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Natural scaffolds-inspired synthesis of CF_3-substituted macrolides enabled by Rh-catalyzed C–H alkylation macrocyclization

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ABSTRACT

The development of innovative strategies and methods to provide natural product-like macrocycles not accessible by biosynthesis, but endowed with novel bioactivities and simplified structure, is highly desirable. Inspired by the key scaffolds of rapamycin and FR252921, herein, we report a Rh(III)-catalyzed C–H alkylation macrocyclization, which enables access to CF_3-substituted macrolides. DFT calculations reveal that the chemoselectivity between C–H alkylation and olefination macrocyclization was highly controllable. Moreover, the unique CF_3-substituted macrolides showed potent anti-inflammation activities against TNF-α, IL-6 and CCL2 mRNA expression.

Macrocyclic natural products have occupied an impressive area of chemical space, and have played an impactful and enduring role in the treatment of a range of serious diseases [1–6]. For instance, rapamycin and FK506 have a unique capacity of modulating protein-protein interactions (Scheme 1A) [7–13], which are difficult to interfere by typically drug-like small molecules. Despite the attractive characteristics offered by macrocyclic natural products, the sustainability of them could be hampered by gene expression limitation of microbes and difficulty of resupply. Therefore, the development of innovative strategies and methods to provide macrocycles not accessible by biosynthesis, but endowed with new biological functionality, still represents an important goal in organic synthesis. Very recently, Liu and co-workers established an elegant compound library of hybrid macrocycles by merging optimized FKBP-binding domains derived from rapamycin and various peptides [7, 14]. Intriguingly, screening of the library led to the discovery of Rapadocin, a highly potent inhibitor of human equilibrative nucleoside transporter 1 (hENT1). The key to this success was the orchestrated design of FKBD mimics tethered with peptides as linker and the use of classic ring-closing metathesis (RCM) as macrocyclization method [15–18]. While traditional macrocyclization methods, such as lactamization or lactonization, RCM, alkyne-azide cycloaddition (Scheme 1B), could serve as powerful tools to construct macrocycles [19–22], in recent years an attractive, cost-effective and atom-economical C–H activation macrocyclization has emerged and added new energies to expedite macrocycle synthesis [23–34]. In this regard, we questioned whether a new class of CF_3-substituted macrolides can be achieved through using FKBD mimics and exploring novel C–H alkylation macrocyclization (Scheme 1C). It is noteworthy that the introduction of -CF_3 into molecules could significantly modify their biological activities and physical properties such as, metabolic stability, lipophilicity, and permeability [35,36]. However, there are two challenging issues to be addressed in this scenario. First, controlling the chemoselectivity between olefination and alkylation remained a formidable challenge. The β-H elimination might preferably lead to the formation of olefination macrocyclization compounds rather than alkylation macrocyclization products, as it has been well-established in previous reported Pd-catalyzed or Rh-catalyzed C–H activation macrocy-

