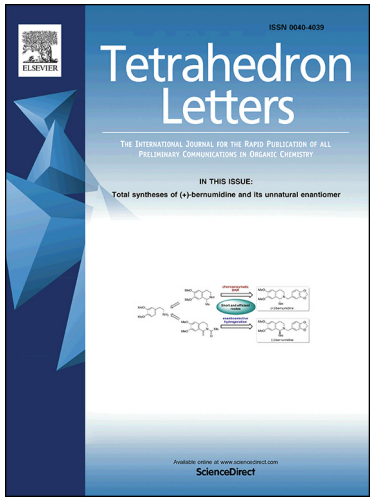

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A short and divergent route to 2-alkenyl-4-quinolones

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4-Quinolones
Alkaloid
Olefination
Horner-Wadsworth-Emmons reaction

Abstract
Alkenyl-4-quinolones were accessed *via* a high-yielding, three-step synthesis starting from 2-methyl-4-quinolones using a one-pot phosphorylation-olefination sequence as the key step and SEM as a convenient protecting group. This protocol tolerates various functional groups and gives the target olefins with complete (*E*)-selectivity.

Introduction

4-Quinolones are a scaffold of significant relevance in medicinal chemistry. Appropriately substituted 4-quinolone-3-carboxylic acids, e.g. ciprofloxacin, are among the most important fully synthetic antibiotics.[1] Furthermore, a considerable number of 4-quinolones have been isolated from biological sources (plants like the *Evodia* species and microorganisms, the most prominent among these are *Pseudomonas* species), and antibacterial, antiplasmodial, and cytotoxic activities have been reported for many of them.[2] These naturally occurring 4-quinolones are characterized by an alkyl or alkenyl group at C-2, and some of them further bear a substituent at C-3. The olefinic double bond in the side-chain can be located at a distal position (e.g. evocarpine), separated from the heterocycle by a methylene group (e.g. burkholone), or in direct conjugation with the heterocycle (e.g. alkaloid Δ^1-pseudene-VII and some homologues[3]). *N*-Hydroxylation was detected in 4-quinolones exhibiting strong antibiotic activity, e.g. YM-30059[4] and aurachin C[5] (Fig. 1).
Naturally occurring 2-alkylquinolones served as lead structures for the synthesis of antimycobacterial analogues,[6] but were catapulted into the spotlight when they were identified as quorum sensing signal molecules in *Pseudomonas* species, controlling the expression of virulence genes as a function of cell population density.[2a] This opens a completely new option for the treatment of multidrug-resistant *Pseudomonas aeruginosa* infections.[7] Furthermore, *N*-unsubstituted 4-quinolones are useful precursors for the synthesis of antibacterial *N*-hydroxy-4-quinolones[8] and antiprotozoal 4-aminoquinolines.[9]

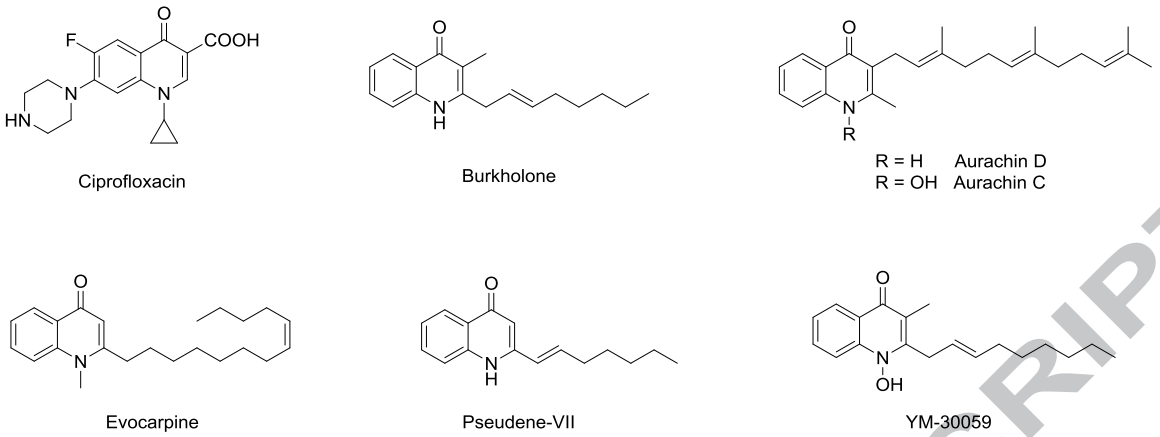


Figure 1. Selected 4-quinolones of pharmaceutical interest. The antibiotic ciprofloxacin and representative 4-quinolone alkaloids bearing unsaturated side-chains: burkholone, aurachin C, aurachin D, evocarpine, Δ^1-pseudene-VII, and YM-30059.

