A General Solution to the Modular Synthesis of Polyketide Building Blocks by Kanemasa Hydroxy-Directed Nitrile Oxide Cycloadditions**

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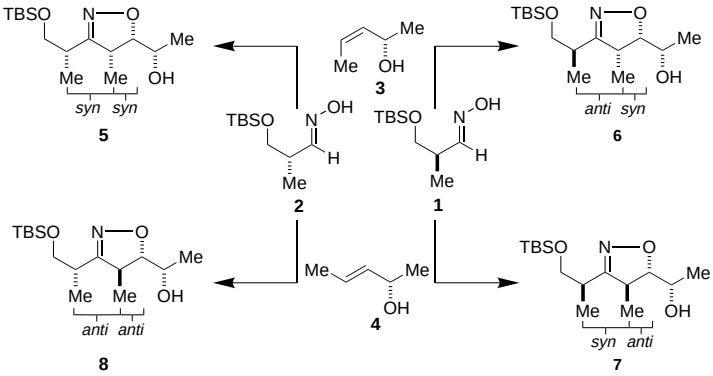
The abundance, structural diversity, and significant biological activity of polyketide-derived natural products has placed at the forefront of chemistry and biology the identification and development of processes permitting their expeditious synthesis.[1, 2] Of particular interest are methods which allow the convergent assembly of stereochemically defined building blocks as well as those which are readily tailored to provide the full spectrum of stereochemical permutations and functional group diversity inherent to these structures. Although the most widely used methods towards this goal employ carbonyl additions reactions,[3–7] numerous alternatives have been advocated.[8] One of the most intriguing proposals is Curran's and Torssell's recognition that the products of nitrile oxide cycloadditions with alkenes, namely isoxazolines, are latent aldol adducts.[9]

Herein we disclose the general, stereo- and regioselective cycloaddition of chiral nitrile oxides and allylic alcohols to provide enantiomerically pure isoxazolines. We demonstrate that this strategy permits the modular preparation of all possible protected dipropionate diastereomers with the same set of reagents and a single reaction protocol affording complex, densely functionalized polyketide building blocks **5**–**8** (Scheme 1).



Scheme 1. Single-step preparation of all possible diastereomers of latent dipropionates. TBS = tBuMe$_2$Si.

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The use of isoxazolines as masked β-hydroxy carbonyl compounds offers considerable advantages over alternative processes for the construction of aldol adducts. These include: the ability to carry out convergent syntheses through the coupling of complex olefin and nitrile oxide fragments;[10] the ease of preparation and stability of the reaction partners; the use of isoxazolines as masked aldol–adducts avoiding superfluous protecting group manipulations; the ability of this heterocycle to function as a platform for stereoselective transformations;[11, 12] and the highly stereospecific nature of the cycloadditions. Despite intense efforts in this field, however, the lack of regio- and stereochemical control in the typical nitrile oxide cycloaddition reaction, the inability to successfully employ substituted olefins, and the lack of a general procedure permitting the preparation of isoxazolines in enantiomerically pure form have to date precluded the widespread adoption of this method in polyketide synthesis.[12]

The basis for the strategy we disclose for the preparation of enantiomerically pure latent dipropionate stereotetrads is the seemingly unnoticed report by Kanemasa et al. on Mg^{II}-directed nitrile oxide cycloadditions with allylic alcohols.[13] Although these studies documented the ability of magnesium alkoxides to promote significant rate acceleration and diastereoselectivity in cycloaddition reactions, this study was limited to the use of benzonitrile oxide. Aliphatic nitrile oxides, which are considerably more capricious than their aromatic counterparts, were not investigated. Consequently, at the onset of our own efforts it was unclear whether this process would be amenable to the use of functionalized aliphatic nitrile oxides of interest to achieve a general surrogate for convergent aldol-equivalent reactions.

