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Stereoselective Alkylation of the Vinylketene Silyl *N,O*-Acetal and Its Application to the Synthesis of Mycocerosic Acid

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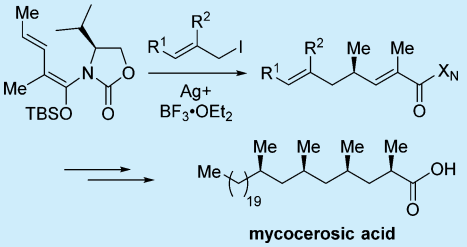
Supporting Information

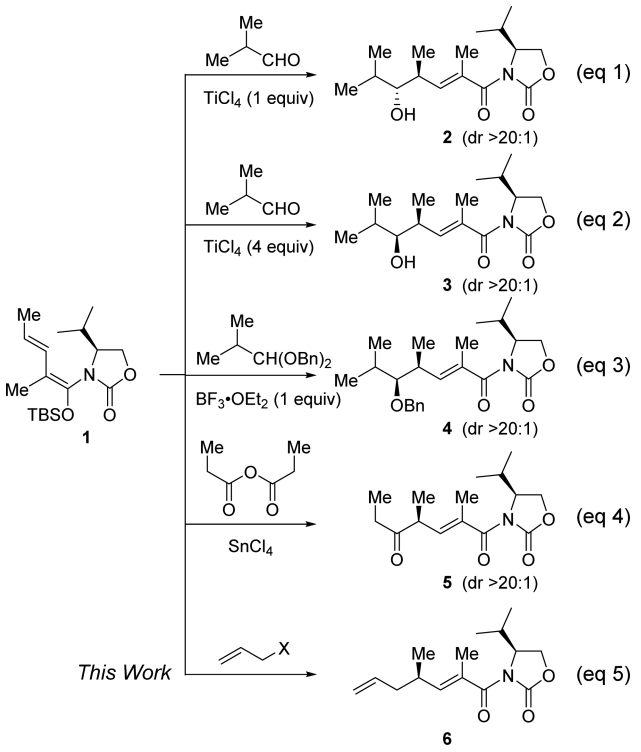
ABSTRACT: Stereoselective alkylation of the vinylketene silyl *N,O*-acetal possessing a chiral auxiliary has been achieved by using activated alkyl halides including allyl iodides, benzyl iodides, and propargyl iodide with Ag(I) ion in the presence of $BF_3{\cdot}OEt_2$. The reaction proceeded to give reduced polyketides in high stereoselectivity. The synthesis of mycocerosic acid, a component of the cell envelope of *Mycobacterium tuberculosis*, has been accomplished by this methodology. During the synthetic studies, 2-methylbenzimidazole was found to be a bulky proton source which worked in the presence of liquid ammonia.



Reduced polyketides are ubiquitous in natural products including secondary metabolites[1] and pheromones of insects.[2] Methodologies toward reduced polypropionates have been developed by several groups. Some of them are iterative routes[3] while others include organometallic reactions.[4] Recently, we reported the stereoselective and short-step synthesis of all isomers of the branched methyl groups of 2,4,6-trimethyloctanoic acid derivatives having a hydroxy group at the C5 position by using our remote asymmetric induction reaction[5] and the regio- and stereoselective reductions.[6] We applied the methodology to accomplish the first total synthesis of septoriamycin A.[6] This methodology is a powerful tool to synthesize partially reduced polyketides having a hydroxy group or a δ-lactone. However, further steps for deoxygenation are required to prepare the reduced polypropionate having no oxygen in their chains. A stereoselective alkylation of a dienolate would be a straightforward and concise method to prepare reduced polypropionates. To the best of our knowledge, there is no precedent of the asymmetric alkylation of the γ-position of a dienolate derived from α,β-unsaturated carboxylic acid.[7] Herein, we report the stereoselective alkylation of the vinylketene silyl *N,O*-acetal possessing a chiral auxiliary and its application to the synthesis of mycocerosic acid [(2*R*,4*R*,6*R*,8*R*)-2,4,6,8-tetramethyloctacosanoic acid], a component of the cell envelope of *Mycobacterium tuberculosis*.

