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Pathway Development and Pilot Library Realization in Diversity-Oriented Synthesis: Exploring Ferrier and Pauson-Khand Reactions on a Glycal Template

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Summary

Through a correlation of the ability of small molecules to bind biological macromolecules and their ability to modulate cellular and organismal processes, chemistry can inform biology and vice versa. Diversity-oriented organic synthesis (DOS), which aims to provide structurally complex and diverse small molecules efficiently, can play a key role in such chemical genetic studies. Here we illustrate the trial-and-error experimentation that can refine an initial pathway-planning exercise and result eventually in an effective diversity pathway. By exploring Ferrier and Pauson-Khand reactions on a glycal template, we have developed efficient and stereoselective syntheses of tricyclic compounds. In this pathway, diversity results from the substituents and their spatial relationships about the tricyclic rings. A pilot split-pool library synthesis of 2500 tricyclic compounds highlights the use of planning considerations in DOS and a "one-bead, one-stock solution" technology platform. Additionally, it illustrates a promising synthetic pathway for future chemical genetic studies.

Introduction

A structurally complex and diverse collection of small molecules can be used for the exploration of cellular and organismal pathways in a process analogous to genetics [1, 2]. Diversity-oriented organic synthesis is an effective method for synthesizing such compounds efficiently [3], and technology platforms that provide efficient interfaces between diversity-oriented synthesis and small-molecule assays are evolving [4, 5, 6, 7]. Many small molecule-based advances in the past (for example, Carlsson's use of chlorpromazine to explore the dopamine receptor [8, 9] and Borisy's use of colchicine to discover tubulin [10, 11]) have been brought to light on a case-by-case basis. In recent years, progress has been made in developing a *systematic* way to explore biology with small molecules; this is the chemical genetic approach [1, 2].

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Diversity-oriented synthesis as a discovery engine for chemical genetics entails two distinct phases, first a "pathway development phase" and then a "library realization phase." Pathway development is aided by a planning algorithm that involves a "forward synthetic analysis," in contrast to retrosynthetic analysis used in target-oriented synthesis (TOS) [12]. Forward synthetic analysis aims to define in a small number of steps potential pathways leading to highly complex products that have highly diverse structures, ideally containing many different skeletal arrays of backbone atoms (scaffolds) [13, 14, 15]. It has been our experience that the initial analysis provides a blueprint at best for an eventual plan and that the actual plan relies heavily on much trial-and-error experimentation in the laboratory. This report describes one such study that was guided by the potential of coupling Ferrier and Pauson-Khand reactions on glycal templates [16, 17]. The plan that is now emerging reflects unforeseen reactivity patterns uncovered in the pathway development phase.

These efforts in pathway development have led us to the library realization phase. Library realization in a form that is well suited for chemical genetics has been aided by the strategy of split-pool synthesis [18, 19, 20] and the development of a technology platform that enables a "one bead-one stock solution" approach to chemical genetics [5, 6, 7]. This platform involves the use of high-capacity (500–600 μm) polystyrene macrobeads equipped with a carbon- and silicon-based linker [4]. It also involves an optimized encoding protocol [5, 7] that uses electrophoretic tags [21, 22], a bead arrayer, liquid-handling robots for preparing stock solutions [6], and one robot each for assembling high-density arrays of small molecules for either phenotypic [23, 24] or protein binding (proteomic) assays [25, 26]. We have performed all solid-phase reactions in the current study for both pathway development and pilot library realization on the high-capacity macrobeads and carbon/silicon linker (designated with the indicated symbol—an asterisk within a circle, Figure 1) [4, 5, 6, 7].

Results and Discussion

Overview

Figure 1 illustrates an overview of our pathway development studies in their present form. The pathway emerged from findings that are presented below in detail. At the outset, we envisioned performing a short and stereoselective synthesis of tricyclic compounds by coupling propargylic alcohols to glycal templates by using a reaction catalyzed by a Lewis acid (Ferrier reaction) [27] followed by $Co_2(CO)_8$-mediated annulation (Pauson-Khand reaction) [28, 29, 30]. Although both *R*- and *S*-propargylic alcohols underwent the Ferrier coupling reaction, the diastereomeric products exhibited different reactivity patterns in subsequent experiments. For example, Mannich reaction of the terminal acetylene [31, 32, 33] of the *R*-diastereomer led to products that

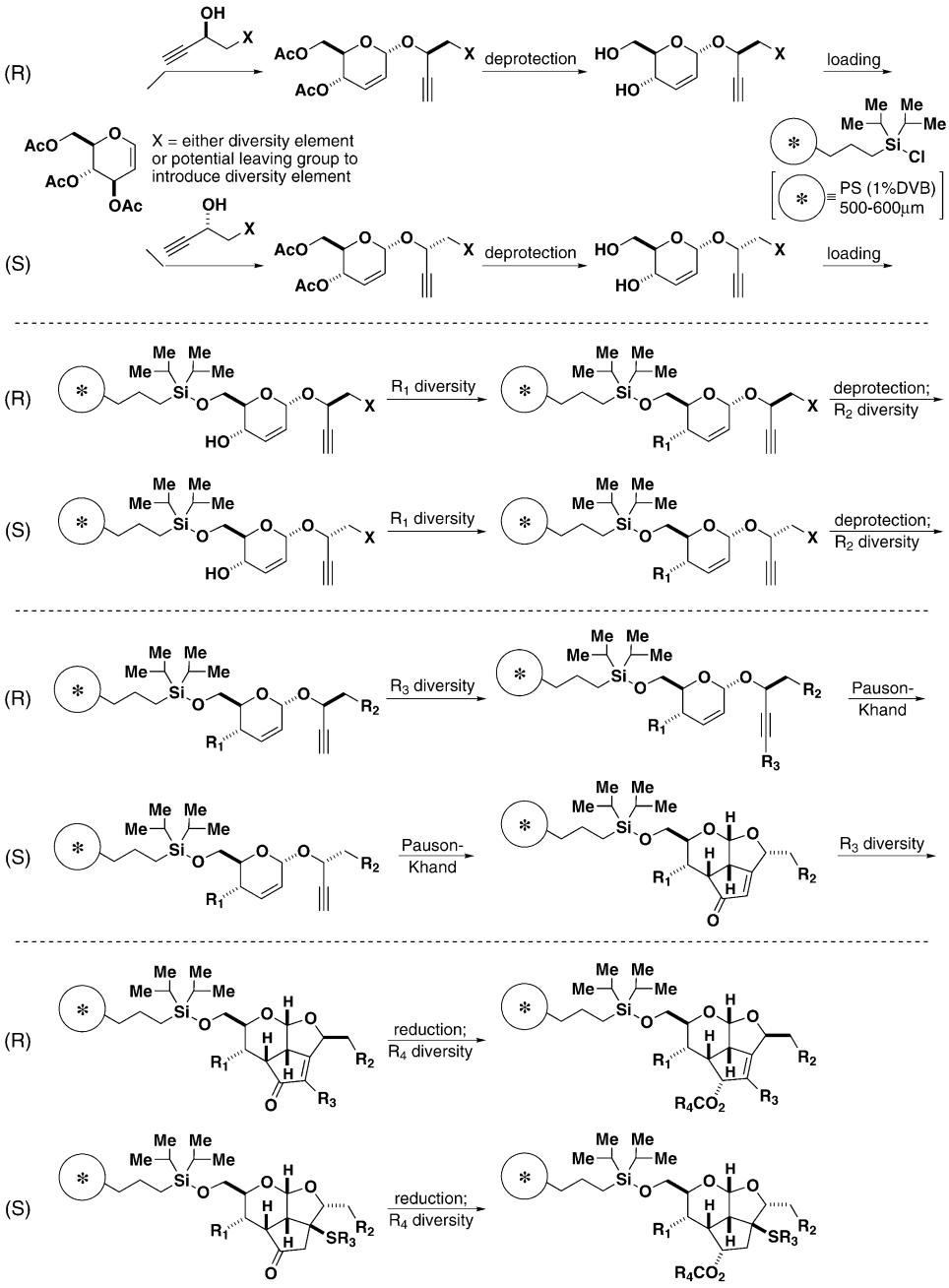


Figure 1. Diversity-Oriented Organic Synthesis: Overall Plan Emerging from Pathway Development Studies

underwent Pauson-Khand cyclizations. Analogous Mannich products in the *S*-diastereomer series failed to undergo Pauson-Khand reactions. In contrast, terminal acetylenes in the *S*-diastereomer series underwent the cyclization reaction. The resulting products underwent subsequent Michael additions, a reactivity pattern not seen with the tricyclic products derived from Mannich and Pauson-Khand reactions in the *R*-diastereomer series. Although we did not anticipate the influence of alcohol stereochemistry on subsequent reactivity, the experiments described below have defined these patterns and allow us to take advantage of them in achieving an actual library synthesis. Knowledge of these patterns allows us to plan a synthesis that should yield products varying not only in the identity of substituents derived from different building blocks but also in their spatial relationships (by varying both hybridization and stereochemistry; Figure 2).

