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Synthesizing Molecules with Linear Tricyclic 5/5/5 and 6/5/5 Skeletons via [5 + 2 + 1]/Ene Strategy

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Cite This: https://doi.org/10.1021/acs.orglett.1c02766 Read Online

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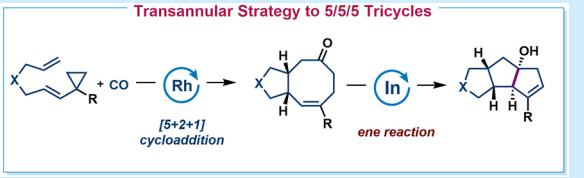
ABSTRACT: Report here is the development of a [5 + 2 + 1]/ene strategy for the synthesis of molecules with linear tricyclic 5/5/5 and 6/5/5 skeletons widely found in natural products. The first step of this strategy is applying a Rh-catalyzed [5 + 2 + 1] reaction of ene-vinylcyclopropanes and CO to synthesize 5/8 and 6/8 bicyclic compounds, which can then be transformed to the final target molecules by an $InCl_3$-catalyzed ene reaction.



There are many natural products with linear tricyclic 5/5/5 and 6/5/5 skeletons (for randomly selected molecules, see Scheme 1a).[1−6] Many of these natural products have significant biological activities and have been becoming either leading compounds for drug discoveries or chemical probes for biological investigations. For example, hypnophilin, displaying effective performance in killing the intracellular forms of *Trypanosoma cruzi* and modulating human peripheral blood mononuclear cells, is now a lead compound for the development of chemotherapeutic agents to treat Chagas disease.[2] HSAF (dihydromaltophilin) is an antifungal natural product with a new mode of action (especially for *Penicillium avellaneum*).[3] A novel nonpeptidic thrombin inhibitor with a tricyclic 5/5/5 skeleton shown in Scheme 1a has comparable activity and selectivity to hirudin and is a promising candidate to treat thrombotic diseases.[4] Therefore, developing more general and efficient strategies and reactions to synthesize both linear 5/5/5 and 6/5/5 tricycles is important, considering that these strategies and reactions could be used to provide required quantities of 5/5/5- and 6/5/5-embedded natural products and analogues and other related compounds as well, which then provide the molecular basis for downstream studies in different disciplines.

However, molecules with 5/5/5 and 6/5/5 tricycles still pose challenges to synthetic chemists, mainly due to their compact structures with various substitutions and stereochemistry. Several elegant approaches and reactions developed in the past can be used to access some of these 5/5/5 molecules.[5] More strategies and reactions are needed for the synthesis of molecules with the 5/5/5 tricyclic structures, especially for those that are either impossible or difficult to obtain using previous strategies and reactions. To the best of our knowledge, the reactions and strategies to 6/5/5 structures have been seldom investigated, and new reactions or strategies for this skeleton are in high demand.[6]