During the course of our synthetic studies on acyclic polyketides, we have developed remote asymmetric induction reactions including the vinylogous Mukaiyama aldol reactions and the acylation reaction (Scheme 1).[5,8] These reactions showed high stereoselectivity, although the reaction position (the terminal carbon of the dienol ether) was directed far from the chiral center of the auxiliary. These reactions construct stereogenic centers and introduce the enone attaching the chiral auxiliary simultaneously, so that they realize short-step syntheses of polypropionates.[6,8c,9] Based on these results, we examined a stereoselective alkylation of silyl dienol ether **1**, which would be a straightforward method to synthesize reduced polyketides.[10]

Scheme 1. Remote Asymmetric Induction Reactions Using the *E,E*-Vinylketene Silyl *N,O*-Acetal 1



At first, we investigated various Lewis acids in the presence of allyl iodide (Table 1). Frequently used Lewis acid including

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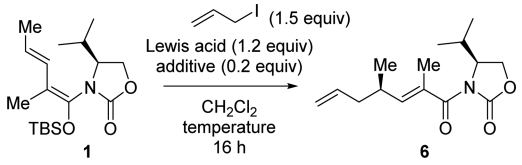
Table 1. Reaction of the *E,E*-Vinylketene Silyl *N,O*-Acetal 1 and Allyl Iodide in the Presence of Lewis Acid



entry	Lewis acid	additive	temp (°C)	yield (%)	dr[a]
1	$TiCl_4$		0	0	
2	$SnCl_4$		0	0	
3	$AlCl_3$		0	0	
4	$BF_3{\cdot}OEt_2$		rt	0	
5	$ZnBr_2$		rt	0	
6	$AgNO_3$		rt	10	10:1
7	Ag_2SO_4		rt	18	6:1
8	$AgClO_4$		0	24	18:1
9	$AgBF_4$		−20	45	10:1
10	AgOTf		−20	46	>20:1
11	AgTFA		−20	58	>20:1
12	AgTFA	$BF_3{\cdot}OEt_2$	−20	65	>20:1
13[b]	AgTFA		−20	80	>20:1
14[b]	AgTFA	$BF_3{\cdot}OEt_2$	−40	83	>20:1

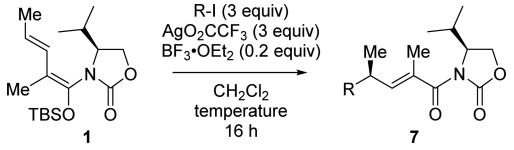
[a]The ratio was determined by 400 MHz ^{1}H NMR. [b]Allyl iodide (3 equiv), AgTFA (3 equiv), and $BF_3{\cdot}OEt_2$ (0.2 equiv) were used.

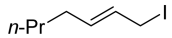
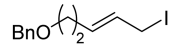
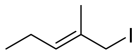
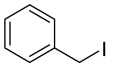
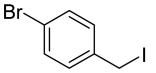
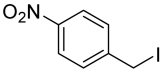
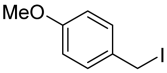
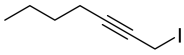
$TiCl_4$, $SnCl_4$, $AlCl_3$, $BF_3{\cdot}OEt_2$, and $ZnBr_2$ did not provide the allylated product **6** (Table 1, entries 1 to 5), while silver(I) salts[11] facilitated the reaction to give γ-adduct **6** with good to excellent stereoselectivity (entries 6−11).[12] Among silver(I) salts, silver trifluoromethanesulfonate (AgOTf) and silver trifluoroacetate (AgTFA) gave the adduct **6** in moderate yield with excellent selectivity (entries 10 and 11). No α-alkylated compound was observed. Addition of a catalytic amount of $BF_3{\cdot}OEt_2$[11a] in the presence of AgTFA gave better yield without affecting the stereoselectivity (entry 12). Increasing the amount of AgTFA and allyl iodide gave a higher yield of **6** (entry 13). After all, the reaction in the presence of $BF_3{\cdot}OEt_2$ proceeded at −40 °C to afford γ-adduct **6** in high yield with excellent regio- and stereoselectivity (entry 14). Therefore, the conditions of entry 14 were employed for the following reactions.