Exploration of Key Reactions in Solution

We first studied the entire planned reaction sequence in solution before adapting it to the solid phase. Our first set of solution-phase studies led us to a stereochemistry-induced diverging reaction pathway. While attempting to annulate the Ferrier products of 3,4,6-tri-*O*-acetyl-*D*-glucal with *R*- and *S*-1-phenylpropargyl

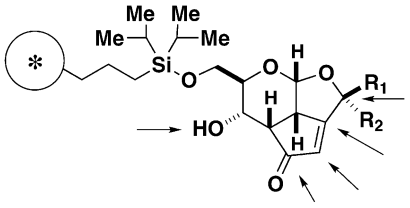


Figure 2. Diversifying Positions of a Tricyclic Scaffold Derived from *D*-Glycal

Variables include stereochemistry, the degree of hybridization, and the identity of substituents at each of the indicated sites.

alcohols, we noticed that only the Ferrier product derived from the *R*-enantiomer undergoes the Pauson-Khand reaction, whereas the one derived from the *S*-enantiomer fails (data not shown). The bulky *endo*-oriented phenyl group probably disfavors formation of the cycloadduct because of repulsive interactions between the phenyl group and the C5 hydrogen. We guessed that insertion of a methylene group between the phenyl and the carbinol carbon would enable both diastereomers to undergo the cycloaddition, and this was indeed the case. Both *R*- and *S*-1-phenyl-3-butyn-2-ol underwent the Ferrier and Pauson-Khand reactions efficiently. Thus, our modified design included this crucial methylene, which enabled both enantiomers to undergo the cycloaddition.

We were then in a position to examine the Ferrier reaction in detail because we were confident that the benzyl fragment would mimic effectively the steric bulk of other replacement substituents. As shown in Figure 3, Ferrier reaction of 3,4,6-tri-*O*-acetyl-*D*-glucal with *R*-1-phenyl-3-butyn-2-ol (**1R**) catalyzed by $BF_3{\cdot}OEt_2$ or trifluoromethanesulfonic acid proceeded stereoselectively to afford the α-anomer **2**, whereas Ferrier reaction with the *S*-enantiomer **1S** gave a mixture of α and β anomers **3** ($\alpha{:}\beta$ = 4:1). This selectivity pattern of Ferrier reactions was also observed with other enantiomeric pairs of propargylic alcohols; the stereoselectivity of Ferrier reactions of 6-*O*-silyl-protected glucals with the *S*-enantiomer **1S**, both in solution and on the solid phase, decreased to $\alpha{:}\beta$ = 1.5–2:1 when Lewis acid [27] or iodine were used as activators [34, 35]. This lack of selectivity is incompatible with our plans for library realization. It suggested that the Ferrier reactions should be carried out in solution, prior to the loading of initial substrates onto the macrobeads, in order to obtain the desired α-anomer by purification.

We next examined the Pauson-Khand reaction for the influence of substituents attached to the remote end of the alkyne. The terminal alkyne can facilitate "reaction-based" diversity. *N*,*N*-dialkylaminomethyl and aromatic moieties can be introduced by Mannich [31, 32, 33] and Sonogashira reactions [36, 37], respectively, and the resulting 1,6-enynes can undergo Pauson-Khand reactions. All three reactions have been reported on the solid phase, but only on small-diameter beads (approximately 50–100 μm) [38, 39].

We investigated several methods for facilitating the Pauson-Khand reaction and found that promotion with 4-methylmorpholine-*N*-oxide in acetonitrile at room temperature gave consistently the highest yields across numerous substrates [40]. The alkynyl Mannich products of *S*-benzyl (**6**) and *R*-benzyl (**8**) substrates exhibited different reactivity patterns in the cyclization reaction. As shown in Figure 4, **6** underwent the Pauson-Khand reaction, but **8** did not. The success of the cycloaddition in the *R*-diastereomer series depended on the alkyne substituent; the *R*-isomer **2** without a terminal alkyne substituent underwent cyclization smoothly. A bulky trimethylsilyl group on the alkyne terminus in **10** thwarted the annulation. These results can be reasonably explained by the repulsive interaction present in alkyne-$Co_2(CO)_6$ complex **12**. The bulky alkyne substituent should be repulsive to the *endo*-oriented benzyl group in **12**, whereas it should not suffer from repulsive interactions with the *exo*-oriented benzyl group in complex **11** [41, 42].

The Pauson-Khand reaction products can be further diversified through a sequence of Michael addition, reduction of the ketones, and acylation of the resulting secondary alcohols. Here again we observed a diverging pattern of reactivity for the stereochemically distinct *R* and *S* series. The tricyclic enone **9** containing the *endo*-benzyl group enabled quantitative addition of ethanethiol and other thiols (but not primary or secondary amines) to the β-carbon of the enone, whereas the *exo*-benzyl group in **13** prevented addition from occurring (Figure 5). This all-or-nothing reaction pattern in the diversity step potentially allows us to pool beads containing either stereochemical series prior to the Pauson-Khand reaction step.

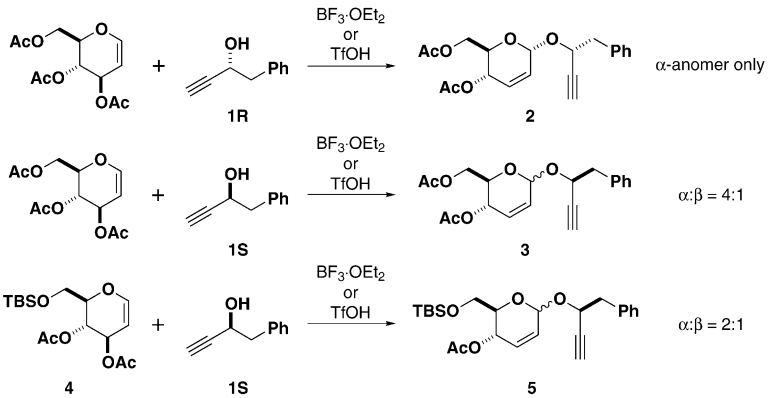


Figure 3. Stereoselectivity of Ferrier Reactions with Enantiomeric Propargylic Alcohols

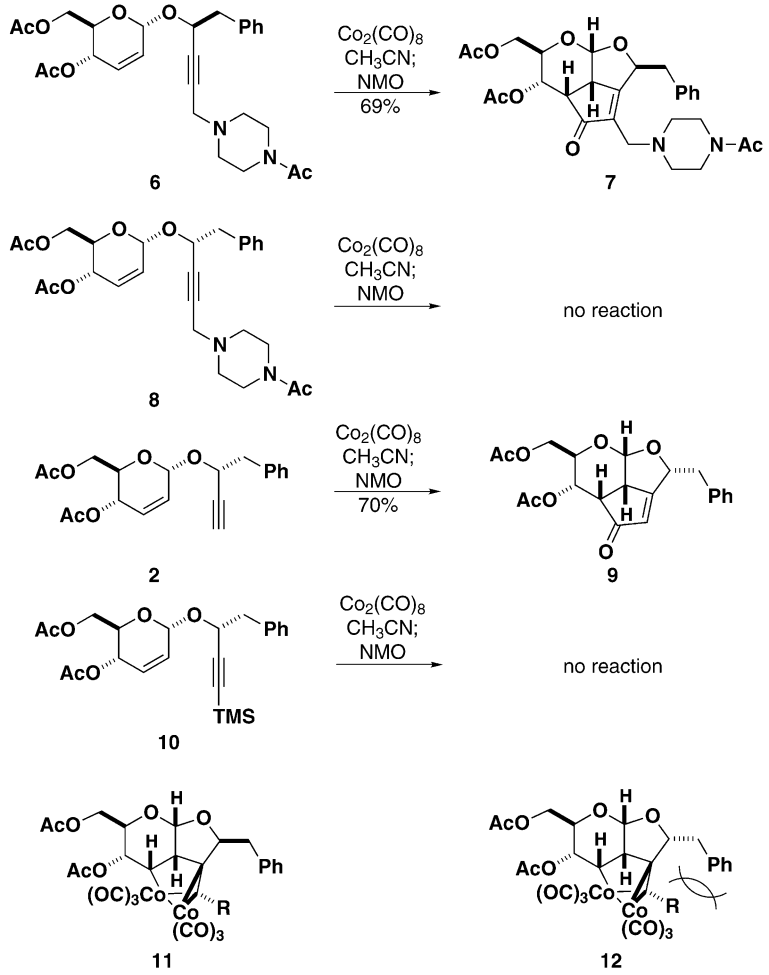


Figure 4. Reactivity Patterns Observed with Enyne Substrates in Pauson-Khand Cyclizations

The reduction of enone **7** with sodium borohydride-cerium(III) chloride [43] proceeded stereoselectively with 1,2-*exo*-hydride addition to afford an *endo*-secondary alcohol at C6. This alcohol could be acylated with benzoyl chloride to provide **15** in good yield (Figure 6). Observation of a long-range through-bond C-H coupling (HMBC) of the benzoate carbonyl to the C6 hydrogen demonstrated that O4-to-O6 acetate migration followed by benzoylation of O4 did not occur. Preliminary studies suggest that ketone **16** also undergoes this stereoselective reduction and acylation. However, transformation of the C6 carbonyl group to a hydrazone is possible only with the Michael adduct, not with the enone.

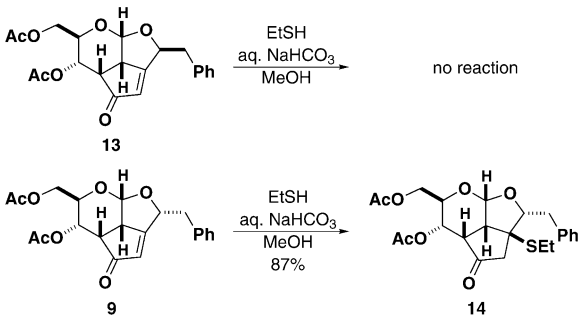


Figure 5. Reactivity Patterns of Enone Substrates in Michael Additions

Loading and Solid-Phase Reactions in the R series

Solid-phase reactions were performed on 500–600 μm polystyrene macrobeads, which we use as inexpensive microreactors in split-pool syntheses [4, 5, 6, 7]. Macrobeads bearing a carbon- and silicon-based linker, after cleavage with HF-pyridine, provide quantities of product sufficient to produce 5 mM stock solutions, which can be used in hundreds of subsequent phenotypic and proteomic assays (the "one bead-one stock solution" chemistry platform).