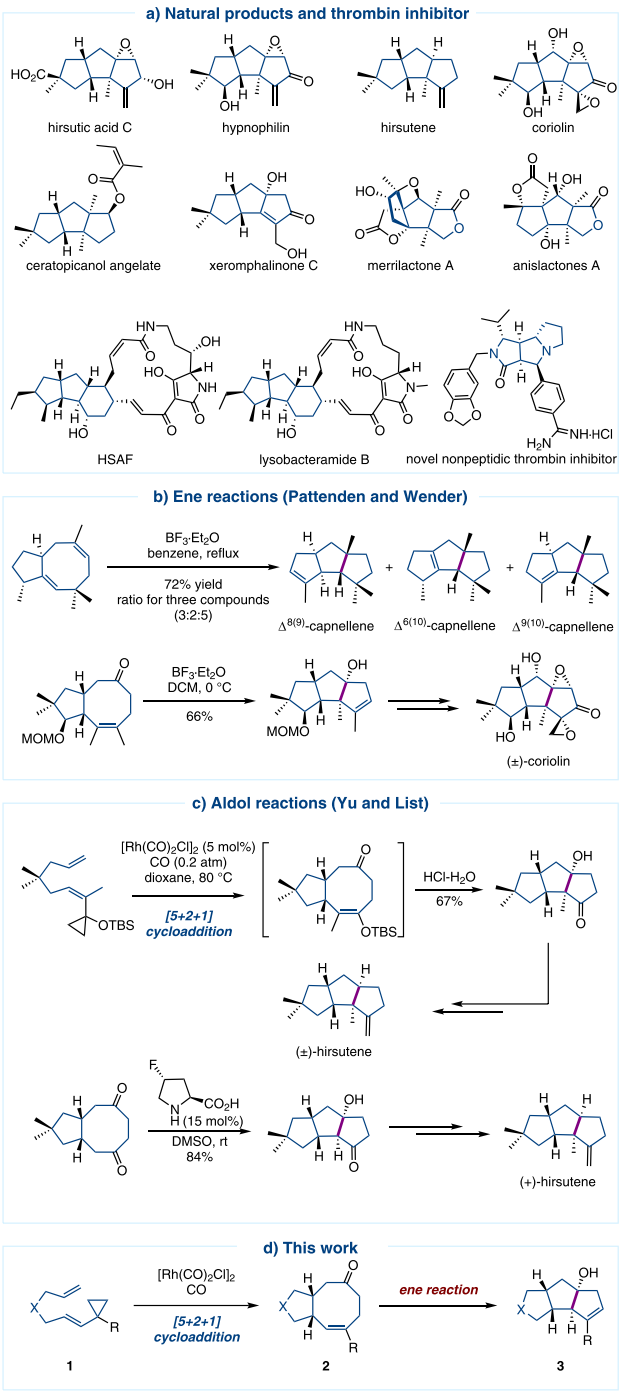
One transannular strategy to obtain the 5/5/5 skeleton is to use bicyclic 5/8 compounds as substrates and apply the ene reaction (Scheme 1b). This strategy was first used by Pattenden's[7] group and Wender's[8] group in the syntheses of capnellane and coriolin, respectively. Another strategy is to use a transannular aldol reaction to reach the 5/5/5 structure, as demonstrated by Yu's[9] and List's[10] syntheses of hirsutene (Scheme 1c). Yu and co-workers also realized the syntheses of two other triquinane natural products, 1-desoxyhypnophilin[9] and hirsutic acid C,[11] by using a [5 + 2 + 1]/aldol reaction.

Inspired by the elegant works from Pattenden and Wender, we wondered whether we could develop a general [5 + 2 + 1]/ene strategy for the synthesis of various linear tricyclic 5/5/5 and 6/5/5 skeletons, considering that Rh-catalyzed [5 + 2 + 1] reaction of ene-vinylcyclopropanes and CO can be used to synthesize 5/8 and 6/8 skeletons,[12,13] which could then undergo ene reaction to access the tricyclic molecules (Scheme 1d). To achieve this, the following three key issues must be resolved. First, the generality of the transannular ene reaction needs to be explored, considering that only two examples using this strategy were reported by Pattenden and Wender. This means that we have to find the appropriate substituents in the eight-membered rings of the 5/8 and 6/8 substrates. Second, which catalyst could be the most effective one for the ene reaction? Even though there are lots of catalysts that can potentially promote this transformation, we have to find an appropriate one for this task. In addition, we also hoped that the selected catalyst would give high regioselectivities, instead of that found in Pattenden's synthesis.[7] Finally, can such a strategy be used to synthesize a 6/5/5 skeleton? In what follows, we report our investigation of how to achieve the

Received: August 18, 2021

https://doi.org/10.1021/acs.orglett.1c02766
Org. Lett. XXXX, XXX, XXX−XXX

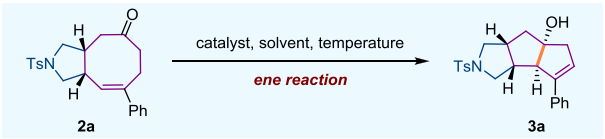
Scheme 1. Selected Molecules with 5/5/5 and 6/5/5 Skeletons and Transannular Reactions to Access Them



efficient synthesis of linear 5/5/5 and 6/5/5 tricycles by using [5 + 2 + 1]/ene strategy.

