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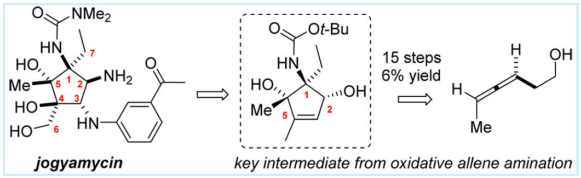
Diastereoselective Synthesis of the Aminocyclitol Core of Jogyamycin via an Allene Aziridination Strategy

Nels C. Gerstner, **Christopher S. Adams**[†], **R. David Grigg**[‡], **Maik Tretbar**, **Jared W. Rigoli**[§], and **Jennifer M. Schomaker**[*]
Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706, United States

Abstract



Oxidative allene amination provides rapid access to densely functionalized amine-containing stereotriads through highly reactive bicyclic methyleneaziridine intermediates. This strategy has been demonstrated as a viable approach for the construction of the densely functionalized aminocyclitol core of jogyamycin, a natural product with potent antiprotozoal activity. Importantly, the flexibility of oxidative allene amination will enable the syntheses of modified aminocyclitol analogues of the jogyamycin core.

Jogyamycin (**1**) was first isolated in 2012 from a culture broth of Streptomyces sp. a-WM-JG-16.2, joining a family of aminocyclopentitols that include pactamycin (**2**), cranomycin (**3**), and TM-026 (**4**) (Figure 1).[1] Jogyamycin itself exhibits potent antiprotozoal activity against important diseases including malaria and African sleeping sickness, while pactamycin and analogs have been shown to possess anticancer, antiviral, and antimicrobial activity in addition to antiprotozoal activity.[1,2] Crystal structures of pactamycin with the ribosomal 30S subunit indicate it acts as a universal inhibitor of translocation in a highly conserved region of the ribosome, explaining the wide range of biological activity exhibited by this family of molecules.[3] Subtle structural changes in the aminocyclitol motif have been shown to alter the activity of these natural products significantly.[2d–g] Further exploration of

[*]**Corresponding Author**schomakerj@chem.wisc.edu..
[†]**Present Address** Intel Corporation, Hillsboro, OR 97124, USA.
[‡]**Present Address** The Dow Chemical Company, Midland, MI 48674, USA.
[§]**Present Address** Dow AgroSciences, Indianapolis, IN 46268, USA.

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Experimental procedures and characterization for all new compounds (PDF)
NMR spectra (PDF)
Crystallographic data for **24** (CIF)
Crystallographic data for a derivative of **25** (CIF)

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the structure–activity relationship of this family of molecules may help attenuate the cytotoxicity that these compounds possess.

In addition to their potent biological activity, jogyamycin and its analogs pose a significant synthetic challenge that has drawn the interest of a number of research groups.[4] All members of this class of compounds exhibit a fully substituted cyclopentane ring system with a heteroatom present on each carbon. Three contiguous quaternary carbons, as well as the dense functionalization around the ring that includes sensitive urea and aniline moieties, have inspired various strategies to achieve the syntheses of these challenging motifs.[4] Pactamycin was the first molecule in this family to yield to total synthesis, as reported by Hanessian and co-workers in 2011 (Scheme 1).[4a] This landmark synthesis converted L-threonine into the oxazoline **5** to set the C-7 stereocenter. This stereochemical information was parlayed to the C-1 stereocenter through an aldol reaction, yielding **6** after a short sequence of steps. A series of functional group interconversions and a Ti-mediated aldol reaction/condensation led to the formation of **7**, which was eventually transformed to **2** in 21 subsequent steps.

The most recent synthesis of pactamycin was completed by the Johnson group in 2013 (Scheme 2).[4b] This fundamentally different strategy first sets the C-2 stereocenter via an asymmetric Mannich reaction between **8** and **9**, albeit with the incorrect configuration. Stereochemistry at the urea-bearing C-1, as well as at C-7, was set using a desymmetrizing β-diketone monoreduction to yield **10**. Intramolecular aldol condensation/selective epimerization of **11** delivered **12** with the correct C-2 stereochemistry, which was then carried on to **2** in 7 steps.