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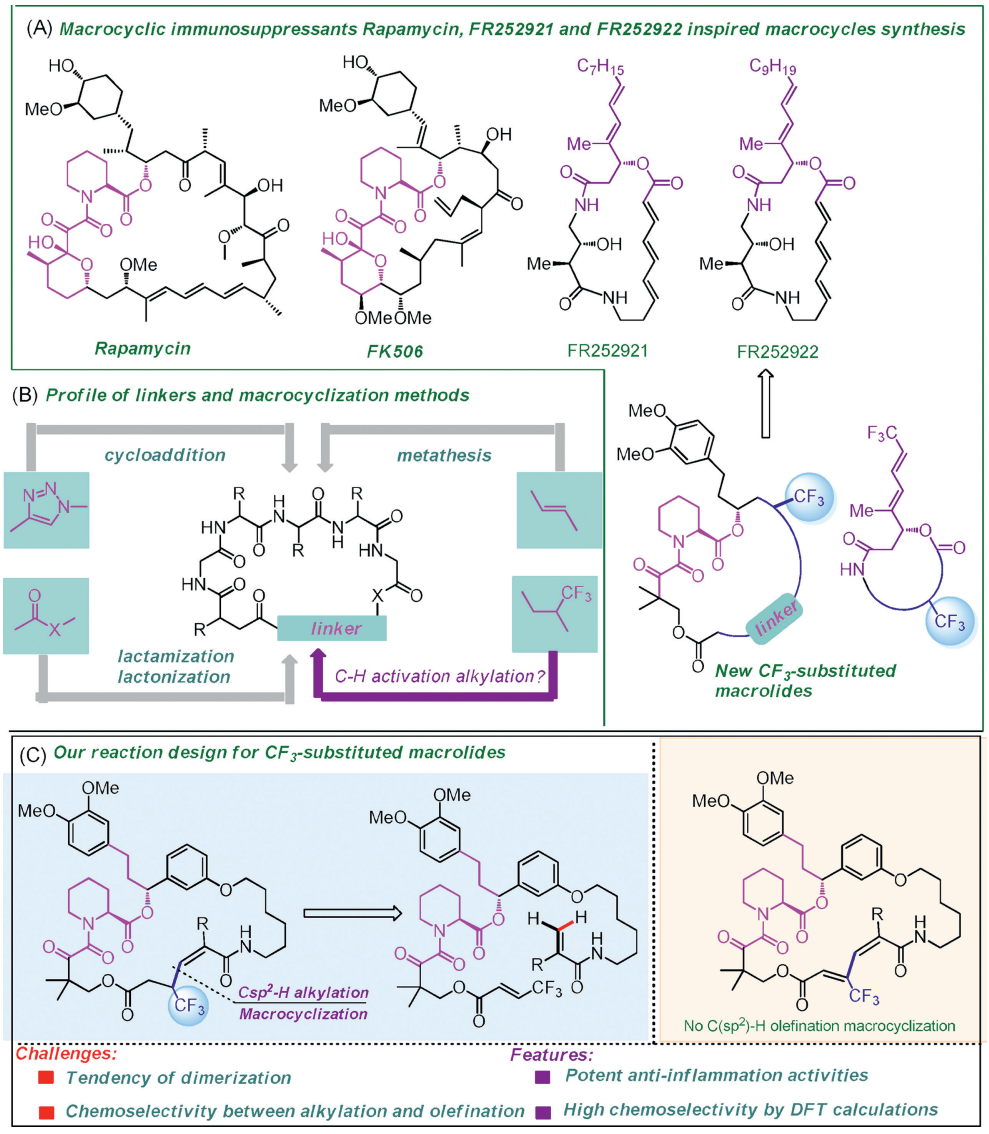


Scheme 1. Natural macrocyclic immunosuppressants and our design for CF_3-substituted macrolides.

clization [37–42]. To the best of our knowledge, the C–H alkylation macrocyclization has not been realized to date. Second, the synthesis of macrocycles *via* C–H activation manifold would be challenged by inter- versus intramolecular competition [29].

As our continuous effort in developing strategies and chemical methods to synthesize pseudo-natural macrocycles with diverse biological functionality [43–45], herein, we detail the successful realization of these ideas through the development of an unprecedented Rh(III)-catalyzed late-stage C–H alkylation macrocyclization (Scheme 1C). The reaction proceeds with very high chemoselectivity and affords a series of C(sp^3)-rich CF_3-substituted macrolides. Moreover, the unique CF_3-substituted macrolides showed potent anti-inflammation activities against TNF-α, IL-6 and CCL2 mRNA expression.