The initial loading element was synthesized readily according to the reactions in Figure 7. Ferrier reaction of 3,4,6-tri-*O*-acetyl-*D*-glucal with *R*-1-[(*tert*-butyldiphenylsilyl)oxy]-3-butyn-2-ol (**18R**) [44, 45] gave the pseudoglucals **19** in a α:β = 5:1 ratio. This solution-phase reaction allowed us to isolate the desired α-anomer **20** by silica gel chromatography after removal of the TBDPS group. On the other hand, Ferrier reaction with *S*-1-[(*tert*-butyldiphenylsilyl)oxy]-3-butyn-2-ol [45] proceeded stereoselectively to afford the α-anomer exclusively.

After the Ferrier reaction, the TBDPS protecting group

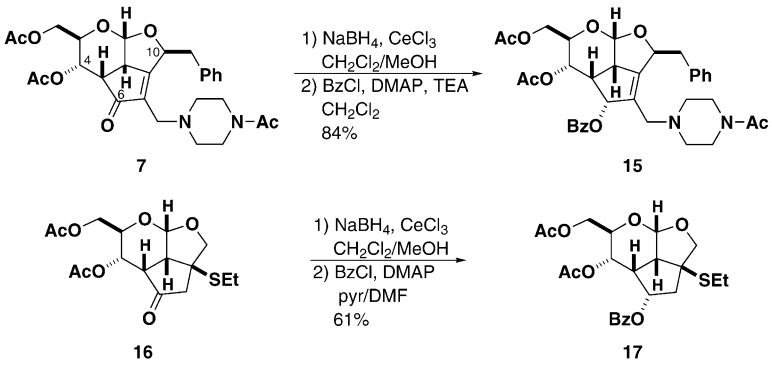


Figure 6. Ketone Reductions and Acylations

had to be converted to a protecting group that could be cleaved without affecting the solid-phase silyl ether-based linking element. The selection was a challenge because the diisopropylalkylsilyl ether linker is not stable to strongly acidic conditions. This suggested a neutral or base-cleavable protecting group. We also had to consider compatibility with electrophoretic tags, which are sensitive to strong oxidative conditions [21, 22]. To our initial surprise, we also determined that hydrophobicity was an essential property of the protecting group; this property was required to achieve high levels of loading of the hydrophilic 4,6-dihydroxypseudoglucal. Presumably, a more hydrophobic protecting group enables greater penetration of the substrate into the hydrophobic polystyrene network. We tried methylthiomethyl (MTM), bis(p-methoxyphenyl)methyl and 3,4-dimethoxybenzyl protecting groups, all of which were unsatisfactory for one reason or another. Ultimately, we found that 4-butoxybenzyl (BOB) ether **22** afforded the highly loaded beads **23.** The BOB group can be removed by standard DDQ oxidation (3 hr) and does not harm the electrophoretic encoding tags (unpublished results), which we remove with ceric ammonium nitrate.

The first solid-phase diversity step in the *R* series is the functionalization of the 4-hydroxy group of the pseudoglucal (Figure 8). Phenyl isocyanate reacted quantitatively to afford the carbamate. The BOB group was removed without incident to afford alcohol **24**, and the second diversity position was introduced. This "deprotection-functionalization" strategy for the propargylic fragment was very useful because it saved us the effort and cost of pre-preparing numerous chiral propargylic alcohols. The hydroxy group can be converted to a variety of functional groups. For example, the alcohol was converted to the triflate in CH_2Cl_2 at low temperature and, after a quick CH_2Cl_2 wash, was treated with benzyl amine to afford secondary amine **25**. Amine **25** was acetylated out of necessity. Solid-phase studies indicated that the subsequent Pauson-Khand reaction with secondary or tertiary amines at this position afforded numerous products, probably due to intramolecular amine coordination to the cobalt complex [46]. However, if the amine was acetylated, the Pauson-Khand reaction proceeded efficiently.

A third reaction-based diversity step involving the introduction of substituents to the terminal alkyne in **26** was developed. For example, the alkyne Mannich reactions were used to introduce *N,N*-dialkylaminomethyl groups, and the Sonogashira reactions were used to introduce aromatic groups. Both Mannich and Sonogashira products, **27** and **29,** respectively, undergo Pauson-Khand cyclizations successfully in this diastereomeric series. We developed new reaction conditions for this latter transformation that enabled efficient penetration of $Co_2(CO)_8$ into the resin. The first step involves formation of the alkyne-$Co_2(CO)_6$ complex, which oc-

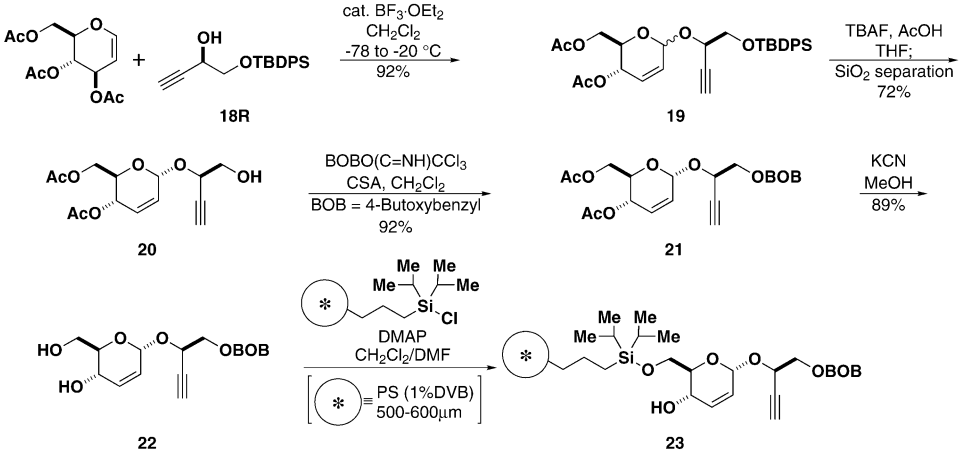


Figure 7. Preparation of Substrate and Loading onto Polystyrene Macrobeads

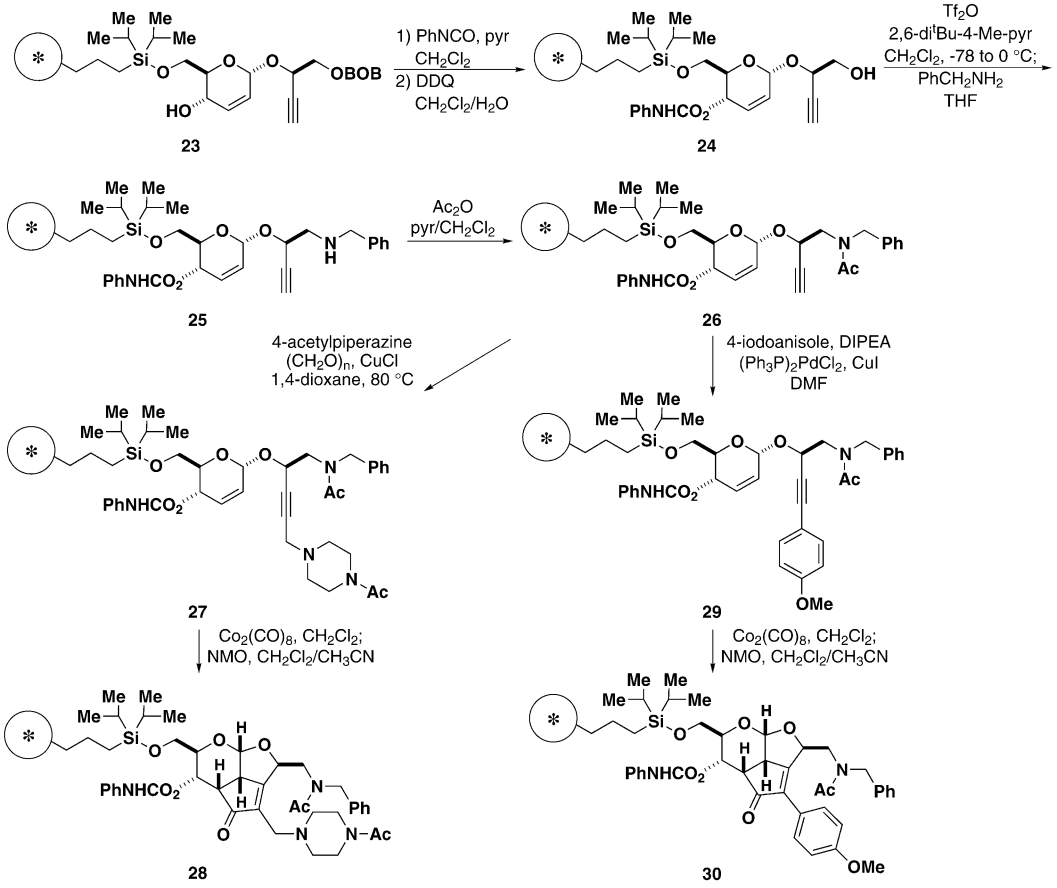


Figure 8. Solid-Phase Synthesis of (*R*)-Series Tricyclic Compounds

curred optimally in CH_2Cl_2. For the second step, we found that NMO in a 4:1 mixture of CH_2Cl_2:CH_3CN gave products **28** and **30** having the highest purity and yields.

