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Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/lsyc20

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To cite this article: Mana Ono , Shouki Abe , Koji Higai , Shoko Higashi , Setsuo Saito & Ryota Saito (2020): An improved and practical synthesis route to antiproliferative (±)-shikonin and its *O*-acyl derivatives, Synthetic Communications, DOI: 10.1080/00397911.2020.1853171

To link to this article: https://doi.org/10.1080/00397911.2020.1853171

Published online: 06 Dec 2020.

SYNTHETIC COMMUNICATIONS®
https://doi.org/10.1080/00397911.2020.1853171

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An improved and practical synthesis route to antiproliferative (±)-shikonin and its *O*-acyl derivatives

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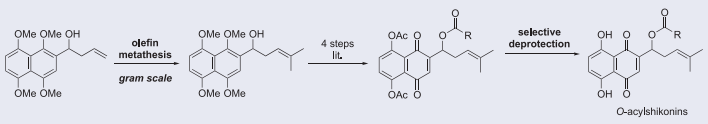
ABSTRACT

Shikonin and its *O*-acyl derivatives are attracting increasing levels of attention among medicinal chemists due to their potencies as highly selective cytotoxic agents against cancer cells. However, providing a large number of shikonin-related samples by organic synthesis remains challenging. In the present study, we developed an improved and practical synthesis route to shikonin derivatives by olefin metathesis that has enabled the gram-scale preparation of a prenylated tetramethylnaphthazaline, a key intermediate in the synthesis of shikonin. In addition, a method for the selective cleavage of the acyl protecting groups at the phenolic positions of tri-*O*-acylated shikonins has been developed that provides concise routes to diverse *O*-acylshikonin derivatives.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 17 August 2020

KEYWORDS
Shikonin; O-acyl shikonin; gram-scale synthesis; olefin metathesis

Introduction

Shikonin, (*R*)-(−)-**1** (Figure 1), was first isolated as acetylshikonin from the roots of the traditional oriental herb, Murasaki (*Lithospermum erythrorhizon*),[1,2] and alkannin,[3] (*S*)-(+)-**1** (Figure 1), is the enantiomer of shikonin. Shikonin has a long history of use as a drug for the treatment of burns, bacterial infections, wounds, and inflammation.[4] Over the last 40 years many *in vitro* and *in vivo* studies have demonstrated the antitumor activities of shikonin against several kinds of cancer cells, including leukemia,[5,6] breast-cancer,[7,8] glioma,[9,10] and bladder-cancer cells.[11]

More recently, shikonin derivatives bearing functional groups in their side chains have exhibited higher anticancer activities than shikonin. For example, sulfonamide derivatives exhibit inhibitory activities against promyelocytic leukemia cells (HL60) that are about 20-times higher than that of shikonin, which has already been shown to be

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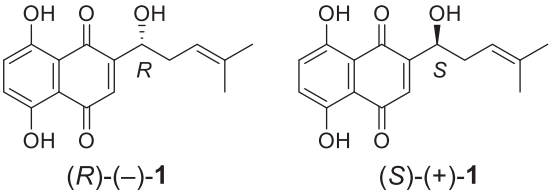


Figure 1. The structures of shikonin and alkannin.

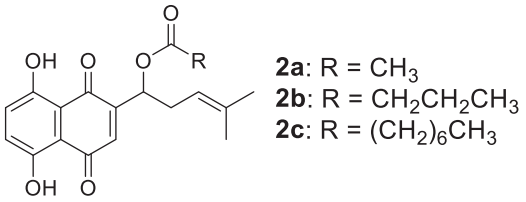


Figure 2. Targeted *O*-acylshikonin derivatives.