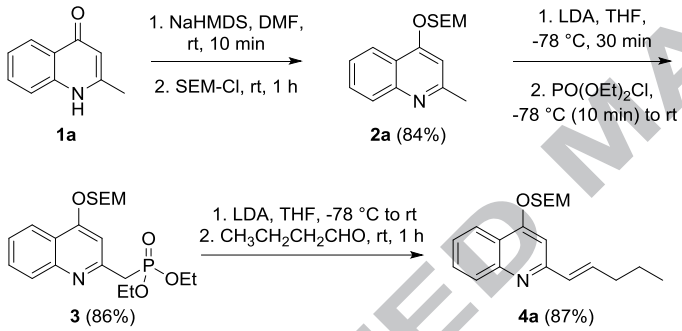
Sophisticated methods have been developed for the industrial production of fluoroquinolone antibiotics, among them one-pot-[10] and flow-chemistry[11] multi-step reactions. 4-Quinolones bearing alkyl or aryl residues at C-2 (and/or C-3) can be prepared following established strategies.[12] The most prominent are the Conrad-Limpach synthesis (from anilines and β–ketoesters), the Camps method (cyclization of *ortho*-acylaminoacetophenones) and the Niementowski reaction (from anthranilamide and ketones as well as variants using isatoic anhydride).[6,13] However, most of these methods are not or only moderately applicable to the synthesis of 4-quinolones bearing olefinic residues, and very few publications describe the synthesis of 2-(1-alkenyl)-4-quinolones other than styryl derivatives.[6,14] A novel rearrangement of anthranilic esters yields 2-alkenyl-3-hydroxy-4-quinolones.[15] Considerable work has been performed on the construction of 2-alkenyl-4-quinolones by the functionalization of pre-built 2-methyl-4-quinolones. Target compounds related to burkholone (Fig. 1) bearing allylic residues at C-2 were obtained *via* the cross-coupling reactions of 2-halomethyl-4-quinolones with vinylic building blocks.[16] For the synthesis of 2-(1-alkenyl)-4-quinolones, very few examples of direct Knoevenagel-type condensations of the 2-methyl group attached to a 4-quinolone are known;[17] only aromatic aldehydes have been condensed under drastic reaction conditions (acetic anhydride, 140 or 145 °C), and the configuration of the resulting olefins is unclear. In other approaches the 2-methyl-4-quinolones were first converted into 4-substituted (methoxy, benzyloxy) 2-methylquinolines by *O*-alkylation. Deprotonation of the now CH-acidic 2-methyl group followed by reaction with diethyl chlorophosphate gave benzylic phosphonates as building blocks for Horner-Wadsworth-Emmons (HWE) olefinations with aldehydes.[18] For 4-benzyloxy derivatives deprotection by catalytic hydrogenation is accompanied by saturation of the 2-alkenyl residue;[18b] deprotection of the 4-methoxy analogues[18a] has not been attempted. 4-Acetoxy-2-methylquinolines were oxidized at the methyl group and further converted over a number of steps into quinolin-2-ylmethyl triphenylphosphonium salts, which gave 2-alkenyl-4-quinolones after Wittig olefination and deprotection.[19]

Results and Discussion

In the present work we intended to develop a new general approach to *N*-unsubstituted 2-alkenyl-4-quinolones, and HWE olefinations of an appropriate building block with aldehydes or ketones appeared to provide a divergent approach to variable olefinic side-chains. However, the acidity of the quinolone NH group impedes HWE olefinations at the stage of the 4-quinolone.[20] Therefore, we decided to convert 2-methyl-4-quinolones into *O*-protected 4-hydroxyquinolines to circumvent this problem. We selected the SEM (2-(trimethylsilyl)ethoxymethyl) protecting group that had previously