One operational challenge of concern in solid-phase syntheses was the removal of the cobalt residue after each Pauson-Khand reaction [38, 39], especially on the high-capacity macrobeads, which tend to have reduced diffusion rates. The use of acetic acid resulted in premature release of the enone products from the resin and inefficient removal of cobalt residue. Screening of cobalt-chelating conditions led to an optimized procedure. Washing with 10% acetylacetone in THF and then with 5% 8-quinolinol in CH_2Cl_2 was found to remove the cobalt residue efficiently, as evidenced by our ability to obtain normal "magic-angle spinning" ^{1}H NMR spectra of these polystyrene beads without observing Co-induced, broad amorphous peaks. Also, after cleavage from the macrobeads with HF-pyridine, the compounds gave sharp and appropriate ^{1}H NMR signals (Figure 9).

In the course of building-block screening, we found that **31**, obtained by reaction of **24** with phenyl isocyanate, when submitted to the Pauson-Khand conditions gave an unexpected and interesting result (Figure 10). Pauson-Khand reaction of **31** afforded not only the expected tricyclic enone but also the tetracyclic product **32**, resulting from intramolecular carbamate cyclization onto the enone and subsequent elimination of the C4 carbamate. This mixture could be driven completely to the tetracyclic product with a catalytic amount of $NaHCO_3$ in a H_2O-THF-MeOH mixture. The tetracyclic product **32** represents a different scaffold from the tricyclic compounds, and thus the reaction producing it is an attractive candidate for an advanced diversity pathway.

Solid-Phase Reactions in the *S* Series

The first two diversity steps of the *S* series can be performed in the same way as the *R* series on solid phase (Figure 11). With enyne **36**, the Pauson-Khand reaction proceeded smoothly. The Michael addition of the resulting tricyclic enone **37** with ethanethiol proceeded under mild conditions. The Michael addition reaction constitutes the third diversity step in the *S* series. Importantly, it serves to alter the three-dimensional structure of the resulting scaffold relative to the *R* series. The cyclopentanone ring in **38** is more puckered, and the third diversity element, the thioether, is oriented perpendicularly to the best plane of the tricycle. In the *R* series, the *N*,*N*-dialkylaminomethyl group in **28** rests within the best plane of the tricycle. The additional solid-phase ketone reduction step is now in progress.

The purity of the final products is largely dependent on the outcome of the Pauson-Khand reactions. Following HF-pyridine release, ^{1}H NMR analyses of Pauson-Khand reaction products suggested that acceptable purity levels were achieved in most cases, as shown in Figure 9.

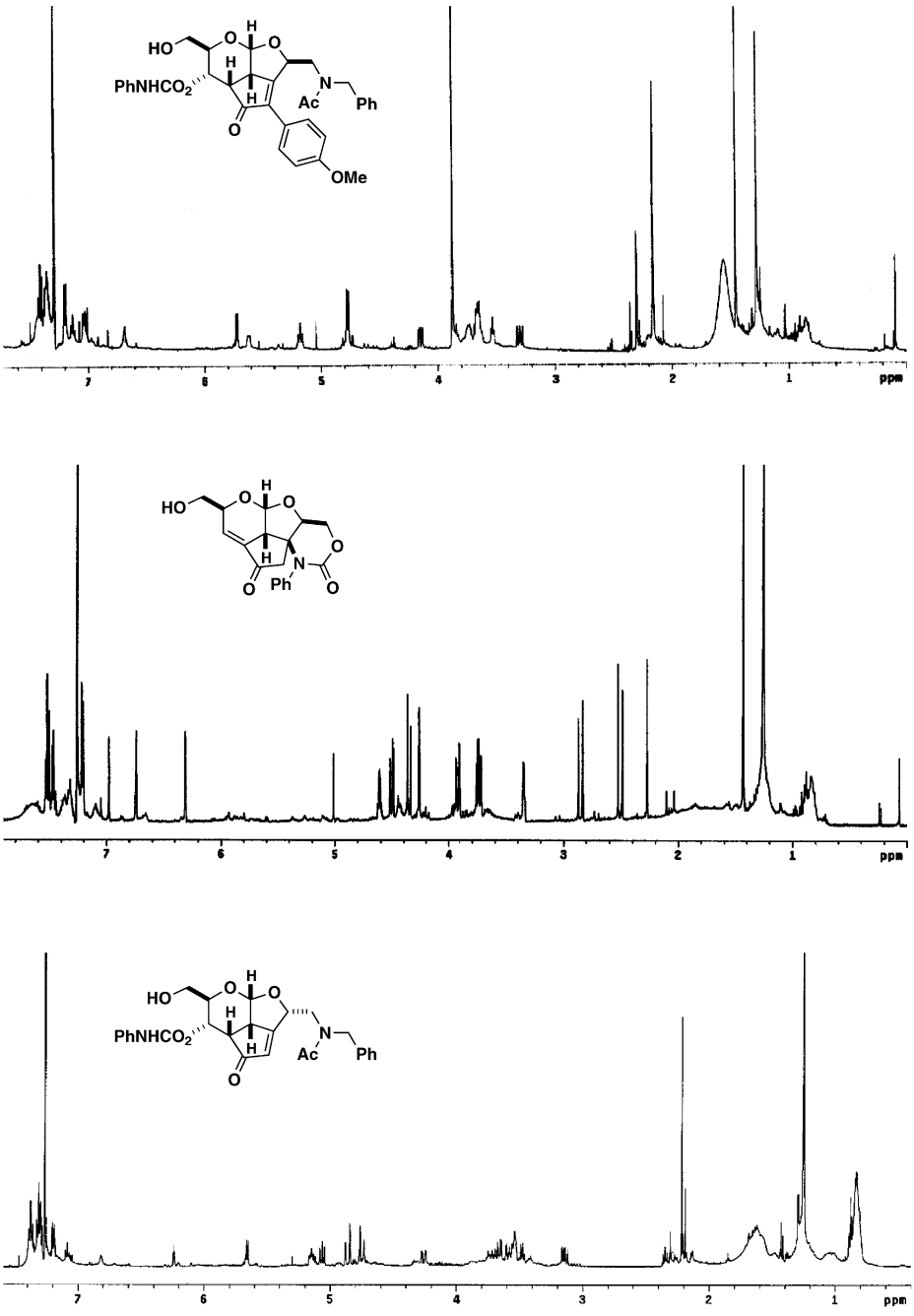
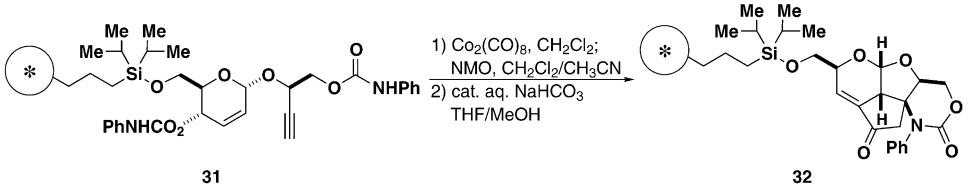


Figure 9. ^{1}H NMR Spectra of Representative Compounds after Release from Macrobeads



31 32

Figure 10. Solid-Phase Synthesis of a Tetracyclic Product

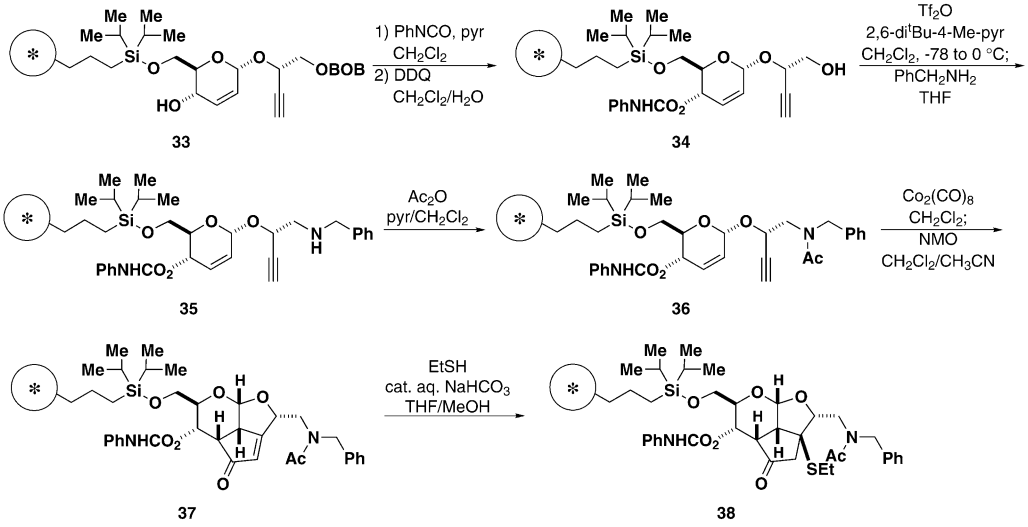


Figure 11. Solid-Phase Synthesis of (*S*)-Series Tricyclic Compounds

Usually, the ^{1}H NMR and LC-MS data show >80% purity of the desired compound.