We first screened the reaction conditions for the ene reaction using a phenyl-substituted 5/8-fused substrate **2a** (Table 1). It was found that the ene reaction can be mediated by using 1.2 equiv of $BF_3{\cdot}Et_2O$, and the corresponding 5/5/5 product **3a** was obtained in 50% yield (Table 1, entry 1).[7] When 1.5 equiv of Me_3Al[14] was used, no desired product was detected (Table 1, entry 2). Fortunately, the reaction yield could reach as high as 95% when 1.5 equiv of Me_2AlCl[15] was used (Table 1, entry 3). To our delight, using other Lewis

Table 1. Study of Reaction Conditions of the Ene Reaction[a]



entry	catalyst	loading (equiv)	solvent	temp (°C)	time (h)	yield[b] (%)
1	$BF_3{\cdot}Et_2O$	1.2	DCM	−78 to rt	22	50
2	Me_3Al	1.5	DCM	−45 to rt	69	trace
3	Me_2AlCl	1.5	DCM	−45 to rt	11.5	95
4	$InCl_3$	0.5	DCE	rt	41	quant
5	$InBr_3$	0.5	DCE	rt	96	quant
6	$InCl_3$	0.5	DCE	80	2	quant
7	**$InCl_3$**	**0.1**	**DCE**	**60**	**1.5**	**95**
8	$InCl_3$	0.1	DCE	40	12	90
9	$InCl_3$	0.05	DCE	60	8	98
10	$InCl_3$	0.01	DCE	60	24	62
11	$InCl_3$	0.1	toluene	60	5	NR
12	$InCl_3$	0.1	dioxane	60	5	NR
13[c]	$InCl_3{\cdot}4H_2O$	0.1	DCE	60	24	89
14[d]	$InCl_3{\cdot}4H_2O$	0.1	DCE	60	12	93
15	$InCl_3{\cdot}4H_2O$	0.05	DCE	60	5	85

[a]Reaction conditions: **2a** (0.1 mmol), concentration (0.05 M), all processes under Ar unless otherwise indicated. [b]Isolated yields. [c]DCE was used without further dehydration. [d]Reaction under air atmosphere and DCE without further dehydration. NR = no reaction.

acids including $InCl_3$[16] and $InBr_3$[17] in 0.5 equiv can accomplish the ene reaction in almost quantitative yields at room temperature (Table 1, entries 4 and 5). Encouraged by these results, we chose $InCl_3$ as the catalyst to conduct further optimization of the reaction. It was exciting to note that elevating the reaction temperature can greatly shorten the reaction time (Table 1, entry 6). Decreasing the catalyst loading to 10 mol % and lowering the reaction temperature to 60 °C together helped the ene reaction to occur smoothly. In this case, product **3a** was obtained in 95% yield in 1.5 h (Table 1, entry 7). Further lowering the reaction temperature or decreasing the catalyst loading did not improve the reaction yields significantly, but required much longer reaction time or led to decreased reaction yields (Table 1, entries 8−10). Neither toluene nor dioxane was found to be suitable for the ene reaction (Table 1, entries 11 and 12). Importantly, the ene reaction was not sensitive to moisture and air because $InCl_3{\cdot}4H_2O$ (by 10 or 5 mol % loading) can catalyze the ene reaction under air atmosphere to give the product in 85−93% yields (Table 1, entries 13−15). Therefore, we chose the optimized reaction conditions for the ene reaction as those shown in Table 1, entry 7 (10 mol % $InCl_3$, DCE as the solvent, reaction temperature of 60 °C).

