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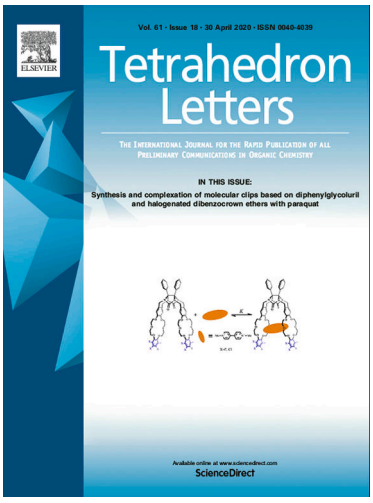

A Simple and Efficient Total Synthesis of Anticancer Indole Alkaloids TMC-205 and Its Analogues

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Graphical Abstract.

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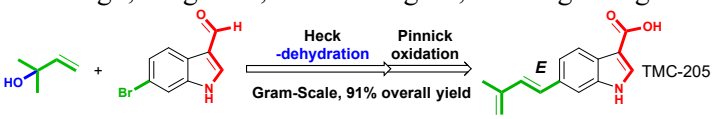
Tao Li [a], Jinjie Song [a], Lihua Wang [a], Ting Lei [a], Shizhi Jiang [a,*], Fusheng Wang [a,*]



- Cheap and readily available feed stock
- Protecting-group-free and redox-economy
- Excellent regio- and stereo-selectivity

2 Steps
VS
5 Steps
(First total synthesis)

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A Simple and Efficient Total Synthesis of Anticancer Indole Alkaloids TMC-205 and Its Analogues

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[a]*College of Pharmacy, Dali University, Dali 671000, China*

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ABSTRACT

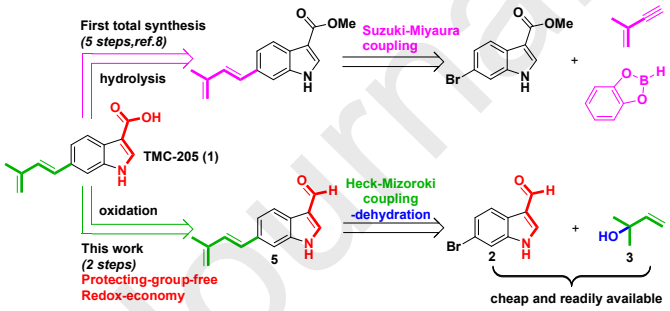
A concise synthesis of TMC-205 was accomplished in two steps via a protecting-group-free (PGF) and redox-economical strategy. In this approach, a high yield Pinnick oxidation and a practical Heck-dehydration reaction with high atom economy as well as a high regio- and stereo-selectivity (*E*-isomer) were used and further applied to the total synthesis of its active analogues. This newly established route would be beneficial for future structure-activity relationship (SAR) and biological studies. The synthetic strategy and methodologies demonstrated in this paper could be extended to related biologically active natural products.

* Corresponding author. E-mail address:jiangshizhi@dali.edu.cn (S.-Z. Jiang);
wfsyn@163.com (F.-S. Wang).

and redox-economical methods have received considerable attention as strategies to improve the efficiency of total synthesis. In addition, this approach provides an "opportunity for invention," as the development of a novel synthesis strategies and synthetic methodologies is essential [1-6]. Herein, we report the successful application of these principles to the total synthesis of TMC-205 and its analogues.

TMC-205 (Scheme 1), an unusual structurally simplified indole-3-carboxylic acid derivative bearing an isoprene-like side chain at the 6-position, is a secondary metabolite of an unidentified fungal strain, TC 1630, which was isolated in 2001 by the Masaaki Sakurai group [7]. TMC-205 shows antiproliferative activity against various human cancer cell lines and also activates the SV40 promoter [7,8]. However, only 3.3 mg of TMC-205 was first isolated from the fermentation broth of TC 1630, and such a small amount of the extract could not be used for SAR and biological studies. The fascinating structural features of TMC-205, along with its potential pharmacological activity and our ongoing interest in the total synthesis of biologically active indole natural products [9-11], prompted us to develop a practical approach to synthesize this attractive indole alkaloid.

