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Paul Massé, Sabine Choppin, Lucia Chiumminto, Gilles Hanquet, Françoise Colobert. Unintended Formation of a 26-Membered Cycle in the Course of a Novel Approach to Myricanol, a Strained [7,0]-metacyclophane. SYNLETT, 2019, 31 (06), pp.559-564. 10.1055/s-0039-1691523 . hal-03075499

HAL Id: hal-03075499

<https://hal.science/hal-03075499>

Submitted on 16 Dec 2020

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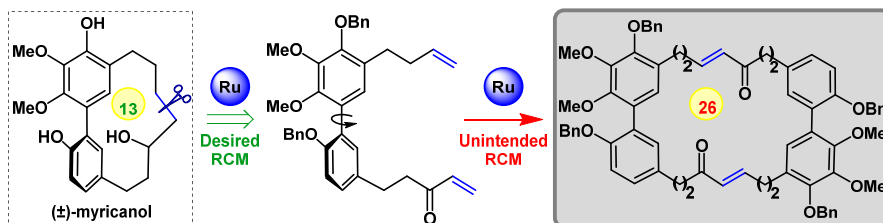
Unintended Formation of a 26-Membered Cycle in the Course of a Novel Approach to Myricanol, a Strained [7,0]-*metacyclophane*

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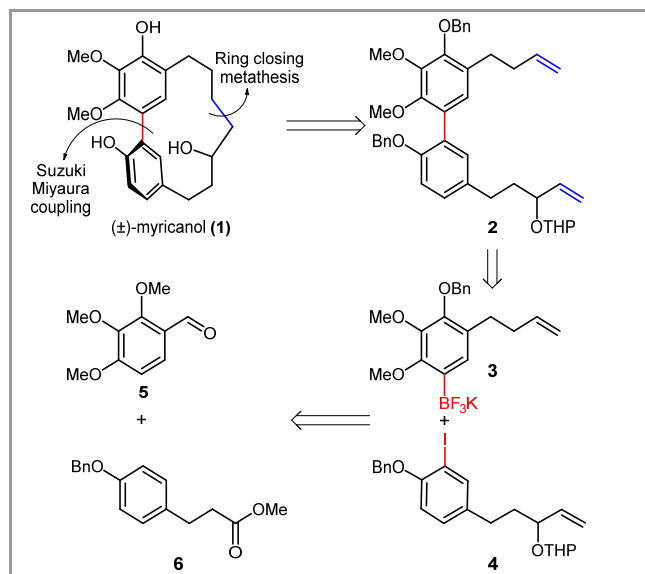
Received:
 Accepted:
 Published online:
 DOI:

Abstract A convergent approach for the synthesis of (±)-myricanol, a strained diarylheptanoid isolated from *Myricaceae*, was undertaken using a Suzuki-Miyaura coupling followed by a RCM. Herein, we report the unintentional formation of a 26-membered macrocycle as RCM product resulting from a head-to-tail dimerization of the *seco*-precursor, even in RRCM conditions.

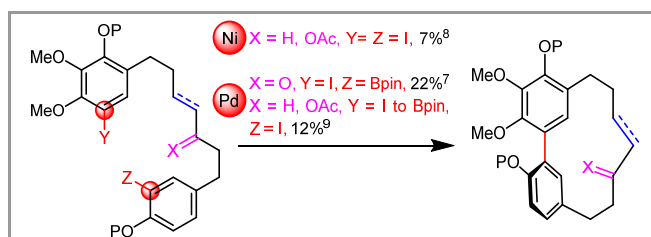
Key words myricanol, target-oriented synthesis, diarylheptanoid, natural product, macrocycle, Suzuki-Miyaura cross-coupling, RCM, Alzheimer's disease biological activities

