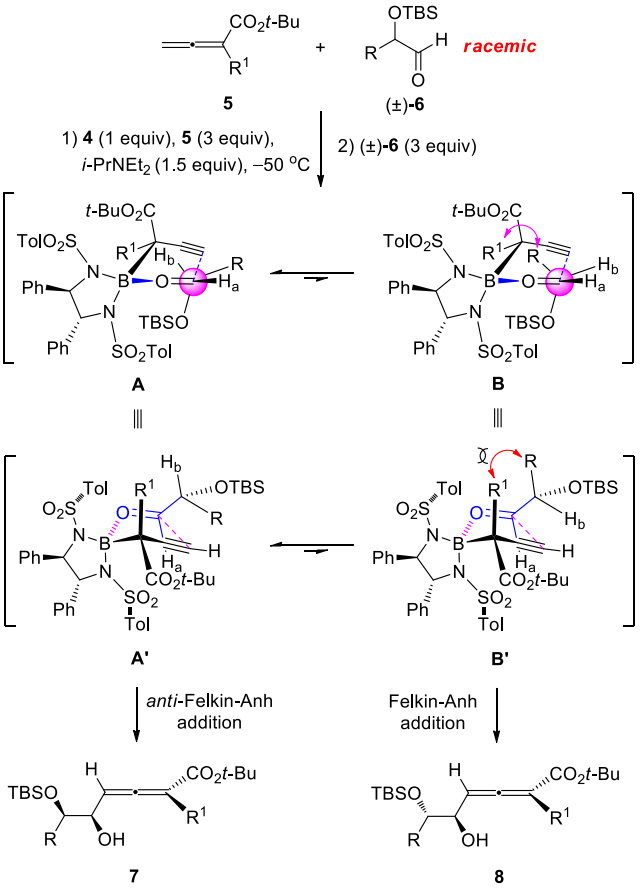


Figure 1. X-ray structure of **7f** (R = *i*-Pr).

rigorously elucidated, Scheme 3 illustrates possible stereochemical routes for *anti*-Felkin–Anh adduct **7** and Felkin–Anh

Scheme 3. Origin of Stereochemical Outcomes



adduct **8** stereoisomers on the basis of our previous observations[4] and the well-defined π-facial selectivity of racemic aldehydes toward various nucleophiles.[8] To explain the preference of the π-facial selectivity of racemic 2-silyloxyaldehydes (±)-**6** through a kinetic resolution in the allenoate γ-addition, we started to analyze two possible stereochemical models **A** and **B** to provide **7** and **8**, respectively, as shown in Scheme 3. Geometrical preference depicted as Newman projections in **A** and **B** can be explained by a stereoelectronic effect: The interaction of the $\pi^*_{C=O}$ orbital with an adjacent perpendicular σ_{C-O} orbital lowers the energy of the lowest unoccupied molecular orbital (LUMO). On the basis of this argument, conformations **A** and **B** summarize the preferred stereochemical models for two possible γ-additions along with a well-established trajectory of an approaching nucleophile under an optimum electronic effect.[11] In general, less steric demand in **B** caused by the interaction between H_a and H_b (Felkin–Anh addition) is favored over model **A** due to the more severe interaction between R and H_a (*anti*-Felkin–Anh). However, our stereochemical models have another steric demand between R^1 and H_b in **A** versus R^1 and R in **B** (Scheme 3).

Stereochemical models **A′** and **B′** with different angles more clearly illustrate the stereochemical routes for the *anti*-Felkin–Anh adduct **7** and the Felkin–Anh adduct **8**, providing major factors. The formation of the *anti*-Felkin–Anh adduct **7** via models **A** and **A′** can be explained by the steric interactions between $R^1 \leftrightarrow H_b$ and $R \leftrightarrow H_a$ in model **A**/**A′** being favored over the steric repulsion between $R^1 \leftrightarrow R$ and $H_a \leftrightarrow H_b$ in model **B**/**B′** for a kinetic resolution of (±)-**6**. Thus the origin of the stereochemical outcomes for **7** might be a subtle geometrical preference and an electronic characteristic in the *anti*-Felkin–Anh model **A**.