Pilot Library Realization of the (*S*)-Tricyclic Compounds

Using the chemical pathways reported herein, we performed a pilot split-pool library synthesis of (*S*)-tricyclic compounds. As a first step of a library realization, building blocks that would provide both electronic and structural diversity were screened with the typical intermediates on macrobeads in Figure 11 for each diversity step. The screening reactions were analyzed by LC-MS and ^{1}H NMR spectra, and the building blocks that provided desired products with >90% purity were selected. Through a series of building-block screening were selected ten isocyanates, five primary amines, three acylating reagents, and eight thiols for use in the library of 2,500 tricyclic compounds (Figure 12).

The pilot library synthesis was initiated with 7,500 polystyrene macrobeads (500–600 μm) to produce, on average, three beads containing each theoretical compound. Allylic alcohol **33** was treated with 10 aromatic and aliphatic isocyanates in ten reaction vessels, and the beads were encoded with tags [5, 7] before they were pooled for DDQ deprotection (Figure 13). Alcohols **39** underwent either sequential triflation, S_N2 reaction with five primary amines, and acylation with three acylating reagents or carbamate formation with ten isocyanates. After the split reactions (S_N2 reaction, acylation, and carbamate formation), the beads in reaction vessels were encoded and then pooled. After Pauson-Khand reaction of enynes **40**, the beads were split into nine

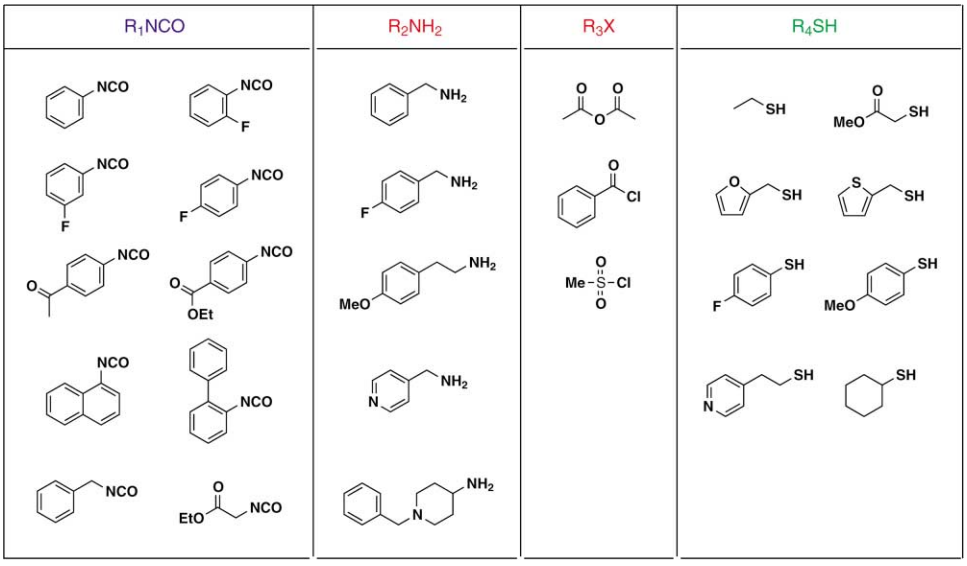


Figure 12. Building Blocks Used for a (*S*)-Series Tricyclic Library

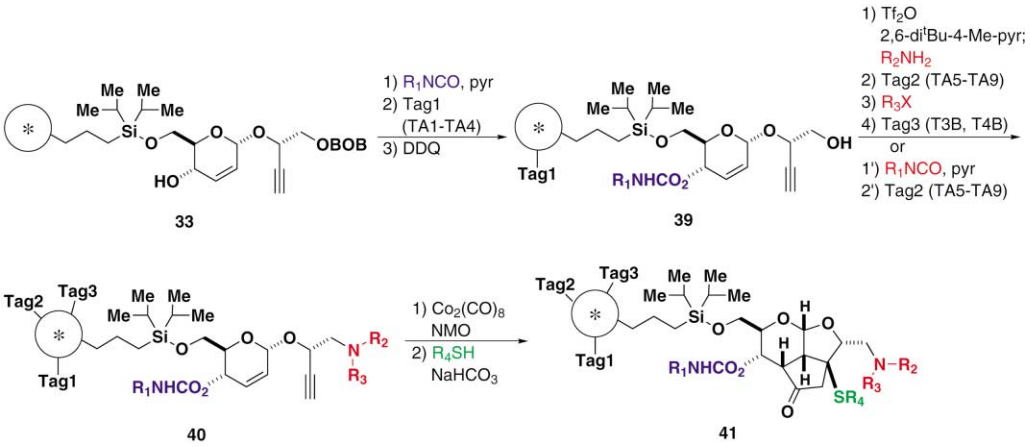


Figure 13. Pilot Library Realization of (*S*)-Series Tricyclic Compounds

reaction vessels. The beads in one reaction vessel were kept as tricyclic α,β-unsaturated ketones, and the ones in the other eight reaction vessels were treated with eight thiols to provide tricyclic sulfides **41**.

After the pilot library synthesis, 30 beads from the above nine pools were treated with HF-pyridine, and the resulting stock solutions were assayed by LC-MS for quality control (Figure 14). About 80% of the stock solutions showed satisfactory purity levels (>80%), which indicates that this pathway is promising for future chemical genetic synthesis.

Significance

"Diversity, complexity, and efficiency" is the mantra of diversity-oriented synthesis. In this study, we developed a short reaction pathway for split-pool syntheses of complex tricyclic and tetracyclic small molecules. Ferrier reactions with two enantiomeric (*R*)- and (*S*)-propargylic alcohols and subsequent Pauson-Khand reactions yielded rigid and highly functionalized tricyclic scaffolds. The propargylic alcohol-derived stereocenter resulted in two distinct reaction pathways leading to small molecules having different spatial arrays of different substituents. Our work highlighted the need to understand the reactivity patterns of both series before performing a split-pool synthesis. For split-pool synthesis, an ideal scenario would be that both *R* and *S* series could be prepared through the same pathway by the use of common building blocks. However, knowledge of the reactivity pattern resulted in a pathway wherein the *R* and *S* series are manipulated separately. To illustrate the feasibility of library realization, we synthesized a pilot library of 2500 (*S*)-tricyclic compounds. Individual compounds were synthesized in good purity levels, as judged by analyses of their resultant stock solutions. We are also investigating other diversity-generating reactions besides the Pauson-Khand reaction to produce additional scaffold diversity from glycal templates. Solution-phase studies

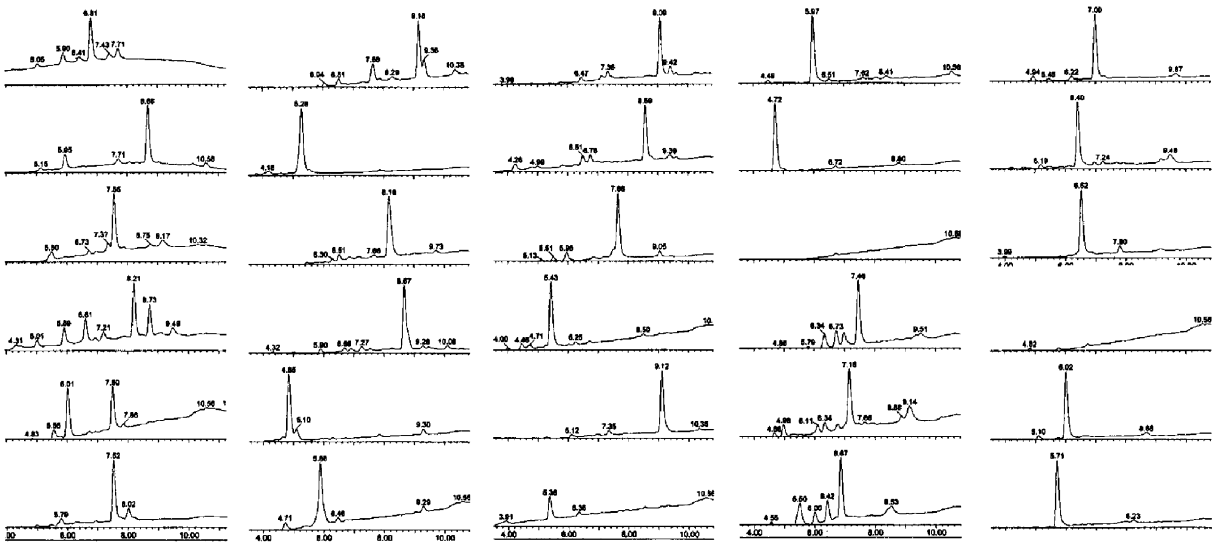


Figure 14. LC-MS Data (UV Absorbance Traces) of Stock Solutions from 30 Beads

of Ni-catalyzed enone-yne-type reactions are currently under investigation and have shown promise [47].

Experimental Procedures

Solution-Phase Chemistry

Starting materials and reagents were purchased from commercial suppliers and were used without further purification except for the following: methylene chloride (CH_2Cl_2), tetrahydrofuran (THF), acetonitrile, dimethylformamide (DMF), and Et_2O, which were passed through two activated alumina columns to remove impurities prior to use. Methanol was distilled from Mg under an argon atmosphere. Dicobalt octacarbonyl ($Co_2(CO)_8$) was exclusively purchased from Strem Chemicals. All reactions were performed in oven-dried glassware, sealed with a rubber septum under an argon atmosphere.