Myricanol **1** was extracted from the stem bark of *Myricaceae* species, trees that produce bayberries, and more particularly from *Myrica Nagi* in 1970 by Whiting and co-workers.¹ There is a vivid interest in the community for this strained *meta,meta*-bridged phenolic diarylheptanoid **1** which displays a very intriguing structure with its biaryl system linked by an oxygenated aliphatic heptyl chain.²⁻³ Besides, it exhibits many different biological activities such as anti-oxidant and anti-androgenic.⁴ Very recently, it was discovered that **1** displays as well anti-inflammatory along with anti-obesity and anti-muscle atrophy properties.⁵ This [7,0]-*metacyclophane* **1** also features anti-cancer virtues. It was shown to undoubtedly strive against human lung adenocarcinoma A549 cells.⁶ Furthermore, Dickey *et al* found that **1** potently reduces the levels of the microtubule-associated protein tau in both cultured cells and *ex vivo* mouse brain slices, which results in an anti-Alzheimer's disease effect, notably owing to the (-)-*aS*,11*R*-myricanol enantiomer which has been separated by chiral HPLC.⁷

7% yield by a nickel-mediated intramolecular oxidative coupling from a linear diiodide diarylheptanoid. Dickey and co-workers reported in 2015 the second total synthesis of racemic myricanol **1**.⁷ They performed an intramolecular Suzuki-Miyaura cross coupling between an aryl boronic acid pinacol ester and an aryl iodide delivering the macrocycle in 22% yield. Colobert *et al* carried out a Suzuki-Miyaura domino reaction to obtain the expected 13-membered cycle in 12% yield (Scheme 1).⁹



Scheme 2 Retrosynthetic analysis of **1**



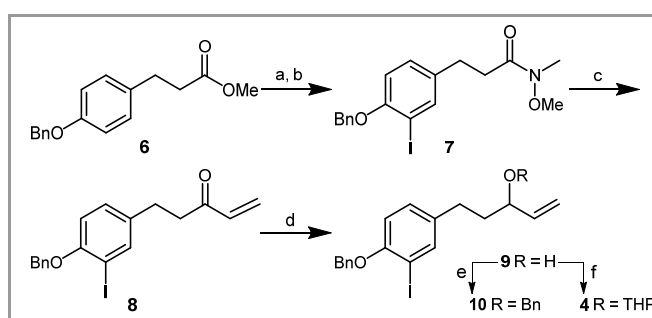
Scheme 1 State-of-the-art on macrocyclizations leading to (±)-myricanol

Three total syntheses have been previously described in a racemic way. The first one was reported by Whiting *et al* in 1983.⁸ They achieved the challenging macrocyclization in

Based on our deep-rooted enthusiasm for the chemistry of bioactive natural products,¹⁰ we were eager to perform the total synthesis of this uncommonly strained compound. *Meta,meta* cyclic diarylheptanoids are considered as congested cyclophanes because of their high ring strain due to the short heptyl bridge.^{2a,3} As for all cyclic compounds, macrocyclization is the most critical step, which determines the overall efficiency of a synthetic route.³ To the best of our knowledge, endeavor of macrocyclization to prepare *meta,meta*-bridged diarylheptanoids in the literature other than by biaryl coupling have failed so far (Heck coupling and Thorpe-Ziegler reaction).¹¹ However, none of those routes have envisioned a convergent approach of this 13-membered strained compound **1** *via* a

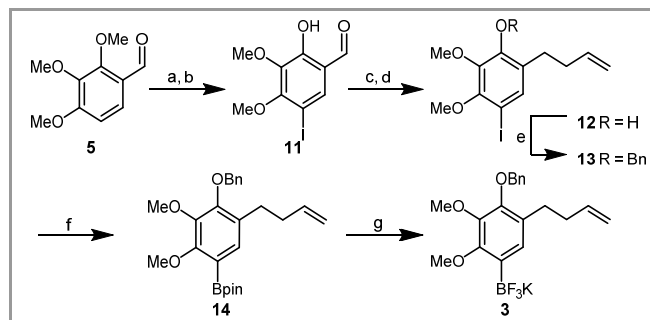
sequence of two key reactions: a Suzuki-Miyaura coupling followed by a ring closing metathesis (RCM). RCM is often efficiently applied for the construction of strained natural compounds and with a large variety of substrates.¹² For instance, Kundig *et al* prepared a strained 12-membered macrolactone bearing an *ortho,meta* diarylheptanoid performing a RCM in presence of HGII in an optimized yield of 37%.¹³

A large variety of catalysts are available for RCM as GII, HGII, but also more exotic catalysts like Mauduit's (Umicore **M71**), Nolan's (Umicore **M2**) and Grela's (**nG-I₂**) which could achieve this challenging macrocyclization (Scheme 5).¹⁴ Herein, we describe a new convergent retrosynthetic pathway of **1** that could be arisen from **2** by RCM, itself stemming from the Suzuki-Miyaura coupling from key building blocks **3** and **4**, envisaged respectively from commercially available compounds **5** and **6** (Scheme 2).