In light of the above results for the kinetic resolution of 2-silyloxyaldehydes (±)-**6** via the allenoate γ-addition, we next turned our attention to the application of this approach for the synthesis of naturally occurring (+)-xylogiblactone A (**1a**). Structurally unique xylogiblactone A along with B and C was isolated from the ethyl acetate extracts of the fermented broth of *Xylotumulus gibbisporus* YMJ863, which exhibits antifungal activities.[4] Structurally related butenolide (+)-hypoxylactone was isolated from a different source, the fermentation broth of the facultative marine *Hypoxylon croceum* together with a new sordarin derivative.[13]

To begin, we undertook the synthesis of (+)-xylogiblactone A (**1a**) starting from the aldehyde (±)-**3a**, readily prepared in quantity from methyl crotonate in four steps.[14] The treatment of (*R*,*R*)-**4** with **5a** at −50 °C for 30 min, followed by the addition of (±)-**3a** (3 equiv) at a somewhat higher temperature −20 °C, presumably due to a steric factor, afforded **2a** as a single stereochemical adduct in 61% yield. The stereochemistry of **2a** was confirmed by X-ray crystallography. The regiospecific cyclization of **2a** by gold catalysis[15] using $Ph_3PAuNTf_2$ (10 mol %) clearly provided the γ-butenolide core **9a** in 83% yield. The known desilylation methods for the *tert*-butyldimethylsilyl (TBS) group encountered unexpected problems such as the decomposition of the product and the partial epimerization of the γ-butenolide core.[16] Fortunately, under acidic conditions (aq. HCl in MeOH) (+)-xylogiblactone A (**1a**) was afforded in 88% yield.[17] However, ^{1}H NMR, ^{13}C NMR, and specific rotation values obtained from synthetic **1a** were not consistent with the literature values.[7]

We speculated that **1a** must be an epimer at the C*–Cl position of the natural product after the analysis of several related structures of butenolides.[9] In this regard, (±)-**3b** was prepared from methyl crotonate in five steps.[18] Reactions were performed again with (±)-**3b**, as described in Scheme 4, and we obtained **1b** as a single product (40.7% overall yield in a three-step sequence). Finally, all physical data, including the specific rotation for **1b**, were exactly consistent with the literature values. Consequently, the structure of naturally occurring (+)-xylogiblactone A was verified unambiguously to be **1b**.

In summary, we describe a highly efficient kinetic resolution of racemic 2-silyloxyaldehydes via the allenoate γ-addition

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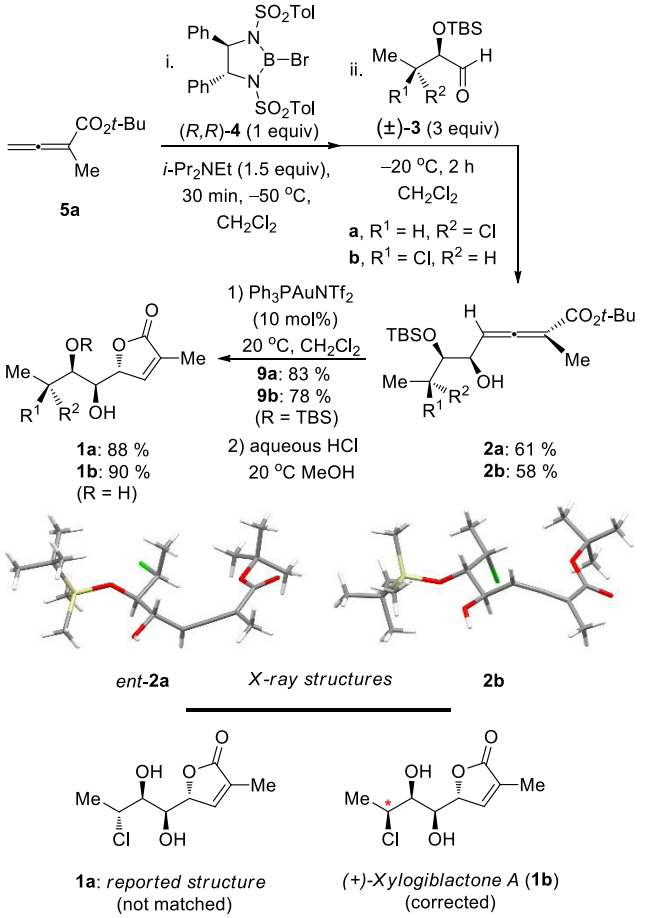
Scheme 4. Synthesis and Correction of (+)-Xylogiblactone A



reaction. We demonstrate that this reaction is general for a variety of aldehydes in an efficient way that promises to be synthetically useful. We observed that the nature of aldehydes plays a crucial role in the stereochemical outcomes for *anti*-Felkin–Anh addition. The concise synthesis of bioactive natural product (+)-xylogiblactone A clearly demonstrates the efficacy and applicability of this method. Studies are in progress for the extension of methods to other racemic aldehydes and their applications to natural product syntheses.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02982.

