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Synthesis of Highly Stereodefined Tetrasubstituted Acyclic All-Carbon Olefins via a *Syn*-Elimination Approach

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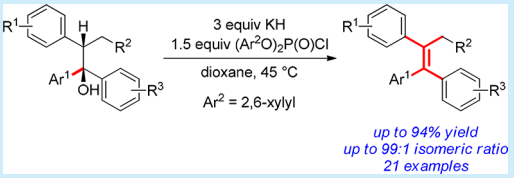
Supporting Information

ABSTRACT: An efficient synthesis of stereodefined tetrasubstituted acyclic all-carbon olefins has been developed via a bis(2,6-xylyl)phosphate formation of stereoenriched tertiary alcohols, followed by in situ *syn*-elimination of the corresponding phosphates under mild conditions. This chemistry tolerates a wide variety of electronically and sterically diverse substrates and generates the desired tetrasubstituted olefins in high yields and stereoselectivities (>95:5) in most cases. This stereocontrolled olefin synthesis has been applied to the synthesis of anticancer drug tamoxifen in three steps from commercially available 1,2-diphenylbutan-1-one in 97:3 stereoselectivity and 78% overall yield.



Stereodefined tetrasubstituted acyclic all-carbon olefins are a fundamental structural motif found in pharmaceuticals,[1a−c] scaffolds for material science, molecular motors, and liquid crystals.[1d−f] Tetrasubstituted olefins bearing a triphenylethylene moiety constitute an important class of molecules critical to the treatment of breast cancer[1a−c] and additional diseases such as multiple sclerosis and infections of fungal, bacterial, and Ebola virus (Figure 1).[2] Several strategies for forming the key C=C double bond are well established,[3] including McMurry coupling,[4] Wittig and Horner−Wadsworth−Emmons reactions,[5] dehydration of alcohols,[6] conjugate addition to activated allenes,[7] iterative Heck coupling of acrylates,[8] functionalization of enolates,[9] and carbometalation of alkynes.[10] However, concerns of stereo- and regioselectivity have limited any specific strategy from being fully adopted for general application. Hence, the preparation of stereodefined tetrasubstituted acyclic all-carbon olefins remains a stimulating challenge for the synthetic organic community.[3]

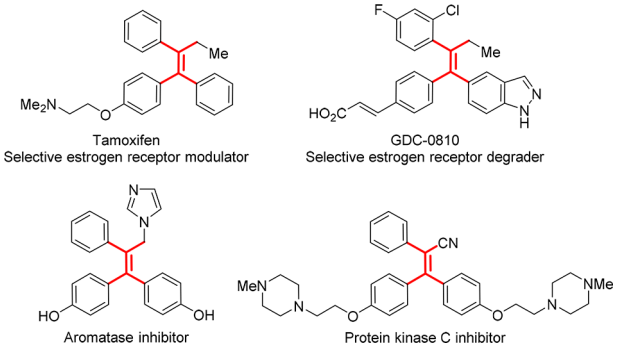
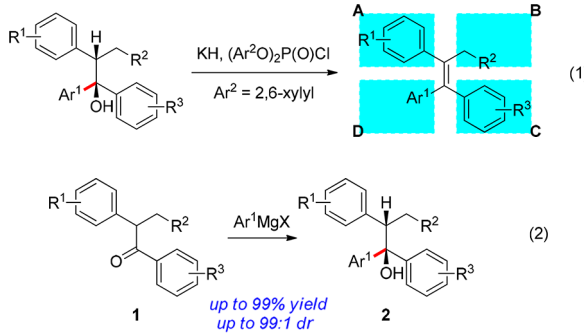


Figure 1. Tetrasubstituted olefins in various pharmacological targets.