Next, we examined the alkylation reaction with a variety of alkyl iodides. Although *n*-Pr-I gave no adducts, activated iodides reacted with dienol ether **1** to provide γ-alkylated compounds (Table 2). Disubstituted allyl iodides gave the corresponding adducts in good yield with excellent stereoselectivity (Table 2, entries 2−4). Trisubstituted allyl iodide gave the adduct in moderate yield but stereoselectivity was high (entry 5). Benzyl iodides including benzyl iodide, *p*-bromobenzyl iodide, and *p*-nitrobenzyl iodide gave adducts in good yield with excellent selectivity (entries 6−8); however, *p*-methoxybenzyl iodide gave moderate yield with good selectivity (entry 9). In this reaction, we observed production of *p*-methoxybenzyl trifluoroacetate as a byproduct. Propargyl iodide also facilitated the reaction to give the corresponding propargyl adduct in good yield with good stereoselectivity (entry 10).

To investigate the reaction mechanism *Z*-olefin **8** was used as an electrophile in the alkylation reaction (Scheme 2). The reaction proceeded at −90 °C and provided a mixture of allylated compounds **9** and **10**. The *E*-isomer **10** was produced about the same amount as *Z*-isomer **9**. Additionally, ethyl iodoacetate did not afford the corresponding adduct (not shown in Scheme 2).

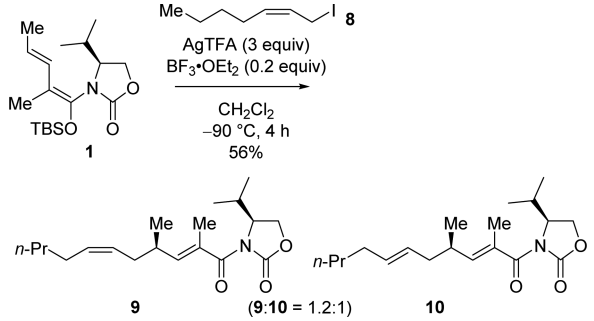
Table 2. Reaction with the *E,E*-Vinylketene Silyl *N,O*-Acetal 1 and Alkyl Halide in the Presence of AgTFA and $BF_3{\cdot}OEt_2$



entry	R-I	temperature (°C)	product	yield (%)	dr[a]
1		−78 to −40	**6**	83	>20:1
2		−78	**7a**	75	>20:1
3		−90	**7b**	77	>20:1
4		−78	**7c**	71	17:1
5		−90	**7d**	43	18:1
6[b]		−78	**7e**	76	>20:1
7		−78 to −40	**7f**	75	16:1
8		−20	**7g**	66	>20:1
9		−90	**7h**	58	9:1
10		−78	**7i**	73	13:1
11		−78 to −40	-	0	-

[a]The ratio was determined by 400 MHz ^{1}H NMR. [b]BnI (1.5 equiv) and AgTFA (1.2 equiv) were employed.

Scheme 2. Alkylation with *Z*-Allyl Iodide 8



These results suggest that the reaction involves cation intermediates.

Based on these results, we applied this alkylation reaction to natural product synthesis. Mycocerosic acid is a component of phthiocerol dimycocerosate (PDIM), a virulent factor of *Mycobacterium tuberculosis* (Figure 1).[13] Tuberculosis is a worldwide problem as a leather infection disease caused by *Mycobacterium tuberculosis*. PDIM is required for further investigation of the infection system of *M. tuberculosis*. The Minnaard group has achieved the total syntheses of mycocerosic acid and PDIM by the iterative catalytic asymmetric conjugate addition of methyl group to α,β-unsaturated thioester.[14] During the course of synthesis of polyketide compounds in our

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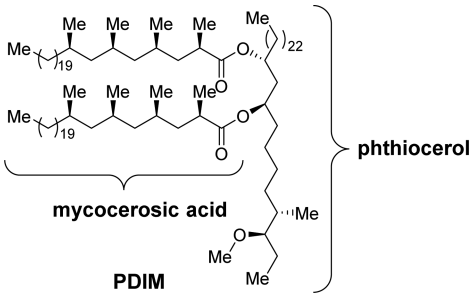
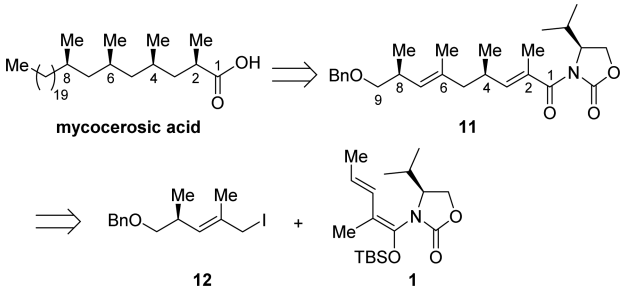


