Facile Generation of Fused Seven-Membered Polycyclic Systems via Ring Expansion and Application to the Total Synthesis of Sesquiterpenoids

Zhimin Xing[1], Bowen Fang[2], Shangwen Luo[1], Xingang Xie[1]* & Xiaolei Wang[1]*

[1] State Key Laboratory of Applied Organic Chemistry, Department of Chemistry, Lanzhou University, Lanzhou 730000, [2] Key Laboratory for Utility of Environment-Friendly Composite Materials and Biomass in University of Gansu Province, Gansu Provincial Biomass Function Composites Engineering Research Center, College of Chemical Engineering, Northwest Minzu University, Lanzhou 730030

*Corresponding Author(s): xiexg@lzu.edu.cn; wangxiaolei@lzu.edu.cn

Abstract

Seven-Membered polycyclic architectures, widely present in natural products and small molecular drugs, are challenging synthetic targets. So far, methods for synthesizing fused medium-sized bicyclo[m.n.0] ring systems, including the benzocycloheptane systems, are still surprisingly underdeveloped due to the lack of a general protocol to access these architectures. Herein we describe a base-induced ring expansion as a general strategy, which enables rapid and efficient construction of a wide range of fused seven-membered ring systems. The application of this method was demonstrated by the efficient total syntheses of two sesquiterpenoids plecarpenene and plecarpenone, both bearing a fused bicyclo[5.3.0]decane skeleton.

Keywords

ring expansion, regioselectivity, hydrogen atom transfer, total synthesis, fused seven-membered ring

Introduction

Molecules with fused seven-membered ring systems have attracted considerable attention due to their extensive presence in biologically active natural products and small molecule drugs, such as daphenylline, aplyviolene, pepluanol A, and ingenol (Figure 1).[1-16] For this reason, methods with high efficiency for the

synthesis of fused ring systems is in great demand. However, those seven-membered ring systems are particularly difficult to prepare due to their typically higher strain barrier than other sized rings. A scarce number of catalytic methods are available to overcome the unfavorable enthalpic and entropic challenges of such organic reactions.[17-18] Over the past decades, a vast array of approaches have been devoted to developing effective strategies for synthesizing the benzocycloheptane motif and other fused bicyclo[m.n.0] ring systems,[19-28] including intramolecular cycloadditions, transition-metal catalyzed intermolecular [5+2] annulation, and other methods (Scheme 1a).[29-32] Very recently, Dong and co-workers reported a straightforward and distinct approach for accessing benzene-fused scaffolds between 1-indanones and ethylene gas or internal alkynes via intermolecular reactions (Scheme 1b).[33,34] Although these strategies have undoubtedly made a significant progress, the requirement of expensive noble metal rhodium, high temperature, high-pressure ethylene gas, and the limited scope of substrates, have severely hindered the application of these methodologies to the construction of highly complex and multi-functionalized structures.

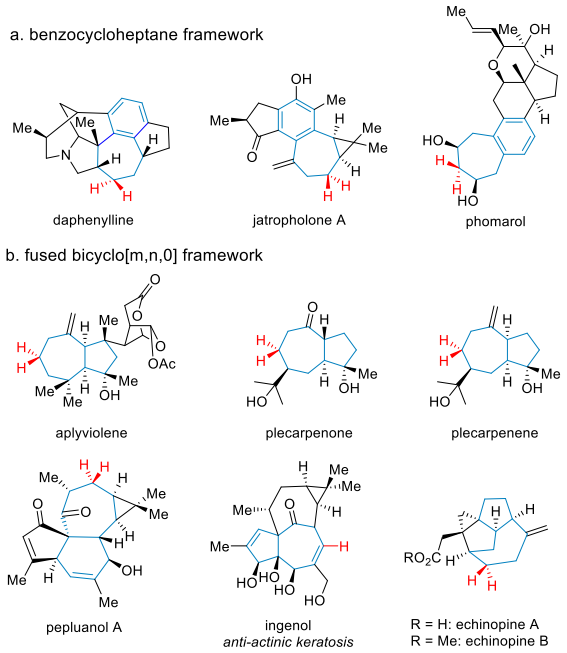
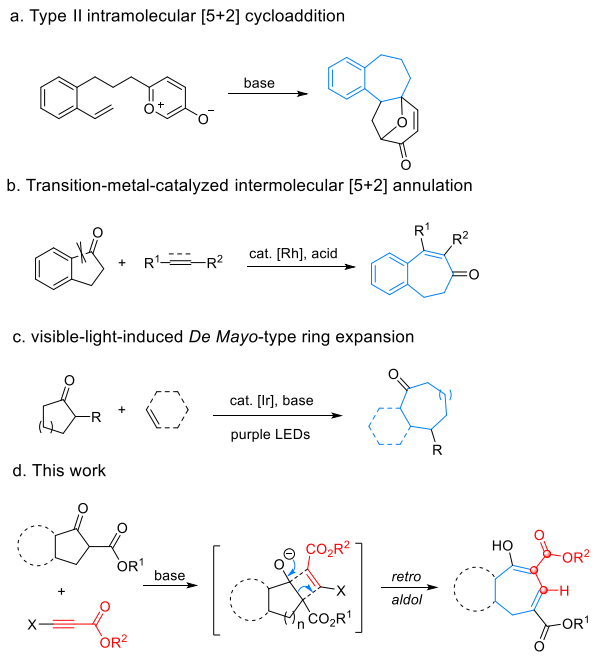