During our process development of GDC-0810, a selective estrogen receptor degrader in clinical studies for the treatment of metastatic breast cancer,[1c] we sought to advance an efficient route to stereodefined tetrasubstituted olefins. Herein we describe a practical and mild protocol to access highly stereodefined tetrasubstituted acyclic all-carbon olefins that can be readily adapted to structural modifications on all four quadrants (arbitrarily assigned clockwise as **A**, **B**, **C** and **D**) of the olefin molecule (eq 1). The synthesis of stereoenriched tertiary alcohols **2** was readily achieved via aryl Grignard addition to ketones **1** in excellent yields and diastereoselectivity in most cases (eq 2).[6] In order to confirm the stereochemical assignments of the tertiary alcohols, we obtained X-ray crystal structures of most of the alcohol products (see the Supporting

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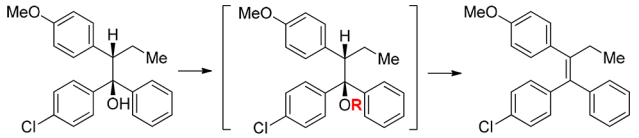
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Optimization of *Syn*-Elimination Reaction[a,b]



2a 3a

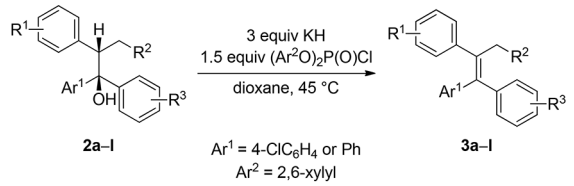
entry	R	temp (°C)	conv (%)	3a (A%)	Z/E ratio
1	C(O)*t*-Bu	150	<5	<5	93:7
2	CO_2*t*-Bu	150	30	16	98:2
3	$C(O)NMe_2$	150	<5	<5	92:8
4	SO_2NMe_2	150	22	17	84:16
5	$P(O)(OPh)_2$	45	68	59	89:11
6	$P(O)(O\text{-}2,6\text{-}xylyl)_2$	45	72	72	96:4
7[c]	$P(O)(O\text{-}2,6\text{-}xylyl)_2$	45	88	84[d]	98:2
8[e]	H	45	92	91	67:33
9[f]	H	45	35	37	57:43

[a]Reactions were performed with alcohol **2a**, KHMDS (3.0 equiv), PhEt (5.0 mL/mmol), and electrophile RCl (1.5 equiv) except for entry 2 where Boc_2O (1.5 equiv) was employed. [b]Conversion, A%, and *Z*/*E* ratio were determined by HPLC analysis. [c]KH (3.0 equiv), bis(2,6-xylyl)phosphoryl chloride (1.5 equiv) in dioxane (5.0 mL/mmol). [d]Isolated yield. [e]Burgess reagent (1.5 equiv) was employed. [f]Martin sulfurane (1.5 equiv) was employed.

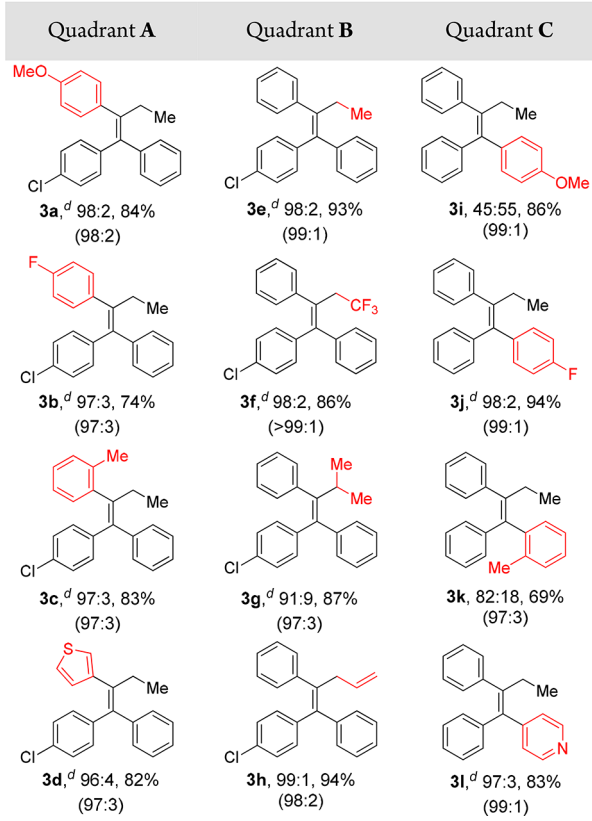
Information). We then investigated the *syn*-elimination of these substrates via direct derivatization, first using alcohol **2a** as a model substrate (Table 1). Elimination of the pivalate of alcohol **2a** did generate tetrasubstituted olefin **3a** in a 93:7 *Z*/*E* ratio; however, the reaction required very high temperature and the conversion was low (Table 1, entry 1). Similarly, the corresponding carbonate, carbamate, and sulfamate also required harsh conditions to afford the elimination product (Table 1, entries 2−4). To our pleasant surprise, alcohol **2a**, upon treatment with diphenylphosphoryl chloride and KHMDS, formed predominantly the *Z* olefin isomer **3a** in an 89:11 *Z*/*E* ratio at a more practical 45 °C (Table 1, entry 5). Further modifying the phosphate to bis(2,6-xylyl)phosphate and employing potassium hydride as the base in dioxane led to the formation of the tetrasubstituted olefin **3a** in 98:2 *Z*/*E* ratio and 84% isolated yield (Table 1, entries 6 and 7). It is worth mentioning that the direct dehydration using Burgess reagent[11a] or Martin sulfurane[11b] without KHMDS produced unsatisfactory conversion and *Z*/*E* ratio (Table 1, entries 8 and 9).