Figure 1. Structure of PDIM.

laboratory, we started the synthesis of PDIM. Herein, we report the concise synthesis of mycocerosic acid by using our stereoselective alkylation reaction. As shown in Scheme 3, we

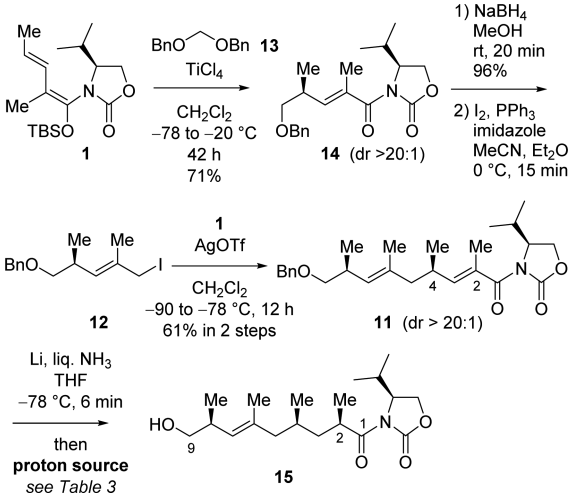
Scheme 3. Synthetic Plan toward Mycocerosic Acid



planned to synthesize mycocerosic acid by regio- and stereoselective reductions of two olefins of imide **11**, which would be synthesized by the stereoselective alkylation reaction with allyl iodide **12** and dienol ether **1**.

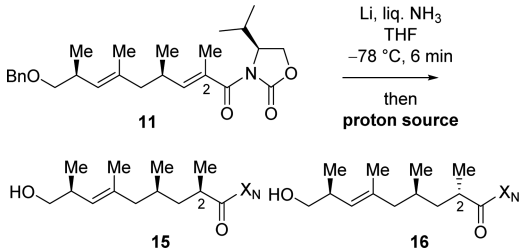
The synthesis started from the remote asymmetric induction reaction using vinylketene silyl *N*,*O*-acetal **1** and dibenzyl acetal **13** (Scheme 4). The reaction proceeded to give **14** in a

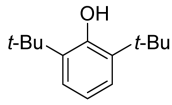
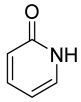
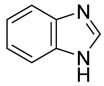
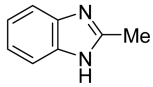
Scheme 4. Synthesis of C1−C9 Moiety of Mycocerosic Acid



stereoselective manner. Reduction of the imide to the primary alcohol, followed by Appel reaction, afforded unstable allyl iodide **12** which was immediately used in the next reaction. The reaction of **12** with vinylketene silyl *N*,*O*-acetal **1** in the presence of silver triflate gave **11** in good yield with good stereoselectivity. Subsequent Birch reduction promoted both reduction of *α*,*β*-unsaturated imide and removal of the benzyl group. In this reaction, we examined the proton source to prepare C2 position of the desired **15** (Table 3). When we added ammonium chloride

Table 3. Birch Reduction of Imide 11



entry	proton source	yield (%)	dr[a] (**15**:**16**)
1	NH_4Cl	72	2:1
2		86	2:1
3		61	4:1
4		86	12:1
5		81	>20:1

[a]The ratio was determined by 400 MHz ^{1}H NMR.

as a proton source, diastereoisomer at the C2 position (**16**) was produced as a minor product in a ratio of 2:1 (Table 3, entry 1). Although we employed 2,6-di-*tert*-butylphenol,[15] a frequently used phenol as a bulky proton source, the diastereoselectivity was not improved (entry 2). 2-Pyridone, reported by the Davies group[16] as a good proton source to react with the enolate attaching an oxazolidinone, improved the diastereoselectivity to 4:1 (entry 3). Considering the acidity of the proton source, we examined benzimidazole (pK_a 12.75[17]), which gave **15** in good yield with high stereoselectivity (entry 4). Finally, we added 2-methylbenzimidazole as a more bulky and commercially available proton source, and the desired **15** was obtained in good yield with excellent selectivity (entry 5).