Figure 1. Selected fused seven-membered ring systems containing natural products.

In order to achieve direct construction of the fused medium-sized ring systems, a *De Mayo*-type ring expansion method was developed. To the best of our knowledge, the *De Mayo* reaction was pioneered by De Mayo[35] and subsequently enriched by De Mayo,[36] Weedon,[37,38] Bach,[39] and other groups.[40-42] Until now, the *De Mayo* reaction has still been a powerful and versatile tool for constructing polycyclic compounds using β-ketoenols and olefins induced by ultraviolet light. Based on this strategy, many complex natural products, and biologically active small molecules have been created.[18,40-44] With the rapid development of photoredox catalysts, radical chemistry has emerged as a vital and powerful platform to achieve multiple and efficient transformations under mild conditions. One prominent example is a more recent study by Glorius and co-workers that showcased a visible-light photocatalyzed two-carbon homologation of carbonyl compounds based on a novel iridium catalyst system to access medium-sized carbocycles (Scheme 1c).[45] Although this protocol presented the important aspect of generality, the unsatisfying regioselectivity has limited its synthetic applications in total synthesis.

Scheme 1. Synthetic Strategies toward the fused seven-membered ring systems.



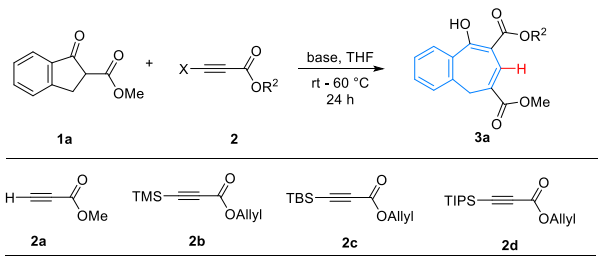
Alternatively, it is considered more appealing and of greater application value to directly generate seven-membered ring systems between β-keto esters and internal alkynes or alkene derivatives using less expensive, more abundant, and environmentally friendly transition metals, or even under metal-free conditions. Significant advances have been made by Proctor,[46,47] Stolz,[48] and others,[49,50] demonstrating the value of this strategy. In order to further extend the generality of this strategy for broader applications, the development of complementary methods is urgently required. To this end, we sought to explore the ring expansion on the unfavorable ring strain fused-cyclic system using alkynes in the presence of a base to afford these synthetically challenging fused seven-membered bicyclic scaffolds (Scheme 1d). This unique method can serve as a straightforward and powerful platform for the synthesis of a variety of functionally fused seven-membered polycyclic systems. Based on this strategy, we realized the total synthesis of two sesquiterpenoid natural products plecarpenene and plecarpenone, and achieved the key core for the total synthesis of echinopines. All the synthesized structures bear a highly strained fused bicyclo[5.3.0]decane motif.