Growing evidence suggests that an increasing number of C(sp^3)-rich scaffolds in the macrocycles can result in proper molecular rigid and flexibility [46], which allow the macrocyclic molecules to adjust conformations and interfere their biological targets. Considering the importance of C(sp^3)-rich scaffolds in macrocycles, we sought to develop a novel macrocyclization process based on C–H alkylation. We speculated that using a native directing group tethered with a proper Michael receptor and an editable C–H crosslink might realize this transformation. To test this hypothesis, we first prepared the model substrate **1a** from a commercial available amino alcohol, 2-phenylacrylic acid and (2*E*)–4,4,4-trifluorobut-2-enoic acid by condensation reaction (Table 1). After an extensive assessment of reaction parameters, the optimal conditions for this C–H alkylation macrocyclization were identified as follows: $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ (10 mol%) as a catalyst, and AgOAc (2.0 equiv.) as an additive in DCE solvent at 100 °C for 12 h, affording the desired product **2a** in 54% isolated yield. A safe assignment of the structure **2a** was unambiguously determined by X-ray crystallography diffraction analysis (see Supporting information). The control experiments showed that the choice of $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ as catalyst was very crucial for the present macrocyclization reaction. No reaction occurred in the absence of the Rh(III) catalyst. Notably, switching to Pd(II), Ir(III) or Co(III) catalysts, which were highly effective in C–H alkylation, had no effect. Screening of different additives indicated that AgOAc was the most favored in this transformation. In the presence of 20 mol% AgOAc, only a trace amount of **2a** was obtained. Both Ag_2CO_3 and $Cu(OAc)_2$ completely shut down the reactivity. In addition, the solvent effect was further explored, and DCE proved to be the best choice.

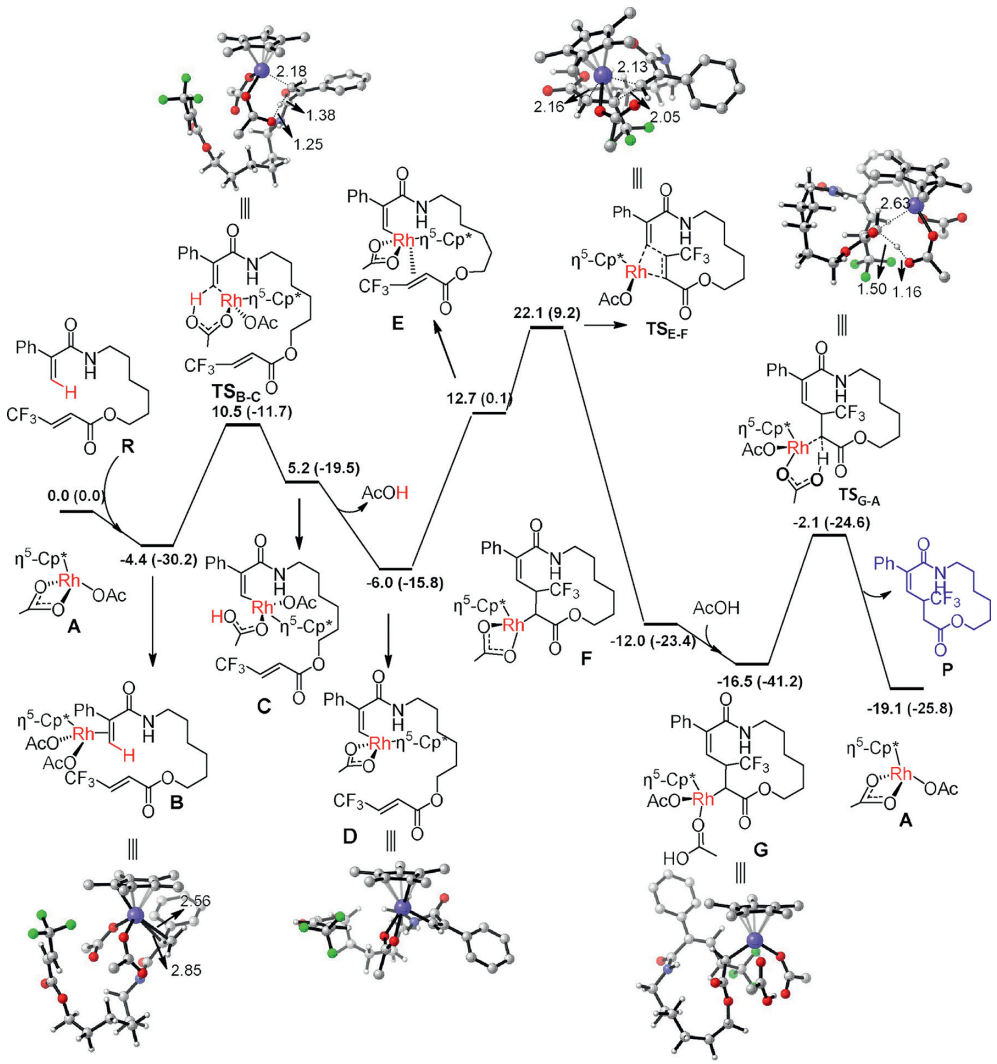
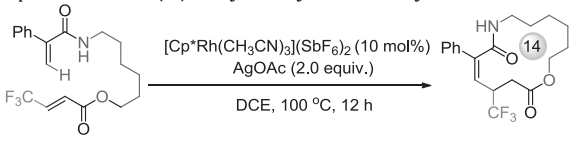