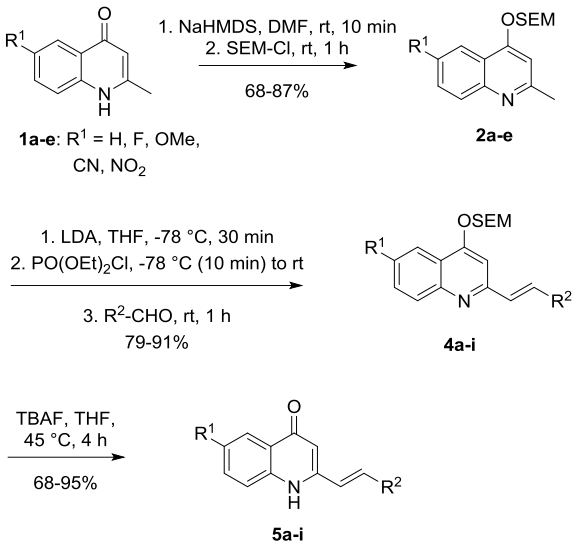
found scarce attention in quinolone chemistry.[21] This protecting group is stable under the anhydrous basic conditions of a HWE reaction, and can, in a final step, be readily removed with aqueous acid or fluoride to release the desired 4-quinolone.

The SEM protecting group was attached to 2-methylquinolone with SEM-Cl and sodium hexamethyldisilazane (84% yield). We were aware of the ambident character of the generated quinolone anion and supposed the SEM protecting group to be linked to the oxygen atom and not to the nitrogen atom. This assumption was confirmed by NOE experiments and 2D-NMR spectroscopy. Inspired by the work of Carran and co-workers[22] on the synthesis of a 2-picoline-derived phosphonate, we converted SEM-protected quinolone (**2a**) into phosphonate **3** by deprotonation of the acidic methyl group using LDA, followed by trapping with diethyl chlorophosphate. Two equivalents of LDA were required for complete conversion, since the product **3** is more acidic than the starting material **2a**. After aqueous work-up phosphonate **3** was isolated in 86% yield. HWE olefination of **3** with *n*-butanal and LDA as a base gave the desired vinylquinoline **4a** in 87% yield (Scheme 1). Fortunately, this conversion of **2a** could also be performed in a one-pot phosphorylation-alkenylation reaction, since during the preparation of intermediate **3** the required deprotonated phosphonate was formed as well. Vinylquinoline **4a** was directly obtained in 87% yield from **2a** (Scheme 2).



Scheme 1. Two-step olefination protocol: Generation of phosphonate **3** and subsequent Horner-Wadswoth-Emmons reaction.

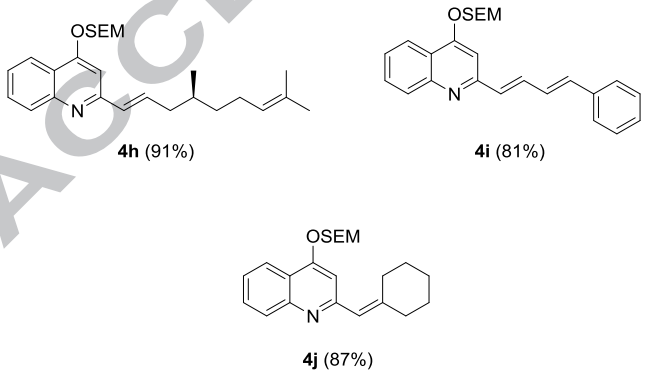
The scope of this one-pot procedure was initially investigated using various carbonyl compounds as starting materials for the HWE reaction. The reaction worked very well (81–91% yield) with aliphatic, aromatic, heteroaromatic and vinylogous aldehydes; even cyclohexanone gave the corresponding alkene **4j** in 87% yield (Scheme 2, Table 1, Scheme 3). The olefins **4a-i** were obtained exclusively with (*E*)-configuration.



Scheme 2. Synthesis of 2-alkenyl-4-quinolones **5a-i** from the corresponding 2-methyl-4-quinolones **1a-e** and aldehydes *via* a one-pot phosphorylation-alkenylation sequence.[23]

Table 1. Yields for the one-pot phosphorylation/HWE reaction of **2a-d** with various aldehydes.