With optimized elimination conditions in place, we first explored the scope and limitations of varying substituents in quadrants **A**, **B**, and **C** (Scheme 1). In quadrant **A**, the elimination reaction to produce olefins **3** occurred with markedly high stereoselectivity (96:4−98:2) and yield (74−84%) regardless of variation of electronic (**3a** vs **3b**) and steric (**3c** vs **3d**) properties of groups or possession of heterocyclic functionality (**3d**). Similarly, varying the electronic properties of groups in quadrant **B** did not have a significant impact on the stereoselectivity (**3e** vs **3f** and **3h**). However, when a larger isopropyl group was installed in quadrant **B**, the stereoselectivity suffered a slight loss to 91:9 (**3g**). Quadrant **C** is more sensitive to both electronic and steric impacts. For example, the elimination reaction was essentially nonselective when an electron-rich substituent 4-$MeOC_6H_4$ was placed in quadrant **C**, resulting in a 45:55 mixture of *E*/*Z* isomers (**3i**), while electron-deficient substituents in quadrant **C** (4-FC_6H_4 and 4-pyridyl) continued to generate excellent stereoselectivity (97:3−98:2) in formation of the olefin products (**3j** and **3l**). When quadrant **C** was

Scheme 1. Elimination Reaction Scope of Quadrants A−C[a−c]



2a–l 3a–l



[a]All reactions were performed with KH (3.0 equiv) and bis(2,6-xylyl)phosphoryl chloride (1.5 equiv) in dioxane (5.0 mL/mmol) at 45 °C, unless otherwise indicated in the SI. The number in parentheses is the dr of the starting alcohol. [b]Measured stereoisomer ratio by HPLC. [c]Isolated yield. [d]Assigned stereochemistry confirmed by X-ray crystallographic analysis.

substituted with a bulky 2-tolyl group, the stereoselectivity of the elimination reaction again deteriorated, giving an 82:18 *E*/*Z* ratio of the olefin products (**3k**).

We subsequently evaluated the substituent scope and limitations of quadrant **D** (Scheme 2). Elimination of the corresponding bis(2,6-xylyl)phosphates derived from alcohols **2m−u** to olefins **3m−u** is noticeably influenced by both steric and electronic components of the substituents, as evident by lower *Z*/*E* ratios observed for products **3n** and **3s**, which bear electron-rich 4-$MeOC_6H_4$ and 3-thienyl moieties, and **3r** which contains a bulky 2-tolyl group. We were nevertheless encouraged to discover that the remaining substrates bearing diverse functionalities displayed high stereoselectivity (≥95:5). Hence, selective elimination via phosphates[12] can be readily extended to a diverse scope of substrates. Furthermore, X-ray crystal structures of several crystalline olefin products not only confirmed our stereochemical assignments but also consistently pointed to a predominant *syn*-elimination process (see the Supporting Information).