Two similarities between the Hanessian and Johnson syntheses are the intramolecular aldol condensations to close the cyclopentene rings and the use of the exocyclic C-7 stereocenter as the linchpin of the synthetic strategy. Hanessian used C-7 to set the important C-1 stereocenter that, in turn, was employed to set all subsequent stereocenters in the synthesis.

Johnson also engaged the C-7 stereocenter to set the correct stereochemistry at C-1 and used both C-1 and C-7 to “correct” the C-2 stereochemistry. This strategic use of the C-7 stereocenter proved vital to both Johnson and Hanessian's work.

In contrast to pactamycin, both jogyamycin **1** and **4** lack a C-7 stereocenter. It has been shown that the subtle changes of the C-1 side chain have a significant effect on the biological activity.[2c,g] Furthermore, attempts by Johnson and co-workers to cleave the alcohol at C-7 during studies directed toward analogue synthesis were unsuccessful.[2f] Therefore, we felt that it would be useful to develop a synthesis of **1** that could accommodate flexibility in the oxidation state at C-7. We also wanted to develop a strategy that would eventually be capable of delivering access to a broad range of jogyamycin analogues where the positioning, identity, and stereochemistry of heteroatoms in the cyclopentane core could be controlled at will. Finally, developing a potentially asymmetric synthesis of **1** would be an interesting challenge in the absence of the diastereocontrol provided by the handle at C-7.[4b]

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With these goals in mind, we proposed to apply our recently developed oxidative allene amination method to the construction of the cyclopentitol core of jogyamycin.[5] The retrosynthetic analysis is shown in Scheme 3. Moving from **1** to **13**, we envisaged that the alcohol at C-4 and the aniline at C-3 could arise through an epoxidation/epoxide opening sequence of **13**. The exocyclic alcohol could be installed via a selective allylic C–H oxidation and the amine at C-2 from a functional group interconversion of the 2° alcohol in the key target **14**. The cyclopentene ring of **14** would arise from a ring-closing metathesis of the diene **15**. The relative stereochemistry at C-5 was predicted to be set through an addition of isopropenyl-magnesium bromide to the carbonyl of **16** through chelation control. The olefin at C-3 of **15** could be formed through a sulfamate cleavage/elimination sequence of **16**. Amino ketone **16** would arise from the allene **17** through an enesulfamate intermediate, as described in more detail in Scheme 4.

Previous work in our group has shown that allene aziridination yields enesulfamate intermediates that serve as tunable and versatile scaffolds for further functionalization (Scheme 4).[5] By using different electrophiles, the installation of various heteroatoms at the three original allene carbons can be accomplished in a stereodefined manner in two steps. In addition to heteroatom diversity, our methods provide stereochemical diversity, as illustrated by work showing all four O/N/O triads are accessible from a single allene precursor.[5b] Effective transfer of the axial chirality of the allene to the triad enables the syntheses of enantiomerically enriched amine products. This flexibility indicated oxidative allene amination would be an ideal vehicle for not only the synthesis of **1**, but more importantly, functionally and stereochemically diverse analogues of **1** that could be employed for SAR studies of jogyamycin.

The substrate homoallenic sulfamate **19** was synthesized in one step from commercially available homoallenic alcohol **18** (Scheme 5).[6] Rh-catalyzed intramolecular aziridination of **19** is observed exclusively at the proximal double bond of the allene in a > 20:1 *E*/*Z* ratio; no aziridination of the distal bond occurs. Due to its relative instability, **20** is not isolated but is subjected to ring opening with water following a quick solvent exchange. The crude alcohol is then protected with a TBS group prior to isolation to furnish the enesulfamate **21** in good yield over the three steps with just a single purification step. This reaction sequence has been performed several times on scales up to 8 g with consistent yields obtained.