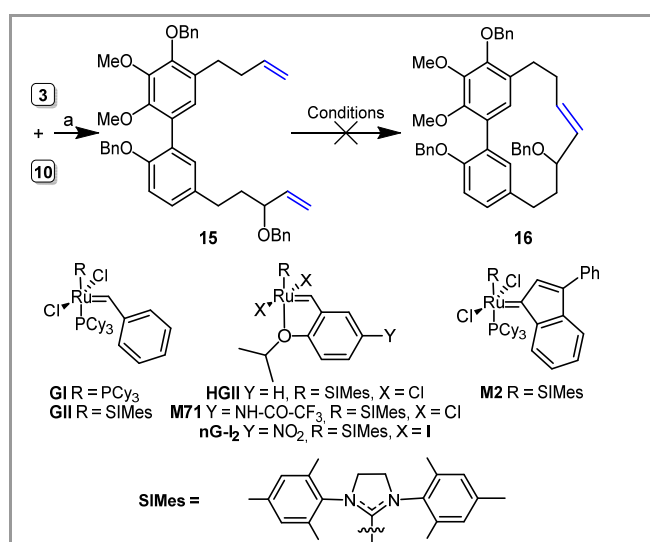
Scheme 3 Preparation of the first building-block **10** Reagents and conditions: (a) $\text{CH}_3\text{NHOCH}_3\cdot\text{HCl}$, AlMe_3 , PhMe, r.t., 24 h, 99%; (b) I_2 , Ag_2SO_4 , CH_2Cl_2 , r.t., 3 days, 83%; (c) vinylmagnesium bromide, THF, 0 °C, 1 h, 99%; (d) NaBH_4 , $\text{CeCl}_3\cdot 7\text{H}_2\text{O}$, MeOH, -78 °C, 0.5 h, 88%; (e) NaH, BnBr, NaI, DMF, 0 °C to r.t., 1.5 h, 91%; (f) DHP, PPTS, CH_2Cl_2 , r.t., 24 h, 79%.

As depicted in Scheme 3, the first building block **10** has been synthesized in 5 steps on a multigram scale without any required purification from the readily available benzyl-protected phenol **6**.¹⁵ The ester moiety was derivatized into the corresponding Weinreb amide in toluene in remarkable yield using AlMe_3 and the corresponding hydroxylamine hydrochloride. The latter underwent a regioselective iodination in *ortho* position of the benzyl ether using I_2 as well as Ag_2SO_4 to give **7** in 83% yield.⁹ Subsequent vinylation of the amide with a Grignard reagent allowed us to isolate the α,β -unsaturated ketone **8** in a quantitative yield upon quick hydrolysis with a strong acid to avoid the formation of a side-product coming from the Michael addition of the released hydroxylamine onto **8**.¹⁶ Luche reduction furnished **9** in 88% yield with complete chemoselectivity. Consecutive protection of the formed allylic carbinol as its corresponding benzyl ether afforded the first building block **10** with an overall yield of 58%. A variant protecting group (**4**, bearing a THP group) was envisaged to perform the remainder of the synthesis.



Scheme 4 Preparation of the second coupling partner **3** Reagents and conditions: (a) AlCl_3 , CH_2Cl_2 , r.t., 3 h, 81%; (b) I_2 , Ag_2SO_4 , CH_2Cl_2 , r.t., 3 days, 51%; (c) allylmagnesium bromide, THF, 0 °C, 0.5 h, 87%; (d) i. TES, TFAA, CH_2Cl_2 , 0 °C, 1.5 h; ii. TBAF, THF, 70%; (e) BnBr, NaH, NaI, DMF, 1.5 h, 0 °C to r.t., 95%; (f) i. *t*-BuLi, hexane, -78 °C; ii. *i*-PrOBpin, -78 °C to r.t., 2.5 h; (g) KHF_2 , H_2O , MeOH, r.t., 1.5 h, 89% (over 2 steps).