Fig. 1. Energy profile calculated according to the proposed mechanism involving deprotonation, olefin insertion and protonation. Relative free energies and electronic energies (in parenthesis) are given in kcal/mol.

Table 1
Optimization of Rh(III)-catalyzed alkylation macrocyclization.[a]



1a 2a

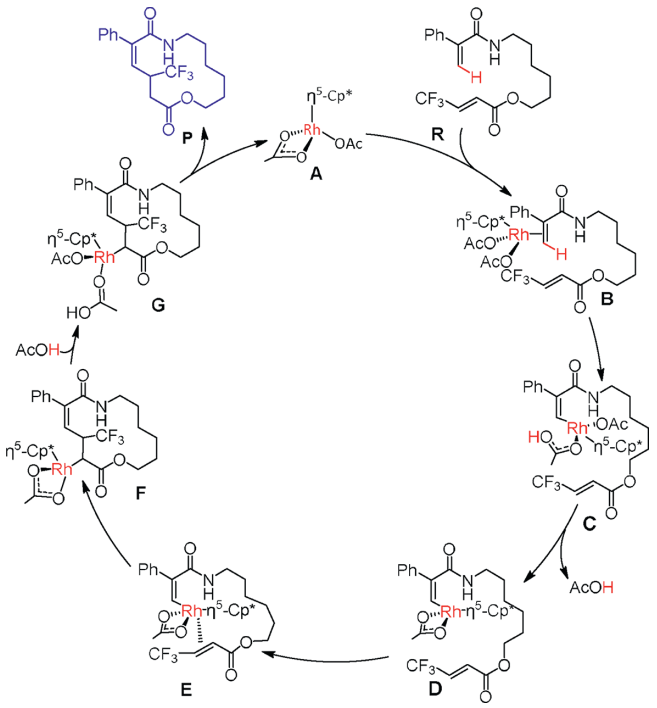
Entry	Variation from the standard reaction conditions	Yield (%)[b]
1	None	54
2	no $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$	0
3	$Pd(OAc)_2$ instead of $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$	0
4	$[Cp^*IrCl_2]_2/AgSbF_6$ instead of $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$	0
5	$[Cp^*Co(CH_3CN)_3](SbF_6)_2$ instead of $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$	0
6	no AgOAc	0
7	20 mol% AgOAc	trace
8	Ag_2CO_3 instead of AgOAc	0
9	$Cu(OAc)_2$ instead of AgOAc	trace
10	$PhCF_3$ instead of DCE	25
11	THF instead of DCE	47

DCE = 1,2-dichloroethane, THF = tetrahydrofuran, $PhCF_3$ = benzotrifluoride.

[a] Reactions were performed by using **1a** (0.1 mmol), $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ (0.01 mmol), AgOAc (0.2 mmol) and 1,2-dichloroethane (8.0 mL) at 100 °C for 12 h under air atomsphere.

[b] Yield of isolated product.