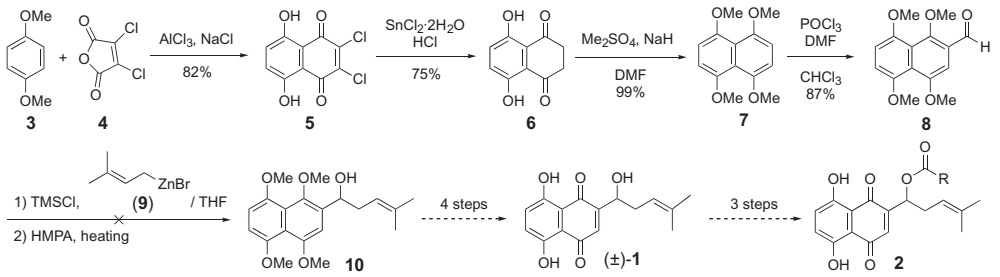
more potent compared to the clinically used drug, VP16.[4] Other derivatives bearing *O*-acyl substituents exhibited growth-inhibition activities against human A875 melanoma cells that are up to 90-times higher than that of shikonin, which is an even better inhibitor than the clinically used colchicine.[12]

Despite these fascinating features, providing large amounts of shikonin samples remains challenging. Most derivatives that have had their bioactivities examined so far were mostly synthesized from shikonin isolated from natural sources,[13–15] making it difficult for researchers to provide practical amounts of shikonin-related compounds and to establish a comprehensive structure-activity relationship study for elucidating the underlying mechanisms of their anticancer actions.

Our research group has also been interested in shikonin derivatives modified with acyl groups at the alcohol moiety in the side chain (Figure 2), since one such derivative showed higher antitumor activity than shikonin during preliminary screening. This preliminary result encouraged us to synthesize further *O*-acylshikonin derivatives in order to study the structure-activity relationship of acylated shikonins as cytotoxic agents. Hence, we began this study by synthesizing shikonin, the key substrate in this project, following an article that reports one of the few examples of the gram-scale synthesis of shikonin.[16,17] However, we found this method to be unreliable; even when we repeatedly examined the reported method with strict care, the reported results could not be reproduced. Consequently, there is an urgent need to develop a new authentic route for the synthesis of shikonin. Herein, we report the development of an alternative synthesis route that enables the preparation of shikonin on the gram scale.

Results and discussion

Our first strategy for producing *O*-acylshikonins (**2**) involved the synthesis of (±)-**1**, followed by its conversion into the targeted compounds by subsequent appropriate protection, acylation, and deprotection reactions.[16,18] This strategy is outlined in Scheme 1.

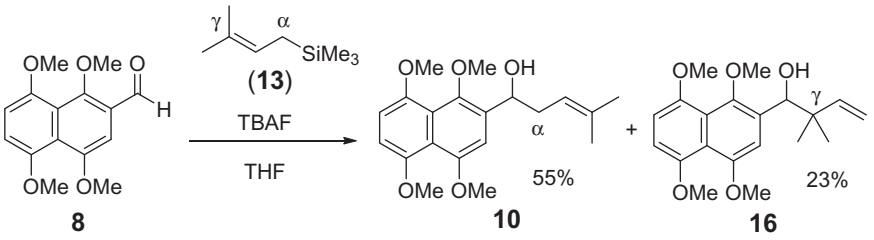


Scheme 1. Synthesis route to shikonin and its *O*-acyl derivatives.[13]

1,4,5,8-Tetramethoxy-2-naphthaldehyde (**8**) was successfully prepared in good yield following literature methods.[18,19] However, we were confronted with some difficulties in the next step. When **8** was reacted with prenylzinc bromide (**9**) and then heated in HMPA,[18,20] the expected alcohol **10** was not observed and the starting material **8** was not recovered. Based on the previous report we referred to, this reaction was anticipated to proceed in good yield (91%).[18] We carefully repeated the reaction under the same conditions, but all attempts were met with failure. One of the reasons for this difficulty might be attributable to that the purity of the reagents used were different from the previous ones. It has been known that trace impurities sometimes affect chemical transformations. If the present reaction in question is in that case, it would be very difficult to find the key substances. Therefore, we decided not to find the cause, but to optimize this step. For this purpose, experiments were conducted with benzaldehyde (**11**) as a model substrate and several metal-prenyl complexes as prenylating agents (Table 1).