Results and Discussion

Based on the analysis of the structures shown in Figure 1 and our hypothesis illustrated in Scheme 1d, we should choose a suitable alkyne to access these architectures. Therefore, the X group of alkyne could be easily switched to a hydrogen atom. Initially, our investigation started by using readily available methyl 1-oxo-2,3-dihydro-1H-indene-2-carboxylate (**1a**) and unprotected terminal alkyne (**2a**) as the model substrates to evaluate the reaction feasibility (Table 1). However, the annulation products were not obtained as expected while using cyclic β-ketoesters and terminal alkynes. This failure was likely a result of self-addition of activated alkynes under basic reaction conditions.[51,52] Consequently, we hypothesized that the installation of a suitable protecting group that can be easily switched to a hydrogen atom, was extremely important for constructing these architectures. Organosilicon compounds have been well recognized as versatile synthetic reagents that can be functionalized or cleaved under mild conditions. Thus, TMS-substituted alkyne (**2b**) was chosen to mimic the terminal alkyne **2a**. Surprisingly, **3a** was generated smoothly with high regioselectivity in 73% yield. The

chemical structure of **3a** was further confirmed via X-ray crystallography. It is of particular note that the steric hindrance of the protecting group for terminal alkynes had a great impact on the reaction. Thus, when alternative silane-protected alkyne **2c** or **2d** was used, the corresponding product was not able to be observed, which indicated that the use of TMS-substituted alkyne was critical for this type of ring expansion reaction. Based on this observation, TMS was chosen as the protecting group for further study.

Table 1. Optimization of the reaction conditions[a,b]



Entry	Base	Substrate ratio	Yield (%)
1	NaH	1/1.3	73
2	DABCO	1/1.3	N.R.
3	Na_2CO_3	1/1.3	N.R.
4	K_2CO_3	1/1.3	tracce
5	NaOH	1/1.3	N.R.
6[c]	NaH	1/1.5	78
7[c]	NaH	1/2	73

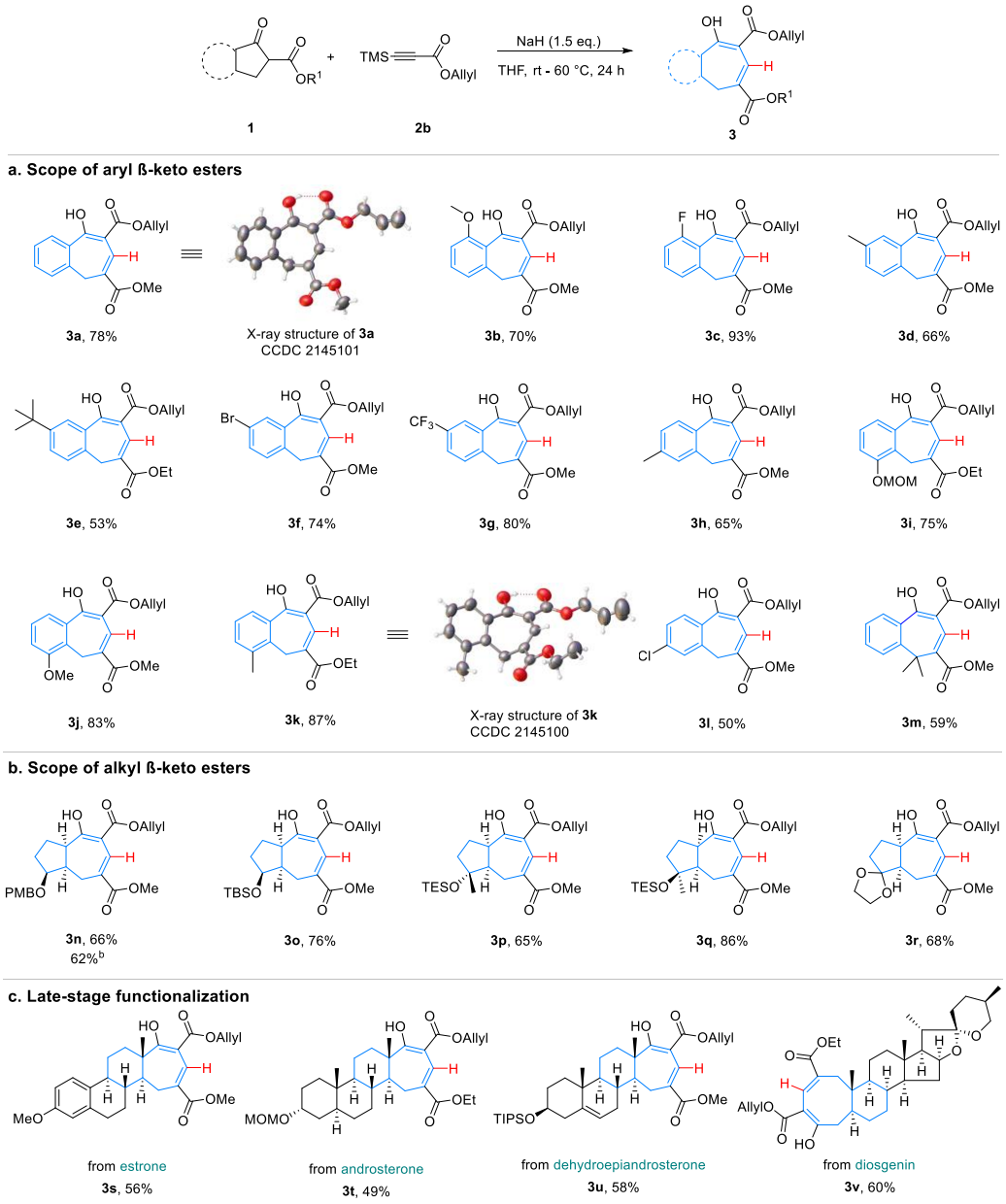
[a] Reaction conditions: **1a** (0.2 mmol) and base (0.24 mmol) in THF (2 mL), rt, 0.5 h; then **2b** (0.26 mmol), 60 °C, 24 h. [b] Isolated yields. [c] base (0.3 mmol) was added. For experimental details see Supporting Information.