The excellent chemoselectivity between C–H alkylation and C–H olefination promoted us to further investigate its energy cause. Remarkably, this Rh(III)-catalyzed C–H alkylation macrocyclization is distinct from Xu and Loh's Rh(III)-catalyzed C–H olefination macrocyclization [37]. According to the outcome, we hypothesized that this alkylation macrocyclization is likely to involve C–H activation, olefin insertion and protonation. Following this hypothesis, we calculated the mechanism with the aid of DFT calculations. The energy profile calculated is shown in Fig. 1, providing support to the hypothesis. The first step is olefin coordination of a substrate molecule to catalyst **A** to form **B**. Then from **B**, C–H activation occurs through a concerted metalation deprotonation (CMD) process to give **C** *via* $\mathbf{TS_{B-C}}$ with an energy barrier of 14.9 kcal/mol. After that, the intermediate **C** releases AcOH to form **D**, accompanying a change in the coordination mode of the remaining acetate ligand from 1 to 2. Then, the remaining C=C double bond of the substrate molecule coordinates to the metal center of **D** forming the intermediate **E**, followed by olefin insertion occurs to give **F** *via* a four-membered ring transition state ($\mathbf{TS_{E-F}}$) with an energy barrier of 28.1 kcal/mol, which was found to be rate-determining. Finally, coordination of AcOH to the intermediate **F** gives the intermediate **G**, followed by protonation *via* a six-membered ring transition-state ($\mathbf{TS_{G-A}}$) to release the final product **P** and regenerate catalyst



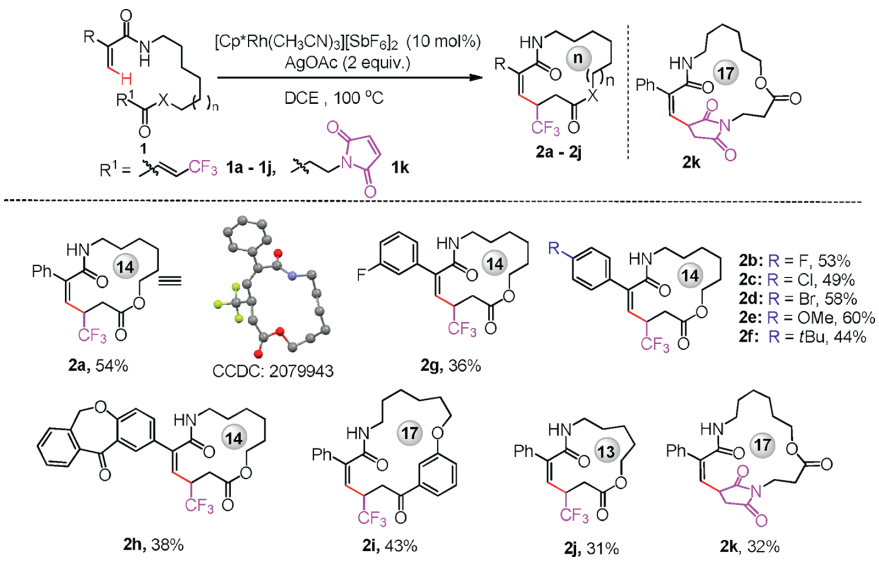
Scheme 2. Schematic catalytic cycle of Rh(III)-catalyzed C–H alkylation macrocyclization.