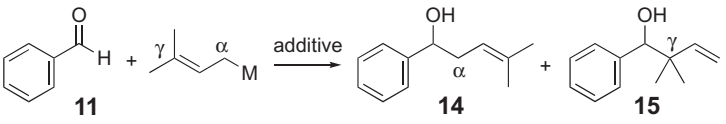
Benzaldehyde (**11**) was first reacted with prenylzinc bromide (**9**) following the literature protocol (entry 1),[20] but the target compound **14** was not obtained. Prenylmagnesium bromide **12** [21] was then examined in the presence of I_2 as a reaction promoter (entry 2). As a result, the γ-adduct **15** was obtained in high yield, but the formation of the desired α-adduct **14** was not observed. Then, prenylsilane **13** [22] was reacted with benzaldehyde (**11**) in the presence of tetra-*n*-butylammonium fluoride (TBAF); as a result the desired α-adduct **14** was obtained in 60% yield, together with the γ-adduct **15** (40%) (Table 1, entry 3). In this reaction, the reactive carbanion, which was produced from **13** by the action of TBAF, presumably attacks the aldehydic carbon with its less hindered carbon to predominantly give the α-adduct. Based on this observation, the reaction between prenylsilane **13** and 1,4,5,8-tetramethoxy-2-naphthaldehyde (**8**) in the presence of TBAF was examined and, as expected, the desired α-adduct **10** was obtained as the major product (Scheme 2).

Despite eventually obtaining **10**, this step is still problematic. In particular, the unsatisfactory yield of **10** from **8** is the most problematic when the cost involved in preparing prenylsilane **13** is considered, since an expensive palladium catalyst is required for its preparation, and significant amounts of costly *n*-pentane are required for the purification step.[22] In addition, the yield of **10** diminished when the prenylation of **8** was performed on a larger scale. Based on these observations, the strategy depicted in Scheme 1 was abandoned and a new synthesis strategy was elaborated. As shown in Table 1, **8** reacted effectively with Grignard reagent **12**. Based on this, aldehyde **8** was reacted with allylmagnesium bromide to afford the corresponding allyl alcohol **17**, which was

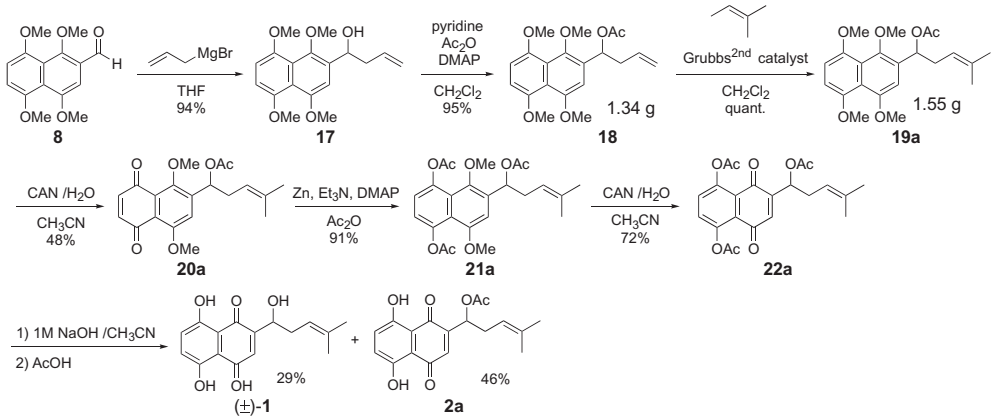


Scheme 2 Reaction of **8** with prenylsilane **13** in the presence of TBAF.

Table 1. Reactions of benzaldehyde (**11**) with several prenylating agents.