In the course of our studies to establish this protocol for a wide range of cycloaddition partners, we have developed convenient, broadly applicable reaction conditions for highly diastereoselective cycloadditions. This protocol permits the use of otherwise problematic aliphatic nitrile oxides by preparation of the corresponding hydroximinoyl chlorides with tBuOCl at $-78\,^{\circ}C$ and direct reaction of this solution with an allylic magnesium alkoxide. Under these conditions nitrile oxides otherwise prone to dimerization or decomposition can be employed successfully as substrates. The magnesium alkoxides, which are unwieldy to prepare as isolated salts, are conveniently generated in situ from the allylic alcohol and a Grignard reagent. The use of isopropanol as an additive improves reaction times and yields otherwise diminished by the ethereal solvent.[14] The operationally simple and remarkably versatile reaction procedure that results is tolerant of a wide range of functionality and olefin substitution [Eq. (1)]. As shown in Table 1, these conditions routinely afford the desired cycloadducts in good yields and high diastereoselectivities. Additionally, we have found this protocol to be amenable to preparative-scale syntheses (>25 mmol).

Optically active oximes **1** and **2** are conveniently and readily prepared from (*R*)- and (*S*)-3-hydroxy-2-methyl propionic acid methyl esters which are commodity chemicals available at $<1\,\$\,g^{-1}$.[15] Each of these oximes reacts smoothly with enantiomerically pure *cis*-allylic alcohol[16] **3** to give the

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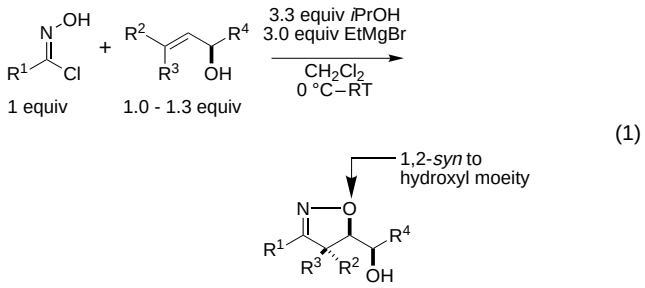
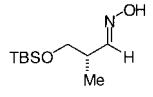
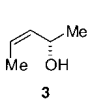
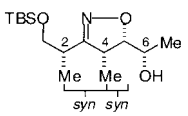
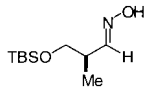
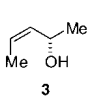
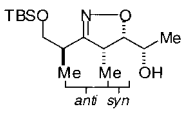
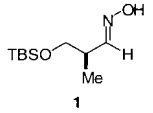
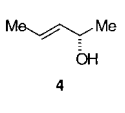
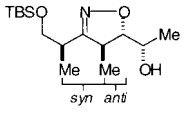
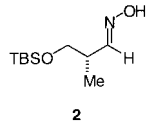
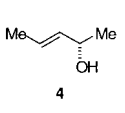
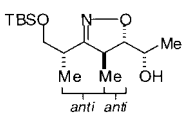
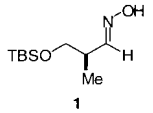
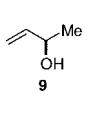
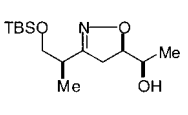


(1)

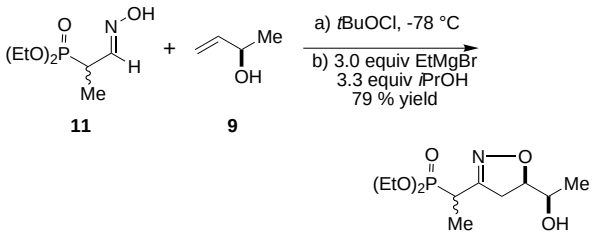
Table 1. Polypropionate building by hydroxy-directed nitrile oxide cycloadditions.[a]

Entry	Oxime	Allylic alcohol	Cycloadduct[b]	Yield [%]
1				82
2[c]				87
3				68
4				73
5				83

[a] All reactions were performed by chlorination of the oxime with 1.0 equivalents of *t*BuOCl at −78 °C followed by addition of this solution to a mixture of the allylic alcohol (1.0–1.3 equiv), isopropanol (3.3 equiv), and EtMgBr (3.0 equiv) in CH_2Cl_2 and stirring 12 h at room temperature. [b] All cycloadducts were regiochemically and stereochemically pure by ^1H and ^{13}C NMR analyses. [c] The structure of a derivative of this cycloadduct was confirmed by X-ray diffraction analysis.