Next, the impact of bases and solvents was evaluated to provide further insights and improvements on this reaction (Table 1). Remarkably, varying the bases from organic bases to inorganic ones suggested sodium hydride to be optimal (Table 1, entries 1-5). In terms of the solvent, THF gave better results than other solvents, such as DMSO, DMF, toluene, 1,4-dioxane, and MeCN (for more details, see Supporting Information, Table S1). Additionally, slightly higher yields were observed when the relative stoichiometry was increased to a 1/1.5 ratio (Table 1, entries 1, 6 and 7).

With the optimized reaction condition in hand, the scope of the reaction was evaluated concerning the benzocycloheptane motifs by performing reactions with aryl β-keto esters. As illustrated in Table 2a, a broad range of aryl-substituted β-keto esters, regardless of the positions and electronic properties of the substituents on the phenyl ring were perfectly compatible with the reaction condition, affording the corresponding products in moderate to excellent yields (**3a**–**3l**). 1-indanone derived substrates with methyl groups at the C4, C5, and C6 positions on the benzene ring are all compatible with the condition (**3d**, **3h** and **3k**). The relative configuration of **3k** was rigorously confirmed by X-ray crystallography. Remarkably, 1-indanone derived substrates with additional functionalities were all shown to be tolerated by this protocol. For example, a wide range of functional groups on the substrate, such as methoxy (**3b** and **3j**), chloro (**3l**), bromo (**3f**), fluoro (**3c**), and trifluoromethyl (**3g**) remained intact toward the transformation into the corresponding products. More interestingly, when the challenging dimethyl substitution located at the aliphatic position of 1-indanones was employed, the desired product (**3m**) was still able to be afforded in an acceptable yields.

Having established that this transformation can tolerate various aryl-substituted substrates, we then turned our attention to the tolerance of the alkyl component. The strained alkyl-substituted β-keto esters bearing different functional groups, such as phenyl ether (**3n**), silyl ether (**3o**-**3q**), and ketal (**3r**), were evaluated. To our delight, all of the substrates smoothly provided the highly strained bicyclo[5.3.0] ring systems in good yields. It is worth mentioning that this protocol can be performed steadily on a gram scale. Thus, 1.59 g of **3n** was easily synthesized from readily available **1n** and **2b**. Moreover, these scaffolds provided versatile synthetic handles for further modifications in natural product synthesis and drug development. In order to explore its prospective potential, this synthetic methodology was applied in the late-stage diversification of natural products and/or complex drug molecules. As shown in Table 2c, under optimized conditions, several natural products can be decorated via our method to afford seven or enight membered polycyclic architectures. These examples further illustrated the advantage of this strategy for the functionalization of biologically active natural products, which plays a significant role in drug development.