After achieving the stereoselective reduction of *α*,*β*-unsaturated imide accompanied by deprotection to give primary alcohol **15**, the stereoselective reduction of the internal olefin was performed by the hydroxy group directed hydrogenation (Scheme 5). Shrock−Osborn catalyst worked very well to produce *all-syn* compound **17** in high yield with excellent stereoselectivity.[18] Oxidation of the primary alcohol was followed by Kocienski olefination to give olefin **18**, which was hydrogenated to give saturated imide **19**. Hydrolysis of the imide afforded mycocerosic acid, spectral data of which were identical to those reported previously[14a] in all respects. Therefore, mycocerosic acid has been synthesized in 10 steps from **1**.

In conclusion, we have established the remote asymmetric induction-type alkylation of vinylketene silyl *N*,*O*-acetal **1** with activated alkyl halides in the presence of silver(I) salt and boron trifluoride diethyl etherate and applied the reaction to synthesize

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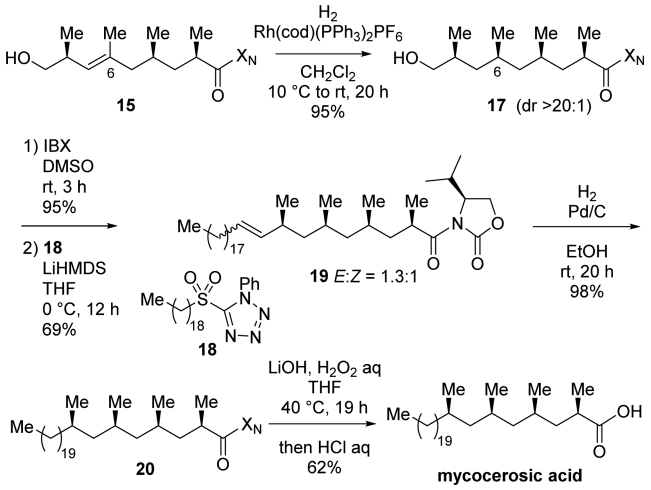
Scheme 5. Synthesis of Mycocerosic Acid



mycocerosic acid. In the Birch reduction of an unsaturated imide, 2-methylbenzimidazole was found to be an effective bulky proton source. These methods are useful to the synthesis of reduced polypropionates. Further application of these method to total synthesis of natural products is in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03422.

Experimental procedure and physical property of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Carmen Paul, M.; Ortega, M. J.; Salva, J. *Tetrahedron* **1997**, *53*, 2303−2308. (b) Kohno, J.; Nishio, M.; Sakurai, M.; Kawano, K.; Hiramatsu, H.; Kameda, N.; Kishi, N.; Yamashita, T.; Okuda, T.; Komatsubara, S. *Tetrahedron* **1999**, *55*, 7771−7786. (c) Schulze, C. J.; Bray, W. M.; Loganzo, F.; Lam, M. H.; Szal, T.; Villalobos, A.; Koehn, F. E.; Linington, R. G. *J. Nat. Prod.* **2014**, *77*, 2570−2574. (d) Tripathi, A.; Schofield, M. M.; Chlipala, G. E.; Schultz, P. J.; Yim, I.; Newmister, S. A.; Nusca, T. D.; Scaglione, J. B.; Hanna, P. C.; Tamayo-Castillo, G.; Sherman, D. H. *J. Am. Chem. Soc.* **2014**, *136*, 1579−1586.

(2) Ando, T.; Yamakawa, R. *Nat. Prod. Rep.* **2015**, *32*, 1007−1041 and references therein.

(3) (a) ter Horst, B.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun.* **2010**, *46*, 2535−2547. and references therein (b) Balieu, S.; Hallett, G. E.; Burns, M.; Bootwicha, T.; Studley, J.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2015**, *137*, 4398−4403.

(4) (a) Sugimura, T.; Sato, Y.; Im, C. Y.; Okuyama, T. *Org. Lett.* **2004**, *6*, 4439−4442. (b) Diez, P. S.; Micalizio, G. C. *Angew. Chem., Int. Ed.* **2012**, *51*, 5152−5156 and references therein.