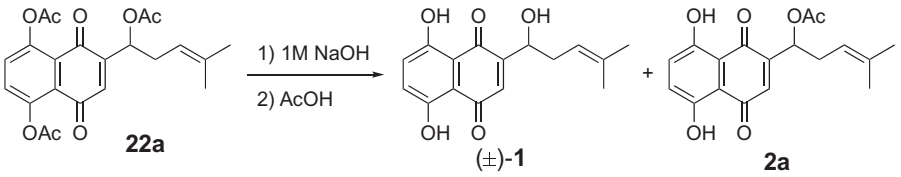
			yield	
Entry	M	Additive	**14**	**15**
1	ZnBr (**9**)	TMSCl	–	–
2	MgBr (**12**)	I_2	–	88%
3	$SiMe_3$ (**13**)	TBAF	60%	40%



Scheme 3. Synthesis of shikonin through the use olefin metathesis as a key reaction.

subsequently acetylated to give the acetate **18** (Scheme 3); these reactions proceeded in good yields. It is noteworthy that the allyl adduct was obtained without the regioselectivity concerns associated with the reactions depicted in Table 1. Subsequently, olefin metathesis between **18** and 2-methyl-2-butene in the presence of Grubbs' second-generation catalyst afforded prenylated **19a** in quantitative yield. In stark contrast to the first strategy (Scheme 1), **19a** was obtained as the sole product in much higher yield. It should be emphasized that this method, based on olefin metathesis, enabled the gram-scale preparation of **19a**, which is a key synthetic intermediate. Intermediate **19a** was converted into the target compound (±)-**1** accompanied by acetylshikonin **2a** in sufficient yield following known procedures.[18,23] Since the total synthesis of shikonin derivatives has been

Table 2. Hydrolysis of triacetylshikonin **22a**.

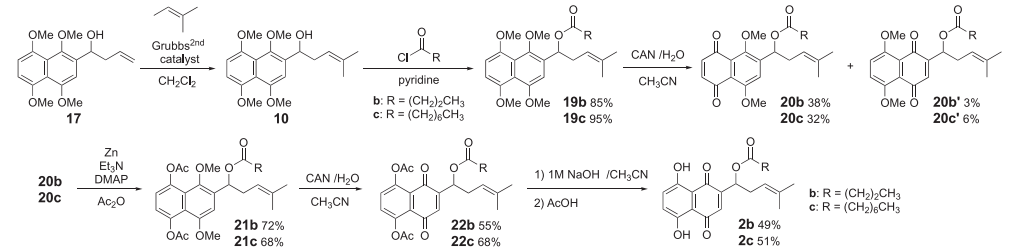


			Yield (%)	
Entry	Equiv. of NaOH	Solvent	(±)-**1**	**2a**
1	3.8	MeCN	29	46
2	4.0	MeCN	4	32
3	3.0	MeCN	–	48
4	3.0	MeOH	–	–
5	2.0	MeCN	–	28

challenging owing to the instability of synthetic intermediates to Brønsted and Lewis acids, light, and oxygen, total yield of this step (73%) was satisfactory result and this proves the usefulness of our synthetic route. During the course of these transformations, we noted that acetylshikonin **2a** was obtained as the main product when the hydrolysis of **22a** was conducted in acetonitrile; in other words, the phenolic acetates in **22a** can be selectively deprotected. Consequently, we optimized the conditions for this selective hydrolysis (Table 2); the highest yield of **2a** was obtained with three equivalents of NaOH in acetonitrile (entry 3).

Inspired by this result, we developed another strategy that involved the synthesis of the desired *O*-acylshikonin derivatives by introducing the required acyl group onto the hydroxyl group of the side-chain prior to hydrolysis. This concept also provides a shorter overall synthesis sequence than that initially proposed, and avoided the consecutive protection, acylation, and deprotection of (±)-**1** depicted in Scheme 1. Based on this idea, an alternative synthesis route to the *O*-acylshikonin derivatives was formulated, as shown in Scheme 4. Hence, compound **17** was converted into **10** by olefin metathesis in excellent yield. Subsequently, **10** was *O*-acylated with the required acyl chloride to give **19 b** or **19c**; these acylated compounds were then subjected to the transformation reactions that led to the acetyl-protected precursors **22 b** and **22c**, respectively.[18,23] Finally, **22 b** and **22c** were selectively deprotected to give the desired *O*-acyl shikonin derivatives, **2 b** and **2c**, respectively, in fewer steps from **8** than shown in Scheme 1.