With significant quantities of **21** in hand, the next goal was to develop conditions for setting the important C-1 stereocenter. Epoxidation of **21**, followed by immediate rearrangement, yielded the imino alcohol **22** in near-quantitative yields but with low *dr* (Table 1). While the stereocenter at C-5 appeared to be of little importance, as it is later destroyed via oxidation to a ketone, this low *dr* could be transferred to the C-1 stereocenter if chelation control operates in the addition of the organometallic reagent to the imine of **22**, which was observed in prior studies. Changing the temperature had little effect on the *dr* of **22**; the greatest effect on *dr* seemed to be the age of the DMDO solution, with older solutions giving decreased *dr*. To complicate the situation, low yields were generally observed when EtMgBr was used as the nucleophile for addition to **22**, as significant competing hydride reduction was observed (Table 1, entry 1). Addition of anhydrous $CeCl_3$ or $LaCl_3$–2LiCl to the EtMgBr did not yield any improvements.[7] Reaction of vinylmagnesium bromide or

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ethynylmagnesium bromide with **22** gave slightly better yields, but the selectivity of the organometallic addition still mirrored that of the DMDO oxidation (entries 2, 3). However, cooling the ethynylmagnesium bromide solution at 0°C for approximately 30 to 60 min prior to addition of **22** resulted in both higher yields and significantly improved *dr* (entry 4). This cooling protocol resulted in the formation of considerable amounts of precipitate, leading to the hypothesis that perturbation of the Schlenk equilibrium yields formation of higher-order species that increase the propensity for attack opposite the bulky –OTBS group, irrespective of the C-5 stereocenter.[4c,5b,8] Addition of acetylides to similar imines has previously proven to be a viable strategy for introducing new functionality that can later be manipulated into the desired functional groups.[9] The stereochemical relationship between C-1 and C-2 of **24** was confirmed by X-ray crystallography (see the Supporting Information (SI) for further details).

Having set the C-1 stereocenter, the alkyne was reduced to form **16** (Scheme 6). Reaction of the carbonyl of **16** with isopropenyl MgBr in the presence of $CeCl_3$ occurred through chelation control to deliver **25** and set the C-5 stereocenter; isopropenyl MgBr alone gave only recovered starting material, likely due to enolization of the sterically encumbered ketone outcompeting the desired nucleophilic addition.[7a] The product **25** was isolated as a single diastereomer in high yield over the two steps. The relative stereochemical relationships between C1–C2–C5 in **25** were confirmed by X-ray crystallography (see the SI for further details).

Next, we set about activating the nitrogen of **25** by installing an electron-withdrawing group to render the sulfamate susceptible to nucleophilic ring opening. Unfortunately, the sulfamate nitrogen of **25** proved resistant to further functionalization using a variety of electrophiles, likely due to the large steric bulk around the nitrogen coupled with its weak nucleophilic character. As this strategy was unsuccessful, attempts to alleviate some of the steric bulk by removing the TBS group were carried out. Although subsequent reaction of the nitrogen still proved difficult, the oxazolidinone **26** could be formed using forcing conditions with triphosgene. With the nitrogen sufficiently activated, the sulfamate of **26** could be cleaved using thiophenol as a pro-nucleophile, followed by extended stirring with aqueous HCl to liberate SO_3 and yield **27**.[10] Selective oxidation to the sulfoxide, followed by thermolysis, yielded **28** and **29** as approximately a 1:1 mixture.[11] Unfortunately, all attempts to cleave the oxazolidinone were unsuccessful, as were attempts to carry out ring closing metathesis.

Due to the inability to cleave the oxazolidinone in **28** and **29**, we opted to avoid such intermediates by attempting to functionalize the less hindered nitrogen prior to addition of the isopropenyl group. The isopropenyl subunit could later be installed after cleavage of the sulfamate. Unfortunately, all attempts to functionalize the nitrogen of **16** led to recovered starting material. Attempts to install the urea directly on **24**, using dimethylcarbamoyl chloride or methyl isocyanate, led to either recovered starting material or complex mixtures of products. However, reaction of **24** with Boc_2O yielded **30** in high yield (Scheme 7). Attempts to hydrogenate **30** to the alkane yielded **16** (see Scheme 6), presumably due to the increased sterics posed by the ethyl group as compared to the alkyne. To circumvent this issue, **30** was reacted directly with thiophenol to yield **31** in near-quantitative yield.