A. A catalytic cycle shown in Scheme 2 summarizes the reaction mechanism discussed above.

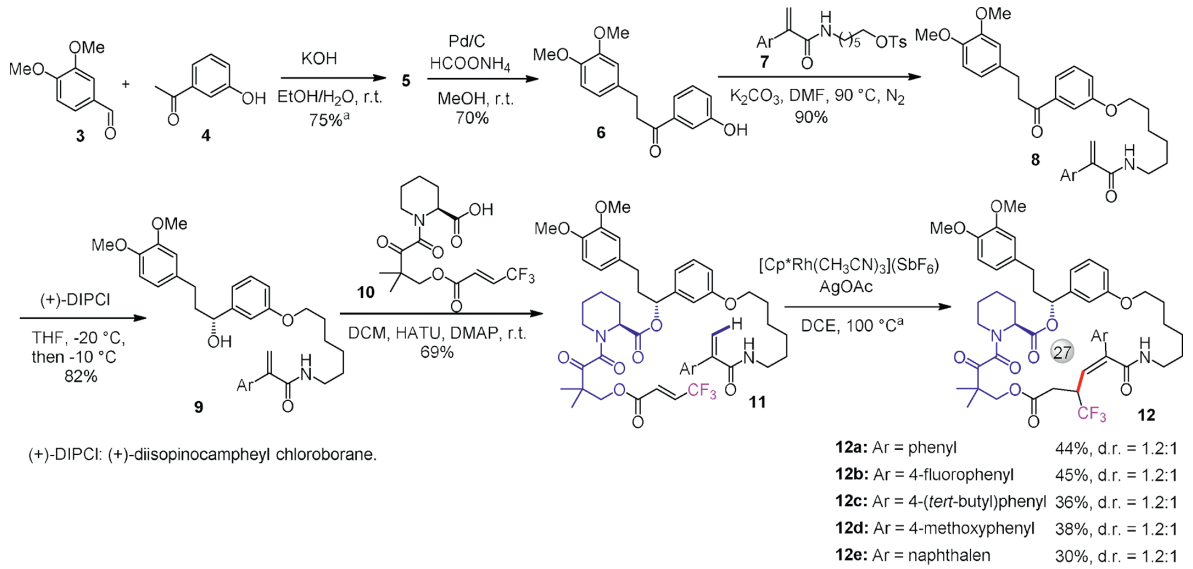
We also considered a pathway starting from the intermediate **G** that undergoes β-H elimination followed by reductive elimination, which was not observed experimentally (Fig. s10 in Supporting information). The β-H elimination was found to require an activation energy of greater than 40 kcal/mol, which is energetically inaccessible and consistent with the experimental observation that this pathway did not occur.

Encouraged by these findings, we turned our attention to studying the generality of this C–H alkylation macrocyclization. As outlined in Scheme 3, substrates bearing electron-withdrawing groups such as fluoro, chloro, and bromo, or electron-donating groups such as methoxyl, and tert–butyl could be well-tolerated to produce 13–17-membered macrocycles in moderate to good isolated yields. In addition, the dibenzo[*b,e*]oxepin-11(6*H*)-one, as an important privileged structure, was incorporated into the substrate, which successfully led to the production of macrolide **2h** in 38% isolated yield. Further studies showed that this method was not limited to the substrates tethered with ester linker, but also compatible with ether linker connected substrates. Apart from the CF_3-substituted moiety, we were delighted that the maleimide used as antibody-drug conjugate (ADC) linker took place smoothly to afford the maleimide-substituted macrolide **2k** in a decent yield, which further highlighted the robustness of this developed C–H alkylation macrocyclization.