Thus far, only one group has achieved the total synthesis of TMC-205 in early 2014; the product was obtained in 5 steps via the longest linear sequence reported (6 total steps) and in 64% overall yield by adopting Friedel-Crafts acylation, esterification (using $TMSCHN_2$), and Suzuki-Miyaura coupling as the key steps [8]. In the first total synthesis, an obvious convergent approach was used for the C6−C9 bond formation via the Suzuki-Miyaura cross-coupling reaction. However, the reported methods required the independent preparation of the isoprene portion and involved multiple steps for finally constructing the 3-carboxy group; in addition, they had inherent limitations such as the requirement of harsh reaction conditions as well as expensive and toxic reagents and starting materials. Hence, the previous synthesis methods are complicated. Here we reveal an effective two-step procedure toward the concise synthesis of TMC-205 from inexpensive and readily available starting materials under mild conditions.



Scheme 1. Retrosynthetic analysis of TMC-205.

Early-stage installation of the 3-carboxy group was not advisable because of the difficulties in controlling the troublesome acidic group. As illustrated in Scheme 1, our retrosynthetic analysis of TMC-205 calls for a late-stage construction of the 3-carboxy group by the oxidation of aldehyde **5**. The crucial step in the synthesis is the construction of the 6-substituted indole moiety and an olefin side chain. In this context, Heck coupling [12] appeared to be the most attractive reaction for introducing a *trans*-alkene, without the participation of the indole enamine moiety and the aldehyde group. Retrosynthetic analysis revealed 6-bromoindole derivative **2** and allyl alcohol **3** as suitable starting materials to install the desired carbon skeleton **5** upon Heck-dehydration reaction [11].

Our synthetic efforts commenced with the use of 6-bromoindole-3-carboxaldehyde **2** as the key starting material. This compound is commercially available and can also be prepared easily from the inexpensive 6-bromoindole via Vilsmeier-Haack formylation [12-15]. Notably, after initial extraction of the crude material, **2** could be purified conveniently by recrystallization on a 10 g scale (See Supporting Information for details).

With substrate **2** in hand, we focused on the Heck-dehydration reaction. Initially, we used CH_3CN as the solvent and treated bromide **2** with $Pd(OAc)_2$ and P(*o*-tol)$_3$ in the presence of Et_3N as a base in a sealed tube at 115°C. After 5 h, the desired diene **5** was obtained in 81% yield with high regio- and stereo-selectivity [11] (Table 1, entry 1). The geometry of the double bond was ascertained as the *E*-isomer by ^1H NMR spectroscopy.

Inspired by the recent systematic investigations of this reaction by our group [11], we attempted to further improve the yield. We began our investigation by screening several readily available palladium catalysts. A slightly increased yield was observed when $Pd_2(dba)_3$ was employed (entry 3), but this was accompanied by a low reaction rate. When $PdCl_2$ and $Pd_2(dba)_3{\cdot}CHCl_3$ were used, both the reaction rate and yields were unsatisfactory (entries 2, 4). Therefore, $Pd(OAc)_2$ was chosen as the optimal catalyst.

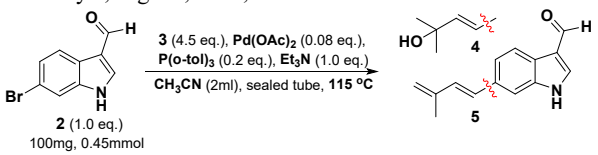
Other phosphorus ligands, PPh_3, P(2-furyl)$_3$, DPEphos, and Xantphos, were also evaluated (entries 5-8), but P(*o*-tol)$_3$ was superior to all of them.

Examination of other trialkylamines, including DIPEA, and (n-C_3H_7)$_3$N, (n-C_8H_{17})$_3$N, indicated that they all performed well (entries 9-11). In particular, in the presence of (n-C_3H_7)$_3$N, the yield of product **5** reached 87% and the reaction time was shortened to 3 h (entry 10). These observations are consistent with those in our previous studies that a tertiary amine base is necessary for an efficient Heck-dehydration reaction [11].