Second, the synthesis of the 5/8 and 6/8 substrates was carried out in order to explore the scope of the $InCl_3$-catalyzed intramolecular transannular ene reaction (Table 2). These substrates were prepared by our [5 + 2 + 1] cycloaddition reaction of ene-vinylcyclopropanes and CO. The [5 + 2 + 1] cycloaddition was carried out in the presence of balloon-pressured mixed gas of 0.2 atm CO + 0.8 atm N_2, with 5 mol %

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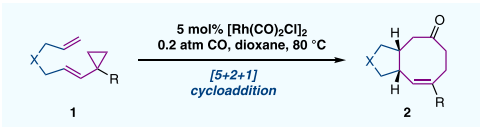
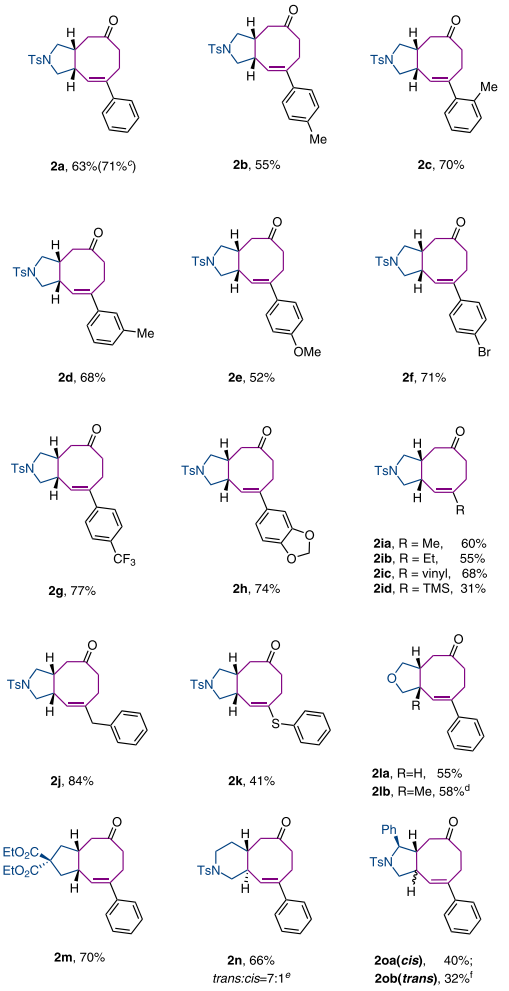
Table 2. Preparation of [5 + 2 + 1] Cycloadducts[a,b]





[a]All reactions used 5 mol % $[Rh(CO)_2Cl]_2$ in 0.05 M of dioxane, under 0.2 atm CO + 0.8 atm N_2 at 80 °C, substrates were 0.43−0.68 mmol scale, and the reported yields represent an average of the yields of the isolated products from two runs. [b]The quality of catalyst from the vendors could be different which affected the yields of the [5 + 2 + 1] reaction (see the Supporting Information for details). [c]1.8 mmol scale reaction with 20.5 h and yield represents an average of two runs. [d][5 + 2] product in 38% yield was obtained. [e]The diastereomeric ratio (dr) value was determined by ^{1}H NMR spectroscopy. [f]Confirmed by X-ray analysis.

$[Rh(CO)_2Cl]_2$ as the catalyst in dioxane at 80 °C.[12] These cycloaddition reactions gave the target products in moderate to good yields (31−84%). Substrates with either an electron-withdrawing or an electron-donating group at the aryl group on the cyclopropyl ring of the substrates had no obvious effect on the reaction yields (Table 2, **2a**−**2h**). A 1.8 mmol scale of [5 + 2 + 1] reaction of **1a** gave 71% of the target compound. Substrate **1e**, with a 4-methoxy phenyl substituent, gave the [5 + 2 + 1] cycloadduct in 52% isolated yield (the crude [5 + 2 + 1] cycloadduct had low solubility and isolation from column chromatography was not satisfactory; this is the reason for the low yield). Substrates with alkyl, vinyl, and benzyl substituents can generate the [5 + 2 + 1] cycloadducts in good yield (Table 2, **2ia**−**2ic** and **2j**). Substrates **1id** (with a TMS group) and **1k** (with a phenylmercapto substituent) delivered the target [5 + 2 + 1] cycloadducts smoothly (Table 2, **2id** and **2k**). Of the same importance, substrates with different tethers such as ether and germinal diester groups can also undergo the [5 + 2 + 1] reaction (Table 2, **2la**, **2lb**, and **2m**).