(1S)-1-[(Tert-Butyldiphenylsiloxy)Methyl]-2-Propynyl 2,3-Dideoxy-4,6-Diacetyloxy-d-Erythro-Hex-2-Enopyranoside *(19)*

To a stirred solution of 3,4,6-tri-*O*-acetyl-*D*-glucal (267 mg, 1.02 mmol) and **18R** [44, 45] (330 mg, 1.02 mmol) in CH_2Cl_2 (10 ml) at −78°C was added $BF_3{\cdot}OEt_2$ (12.7 μl, 0.1 mmol). The solution was allowed to warm to −20°C over the course of 1 hr. The reaction mixture was treated with saturated $NaHCO_3$, and the aqueous layer was extracted with Et_2O (×3). The combined organics were washed with brine, dried over $MgSO_4$, and purified by flash chromatography (6/1 hexanes/ethyl acetate) to give **19** (501 mg, 92%, α anomer:β anomer = 5:1) as a colorless oil. Data for the α-anomer are as follows: IR (film) 2931, 1746, 1370, 1239, 1113, 1032, 704 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.64–7.72 (m, 4H, Ph), 7.35–7.45 (m, 6H, Ph), 5.93 (d, *J* = 10.3 Hz, 1H, H-3), 5.80 (dt, *J* = 10.4, 2.0 Hz, 1H, H-2), 5.41 (dd, *J* = 1.6, 9.6 Hz, 1H, H-4), 5.33 (s, 1H, H-1), 4.53 (m, 1H, OC*H*RCCH), 4.32 (dd, *J* = 4.0, 12.0 Hz, 1H, H-6), 4.23 (m, 1H, H-5), 4.19 (dd, *J* = 2.0, 12.0 Hz, 1H, H-6), 3.82 (m, 2H, CH_2OSi), 2.40 (d, *J* = 2.4 Hz, 1H, CC*H*), 2.04 (s, 3H, Ac), 2.04 (s, 3H, Ac), 1.05 (s, 9H, *tert*-Bu); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.9, 170.3, 135.5, 132.9, 129.8, 127.7, 93.6, 80.6, 74.0, 69.5, 67.0, 66.9, 65.1, 62.5, 26.6, 20.9, 20.8, 19.1; HRMS (FAB^+) calculated for $(C_{30}H_{36}O_7Si + Na)^+$: 559.2128, found: 559.2147.

(1S)-1-(Hydroxymethyl)-2-Propynyl 2,3-Dideoxy-4,6-Diacetyloxy-α-d-Erythro-Hex-2-Enopyranoside *(20)*

To a stirred solution of **19** (23.9 g, 44 mmol, α anomer:β anomer = 5:1) in THF (300 ml) at 0°C were added acetic acid (3.0 ml, 53 mmol) and TBAF (1 M in THF, 49 ml, 49 mmol). The mixture was allowed to warm to room temperature and was stirred for 2 hr. The solution was concentrated in vacuo, diluted with Et_2O, and washed with saturated $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, concentrated, and purified by flash chromatography (1/1 hexanes/Et_2O) to furnish the α-anomer **20** (8.19 g, 72%). $[\alpha]^{23}D$ +73.3° (c 1.05, MeOH); IR (film) 3502, 3273, 1741, 1238, 1031 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.93 (d, *J* = 9.6 Hz, 1H, H-3), 5.84 (dt, *J* = 9.6, 2.0 Hz, 1H, H-2), 5.36 (s, 1H, H-1), 5.33 (m, 1H, H-4), 4.49 (m, 1H, OC*H*RCCH), 4.15–4.25 (m, 3H, H-5, H-6), 3.77 (m, 2H, CH_2OSi), 2.59 (d, *J* = 6.4 Hz, 1H, OH), 2.52 (d, *J* = 2.4 Hz, 1H, CC*H*), 2.10 (s, 3H, Ac), 2.09 (s, 3H, Ac); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.8, 170.2, 129.6, 127.2, 93.5, 79.7, 75.3, 70.1, 67.4, 65.0, 64.9, 62.8, 20.9, 20.7; HRMS (TOF MS ES^+) calculated for $(C_{14}H_{18}O_7 + Na)^+$: 321.0950, found: 321.0938.

(1S)-1-[[4-Butyloxy]Benzyloxy)Methyl]-2-Propynyl 2,3-Dideoxy-4,6-Diacetyloxy-α-d-Erythro-Hex-2-Enopyranoside *(21)*

To a suspension of 60% sodium hydride (44 mg, 1.1 mmol) in Et_2O (10 ml) was added 4-butyloxybenzyl alcohol (2.0 g, 11.1 mmol) at 0°C, and the mixture was stirred for 15 min. The solution was treated with trichloroacetonitrile (1.11 ml, 11.1 mmol) dropwise. The reaction mixture was allowed to warm to room temperature and was stirred for 2 hr. The mixture was treated with saturated $NaHCO_3$, and the aqueous layer was extracted with Et_2O (×3). The combined organics were washed with brine and dried over $MgSO_4$. After filtration, the solution was concentrated in vacuo to give the crude trichloroacetimidate (3.6 g). To a stirred solution of **20** (2.49 g, 8.4 mmol) and the crude trichloroacetimidate in CH_2Cl_2 (15 ml) was added *d*-camphorsulfonic acid (194 mg, 0.84 mmol). The mixture was stirred for 4 hr and poured into saturated $NaHCO_3$. The mixture was extracted with Et_2O (×3). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. A mixture of solvent (9/1 hexanes/benzene) was added to the residue, and the precipitate was filtered. The filtrate was concentrated and purified by flash chromatography (5/1 hexanes/ethyl acetate) to give the BOB ether **21** (3.55 g, 92%) as a colorless oil. $[\alpha]^{23}D$ +30.5° (c 1.3, MeOH); IR (film) 3276, 2958, 1742, 1513, 1244, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.22 (d, *J* = 8.8 Hz, 2H, Ar), 6.87 (d, *J* = 8.8 Hz, 2H, Ar), 5.90 (d, *J* = 8.4 Hz, 1H, H-3), 5.85 (dt, *J* = 8.4, 2.0 Hz, 1H, H-2), 5.40 (d, *J* = 9.2 Hz, 1H, H-4), 5.26 (d, *J* = 2.0 Hz, 1H, H-1), 4.54 (m, 1H, OC*H*RCCH), 4.52 (d, *J* = 12.0 Hz, 1H, CH_2Ar), 4.50 (d, *J* = 12.0 Hz, 1H, CH_2Ar), 4.29 (dd, *J* = 4.4, 12.0 Hz, 1H, CH_2OCH$_2$Ar), 4.23 (m, 1H, H-5), 4.20 (dd, *J* = 2.4, 12.0 Hz, 1H, CH_2OCH$_2$Ar), 3.95 (t, *J* = 6.4 Hz, 2H, ArOCH_2), 3.63 (m, 2H, H-6), 2.45 (d, *J* = 2.4 Hz, 1H, CC*H*), 2.10 (s, 3H, Ac), 2.08 (s, 3H, Ac), 1.77 (m, 2H, ArOCH$_2$CH_2C$_2$H$_5$), 1.47 (m, 2H, ArOC$_2$H$_4$CH_2CH$_3$), 0.97 (t, *J* = 7.2 Hz, 2H, ArOC$_3$H$_6$CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.9, 170.3, 158.9, 129.6, 129.2, 127.3, 114.4, 95.1, 80.6, 74.1, 73.1, 72.5, 67.8, 67.7, 67.0, 65.0, 62.4, 31.3, 21.0, 20.8, 19.2, 13.8; HRMS (TOF MS ES^+) calculated for $(C_{25}H_{32}O_8 + Na)^+$: 483.1995, found: 483.2017.

(1S)-1-[[[4-Butyloxy]Benzyloxy)Methyl]-2-Propynyl 2,3-Dideoxy-4,6-Dihydroxy-α-d-Erythro-Hex-2-Enopyranoside *(22)*

To a stirred solution of **21** (3.50 g, 7.6 mmol) in methanol (20 ml) was added potassium cyanide (60 mg, 0.92 mmol). The mixture was stirred for 2 hr, and the solvent was removed in vacuo. The residue was purified by flash chromatography (1/1 hexanes/ethyl acetate) to afford diol **22** (2.55 g, 89%) as a colorless oil. $[\alpha]^{23}D$ +17.6° (c 1.0, MeOH); IR (film) 3420, 3287, 2932, 1512, 1246, 1026 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.23 (d, *J* = 6.4 Hz, 2H, Ar), 6.86 (d, *J* = 6.4 Hz, 2H, Ar), 5.98 (d, *J* = 10.4 Hz, 1H, H-3), 5.76 (dt, *J* = 10.4, 2.0 Hz, 1H, H-2), 5.21 (s, 1H, H-1), 4.53 (d, *J* = 11.6 Hz, 1H, CH_2Ar), 4.51 (d, *J* = 11.6 Hz, 1H, CH_2Ar), 4.49 (m, 1H, OC*H*RCCH), 4.22 (m, 1H, H-4), 3.94 (t, *J* = 6.4 Hz, 2H, ArOCH_2), 3.8–4.0 (m, 3H, H-5, CH_2OCH$_2$Ar), 3.67 (d, *J* = 11.2, 1H, H-6), 3.64 (d, *J* = 11.2, 1H, H-6), 2.48 (d, *J* = 2.0 Hz, 1H, CC*H*), 1.76 (m, 2H, ArOCH$_2$CH_2C$_2$H$_5$), 1.49 (m, 2H, ArOC$_2$H$_4$CH_2CH$_3$), 0.97 (t, *J* = 7.2 Hz, 2H, ArOC$_3$H$_6$CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.9, 133.7, 129.5, 129.3, 125.8, 114.4, 95.0, 80.9, 74.3, 73.1, 72.4, 71.9, 68.1, 67.7, 64.3, 62.7, 31.3,19.2, 13.9; HRMS (TOF MS ES^+) calculated for $(C_{21}H_{28}O_6 + Na)^+$: 399.1784, found: 399.1802.