(5) Shirokawa, S.; Kamiyama, M.; Nakamura, T.; Okada, M.; Nakazaki, A.; Hosokawa, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 13604−13605.

(6) Nakamura, T.; Harachi, M.; Kano, T.; Mukaeda, Y.; Hosokawa, S. *Org. Lett.* **2013**, *15*, 3170−3173.

(7) To the best of our knowledge, only one example of the catalytic asymmetric allylic substitution of silyl dienolates from dioxinones has been reported, which yielded allylated dioxinones. See: Chen, M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2014**, *53*, 12172−12176.

(8) (a) Mukaeda, Y.; Kato, T.; Hosokawa, S. *Org. Lett.* **2012**, *14*, 5298−5301. (b) Tsukada, H.; Mukaeda, Y.; Hosokawa, S. *Org. Lett.* **2013**, *15*, 678−681. (c) Takahashi, Y.; Otsuka, M.; Harachi, M.; Mukaeda, Y.; Hosokawa, S. *Org. Lett.* **2014**, *16*, 4106−4109.

(9) (a) Hosokawa, S. *Yuki Gosei Kagaku Kyokaishi* **2009**, *67*, 24−37. and references therein (b) Kato, T.; Sato, T.; Kashiwagi, Y.; Hosokawa, S. *Org. Lett.* **2015**, *17*, 2274−2277.

(10) For the alkylation of silyl enol ethers, see: (a) Paterson, I. *Tetrahedron Lett.* **1979**, *20*, 1519−1520. (b) Fleming, I.; Goldhill, J.; Paterson, I. *Tetrahedron Lett.* **1979**, *20*, 3209−3212. (c) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 96−108. and references therein (d) Reetz, M. T.; Walz, P.; Hubner, F.; Huttenhain, S. H.; Heimbach, H.; Schwellnus, K. *Chem. Ber.* **1984**, *117*, 322−335. (e) Maruoka, K.; Sato, J.; Yamamoto, H. *J. Am. Chem. Soc.* **1992**, *114*, 4422−4423.

(11) (a) Takagaki, H.; Yasuda, N.; Asaoka, M.; Takei, H. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1241−1242. (b) Jefford, C. W.; Sledeski, A. W.; Boukouvalas, J. *Tetrahedron Lett.* **1987**, *28*, 949−950. (c) Jefford, C. W.; Sledeski, A. W.; Boukouvalas, J. *J. Chem. Soc., Chem. Commun.* **1988**, 364−365. (d) Padwa, A.; Ishida, M. *Tetrahedron Lett.* **1991**, *32*, 5673−5675. (e) Angers, P.; Canonne, P. *Tetrahedron Lett.* **1994**, *35*, 367−370.

(12) The absolute configuration of compound **6** was determined by conversion into the known compound. See the Supporting Information.

(13) (a) Noll, H. *J. Biol. Chem.* **1957**, *224*, 149−164. (b) Polgar, N.; Smith, W. *J. Chem. Soc.* **1963**, 3081−3085. (c) Jacobs, W. R., Jr.; Cox, J. S.; Chen, B.; McNeil, M. *Nature* **1999**, *402*, 79−83. (d) Camacho, L. R.; Ensergueix, D.; Perez, E.; Gicquel, B.; Guilhot, C. *Mol. Microbiol.* **1999**, *34*, 257−267.

(14) (a) ter Horst, B.; Feringa, B. L.; Minnaard, A. J. *Chem. Commun.* **2007**, 489−491. (b) Casas-Arce, E.; ter Horst, B.; Feringa, B. L.; Minnaard, A. J. *Chem. - Eur. J.* **2008**, *14*, 4157−4159.

(15) (a) Davies, S. G.; Garrido, N. M.; Ichihara, O.; Walters, I. A. S. *J. Chem. Soc., Chem. Commun.* **1993**, 1153−1155. (b) Hanessian, S.; Reinhold, U.; Gentile, G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1881−1884.

(16) Beddow, J. E.; Davies, S. G.; Ling, K. B.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2007**, *5*, 2812−2825.

(17) Eicher, T.; Hauptmann, S.; Speicher, A. *The Chemistry of Heterocycles*; John Wiley & Sons, 2003; Chapter 5, Section 35.

(18) Evans, D. A.; Morrissey, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 3866−3868.

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