Table 2. Substrate scope with respect to the cyclic β-dicarbonyl derivatives[a]



[a] Unless noted otherwise, the reactions were performed using cyclic β-dicarbonyl (0.2 mmol), **2b** (0.3 mmol) and NaH (0.3 mmol) in THF (2 mL) at 60 °C. See Supporting Information for detailed procedures. [b] Ran on a 5 mmol scale.

To further explore the catalytic potentials of the present methodology, we applied this reaction to the total synthesis of plecarpenene and plecarpenone (Figure 2a), two guaiane natural sesquiterpenoids isolated from *Pleocarphus revolutus* in 1976.[53-55] Due to the lacking of an efficient strategy for the preparation of bicyclo[5.3.0]decane ring systems, only the Snapper group has reported their total synthesis so far.[56] First, ester **3p** was subjected to a decarboxylation reaction under the Tsuji conditions[57,58] to afford the desired ketone **4** in 76% yield. Ketone **4** was then reduced by $NaBH_4$ followed by a treatment with excess of MeLi to produce the olefin **5** in 86% yield over 2 steps. With sufficient quantity of olefin **5** in hand, we next sought to saturate the olefin group to install the last stereo-center of the natural product. However, elaboration of olefin **5** was shown to be highly challenging. As outlined in Table 3, the saturation of olefin **5** with conventional hydrogenation reaction using Pd/C as the catalyst failed to give the desired product due to the steric hindrance (Table 3, entry 1). Moreover, similar results were observed when Crabtree's or Wilkinson's catalyst was used (Table 3, entries 2 and 3). Unfortunately, further reaction condition screening revealed that hydrogenation using the highly reactive PtO_2 (Table 3, entry 4) in ethyl acetate produced the undesired diastereomer **7** as the single product. Our pioneering attempts indicated that the desired diol **6** was not able to be obtained via currently available stereo-controlled hydrogenation methods. Thus, the radical reduction reaction initiated by metal-catalyzed hydrogen atom transfer (MHAT) was used as the alternative reduction method.[59,60] We set out to forge the last stereo-center by the procedure developed by Shenvi and co-workers ($Mn(dpm)_3$, $PhSiH_3$, TBHP). To our delight, this reaction produced the desired diol **6** (48% yield) and its diastereomer **7** (29% yield) (entry 5). The major isomer diol **6** was further elaborated by Ley-Griffith oxidation to afford the advanced intermediate ketone **8**. An expected two fold Peterson olefination process occurred upon the treatment of ketone **8** with $TMSCH_2Li$ followed by a treatment with *p*-toluenesulfonic acid in methanol, furnishing the natural product plecarpenene in 69% isolated yield. Alternatively, we also realized the total synthesis of plecarpenone via the base promoted epimerization of the C5 stereo-center followed by a desilylation. The natural product plecarpenone was successfully produced in 96% yield by two steps. All the spectroscopic data (^1H and ^{13}C NMR, HRMS) of synthetic plecarpenene and plecarpenone were in good agreement with those previously reported by Snapper group.[23]