Solid-Phase Chemistry

500–600 μm polystyrene macrobeads with a diisopropyl(4-methoxyphenyl)silyl linker were prepared according to the literature [4]. All reactions were performed in oven-dried glassware, sealed with a rubber septum under an argon atmosphere.

Loading of 22 onto Resin

Silicon functionalized resin (1.41 mequiv. Si/g) that had been dried under hi-vac for 12 hr was weighed (1.10 g, 1.53 mmol) into a 100 ml conical flask and swollen in CH_2Cl_2 (20 ml). HCl gas was bubbled at 0°C until saturation was reached, and the reaction mixture was allowed to warm to room temperature for 30 min with an occasional agitation and leakage of HCl gas. The solvent was drained under positive argon pressure, and the resin was washed successively with CH_2Cl_2 (20 ml, ×3), Et_2O (20 ml, ×3), and CH_2Cl_2 (20 ml, ×3). The resin was treated with 4-dimethylaminopyridine (563 mg, 4.6 mmol) in CH_2Cl_2 (10 ml) and **22** (1.73 g, 4.6 mmol) in DMF (10 ml). The resultant solution was occasionally agitated for 48 hr. The solvent was drained, and the beads were washed with CH_2Cl_2 (20 ml, ×3), THF (20 ml, ×3) and CH_2Cl_2 (20 ml, ×3) and dried to afford beads **23** (1.45 g). Beads **33** were prepared in a similar manner. The loading level was estimated to be 80% based on the weight of the cleaved compound.

Cleavage of 23 from the Resin

Twelve beads of **23** in an Eppendorf tube were treated with a freshly prepared cleavage cocktail (HF-pyridine [5%]/ pyridine [10%]/ THF [85%], 0.1 ml), and the mixture was agitated for 1 hr. The mixture was treated with methoxytrimethylsilane (0.1 ml) and further agitated for 30 min. The solvent was concentrated, and the beads was washed with acetonitrile (0.2 ml, ×2). The combined solution was concentrated in vacuo.

Carbamate Formation and BOB Deprotection of 23

To beads **23** (1.14 g) in CH_2Cl_2 (40 ml) were added pyridine (1.33 ml, 16.5 ml) and phenylisocyanate (1.38 ml, 12.7 mmol). The mixture was gently agitated for 17 hr, and the solvent was drained. The

beads were washed with CH_2Cl_2, THF, and CH_2Cl_2 and dried to afford the carbamate on beads (1.25 g). To the carbamate on beads (1.18 g, 1.2 mmol) in CH_2Cl_2 (100 ml)/H_2O (10 ml) was added DDQ (1.27 g, 5.6 mmol). The reaction mixture was gently agitated for 3 hr. The solvent was drained, and the beads were washed with CH_2Cl_2/THF (1/2) and THF-cocktail (10/1:ascorbic acid [70 mg], citric acid [126 mg], and sodium hydroxide [92 mg] in H_2O [10 ml]) [48, 49]. The resulting pale-yellow beads were washed successively with THF/H_2O (10/1), THF and CH_2Cl_2, and dried to afford beads **24** (1.04 g).

Triflation, Amine Displacement, and Acylation

To beads **24** (30 mg, 34 μmol) in CH_2Cl_2 (1.2 ml) were added 2,6-di-*tert*-butyl-4-methylpyridine (24 mg, 120 μmol) and trifluoromethanesulfonic anhydride (10.2 μl, 60 μmol) at −78°C. The reaction mixture was allowed to warm to 0 °C over the course of 2 hr. The solvent was removed via cannula under positive argon pressure, and beads were quickly washed with CH_2Cl_2. Benzylamine (40 μl, 0.4 mmol) in THF (6 ml) was added to the beads at room temperature, and the resultant mixture was agitated for 19 hr. The solvent was drained, and the beads were washed with CH_2Cl_2 and dried to afford beads **25**. To beads **25** in CH_2Cl_2 (300 μl) were added pyridine (300 μl, 3.72 mmol) and acetic anhydride (10 μl, 0.1 mmol). The mixture was agitated for 24 hr, and the solvent was drained. The beads were washed with CH_2Cl_2 and dried to afford beads **26** (36 mg).

Alkynyl Mannich Reaction

To beads **26** (10 mg, 10 μmol) in degassed 1,4-dioxane (0.5 ml) were added cuprous chloride (0.4 mg, 4 μmol), 1-acetylpiperazine (5.4 mg, 42 μmol) and paraformaldehyde (1.3 mg, 43 μmol). The reaction mixture was heated to 80°C for 3.5 hr with occasional agitation, cooled to room temperature, and treated with CH_2Cl_2. The beads were collected by decantation, washed with THF/isopropylamine (10/1), THF, and CH_2Cl_2, and dried to afford beads **27** (11 mg).

Sonogashira Reaction

To beads **26** (10 mg, 10 μmol) in degassed DMF (0.6 ml) were added dichlorobis(triphenylphosphine)palladium (7.7 mg, 1 μmol), cuprous iodide (4.2 mg, 22 μmol) and (triisopropylsilyl)acetylene (2.5 μl, 11 μmol). The reaction mixture was allowed to stand for 15 min, treated with 4-iodoanisole (46.8 mg, 0.2 mmol) and diisopropylethylamine (52 μl, 0.3 mmol), and agitated for 90 min. The solvent was drained, and the beads were washed with DMF, THF, and CH_2Cl_2 and dried to afford beads **29** (11 mg).

Pauson-Khand Reaction

Beads **29** (5.5 mg, 5 μmol) were treated with $Co_2(CO)_8$ (5.7 mg, 16 μmol) in CH_2Cl_2 (0.3 ml), and the mixture was gently agitated for 3 hr. The solvent was drained, and the beads were washed with CH_2Cl_2. To the beads was added an ice-cooled solution of 4-methylmorpholine N-oxide (3.9 mg, 33 μmol) in CH_2Cl_2 (200 μl)/acetonitrile (50 μl), and the reaction mixture was agitated for 14 hr. The solvent was drained, and the beads were treated with CH_2Cl_2 and collected by decantation. The beads were washed with THF/acetylacetone (10/1, ×3, total 16 hr), 5% 8-quinolinol in CH_2Cl_2 (8 hr), and CH_2Cl_2 and dried to afford beads **30**.

Michael Addition of Thiol

To enone **37** (10 mg) were added 0.5% aqueous $NaHCO_3$ in THF/MeOH (1/1, 1 ml) and EtSH (10 μl, 0.14 mmol). The reaction mixture was allowed to agitate for 4 hr, washed with THF/water (4/1, 2 ml ×3), THF (2 ml ×3), and CH_2Cl_2 (2 ml ×3), and dried to afford thioether **38**.