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Oxidation to the sulfoxide permitted reduction of the alkyne under high pressures of H_2 which, after thermolysis, yielded **32** in good yield. Addition of the isopropenyl subunit to C-5 of **32** to deliver **33** initially proved more difficult than anticipated due to oxazolidinone formation with the tertiary alkoxide resulting from nucleophilic addition to the ketone. Ultimately, we found that performing the addition in the presence of $CeCl_3$–2LiCl at −40 °C slowed down the attack of the resulting alkoxide on the Boc group such that diene **33** could be isolated as the major product in >20:1 *dr*.[7b] Desilylation of **33**, followed by ring closing metathesis using the Grubbs II catalyst, delivered **14** in excellent yield. The configuration of the C-5 stereocenter was confirmed by 1D nOesy analysis, indicating that the organometallic addition to **32** proceeds through chelation control, where the C-5 stereochemistry is dictated by the configuration at C-1.

In conclusion, we have established a reliable route to a densely functionalized cyclopentene motif **14** which maps onto the core of jogyamycin. The challenging C-5 and C-1 quaternary stereocenters are set at an early stage using oxidative allene aziridination as a key step. Employing this approach allows deoxygenation to be achieved at C-7 of jogyamycin, which has proven challenging using reported routes to pactamycin. Another nice feature of this strategy is our anticipated ability to utilize different allene substrates, easily install diverse nucleophiles at either the C1 or C-2 stereocenters, introduce different side chains at C5, and manipulate oxidation of the alkene of the cyclopentene core to enable the versatile syntheses of novel analogues. Work to complete the synthesis of jogyamycin is currently underway and is focused on amination at the C-2 position, oxidation of the C-6 position, and establishment of the C-3 and C-4 stereocenters. The beautiful work carried out in the total syntheses of pactamycin will aid us in this endeavor.[4a–c]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

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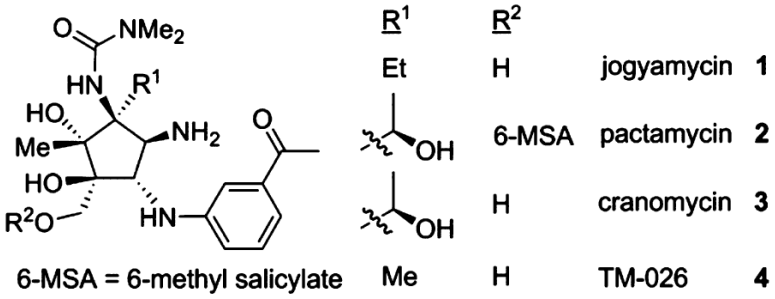
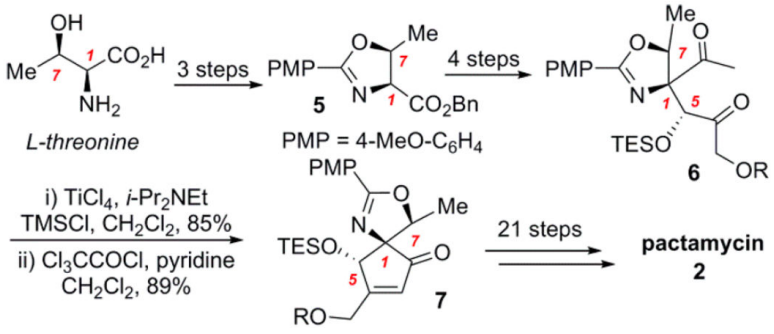


Figure 1.
Biologically active aminocyclitol natural products.



Scheme 1.
Hanessian's Approach to Pactamycin

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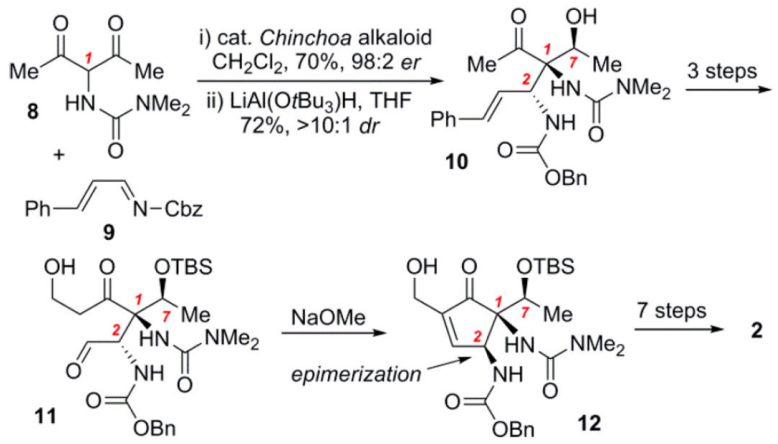