Detailed experimental procedures and full spectroscopic and crystal structures of *ent*-**2a**, **2b**, and **7f** (PDF)

Accession Codes

CCDC 1948595, 1948601, and 1948603 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 Authors

*E-mail: jiminkim@chonnam.ac.kr (J.K.).
*E-mail: cmyu@skku.edu (C.-M.Y.).

ORCID

Jimin Kim: 0000-0003-3223-9983
Chan-Mo Yu: 0000-0002-5213-2529

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For recent reviews, see: (a) Wender, P. A.; Miller, B. L. Synthesis at the Molecular Frontier. *Nature* **2009**, *460*, 197–201. (b) Kuttruff, C. A.; Eastgate, M. D.; Baran, P. S. Natural Product Synthesis in the Age of Scalability. *Nat. Prod. Rep.* **2014**, *31*, 419–432.

(2) For reviews, see: (a) Ma, J.-A.; Cahard, D. Towards Perfect Catalytic Asymmetric Synthesis: Dual Activation of the Electrophile and the Nucleophile. *Angew. Chem., Int. Ed.* **2004**, *43*, 4566–4583. (b) Vogl, E. M.; Gröger, H.; Shibasaki, M. Towards Perfect Asymmetric Catalysis: Additives and Cocatalysts. *Angew. Chem., Int. Ed.* **1999**, *38*, 1570–1577. (c) Sorensen, E. J. A Biochemical Messenger Made Easily. *Nature* **2012**, *489*, 214–215.

(3) For recent reviews, see: (a) Pritchett, B. P.; Stoltz, B. M. Enantioselective Palladium-Catalyzed Allylic Alkylation Reactions in the Synthesis of Aspidosperma and Structurally Related Mono-terpeneIndoleAlkaloides. *Nat. Prod. Rep.* **2018**, *35*, 559–574. (b) Sorensen, E. J. A Biochemical Messenger Made Easily. *Nature* **2012**, *489*, 214–215.

(4) Bang, J.; Oh, C.; Lee, E.; Jeong, H.; Lee, J.; Ryu, J.; Kim, J.; Yu, C.-M. A Regulation of Regiodivergent Routes for EnantioselectiveAl-dol Addition of 2-Alkyl Allenoates with Aldehydes: BBAddition versus A-Addition. *Org. Lett.* **2018**, *20*, 1521–1525.

(5) For a recent example of the migration of *O*-boroneenolate to C-borane, see: Ng, E. W. H.; Low, K.-H.; Chiu, P. Synthesis and Applications of Unquaternized C-Bound Boron Enolates. *J. Am. Chem. Soc.* **2018**, *140*, 3537–3541.

(6) For recent examples, see: Mao, B.; Fañanás-Mastral, M.; Feringa, B. L. Catalytic Asymmetric Synthesis of Butenolides and Butyr-olactones. *Chem. Rev.* **2017**, *117*, 10502–10566. (b) Montgomery, T. P.; Hassan, A.; Park, B. Y.; Krische, M. J. Enantioselective Conversion of Primary Alcohols to c-exo-Methylene –Butyrolactones via Iridium-Catalyzed C-C Bond-Forming Transfer Hydrogenation:2-(Alkoxycarbonyl)allylation. *J. Am. Chem. Soc.* **2012**, *134*, 11100–11103.

(7) Chang, Y.-C.; Lu, C.-K.; Chiang, Y.-R.; Wang, G.-J.; Ju, Y.-M.; Kuo, Y.-H.; Lee, T.-H. Diterpene Glycosides and Polyketides from *Xylotumulusgibbisporus*. *J. Nat. Prod.* **2014**, *77*, 751–757.

(8) For comprehensive discussions, see: Carreira, E. M.; Kvaerno, L. Classics in Stereoselective Synthesis. In *Carbonyl Addition Reactions*; Wiley-VCH: Weinheim, Germany, 2009; pp 19–68.

(9) (a) Tosaki, S.-Y.; Hara, K.; Gnanadesikan, V.; Morimoto, H.; Harada, S.; Sugita, M.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. Mixed La-Li Heterobimetallic Complexes for Tertiary Nitroaldol Resolution. *J. Am. Chem. Soc.* **2006**, *128*, 11776–11777. (b) Arisetti, N.; Reiser, O. Traceless Stereoinduction for the Enantiopure Synthesis of Substituted-2-Cyclopentenones. *Org. Lett.* **2015**, *17*, 94–97.