To achieve the 6/5/5 tricyclic skeleton using the present [5 + 2 + 1]/ene strategy, we synthesized substrate **1n**. The 6/8-fused bicyclic product **2n** can be generated successfully through the [5 + 2 + 1] reaction in a moderate yield, with the *trans*-6/8 bicyclic product as the major one (Table 2, **2n**). For substrate **1o** with a phenyl substituent on the allylic position of ene moiety, the [5 + 2 + 1] cycloaddition took place smoothly as well, generating **2oa** and **2ob** as two isomers in 40% and 32% isolated yields, respectively (Table 2, **2oa** and **2ob**).

Finally, we turned our attention to investigate the generality of $InCl_3$-catalyzed intramolecular transannular reaction using substrates in Table 2. We were excited to observe that all 5/8-substrates with an aryl group can give the desired 5/5/5 tricyclic products in high yields, no matter whether the substituents in the aryl ring are electron-rich, electron-poor, or electron-neutral (Table 3, **3a**-**3h**). To our delight, for 5/8 substrate **2ia** with a methyl group, the corresponding ene reaction gave the desired product in 72% (Table 3, **3ia**). The ene reaction for substrate **2ic** with a vinyl group gave the final product in 17% yield due to the decomposition of the substrate under the reaction conditions (Table 3, **3ic**). For substrates **2id** with R=TMS group and **2p** with R=H (see Scheme 2 and later on discussion), their ene reactions failed, and the possible reasons have been proposed with the aid of DFT calculations (see the Supporting Information). Substrates **2j** (with a benzyl group) and **2ib** (with an ethyl group) can undergo the ene reactions, giving a mixture for the former and the 5/5/5 product with some impurities for the latter, respectively (Table 3, **3j** and **3ib**). We hypothesized that there were two different allylic hydrogen atoms participating in the hydrogen transfers in the ene reaction of **2j**, and then mixtures could be obtained[18] (other unknown side reactions for the substrate **2j** could also happen). Therefore, the aryl groups, compared to alkyl groups in the 5/8 substrates, were better for the present ene reaction. This can be understood from the following two points. First, there is no regiochemistry issue for the ene reaction. Second, the ene reaction could be easier with an aryl group due to the conjugation of the aryl substituent with the alkene in both the 5/8 substrates and 5/5/5 products. Gratifyingly, [5 + 2 + 1] cycloadduct with heteroatom substitution can give the desired product in 44% yield (Table 3, **3k**).

The tether group in the substrate for the ene reaction can be either an ether group or a *gem*-diester group (Table 3, **3la**, **3lb**, and **3m**). To our delight, the *trans*-fused 6/8 bicycle substrate **2n** reacted smoothly at 80 °C, and its corresponding *trans,cis*-fused 6/5/5 tricycle product was obtained in an excellent yield (its structure was determined by X-ray analysis), supporting that the present strategy provides an efficient way to synthesize 6/5/5 embedded-natural products and analogs (Table 3, **3n**). Substrate **2oa** with a phenyl group at the α-position of the sulfonamide tether could also undergo the ene reaction at a raised temperature of 80 °C (Table 3, **3oa**). We emphasize here that the ene reaction can be scaled to 1 mmol scale, as