Scheme 2.
Johnson's Approach to Pactamycin

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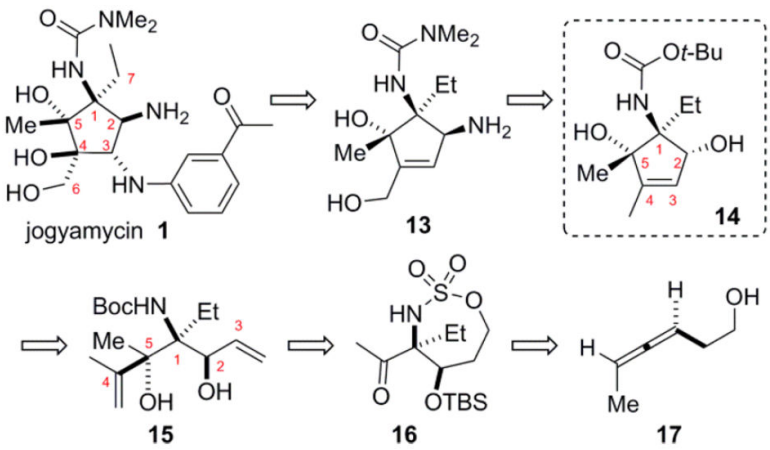
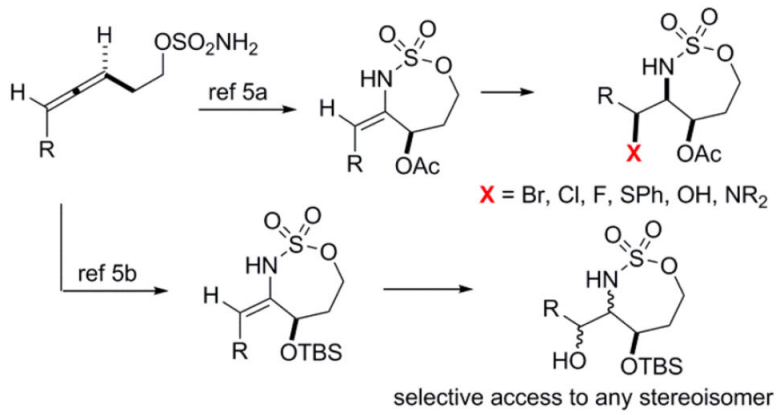


Scheme 3.

Proposed Retrosynthetic Approach towards the Jogyamycin Core Using Oxidative Allene Amination



Scheme 4.

Oxidative Allene Amination for the Synthesis of Densely Functionalized Amine Triads

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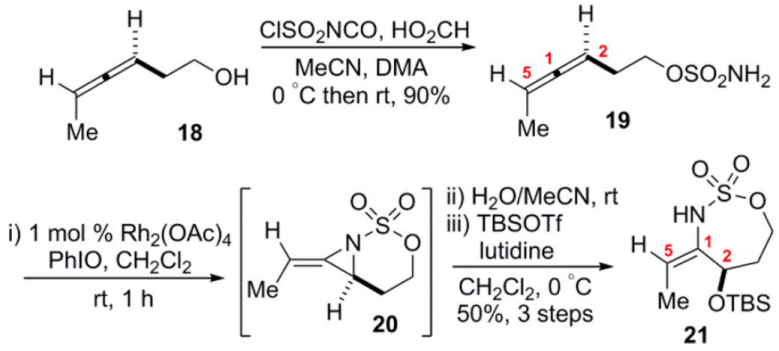