corresponding cycloadducts with complete regio- and stereoselectivity (Table 1, entries 1, 2), affording 4,5-*syn* adducts.[17] Likewise, the use of the *trans*-allylic alcohol **4** provides direct access to the complementary stereochemical family of 4,5-*anti* products (Table 1, entries 3, 4). In all cases the isoxazolines were isolated as single compounds without detectable amounts of other diastereomers or regioisomers (^1H and ^{13}C NMR analyses). In contrast to carbonyl addition methodologies, we did not observe any complications due to mismatched stereochemistries of the reaction partners. Equally noteworthy is the facile application of this nitrile oxide cycloaddition to the synthesis of the methyl ketone aldol equivalents (**10**, Table 1, entry 5) which in general are particularly onerous to accomplish by carbonyl addition methodologies. The ability to selectively prepare all eight of the possible stereoisomers[18] from the same set of reagents (*cis*- or *trans*-allylic alcohols and nitrile oxides) and under a single set of reaction conditions offers great potential for the development of a general synthesis of polyketide structures.[19, 20]

Preliminary results on the use of highly functionalized nitrile oxides and olefins additionally highlight the unique features of this protocol. Despite potential complications due to its C–H acidity, phosphonate oxime **11** cleanly affords the cycloadduct **12** [Eq. (2)]; importantly, the presence of a phosphonate in the product facilitates functionalization and synthetic elaboration. Additionally, the previously unreported *C*-alkynyl nitrile oxides can successfully participate in the cycloaddition, giving adducts amenable to a wide range of transformations [Eq. (3); TMS = Me_3Si].[21]



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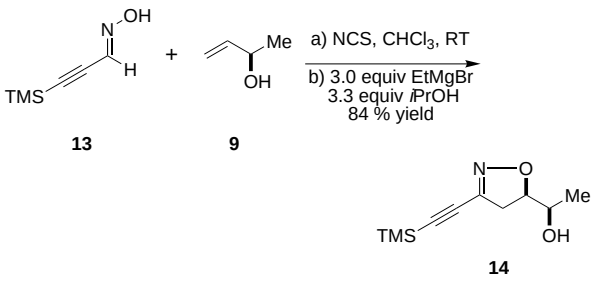
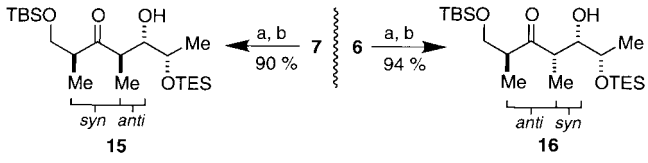


(3)

Although the optically active isoxazoline cycloadducts are in themselves useful synthetic intermediates, we have carried out their conversion to the corresponding hydroxy ketones without loss of stereochemical integrity (Scheme 2). Isoxazolines **6** and **7** undergo N–O bond cleavage and imine

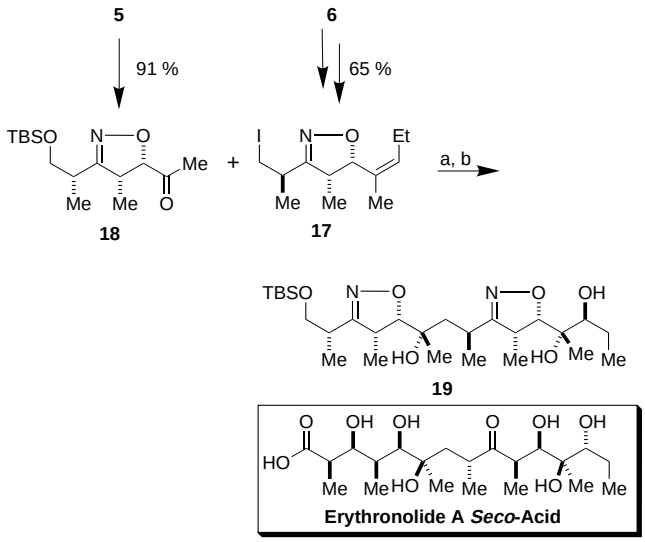


Scheme 2. Facile conversion of isoxazolines **6** and **7** to β-hydroxy ketones. a) TESCl, NEt_3, CH_2Cl_2; b) W2 Ra-Ni, $B(OH)_3$, H_2, MeOH–H_2O. TES = Et_3Si.

hydrolysis upon exposure to Curran's conditions (Raney-Ni, $B(OH)_3$),[22] furnishing β-hydroxy ketones related to those typically used for the synthesis of complex polypropionates.[23]