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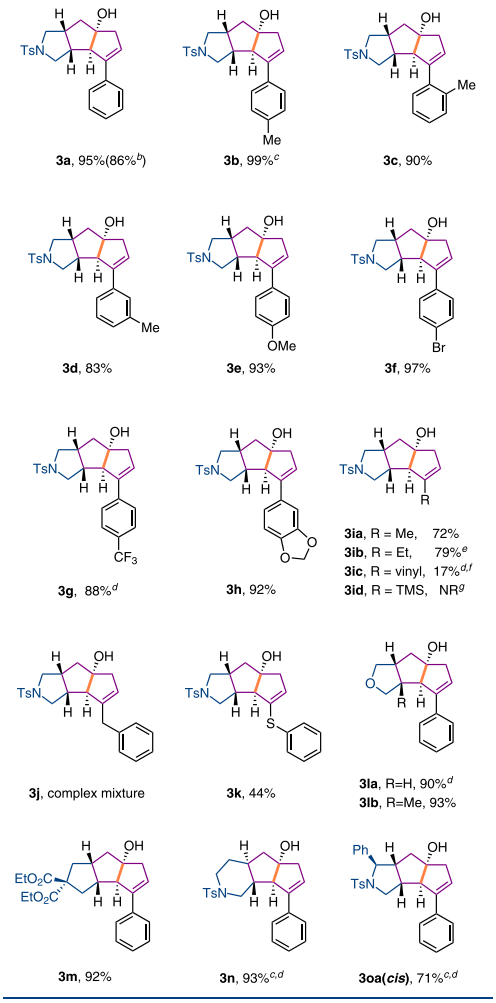
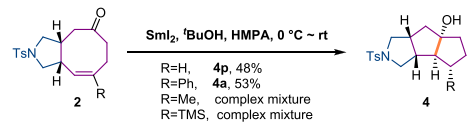
Table 3. Scope of $InCl_3$-Catalyzed Intramolecular Transannular Ene Reaction[a]



[a]All reactions used 10 mol % $InCl_3$ in 0.05 M of DCE, under Ar at 60 °C. The used substrates were 0.1 mmol. The reported yields represent an average of the yields of the isolated products from two runs. [b]1 mmol scale reaction with 29 h and the yield represents average of two runs. [c]Confirmed by X-ray analysis. [d]Reaction carried out at 80 °C. [e]The product was mixed with some inseparable impurities (see the Supporting Information for details). [f]20 mol % $InCl_3$. [g]NR = no reaction (see DFT part of the Supporting Information).

Scheme 2. SmI_2-Mediated Cyclization to Form 5/5/5 Products



demonstrated by the transformation of **2a** to **3a** in 86% yield with extended time (29 h) at 60 °C.

Substrate **2p** with R = H cannot be converted to 5/5/5 product by the $InCl_3$-catalyzed ene reaction, but it can give product **4p** when mediated by SmI_2 (Scheme 2). [5 + 2 + 1] cycloadduct **2a** with R = Ph can also give 5/5/5 product, but **2ia** and **2id** cannot (Scheme 2). These results suggested that the double bond reduced products of **3** for R = H and aryl groups can be obtained by a radical process mediated by SmI_2.[19]

We point out that the tosyl group in the final 5/5/5 products can be removed by Na/naphthalene reduction, as demonstrated by one example (see the Supporting Information). In addition, DFT calculations have been applied to investigate the mechanism of the present ene reaction, showing that this is a stepwise process catalyzed by $InCl_3$ (substituent effects for the ene reaction have also been studied, all of the DFT studies are given in the Supporting Information).

In conclusion, we have developed an efficient strategy to construct linear tricyclic 5/5/5 and 6/5/5 skeletons through a rhodium-catalyzed [5 + 2 + 1] cycloaddition, converting ene-vinylcyclopropanes and CO to 5/8 and 6/8 bicyclic cycloadducts, and an $InCl_3$-catalyzed intramolecular transannular ene reaction, transforming [5 + 2 + 1] cycloadducts to tricyclic 5/5/5 and 6/5/5 products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02766.

Experimental procedures,characterization data for all new compounds and DFT study (PDF)

Accession Codes

CCDC 2047673−2047676 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Beijing Municipal Natural Science Foundation (No. 19B10067) and High-Performance Computing Platform of Peking University. Mr. Lu-Ning Wang (for proofreading) and Dr. Yi Wang and Mr. Weiming Shi (for preparing some substrates), all from Peking University, are highly appreciated.

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https://doi.org/10.1021/acs.orglett.1c02766
Org. Lett. XXXX, XXX, XXX−XXX