The obtained shikonin derivatives **2a**–**c** were subjected to antiproliferative activity tests against human liver hepatocellular carcinoma (HepG2) cell and human colorectal carcinoma HT-29 cell were investigated. Among the three compounds, the bioactivities of acetylshikonin (**2a**) against HepG2 [24] and HT-29 [25] have already known, and thus **2a** acted as a standard. As shown in Figure 3, proliferations of both HepG2 and HT-29 cells treated with different doses of **2a**–**c** were inhibited in a dose-response manner, indicating these shikonin derivatives have antiproliferative activity against the tested cancer cells. The half-maximal inhibition concentration (IC_{50}) values on individual compound against HepG2 and HT-29 cells were then determined and listed in Table 3. No proportional relationship between the chain length of the acyl group and the antiproliferative activity was observed, and the derivative with *n*-



Scheme 4. An alternative route to the target *O*-acylated shikonins.

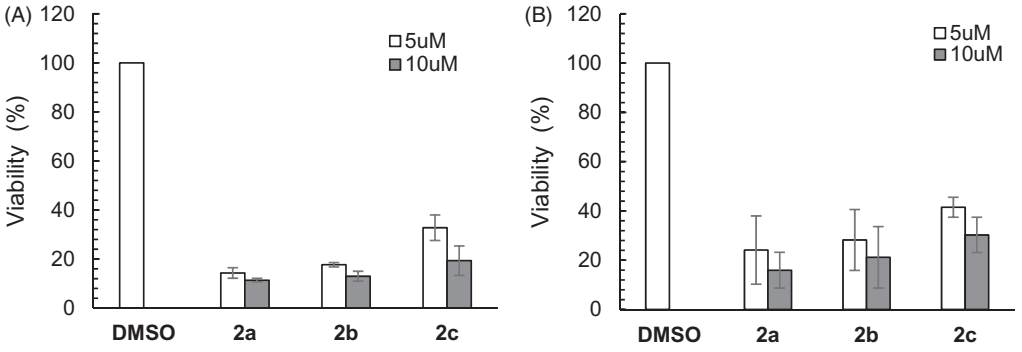


Figure 3. Cell viability of HepG2 (**A**) and HT-29 (**B**) in the presence and the absence of the *O*-acylated shikonin derivatives **2a**–**c**.

Table 3. IC_{50} values of **2a**–**c** on the proliferation of human cancer cells.

	IC_{50} /μM (Mean ± SD)[a]	
Compound	HepG2	HT-29
2a	2.15 ± 0.21	2.07 ± 0.53
2 b	1.37 ± 0.08	0.90 ± 0.04
2c	5.80 ± 1.92	3.87 ± 2.16

[a]IC_{50} = compound concentration required to inhibit cancer cell proliferation by 50%. Data are expressed as the mean ± SD (standard deviation) from the dose response curves of at least three independent experiments.

butanoyl side arm was proved to be the most effective among the tested compound against both HepG2 and HT-29.

Conclusion

In the present study, we found that the previously reported method, in which an efficient synthesis method for the preparation of shikonin (**1**) is described, was unable to be reproduced. Consequently, we developed an alternative, more-practical synthesis route to (±)-**1** and its *O*-acyl derivatives **2a**–**c**. The key step in this novel route involved an olefin metathesis that facilitated the preparation of key intermediate **19a** as the sole product on a gram-scale, under catalytic conditions, and in excellent yield. In addition, we found that the acyl protecting groups at the phenolic positions of the triacylated shikonins **22** are selectively deprotectable. These findings enabled us to synthesize shikonin derivatives bearing *O*-acyl groups on their side chains more efficiently than previously

reported. The present *O*-acylshikonin derivatives were preliminary tested their antiproliferative activity assay against two human cancer cells, and found that all of the derivatives were potential antiproliferative agents. Future goals in this project involve the construction of a library of *O*-acylshikonin derivatives using this new method, and the evaluation of their pharmacological activities in order to gain knowledge about the relationships between the side-chain structures of these shikonin derivatives and their biological activities, including cytotoxicity.