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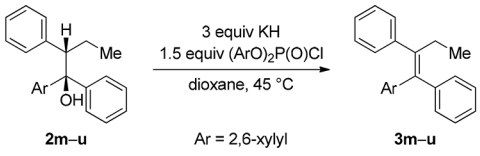
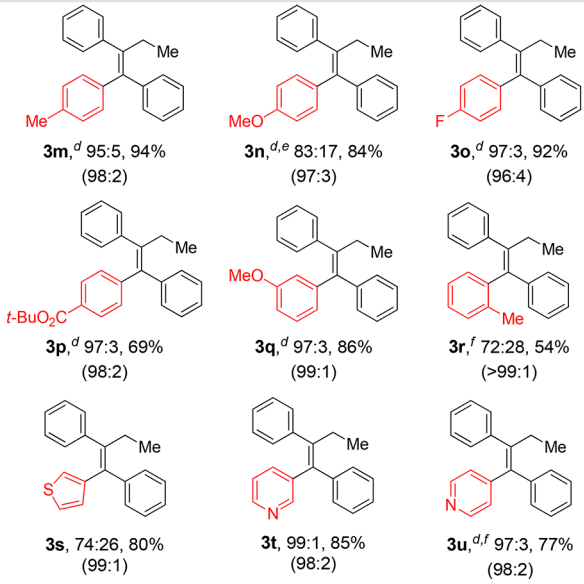
Scheme 2. Elimination Reaction Scope of Quadrant D[a−c]



Tetrasubstituted olefins



[a]All reactions were performed with KH (3.0 equiv) and bis(2,6-xylyl)phosphoryl chloride (1.5 equiv) in dioxane (5.0 mL/mmol) at 45 °C, unless otherwise indicated. The number in parentheses is the dr of the starting alcohol. [b]Measured *Z*/*E* ratio by HPLC. [c]Isolated yield. [d]Assigned stereochemistry confirmed by X-ray crystallographic analysis. [e]Reaction performed at 80 °C. [f]Reaction performed at 70 °C.

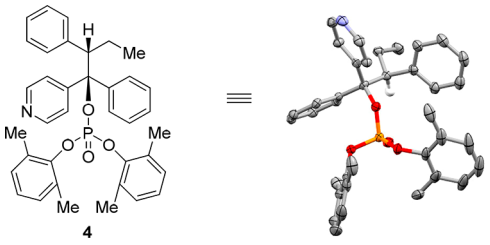
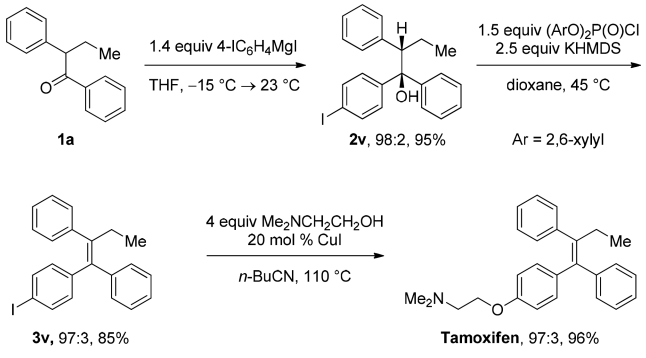


Figure 2. X-ray structure of bis(2,6-xylyl)phosphate **4**.

Scheme 3. Highly Stereoselective Synthesis of Tamoxifen



By performing the phosphorylation reaction at 23 °C, we were able to isolate phosphate intermediate **4** in 61% yield by subjecting alcohol **2u** with an electron-deficient 4-pyridyl substituent in quadrant **D** to the elimination conditions. The X-ray crystal structure of **4** (Figure 2) shows a *syn* relationship between the phosphate and the benzylic proton, consistent with a *syn*-elimination pathway occurring via discrete phosphate intermediate. This phosphate species then could undergo a further elimination reaction upon heating at 70 °C, producing the tetrasubstituted olefins in 97:3 *Z*/*E* ratio and 77% yield (**3u**).

To demonstrate the synthetic utility of our chemistry, we applied the phosphate elimination strategy to the synthesis of tamoxifen (Scheme 3).[13] Commercially available ketone 1,2-diphenylbutan-1-one was treated with 4-iodophenylmagnesium iodide, producing alcohol **2v** with 98:2 dr in 95% yield. Alcohol **2v** was then readily transformed to olefin **3v** in high yield (85%) and *Z*/*E* selectivity (97:3) using slightly modified phosphate elimination conditions.[14] Subsequent copper-catalyzed C−O coupling with *N*,*N*-dimethyl-2-hydroxyethylamine furnished the target tamoxifen in 96% yield and with no erosion of the *Z*/E ratio.