The free alcohol present in the cycloaddition products provides a convenient synthetic handle for further transformation to more elaborate structures. The unique ability of the enantiomerically pure isoxazolines to function as protecting groups as well as a stereochemical controlling element is one of the strengths of this method, enabling the rapid and

highly convergent assembly of complex polyketide structures through diastereoselective fragment couplings. This is illustrated with the use of **5** and **6** (Table 1) in the expeditious assembly of a representative polyproporionate. Diastereoselective coupling of **17** and **18** (d.r. > 10:1) followed by reagent-controlled catalytic dihydroxylation affords **19**, which contains the dense stereochemical array found in *ent*-erythronolide A (Scheme 3).[24]



Scheme 3. The rapid, convergent, and diastereoselective assembly of the erythronolide A stereochemical array. a) *t*BuLi, $MgBr_2$, $-78\,^{\circ}C$; then **14**, THF, $-78\,^{\circ}C$, 50%; b) AD-Mix β, $CH_3SO_2NH_2$, 65%.

In conclusion, we have described the preparation of enantiomerically pure, protected β-hydroxy ketones. The nature of this approach allows the modular preparation of the entire spectrum of functionalization and stereochemical permutations found in polyketide-derived structures. Importantly, the building blocks obtained possess the appropriate functionality for elaboration and stereoselective fragment coupling necessary for the rapid assembly of complex natural and unnatural polyketides.

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[14] A solution of EtMgBr (3.0 M in Et_2O) is used for the in situ preparation of the magnesium alkoxides.

[15] The synthesis of the corresponding aldehydes have been reported: a) A. Gaucher, J. Ollivier, J. Marguerite, R. Paugam, J. Salaün, *Can. J. Chem.* **1994**, *72*, 1312; b) in contrast to the corresponding aldehydes, which are unstable towards decomposition, we have found the oximes to be stable and amenable to prolonged storage.

[16] a) Several preparations of chiral olefins **3** and **4** have been reported in both enantiomeric forms. For our purposes they were prepared from enantiomerically pure 2-hydroxy-3-pentene, itself prepared by the method of Noyori et al.: K. Matsumura, S. Hashiguchi, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1997**, *119*, 8738; b) for another procedure, see O. Hamed, P. M. Henry, *Organometallics* **1997**, *16*, 4903.

[17] In all cases the resulting cycloadducts are formed *syn* to the existing hydroxy group. Although Kanemasa et al. have established that the cycloaddition typically proceeds in > 99:1 *syn*:*anti* diastereomer ratio, we have confirmed this sense of induction by X-ray diffraction analysis of a derivative of **6** and by a synthetic application of **12** (see ref. [11c]).

[18] The use of the readily available enantiomers of allylic alcohols **3** and **4** provides a direct entry to the enantiomeric polypropionate building blocks.

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[21] a) We speculate that the supposed tendency for alkyne-derived nitrile oxides to undergo dimerization or polymerization has precluded their prior use. b) Although oxime **13** is a readily prepared, known compound (L. P. Safronova, A. S. Medvedeva, N. S. Vyazankin, *J. Gen. Chem. USSR Engl. Transl.* **1983**, *53*, 1177) it is unstable towards prolonged storage.

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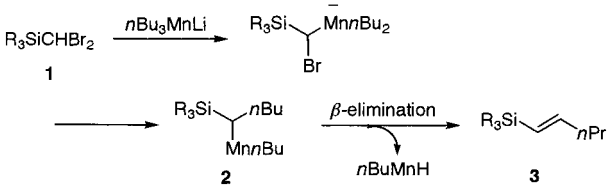
[24] Iodide **17** was prepared by oxidation of **6** followed by Wittig olefination, deprotection, and iodide formation in 65% overall yield. Ketone **18** was prepared by oxidation of **5** in 91% yield.