Materials and methods

General

^{1}H-NMR spectra were recorded on an ECP-400 spectrometer (JEOL Ltd., Japan). Chemical shifts (δ) are reported in ppm using tetramethylsilane or an undeuterated solvent as the internal standard in the deuterated solvent used. Coupling constants (J) are given in Hz. ^{13}C-NMR spectra were recorded on an ECP-100 spectrometer (JEOL Ltd., Japan). Chemical shift multiplicities are reported as s = singlet, d = doublet, t = triplet, m = multiplet. High-resolution electrospray ionization mass spectra (HRMS) were recorded on a JEOL JMS-T100CS mass spectrometer.

Column chromatography was carried out on silica gel (particle size; 46–50 μm; Fuji Silysia Chemical Ltd.)

Experimental procedures for key reactions

Synthesis of 1-(1,4,5,8-tetramethoxynaphthalen-2-yl)but-3-en-1-ol (17)

Under an argon atmosphere, allylmagnesium bromide (32 mL, 32 mmol) was added to 2-formyl-1,4,5,8-tetramethoxynaphthalene (**8**, 4.26 g, 15.4 mmol) in THF (194 mL). After stirring at room temperature for 160 min, sat. NH_4Cl (120 mL) was added with cooling in an ice bath. The mixture was diluted with water (200 mL) and extracted with chloroform (100 mL, then 70 mL). The combined chloroform phases were washed with brine (230 mL) and dried over Na_2SO_4. Evaporation of the solvent gave a brown sirup, which was purified by silica-gel column chromatography (120 g) with 1:1 hexane:ethyl acetate as the eluent to give **17** as a brown sirup (4.59 g, 94%). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.01 (s, 1H), 6.82 (s, 2H), 5.96–5.85 (m, 1H), 5.28–5.13 (m, 3H), 3.94 (s, 3H), 3.93 (s, 3H), 3.89 (s, 3H), 3.75 (s, 3H), 2.64–2.45 (m, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 153.5, 151.4, 150.3, 146.5, 135.1, 133.7, 122.6, 120.3, 118.2, 108.3, 107.7, 105.8, 67.9, 62.9, 57.9, 57.2, 57.0, 43.1. The spectroscopic data for this compound are consistent with the data available in the literature.[26]

Synthesis of 4-methyl-1-(1,4,5,8-tetramethoxynaphthalen-2-yl)pent-3-en-1-yl acetate (19a)

Under an argon atmosphere, 2-methyl-2-butene (60 mL, 573 mmol) was added to a solution of 1-(1,4,5,8-tetramethoxynaphthalen-2-yl)but-3-en-yl acetate (**18**, 1.34 g, 3.73 mmol) in degassed CH_2Cl_2 (10 mL) followed by the Grubbs 2nd generation catalyst (31.2 mg, 36.8 μmol). The orange mixture was then stirred at room temperature for 14 h

and then concentrated *in vacuo*. Purification of the resulting oil by silica-gel column chromatography with 7:3 hexane:ethyl acetate as the eluent gave **19a** as a yellow oil (1.55 g, quant.). ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 6.88 (s, 1H), 6.83 (s, 2H), 6.35 (dd, $J = 5.8$ and 7.2 Hz, 1H), 5.15 (t, $J = 6.8$ Hz, 1H), 3.93 (s, 6H), 3.89 (s, 3H), 3.84 (s, 3H), 2.64–2.51 (m, 2H), 2.10 (s, 3H), 1.67 (s, 3H), 1.56(s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 170.3, 153.4, 151.4, 150.5, 146.9, 134.7, 130.7, 122.7, 120.6, 119.3, 108.6, 107.8, 106.2, 70.9, 62.6, 57.9, 57.4, 57.0, 34.6, 25.8, 21.4, 18.0. The spectroscopic data for this compound are consistent with data available in the literature.[27]

Full experimental details and appropriate characterization data for all new compounds can be found through the "Supplementary Content" section of this article's webpage.

Acknowledgement

The authors would like to thank Editage (www.editage.jp) for English language editing.

Funding

This research was partially supported by the MEXT-Supported Program for the Strategic Research Foundation at Private Universities at Toho University, 2012–2016 [S1201034].

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