After ascertaining that tripropylamine was the best base for the reaction, we next investigated the role of the solvent. A screening various solvents such as DMF, THF, 1,4-dioxane, DCE, and toluene, we found that polar solvents led to the formation of diene **5** in good yield (entries 1, 12-14). In particular, the yield of **5** reached 85% in the presence of 1,4-dioxane (entry 14). A slightly decreased yield were observed when DCE and toluene was employed (entries 15, 16).

Various additives (polymerization inhibitor) were further screened to boost the transformation (entries 17-19). All of them had a positive effect on this reaction; especially, the addition of BHT led to an improved yield of up to 86% (entry 17).

Table 1. Investigating the Effect of the Catalyst, Ligand, Base, Solvent and Additives.



Entry	variable	*t* [h]	R.S.M. **2**%[a]	yield **4**%[a]	yield **5**%[a]
1	**None**	5	-	-	81
2	$PdCl_2$	8	22	15	60
3	$Pd_2(dba)_3$[b]	8	-	7	83

5	PPh_3	8	8	24	32
6	P(2-furyl)$_3$	8	12	6	35
7	DPEphos[c]	8	9	21	65
8	Xantphos[d]	6	8	4	45
9	DIPEA[e]	8	-	9	86
10	(n-C_3H_7)$_3$N	3	-	3	87
11	(n-C_8H_{17})$_3$N	5	6	9	82
12	DMF	8	12	4	82
13	THF	8	8	10	80
14	1,4-dioxane	8	7	0	85
15	DCE[f]	5	25	2	72
16	Toluene	8	22	-	51
17	BHT[g] (0.1/0.3/0.03eq.)	8	6/8/6	5/15/5	86/70/81
18	TBX[h] (0.1 eq.)	8	3	5	83
19	TBC[i] (0.1 eq.)	8	7	3	84

R.S.M.=Recovered Starting Material.

"-" = Not Detected

[a] Isolated yield.

[b] 0.04 eq.

[c] Bis(2-diphenylphosphinophenyl)ether

[d] 9,9-Dimethyl-4,5-bis(diphenylphosphino)xanthene

[e] N,N-diisopropylethylamine.

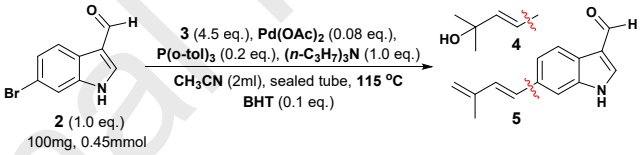
[f] Dichloroethane.

[g] 2,6-di-*tert*-butyl-*p*-cresol.

[h] 2-*tert*-butyl-4,6-dimethylphenol.

[i] *p*-*tert*-butylcatechol..

Table 2. Further Study in the Synthesis of diene **5**.



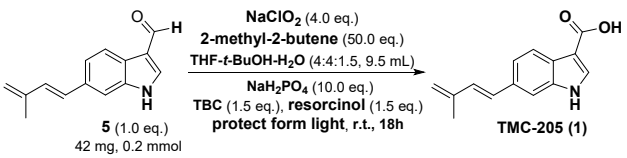
Entry	variable	t [h]	R.S.M. **2**%[a]	Yield **4**%[a]	Yield **1**%[a]
1	**None** (CH_3CN as solvent)	5(**7**[b])	4(**3**[b])	-(-[b])	94(**93**[b])
2	1,4-dioxane	5(**10**[b])	12(**4**[b])	-(-[b])	91(**94**[b])
3	DMF	5	8	-	91
4	DMF;atmospheric pressure	8(**10**[b])	15(**11**[b])	3(**4**[b])	80(**82**[b])
5[c]	Pd(OAc)$_2$(0.04eq.)	5	5	2	92

[a] Isolated yield.

[b] **gram-scale (1.34 g)**.

[c] P(o-tol)$_3$ (0.1 eq.).

Table 3. Study on Pinnick-oxidation of **5**.