Alkylative Preparation of α-Silylalkylmagnesium from $R_3SiCHBr_2$ Using a Magnesate Reagent**

Junichi Kondo, Atsushi Inoue, Hiroshi Shinokubo, and Koichiro Oshima*

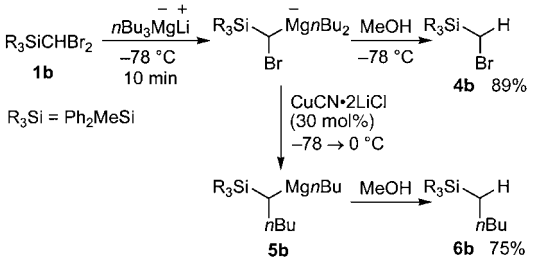
The Peterson olefination reaction utilizing α-silylalkylmetals has been established as a highly stereoselective method to prepare alkenes.[1] Therefore, α-silylalkylmetal species have gained importance as reagents for organic synthesis.[2] Methods for the preparation of α-silylalkylmetals are usually based on 1) deprotonation,[3] 2) halogen–metal exchange with metals (Li or Mg) or organometallic compounds (BuLi or RMgX),[4] or 3) addition of an organometallic species to vinylsilanes.[5] Deprotonation methods require strong bases (typically *t*BuLi) and are not effective for the deprotonation of alkylsilanes which lack an activating group (such as a carbonyl group). The requisite α-haloalkylsilanes for halogen–metal exchange reactions are not readily available; the most efficient method for their preparation is the addition of an organometallic species to a vinylsilane.

Metal carbenoid species are well-known to undergo alkylation by the action of alkylmetals.[6] Therefore, the alkylation of silyl-substituted carbenoids could be an attractive route to α-silylalkylmetals. We have previously reported the synthesis of 1-alkenylsilanes **3** from dibromomethylsilanes **1**[7] via manganese carbenoids (Scheme 1).[8] The α-silylalkylmanganese **2** formed in this reaction cannot be trapped with electrophiles because of its rapid conversion into alkenylsilane **3** by β-hydride elimination. We then investigated alternative methods to generate α-silylalkylmetallic compounds. Herein we report a copper-catalyzed alkylative preparation of α-silylalkylmagnesium compounds via trialkylmagnesium ate complexes and its application to the synthesis of α-silyl ketones.



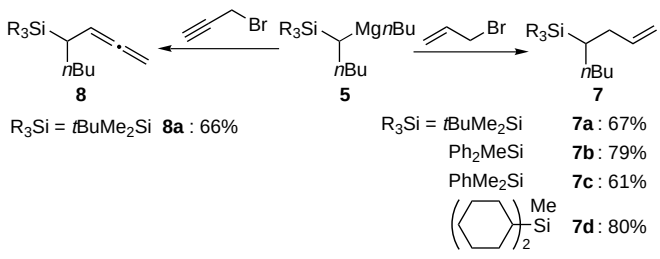
Scheme 1. Reaction of dibromomethylsilanes **1** with tributylmanganate.

We examined the reaction of dibromomethylsilane **1** with trialkylmagnesate (Scheme 2).[9, 10] Tributylmagnesate (nBu$_3$MgLi) was easily prepared by mixing butyllithium



Scheme 2. Bromine–magnesium exchange and the subsequent migration of an alkyl group.

(2.0 equiv) and butylmagnesium bromide (1.0 equiv) in THF at 0 °C. Treatment of dibromomethylsilane **1** with a magnesium ate complex induced clean bromine–magnesium exchange to provide bromomethylsilane **4** upon quenching with methanol at −78 °C.[11] Warming the reaction mixture to room temperature before quenching resulted in the migration of the butyl group to yield α-silylpentylmagnesium **5**.[12, 13] This migration was facilitated by a copper salt.[14] The addition of CuCN·2LiCl (30 mol%) to the reaction mixture induced smooth migration of the butyl group at lower temperatures (−30 °C for **1a** and 0 °C for **1b**) to afford **5** in good yield. The use of butyllithium or *n*BuMgBr instead of tributylmagnesate also induced the metalation and the subsequent butylation. Under these conditions, however, the yields of the desired products were quite low. The α-silylpentylmagnesium **5** could be trapped with allyl bromide to give **7** in good yield (Scheme 3). The reaction with propargyl bromide furnished exclusively the allenylated product **8**.



Scheme 3. Reaction of α-silylalkylmagnesium compounds **5** with allyl or propargyl bromide.

α-Silyl ketones are quite useful intermediates in organic synthesis.[15] Therefore, we undertook the preparation of α-silyl ketones using this new methodology.[16] The reaction of α-silylalkylmagnesiums **5** with various acyl chlorides was

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