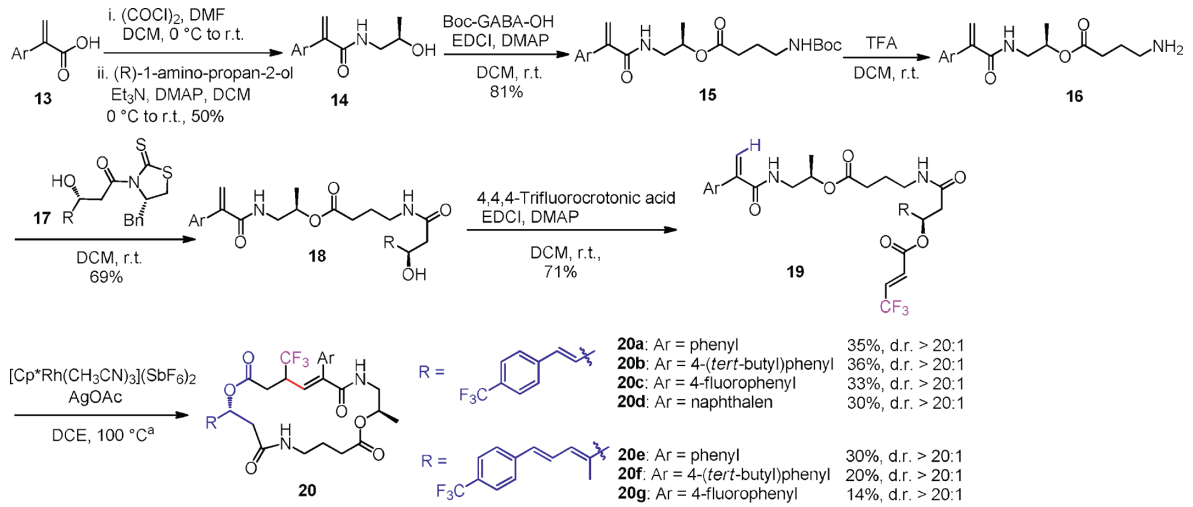
Designing new but simplified *pseudo*-natural macrocycles using function-oriented synthesis strategy and novel protocol is our important goal. Consequently, we set out to create CF_3-substituted macrolides by merging FKBP mimics. The synthesis of compound **10** commenced with nucleophilic substitution of *N*-Boc homoproline, followed by *N*-Boc deprotection to generate **s4**, which reacted with dihydro-4,4-dimethyl-2,3-furandione to form a primary alcohol **s5** in 80% yield over 3 steps. Compound **s5** was then treated with (2**E**)−4,4,4-trifluorobut-2-enoic acid followed by Pd-catalyzed Tsuji-Trost reaction to deliver **10** in 56% yield over 2 steps (see the Supporting information for more details). With **10** secured, we moved our attention toward the preparation of chiral alcohol **9** (Scheme 4). An aldol condensation reaction between 3,4-dimethoxybenzaldehyde and 1-(3-hydroxyphenyl)ethan-1-one led to α,β-unsaturated ketone **5**, which then underwent Pd/C-catalyzed reduction to provide **6**. The route to **7** requires 3 steps from simple building blocks and it proceeds in 44% overall yield in multi-gram scale (Supporting information for more details). Gratifyingly, nucleophilic attack of **6** on **7** proceeded smoothly, giving **8** in 90% yield. Subsequently, **8** was subjected to enantioselective ketone reduction to produce secondary alcohol **9**. The free alcohol moiety of **9** was then esterified with acid **10** to provide ester **11**. With the macrocyclic precursor **11** in place, we moved on to investigate the last synthetic challenge, that is, utilization of Rh(III)-catalyzed C–H alkylation macrocyclization to construct CF_3-containing macrolides **12**. To our delight, a range of simplified non-natural macrolides can be accessed under the standard conditions.



Scheme 3. Substrate scope of Rh(III)-catalyzed intramolecular C–H alkylation macrocyclization. Reaction conditions: reactions of substrate **1** (0.1 mmol), $[Cp^*Rh(CH_3CN)_3][SbF_6)_2$ (0.01 mmol) and AgOAc (0.2 mmol) were carried out in DCE (8.0 mL) at 100 °C for 12 h under air atomsphere. Isolated yields.



Scheme 4. Synthesis of macrolides bearing FKBP mimic. Isolated yield by column chromatography. Compounds **7** and **10** are prepared by the general procedures available in Supporting Information. [a] Reactions of precursor **11** (0.1 mmol), $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ (0.01 mmol) and AgOAc (0.2 mmol) were carried out in DCE (8.0 mL) at 100 °C for 16 h under air atomsphere.



Scheme 5. Synthesis of CF_3-substituted macrolides. Isolated yield by column chromatography. General procedures for preparation of compound **17** are available in Supporting information. [a] Reactions of precursor **19** (0.1 mmol), $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ (0.01 mmol) and AgOAc (0.2 mmol) were carried out in DCE (8.0 mL) at 100 °C for 16 h under air atomsphere.

Very recently, Maulide and co-workers described a fascinating Suzuki–Miyaura/4π-electrocyclic ring-opening macrocyclization method and successfully constructed FR252921 and its analogues which exhibited potent inhibition of T-lymphocyte proliferation [47–50]. Inspired by these unique architecture and biological activity, our next task was to create CF_3-containing macrolides using Rh(III)-catalyzed C–H alkylation macrocyclization. As shown in Scheme 5, our synthesis started with the amidation between easily accessible chiral amino alcohol and **13**, providing **14** in 50% yield. Treatment of **14** with long-chain amino acid *via* esterification, followed by the removal of Boc, gave rise to **16**. Gratifyingly, subjecting **16** and **17** to Maulide's conditions could furnish the desired secondary alcohol **18** in 69% yield with high diastereoselectivity (> 20:1). Subsequently, alcohol **18** was readily coupled with (2**E**)–4,4,4-trifluorobut-2-enoic acid in the presence of EDCI and DMAP to generate macrocyclic precursor **19**. Eventually, building on the power of this Rh(III)-catalyzed C–H alkylation macrocyclization, we were pleased to find that the desired CF_3-containing macrolide **20** could be obtained successfully in decent yield.