Entry	**Optimization of ref. [16]**[b,e]	t [h]	R.S.M. **5**%[a]	yield **1**%[a]
1	**None**	20	20	21
2[c]	$NaClO_2$ (4.0 eq.); + resorcinol	11	14	34

4	"Entry 3"; at -18 °C	48	33	62
5	"Entry 3" ; + TBX	18	33	66
6	"Entry 3" ; + TBX; at -18 °C	48	35	64
7	"Entry 3" ; + BHT	18	36	62
8	"Entry 3" ; + TBC	18(**27**[f])	19(**21**[f])	78[g](**76**[f, g])

[a] Isolated yield.

[b] $NaClO_2$ (20.0 eq.), 2-methyl-2-butene (250.0 eq.), THF-*t*-BuOH-H_2O (0:4:2.0, 6.0 mL), NaH_2PO_4 (20.0 eq.).

[c] $NaClO_2$ (4.0 eq.), 2-methyl-2-butene (50.0 eq.), THF-*t*-BuOH-H_2O (0:4:1.5, 5.5 mL), NaH_2PO_4 (10.0 eq.).

[d] $NaClO_2$ (4.0 eq.), 2-methyl-2-butene (50.0 eq.), THF-*t*-BuOH-H_2O (4:4:1.5, 9.5 mL), NaH_2PO_4 (10.0 eq.).

[e] Without premixing.

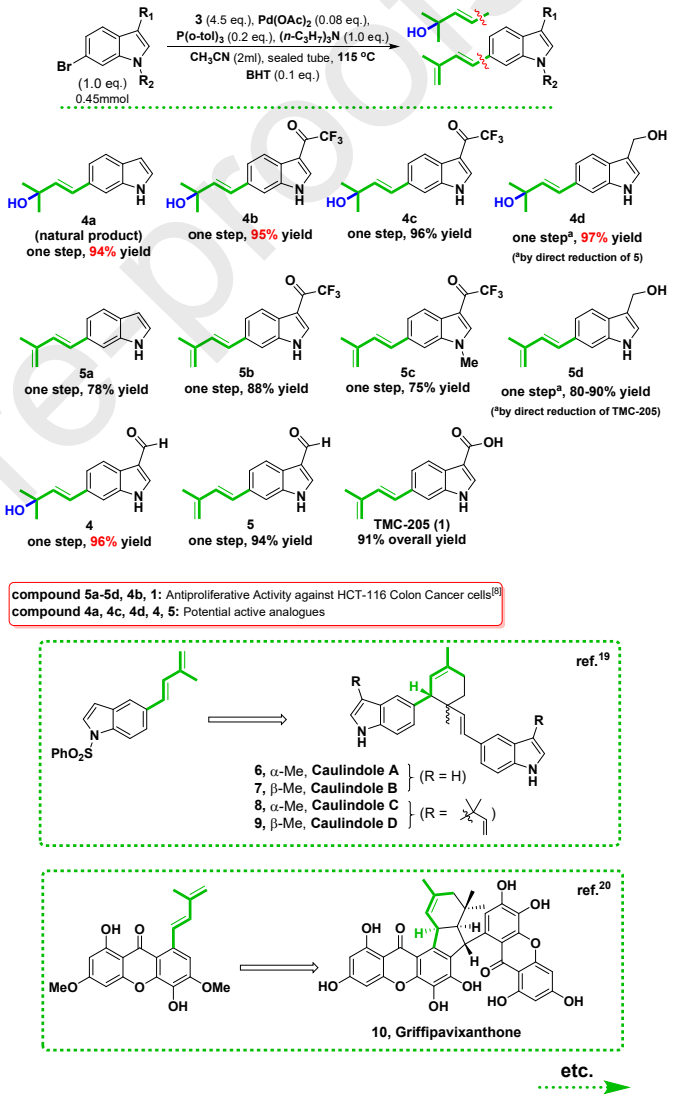
[f] **Gram-scale (1.27 g)**

[g] 97% yield, based on recovered starting material (brsm) .