(10) (a) Ward, D. E.; Becerril-Jimenez, F.; Zahedi, M. M. Rational Design of Aldol Reactions That Proceed via Kinetic Resolution with

DOI: 10.1021/acs.orglett.9b02982
Org. Lett. XXXX, XXX, XXX–XXX

Switchable Enantioselectivity. *J. Org. Chem.* **2009**, *74*, 4447−4454. (b) Corbett, M. T.; Johnson, J. S. Dynamic Kinetic Asymmetric Transformations of t-Stereogenic–Ketoesters by Direct Aldolization. *Angew. Chem., Int. Ed.* **2014**, *53*, 255−259. (c) Bergeron-Brlek, M.; Teoh, T.; Britton, R. A Tandem Organocatalytic a-Chlorination-Aldol Reaction That Proceeds with Dynamic Kinetic Resolution: A Powerful Tool for Carbohydrate Synthesis. *Org. Lett.* **2013**, *15*, 3554−3557. (d) Ward, D. E.; Kazemeini, A. Aldol Reactions with Kinetic Resolution: Scope and Limitations of Ketal- and Dithioketal-Protected h-Ketoaldehydes. *J. Org. Chem.* **2012**, *77*, 10789−10803.

(11) (a) Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G.; Wu, Y.-D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R. J. Theory and Modeling of Stereoselective Organic Reactions. *Science* **1986**, *231*, 1108−1117. (b) Mengel, A.; Reiser, O. Around and beyond Cram's Rule. *Chem. Rev.* **1999**, *99*, 1191−1223. (c) O'Brien, A. G. Recent Advances in Acyclic Stereocontrol. *Tetrahedron* **2011**, *67*, 9639−9667.

(12) Nicolaou, K. C.; Snyder, S. A. Chasing Molecules That Were Never There: Misassigned Natural Products and the Role of Chemical Synthesis in Modern Structure Elucidation. *Angew. Chem., Int. Ed.* **2005**, *44*, 1012−1044.

(13) (a) Daferner, M.; Mensch, S.; Anke, T.; Sterner, O. Hypoxysordarin, a New Sordarin Derivative from Hypoxyloncroceum. *Z. Naturforsch., C: J. Biosci.* **1999**, *54c*, 474−480. (b) Bugni, T. S.; Ireland, C. M. Marine-Derived Fungi: a Chemically and Biologically Diverse Group of Microorganisms. *Nat. Prod. Rep.* **2004**, *21*, 143−163.

(14) (a) Akaike, H.; Horie, H.; Kato, K.; Akita, H. Total Synthesis of (+)-Asperlin. *Tetrahedron: Asymmetry* **2008**, *19*, 1100−1105. (b) Akita, H.; Kawaguchi, T.; Enoki, Y.; Oishi, T. Formal Total Synthesis of (−)-Indolmycin. *Chem. Pharm. Bull.* **1990**, *38*, 323−328.

(15) (a) Pflästerer, D.; Hashmi, A. S. K. Gold Catalysis in Total Synthesis-Recent Achievements. *Chem. Soc. Rev.* **2016**, *45*, 1331−1367. (b) Krause, N.; Winter, C. Gold-Catalyzed Nucleophilic Cyclization of Functionalized Allenes: A Powerful Access to Carbo- and Heterocycles. *Chem. Rev.* **2011**, *111*, 1994−2009.

(16) Borg, T.; Danielsson, J.; Mohiti, M.; Restorp, P.; Somfai, P. DiastereoselectiveNucleophilic Addition to Aldehydes with Polar h- and ——Substituents. *Adv. Synth. Catal.* **2011**, *353*, 2022−2036. (b) Nilewski, C.; Deprez, N. R.; Fessard, T. C.; Li, D. B.; Geisser, R. W.; Carreira, E. M. Synthesis of Undecachlorosulfolipid A: Re-evaluation of the Nominal Structure. *Angew. Chem., Int. Ed.* **2011**, *50*, 7940−7943.

(17) Kanady, J. S.; Nguyen, J. D.; Ziller, J. W.; Vanderwal, C. D. Synthesis and Characterization of All Four Diastereomers of 3,4-Dichloro-2-pentanol, Motifs Relevant to the Chlorosulfolipids. *J. Org. Chem.* **2009**, *74*, 2175−2178.

(18) (a) Huang, J.; Corey, E. J. A Mechanistically Guided Design Leads to the Synthesis of an Efficient and Practical New Reagent for the Highly Enantioselective, Catalytic Dihydroxylation of Olefins. *Org. Lett.* **2003**, *5*, 3455−3458. (b) Hoffman, R. V.; Kim, H. O. Synthesis and Reactions of 3-Hydroxy-2-nosyloxy Esters Produced by the Stereoselective Reduction of 2-Nosyloxy-3-keto Esters. *J. Org. Chem.* **1991**, *56*, 6759−6764.

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Org. Lett. XXXX, XXX, XXX−XXX