Product	R^1	R^2	Yield
4a	H	*n*-propyl	87%
4b	F	*n*-propyl	82%
4c	OMe	*n*-propyl	80%
4d	CN	*n*-propyl	79%
4e	H	phenyl	85%
4f	H	2-furyl	84%
4g	H	*n*-heptyl	85%



Scheme 3. SEM-protected 2-alkenyl-4-quinolines obtained from **1a** and unsaturated aldehydes (citronellal for **4h**, cinnamaldehyde for **4i**), and cyclohexylidene analogue **4j** obtained in an analogous manner utilizing cyclohexanone as the carbonyl component.

Furthermore we investigated the impact of different substituents on the benzene moiety of the quinolone ring on the outcome of the one-pot phosphorylation-alkenylation protocol. Substituents with

electron withdrawing (fluorine, cyano) or electron donating properties (methoxy) were expected to influence the acidity of the methyl group in intermediates **2b-d**, and might thus affect the overall yield. Fortunately, in each case the reaction proceeded very well and good yields (79–82%) of products **4b-d** were obtained (Table 1). Therefore, this method is insensitive to electronic effects, and overall has a broad scope. Only one attempt starting with the 6-nitro analogue **2e** failed, but this was due to solubility problems.

The SEM protecting group in intermediates **4a-j** was conveniently removed with tetrabutylammonium fluoride (TBAF) to give the desired alkenylquinolones **5a-j** in good to excellent yields (68–95%) with preservation of the (*E*)-configuration of the vinyl groups. The overall reaction sequence is summarized in Scheme 2.

One of the obtained products, (*E*)-2-(non-1-en-1-yl)quinolin-4(1*H*)-one (**5g**; also known as Pyo III), obtained from **1a** and *n*-octanal (64% yield over 3 steps), is an alkaloid produced by *Pseudomonas aeruginosa*.[3,24] This compound shows antibiotic[24] and antimalarial[25] properties. Previous total syntheses of **5g** using a Conrad-Limpach synthesis[26] as well as a multi-step route *via* 2-nonylcinchoninic acid[27] yielded this alkaloid in very poor overall yields.

In conclusion, this new 3-step protocol provides a useful synthetic tool for the synthesis of the hitherto poorly accessible 2-alkenylquinolones. The method is mild, gives high overall yields, is insensitive to electronic effects in the starting 2-methylquinolone building block, and is applicable to the introduction of a broad variety of vinylic groups. Due to the stereoselectivity of the HWE olefination step, it is suitable for the controlled production of (*E*)-configured 2-alkenyl-4-quinolones, the geometry typically occurring in natural products of this chemotype. This method should find broad application in the synthesis of bioactive 2-alkenyl-4-quinolones.

Supplementary data

Supplementary data (experimental procedures and copies of ^{1}H and ^{13}C NMR data for all new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/.....

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23. General procedure for the one-pot phosphorylation-olefination step: A solution of the SEM-protected 2-methylquinolin-4(1*H*)-one (1.0 mmol, **2a-d**) in dry THF (3 mL) under a nitrogen atmosphere was cooled to –78 °C and a LDA solution (1.0 mL, 2M in THF, heptane, ethylbenzene; 2.0 mmol) was added dropwise over a period of 10 minutes. After 30 minutes of stirring diethyl chlorophosphate (0.16 mL, 1.1 mmol) was added and the mixture was stirred for 10 minutes at –78 °C. The cooling bath was removed and the mixture was allowed to reach room temperature. Then the carbonyl compound (0.9 mmol) was added and the mixture was stirred for 60 minutes at room temperature. After addition of water (4 mL) the organic layer was separated and the aqueous layer extracted with dichloromethane (3 × 2 mL). The combined organic layers were dried over sodium sulfate and after removal of the solvent the residue was purified by flash column chromatography with a mixture of ethyl acetate and hexanes.

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Highlights

- Novel three-step synthesis of poorly accessible 2-alkenylquinolones developed
- High-yielding synthesis starting from easily available 2-methylquinolones
- High functional group compatibility
- Suitable for the production of pure (*E*)-configured 2-alkenylquinolones

Graphical Abstract

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