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References

1. Schreiber, S.L. (1998). Chemical genetics resulting from a passion for synthetic organic chemistry. Bioorg. Med. Chem. *6*, 1127–1152.
2. Mitchison, T.J. (1994). Towards a pharmacological genetics. Chem. Biol. *1*, 3–6.
3. Schreiber, S.L. (2000). Target-oriented and diversity-oriented organic synthesis in drug discovery. Science *287*, 1964–1969.
4. Tallarico, J.A., Depew, K.M., Pelish, H.E., Westwood, N.J., Lindsley, C.W., Shair, M.D., Schreiber, S.L., and Foley, M.A. (2001). An alkylsilyl-tethered, high-capacity solid support amenable to diversity-oriented synthesis for one-bead, one-stock solution chemical genetics. J. Comb. Chem. *3*, 312–318.
5. Blackwell, H.E., Pérez, L., Stavenger, R.A., Tallarico, J.A., Eatough, E.C., Schreiber, S.L., and Foley, M.A. (2001). A one-bead, one-stock solution approach to chemical genetics: part 1. Chem. Biol., *8*, 1167–1182.
6. Clemons, P.A., Koehler, A.N., Wagner, B.K., Sprigings, T.G., Spring, D.R., King, R.W., Schreiber, S.L., and Foley, M.A. (2001). A one-bead, one-stock solution approach to chemical genetics: part 2. Chem. Biol., *8*, 1183–1195.
7. Blackwell, H.E., Pérez, L., and Schreiber, S.L. (2001). Decoding products of diversity pathways from stock solutions derived from single polymeric macrobeads. Angew. Chem. Int. Ed. *113*, 3421–3425.
8. Nilsson, J.L.G., and Carlsson, A. (1982). Dopamine-receptor agonist with apparent selectivity for autoreceptors: a new principle for antipsychotic action. Trends Pharmacol. Sci. *3*, 322–325.
9. Carlsson, A. (1993). Thirty years of dopamine research. Adv. Neurol. *60*, 1–10.
10. Borisy, G.G., and Taylor, E.W. (1967). The mechanism of action of colchicine. Binding of colchincine-3H to cellular protein. J. Cell Biol. *34*, 525–533.
11. Borisy, G.G., and Taylor, E.W. (1967). Mechanism of action of colchicine. Colchicine binding to sea urchin eggs and mitotic apparatus. J. Cell Biol. *34*, 535–548.
12. Corey, E.J., and Cheng, X.-M. (1989). The Logic of Chemical Synthesis. (New York: John Wiley & Sons).
13. Tan, D.S., Foley, M.A., Shair, M.D., and Schreiber, S.L. (1998). Stereoselective synthesis of over two million compounds having structural features both reminiscent of natural products and compatible with miniaturized cell-based assays. J. Am. Chem. Soc. *120*, 8565–8566.
14. Lee, D., Sello, J., and Schreiber, S.L. (1999). A strategy for macrocyclic ring closure and functionalization aimed toward split-pool syntheses. J. Am. Chem. Soc. *121*, 10648–10649.
15. Nicolaou, K.C., Pfefferkorn, J.A., Mitchell, H.J., Roecker, A.J., Barluenga, S., Cao, G.-Q., Affleck, R.L., and Lillig, J.E. (2000). Natural product-like combinatorial libraries based on privileged structures. 2. Construction of a 10,000-membered benzopyran library by directed split-and-pool chemistry using NanoKans and optical encoding. J. Am. Chem. Soc. *122*, 9954–9967.
16. Marco-Contelles, J. (1994). The Pauson-Khand reaction on carbohydrate templates. 1. Synthesis of bis-heteroannulated-pyranosides. Tetahedron Lett. *35*, 5059–5062.
17. Marco-Contelles, J., and Ruiz-Caro, J. (1999). Iridoids from carbohydrates via Pauson-Khand reaction: synthesis of advanced highly oxygenated cyclopentane-annulated pyranosides from D-glucal derivatives. J. Org. Chem. *64*, 8302–8310.
18. Furka, Á., Sebestyén, F., Asgedom, M., and Dibó, G. (1991). General method for rapid synthesis of multicomponent peptide mixtures. Int. J. Pept. Protein Res. *37*, 487–493.
19. Lam, K.S., Salmon, S.E., Hersh, E.M., Hruby, V.J., Kazmierski, W.M., and Knapp, R.J. (1991). A new type of synthetic peptide library for identifying ligand-binding activity. Nature *354*, 82–84.
20. Houghten, R.A., Clemencia, P., Blondelle, S.E., Appel, J.R., Dooley, C.T., and Cuervo, J.H. (1991). Generation and use of synthetic peptide combinatorial libraries for basic research and drug discovery. Nature *354*, 84–86.
21. Ohlmeyer, M.H.J., Swanson, R.N., Dillard, L.W., Reader, J.C., Asouline, G., Kobayashi, R., Wigler, M., and Still, W.C. (1993). Complex synthetic chemical libraries indexed with molecular tags. Proc. Natl. Acad. Sci. USA *90*, 10922–10926.

22. Nestler, H.P., Bartlett, P.A., and Still, W.C. (1994). A general method for molecular tagging of encoded combinatorial chemistry libraries. J. Org. Chem. *59*, 4723–4724.
23. Stockwell, B.R., Haggarty, S.J., and Schreiber, S.L. (1999). High-throughput screening of small molecules in miniaturized mammalian cell-based assays involving post-translational modifications. Chem. Biol. *6*, 71–83.
24. Mayer, T.U., Kapoor, T.M., Haggarty, S.J., King, R.W., Schreiber, S.L., and Mitchison, T.J. (1999). Small molecule inhibitor of mitotic spindle bipolarity identified in a phenotype-based screen. Science *286*, 971–974.
25. MacBeath, G., Koehler, A.N., and Schreiber, S.L. (1999). Printing small molecules as microarrays and detecting protein-ligand interactions *en masse.* J. Am. Chem. Soc. *121*, 7967–7968.
26. Hergenrother, P.J., Depew, K.M., and Schreiber, S.L. (2000). Small molecule microarrays: covalent attachment and screening of alcohol-containing small molecules on glass slides. J. Am. Chem. Soc. *122*, 7849–7850.
27. Ferrier, R.J., and Prasad, N. (1969). Unsaturated carbohydrates. Part 9. Synthesis of 2,3-dideoxy-alpha-D-erythro-hex-2-enopyranosides from tri-O-acetyl-D-glucal. J. Chem. Soc., series C, 570–575.
28. Geis, O., and Schmalz, H.-G. (1998). New developments in the Pauson-Khand reaction. Angew. Chem. Int. Ed. *37*, 911–914.
29. Brummond, K.M., and Kent, J.L. (2000). Recent advances in the Pauson-Khand reaction and related [2+2+1] cycloadditions. Tetrahedron *56*, 3263–3283.
30. Fletcher, A.J., and Christie, S.D.R. (2000). Cobalt mediated cyclisations. J. Chem. Soc. Perkin Trans. *1*, 1657–1668.
31. Youngman, M.A., and Dax, S.L. (1997). Mannich reactions of a resin-bound terminal alkyne. Tetrahedron Lett. *38*, 6347–6350.
32. McNally, J.J., Youngman, M.A., and Dax, S.L. (1998). Mannich reactions of resin-bound substrates: 2. Tetrahedron Lett. *39*, 967–970.
33. Dyatkin, A., and Rivero, R.A. (1998). The solid phase synthesis of complex propargylamines using the combination of Sonogashira and Mannich reactions. Tetrahedron Lett. *39*, 3647–3650.
34. Banik, B.K., Manhas, M.S., and Bose, A.K. (1994). Stereospecific glycosylation via Ferrier rearrangement for optical resolution. J. Org. Chem. *59*, 4714–4716.
35. Koreeda, M., Houston, T.A., Shull, B.K., Klemke, E., and Tuinman, R.J. (1995). Iodine-catalyzed Ferrier reaction. 1. A mild and highly versatile glycosylation of hydroxyl and phenolic groups. Synlett *1*, 90–92.
36. Sonogashira, K., Tohda, Y., and Hagihara, N. (1975). Convenient synthesis of acetylenes: catalytic substitutions of acetylenic hydrogen with bromoalkenes, iodoarenes, and bromopyridines. Tetrahedron Lett. 4467–4470.
37. Thorand, S., and Krause, N. (1998). Improved procedures for the palladium-catalyzed coupling of terminal alkynes with aryl bromides (Sonogashira coupling). J. Org. Chem. *63*, 8551–8553.
38. Bolton, G.L. (1996). Solid phase synthesis of azabicyclo[4.3.0]-nonen-8-one amino acid derivatives via intramolecular Pauson-Khand cyclization. Tetrahedron Lett. *37*, 3433–3436.
39. Bolton, G.L., Hodges, J.C., and Rubin, J.R. (1997). Solid phase synthesis of fused bicyclic amino acid derivatives via intramolecular Pauson-Khand cyclization: versatile scaffolds for combinatorial chemistry. Tetrahedron *53*, 6611–6634.
40. Shambayati, S., Crowe, W.E., and Schreiber, S.L. (1990). N-oxide promoted Pauson-Khand cyclizations at room temperature. Tetrahedron Lett. *31*, 5289–5292.
41. Magnus, P., Exon, C., and Albaugh-Robertson, P. (1985). Dicobaltoctacarbonyl-alkyne complexes as intermediates in the synthesis of bicyclo[3.3.0]octenones for the synthesis of coriolin and hirsutic acid. Tetrahedron *41*, 5861–5869.
42. Mukai, C., Kim, J.S., Uchiyama, M., Sakamoto, S., and Hanaoka, M. (1998). Stereoselective construction of optically active bicyclo[3.3.0]octenone derivatives based on the Pauson-Khand reaction. J. Chem. Soc. Perkin Trans. *1*, 2903–2915.
43. Luche, J.-L., Rodriguez-Hahn, L., and Crabbé, P. (1978). Reduction of natural enones in presence of cerium trichloride. J. Chem. Soc., Chem. Commun. 601–602.
44. Janson, M., Kvarnström, I., Svensson, S.C.T., Classon, B., and Samuelsson, B. (1993). New routes to isomerically pure cyclopentanes. Synthesis of (3S,4S)-3,4-bis(benzoyloxymethyl)-cyclopentan-1-ol using palladium-catalyzed [2+3] cycloaddition. Synthesis 129–133.
45. Gooding, O.W., Beard, C.C., Jackson, D.Y., Wren, D.L., and Cooper, G.F. (1991). Enantioselective formation of functionalized 1,3-disubstituted allenes: synthesis of α-allenic ω-carbomethoxy alcohols of high optical purity. J. Org. Chem. *56*, 1083–1088.
46. Krafft, M.E., Scott, I.L., Romero, R.H., Feibelmann, S., and Van Pelt, C.E. (1993). Effect of coordinating ligand on the Pauson-Khand cycloaddition: trapping of an intermediate. J. Am. Chem. Soc. *115*, 7199–7207.
47. Chowdhury, S.K., Amarasinghe, K.K.D., Heeg, M.J., and Montgomery, J. (2000). Diverse reactivity manifolds of alkynyl enone- and alkynyl enal-derived nickelacycles: discovery of nickel-promoted [3+2] and [2+1] cycloadditions. J. Am. Chem. Soc. *122*, 6775–6776.
48. Fukase, K., Yoshimura, T., Kotani, S., and Kusumoto, S. (1994). Synthetic study of lipoteichoic acid of gram-positive bacteria. 2. Synthesis of the proposed fundamental structure of enterococcus hirae lipoteichoic acid. Bull. Chem. Soc. Jpn. *67*, 473–482.
49. Deegan, T.L., Gooding, O.W., Baudart, S., and Porco, J.A., Jr. (1997). Non-acidic cleavage of Wang-derived ethers from solid support: utilization of a mixed-bed scavenger for DDQ. Tetrahedron Lett. *38*, 4973–4976.