Considering the above findings, a high yield of diene **5** (Table 2, 94%, entry 1; 91%, entries 2, 3) was obtained in 5 h when adopting tripropylamine as the base, BHT as the additive, and CH_3CN as the solvent (or 1,4-dioxane, DMF). To evaluate the efficiency of this reaction on a larger-scale, we performed the reaction using 1.34 g of substrate **2**. Pleasingly, **5** was isolated in excellent yield (93%, CH_3CN; 94%, 1,4-dioxane) without loss of efficiency, as opposed to the small-scale reaction. Nevertheless, we were dissatisfied with the use of a sealed tube, which is not ideal for large-scale synthesis. Therefore, we further attempted to develop a more practical method. Process development demonstrated that the reaction could also performed at atmospheric pressure in DMF (80% or 82% on a gram scale, entry 4), without the need for higher temperatures to compensate for the reduction in reaction pressure. Furthermore, good performance was achieved by using only 4 mol% of the catalyst (92%, entry 5). As shown above, the Heck-dehydration reaction is a more efficient and reliable method than previous reaction [8] for introducing a isoprene unit toward the synthesis of TMC-205.

Having assembled the desired carbon skeleton, we turned our attention to oxidizing the 3-aldehyde group into a carboxyl group en route to the desired TMC-205. Oxidation of the aldehyde group of **5** via Pinnick oxidation under the literature conditions [16] afforded TMC-205 in 21% yield along with the starting material in 20% yield, after flash column chromatography. The spectroscopic data for the synthetic TMC-205 were in agreement with those reported for the natural product [7]. To achieve an efficient transformation, we decided to explore a high-yield Pinnick oxidation. After many experimental trials [17] (Table 3), we achieved the desired result with resorcinol [18] and TBC as the additives in a mixed solvent system (THF-*t*-BuOH-H_2O) and obtained TMC-205 in 78% yield (or 97% brsm, entry 8). The reaction also performed well on the gram scale. The Pinnick oxidation reported in this paper is beneficial and valuable for further application of this reaction in the field of organic synthesis. The two-step synthesis of TMC-205 was finally realized via a practical Heck-dehydration reaction, followed by a well-studied Pinnick oxidation on a gram scale, in excellent yield without the need for protecting groups.

Scheme 2. Synthesis of active analogues.



Following the above optimized Heck-dehydration reaction, we decided to embark on the synthesis of the active analogues of TMC-205 so that its pharmacological activity could be better examined and the synthetic utility of this reaction could be demonstrated. As shown in Scheme 2, the reaction proceeded well with a wide range of substrates, furnishing a series of the desired tertiary allylic alcohol or isoprene products in good yields (**4a-4d or 5a-5d, 4, 5**). Although **5a−5d, 4b, 1** have been previously synthesized [8], the synthetic route was not as efficient as that employed by our group. The yields of **5d** were variable due to the instability of the butadiene and enol. Additionally, attempts to

synt 72, difficult due to the unstable nature of (6-bromo-1*H*-indol-3-yl) methanol. Further application of this methodology to the total syntheses of other natural products (such as 6-10 [19, 20] and so on) are under investigation and will be reported in due course.

In summary, a concise and practical total synthesis of TMC-205 (on a gram scale) was achieved in two steps and in 91% overall yield from simple, readily available starting materials and reagents. The short and efficient synthesis features a successful PGF and a redox-economical strategy, thus demonstrating the pursuing values of modern organic synthesis. Through optimization of the reaction parameters, a high-yield Pinnick oxidation has been achieved. The *trans*-(3-methyl-l, 3-butadienyl) unit is effectively introduced via a novel Heck-dehydration reaction, with high atom economy as well as high regio- and stereo-selectivity. Based on the key reaction, a series of active analogues of TMC-205, including another natural product, have also been synthesized in good yields. Moreover, the strategy and methodologies adopted in this synthesis would be beneficial for the preparation of other relevant natural products. The gram-scale synthesis of TMC-205 will facilitate the testing of its biological properties and SAR studies. Efforts related to these aspects will be the focus of our future studies.

Acknowledgments

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Highlights

- A concise and efficient total synthesis of TMC-205 is achieved.
- A protecting-group-free and redox-economical strategy has been used.
- This practical reaction was further applied to the synthesis of TMC-205 analogues.