Scheme 5.
Synthesis of the Key Enesulfamate 21

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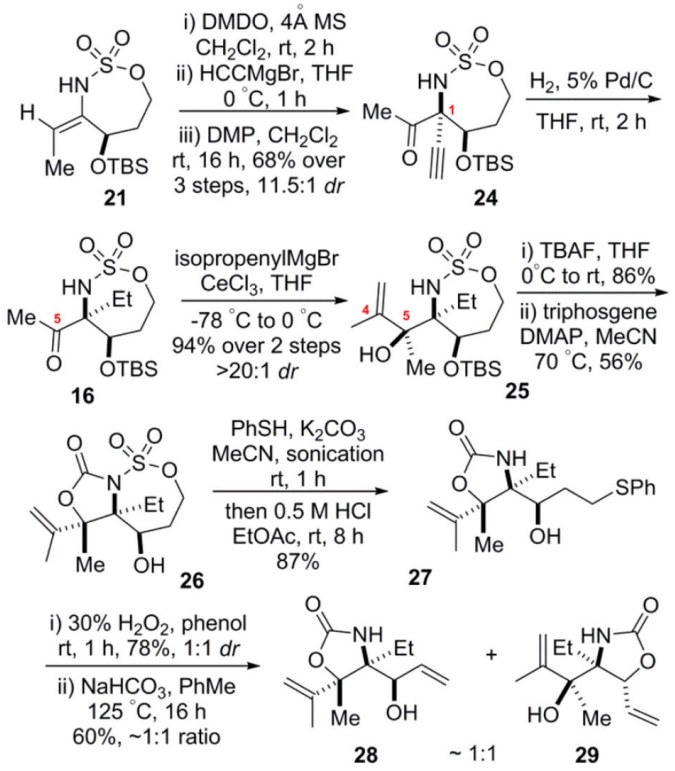
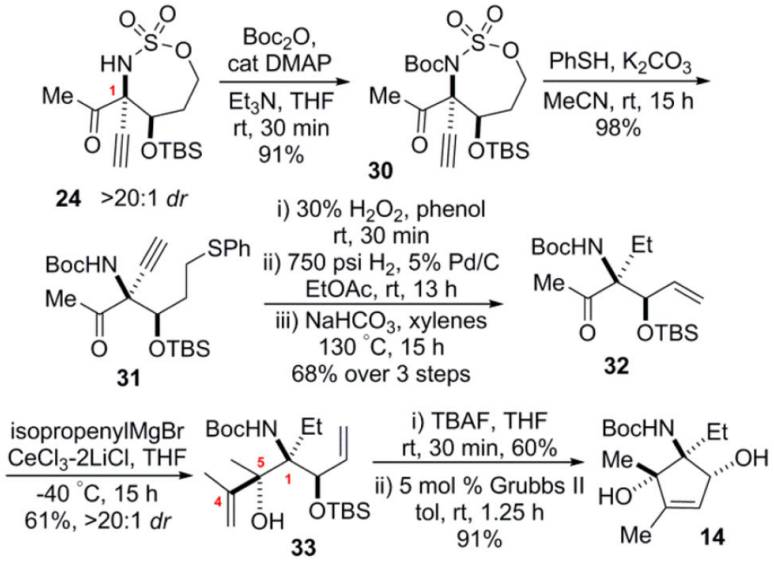


Scheme 6.
First Attempted Route to the Key Core 14



Scheme 7.
Successful Route to the Key Core Structure 14

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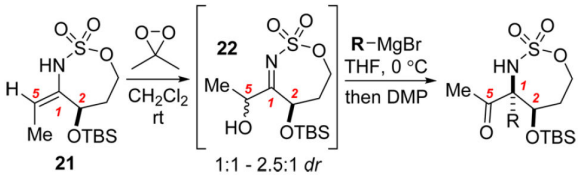
Table 1

Setting the Relative Stereochemistries at C1 and C2



entry	R	product	yield	*dr* [a]
1[b]	Et	**16**	29%[c]	1.9:1
2	$CH{=}CH_2$	**23**	45%	2:1
3	C≡CH	**24**	48%	2.3:1
4[d]	C≡CH	**24**	68%	11.5:1

[a] Based on ^{1}H NMR analysis of crude product.

[b] Reaction using CH_2Cl_2 as the solvent.

[c] Isolated yield and *dr* are before DMP oxidation. Hydride reduction was a significant byproduct observed in 18% yield.

[d] Grignard prestirred at 0 °C for 1 h prior to addition. Yield refers to isolated material.