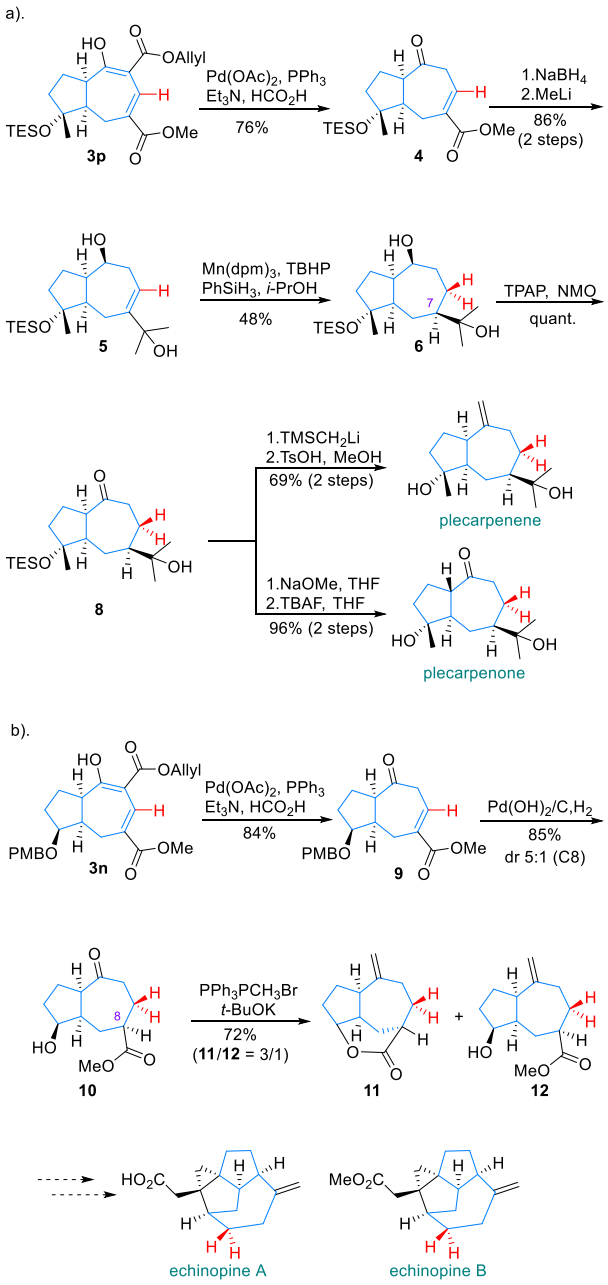
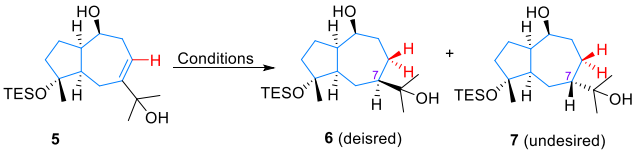


Figure 2. Synthesis of the cores of echinopines and total syntheses of plecarpenene and plecarpenone.

To seek broader applications of our methodology, the highly strained *cis*-fused bicyclic core of echinopines, isolated from the root of the plant *Echinops spinosus* in 2008,[61] was synthesized using this reaction (Figure 2b). Biosynthetically, echinopines A and B were proposed to originate from a guanine type precursor through a

series of rearrangements.[61] Inspired by the biosynthetic pathway, the phenyl ether derivative of **3n** was easily transformed into the corresponding ketone **9**. Then a reduction of the α,β-unsaturated ester group of **9** by palladium-catalyzed hydrogenation reaction generated a pair of diastereomers **10** and C8-*epi*-**10** in 71% and 14% yield respectively. Treatment of the ketone **10** with a Wittig reaction provided the lactone **11** and the olefine **12** in 72% overall yield (dr 3:1), which contained the core moiety of guanine type triterpenoids with a highly strained *cis*-fused bicyclo[5.3.0]decane ring system. The similar intermediate was reported by Liang and co-workers previously.[62]

Table 3. Screening of conditions for the reduction[a]



5 **6** (deisred) **7** (undesired)

Entry	Conditions	Yield (%)
1	H_2, 5% Pd/C, MeOH, rt	N.R.
2	H_2, Crabtree's cat., DCM	N.R.
3	H_2, Wilkinson's cat., toluene, 50 °C	N.R.
4	H_2, PtO_2, EtOAc, rt	**7** (87%)
5[b]	$Mn(dpm)_3$, TBHP, $PhSiH_3$, *i*-ProH,rt	**6** (48%) + **7** (29%)

[a] Isolated yields, reactions ran on 0.012 mmol scale unless otherwise specified. [b] Reaction ran on 1.0 mmol scale.

Conclusion

In summary, a convenient approach for constructing fused seven-membered polycyclic architectures widely found in natural products and small molecule drugs was developed. This synthetic protocol proceeded with the merits of mild conditions, broad substrate scope, operation simplicity, and excellent regioselectivity. Based on this method, we accomplished the total syntheses of plecarpenene and plecarpenone in an extraordinarily efficient manner. To further demonstrate the applicability of this method, the key core of the echinopine natural

products was successfully assembled. Further studies to expand the reaction patterns and the applications in synthesizing complex natural products and other bioactive molecules are still ongoing in our laboratory.

Supporting Information

Supporting Information is available and includes optimization tables, experimental procedures, characterization data, X-ray data, and ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR for the products.

Conflict of Interest (required)

There is no conflict of interest to report.

Funding Information (required)

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