We conducted DFT calculations on the elimination of **4** (Figure 2) to further elucidate the mechanism of the elimination reaction. We were unable to locate transition-state structures (TSSs) for concerted *syn*-elimination, likely a result of the very crowded core of such putative TSSs and the tight grouping of multiple aromatic rings leading to atypical reactivity.[15] Instead, two-step (E1) elimination was predicted to dominate, but the intermediate complex in this process is predicted to reside on a flat region of the potential energy and free energy surfaces (Figure 3); effectively, the reaction is concerted but the dissociation and deprotonation events occur very asynchro-

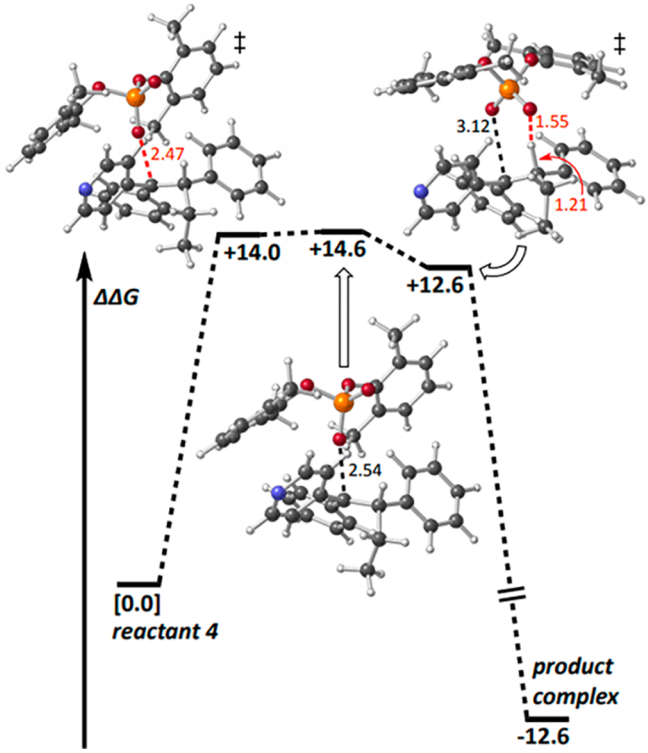


Figure 3. Structures along the reaction coordinate for *syn*-elimination of bis(2,6-xylyl)phosphate **4**. Geometries for TSS for P−O bond cleavage, carbocation−phosphate complex, and TSS for deprotonation (selected distances in Å) and relative free energies (kcal/mol) are shown; note that the TSSs are only TSSs on the potential energy surface, not the free energy surface.

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Org. Lett. XXXX, XXX, XXX−XXX

nously.[16] As result, deprotonation is expected to be much faster than dissociation of the complex and stereochemistry is expected not to be scrambled.

In conclusion, we have developed a stereoselective synthesis of tetrasubstituted acyclic all-carbon olefins by elimination of in situ produced bis(2,6-xylyl)phosphates from stereoenriched tertiary alcohols. The synthetic utility of this chemistry was further demonstrated by a highly stereoselective three-step synthesis of tamoxifen from 1,2-diphenylbutan-1-one in 97:3 *Z*/*E* selectivity and 77% overall yield. Our computational studies indicate that the elimination reaction involves a stepwise or concerted/asynchronous *syn*-elimination that preserves stereochemical information because the lifetime of the carbocation−phosphate complex is exceedingly short. We believe that the highly stereoselective synthesis of tetrasubstituted acyclic all-carbon olefins under mild conditions disclosed here will provide a very useful synthetic tool for organic chemists.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03141.

Experimental details and ^{1}H and ^{13}C NMR spectra (PDF)
Computational data (PDF)
X-ray crystallographic data (PDF)
X-ray crystallographic data in CIF format (ZIP)

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Notes

The authors declare no competing financial interest.

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Org. Lett. XXXX, XXX, XXX−XXX