Elevation of inflammatory gene expression is a well-known response of macrophages to LPS stimulation [51–53]. Therefore, we assessed the suppressive effect of these compounds on the representative inflammatory genes such as CCL2, TNF-α, IL-6 in transcript level, which are critically involved in the process of cancer and metabolic diseases. In comparison to the cells incubated with vehicle, the LPS treatment led to a significant increase in the level of all cytokines. As shown in Fig. 2, compounds **12b**, **12d**, **20d**, **20a**, **12a**, **12e**, **20e**, **20b**, **20g**, **12c** and **20f** significantly suppressed LPS-induced TNF-α expression. In addition, **20d**, **12a**, **12c**, **20f** decreased LPS induced CCL2 mRNA expression (100%) to nearly 25%. In comparison to the cells treated only with LPS, co-treatment with 5 μmol/L of **20d**, **20g**, **12c**, **20f** significantly blunted (87.36%, 73.22%, 88.45%, 90.17%) the expression of IL-6, respectively, while that of the positive control, NF-κB inhibitor BAY-11–7082 is 80.82%.

In summary, we have developed a novel Rh(III)-catalyzed C–H alkylation macrocyclization for the highly chemeoselective synthesis of C(sp^3)-rich CF_3-subsituted macrolides. Our DFT calculations

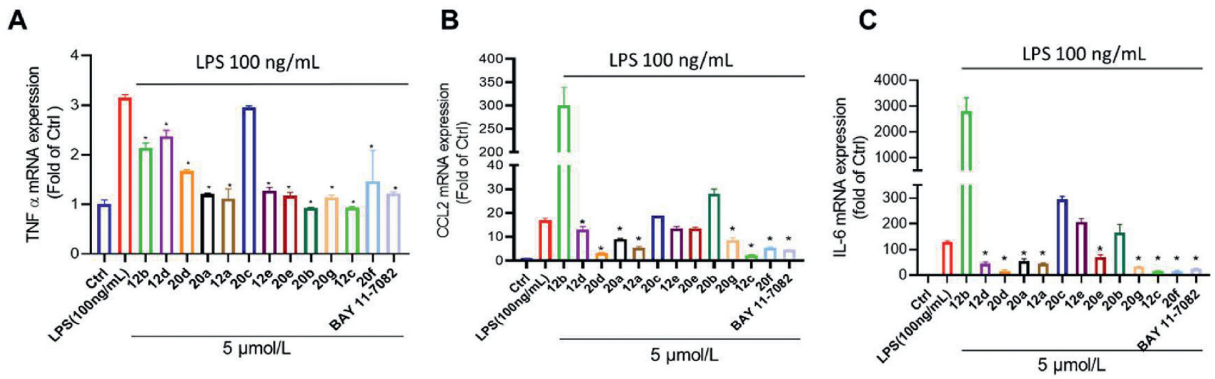


Fig. 2. The anti-inflammation effect of CF_3-substituted macrolides. Raw264.7 cells were treated with indicated concentrations of LPS (100 ng/mL) and various compounds for 24 h. The mRNA levels of associated inflammatory factors including TNF-α, CCL2 and IL-6 were analyzed by qRT-PCR and normalized by GAPDH. Data were analyzed with one-way ANOVA, followed by fisher's LSD tests with two tailed distributions. Bar groups represent the mean ± SEM; $^*P < 0.05$.

provided in-depth insights into the controllable chemoselectivity between C–H alkylation and olefination macrocyclization. Moreover, the functionality of these novel C(sp^3)-rich CF_3-containing macrocycles was highlighted by inhibiting inflammatory factors, such as TNF-α, IL-6 and CCL2 mRNA expression. As such, we anticipate that this noteworthy reaction will facilitate modular, rapid access to other pseudo-natural macrocycles construction.

Declaration of competing interest

All authors declare no competing financial interest.

Acknowledgments

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2021.10.043.

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