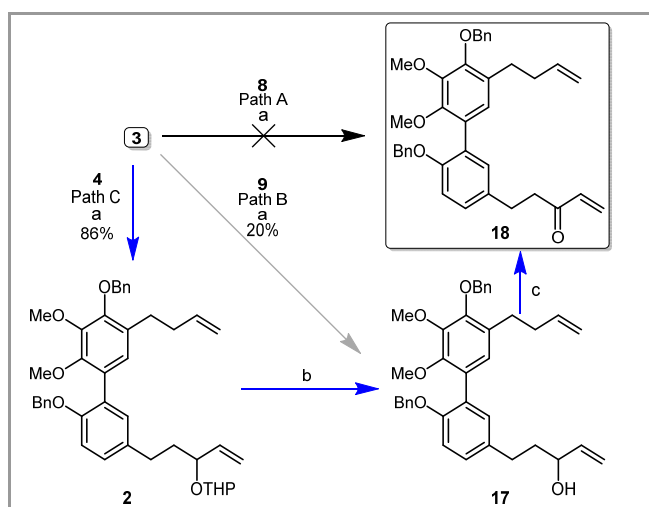
As outlined in Scheme 4, the synthesis of the second key coupling partner **3** started with commercially available trimethoxybenzaldehyde **5** which was regioselectively demethylated in *ortho* position of the aldehyde using a Lewis acid. The reaction has to be performed under 20 °C to avoid a second competitive demethylation. Then, regioselective iodination of the aromatic cycle was accomplished and provided **11** exclusively in 51% yield. It should be noted that a complete conversion was observed; however, aryl iodide was trapped in the silver salts and remained unextractable; many experimental conditions were screened to improve yield, without any success. Upon allylation on the aldehyde with a Grignard reagent, homoallylic alcohol was afforded in excellent yield. Thereupon, the formed carbinol was cleaved using triethylsilane in acidic medium,¹⁷ followed by the addition of a solution of TBAF due to the resulting partial triethylsilylation of the phenol group, thus affording **12**. Subsequently, the latter was subjected to a protection to give its corresponding benzyl ether **13** in 95% yield. Aryl iodide **13** was treated with *t*-BuLi and isopropoxy-pinacolborane at -78 °C in dry hexane to provide **14** as a boronic acid pinacol ester. Finally, **3** was prepared on exposure to an aqueous solution of KHF_2 in MeOH in 89% yield over two steps. **3** was reached in 7 steps with an overall yield of 25%.¹⁸



Scheme 5 First RCM attempts. Reagents and conditions: (a) $\text{Pd}(\text{PPh}_3)_4$, K_2CO_3 , TBAB, H_2O , 100 °C, 16 h, 83%.

With both partners **3** and **10** in hand, we were able to synthesize the biaryl **15** by Suzuki-Miyaura coupling in the presence of palladium(0) (Scheme 5). We have to point out that with the pinacol boronic ester **14**, no reaction occurred; also, we were never able to synthesize the corresponding boronic acid, justifying the selection of the more reactive trifluoroborate salt.¹⁹ Moreover, the yield was low when the reaction was performed in dioxane (28%). By modifying the ratio dioxane/H₂O up to H₂O only, yield was increased to 83%. With Buchwald conditions (palladium(II) acetate and SPhos ligand), we ended up with the isomerization of the terminal double bond.

To finalize the preparation of myricanol **1**, first RCM assays were next attempted with the *seco*-precursor **15** by screening various solvents (CH₂Cl₂, PhMe, DCE, Et₂O, H₂O) catalysts (**GII**, **GII**, **HGII**, **M71**, **M2**) and temperatures (from 25 to 110 °C). None of those experimental conditions gave us rise to the expected cyclized compound **16** even in the required high dilution conditions (Scheme 5). The benzyl-protected allylic alcohol being a type III olefin,²⁰ hence less reactive, we therefore tried with the free allylic alcohol along with its corresponding α,β -unsaturated ketone (likely to be more prone to macrocyclize due to the presence of the sp² carbon center). Notwithstanding, it was impossible to deprotect regioselectively the benzyl group on the allylic alcohol *versus* the benzyl-protected phenols. Consequently, we tried the Suzuki-Miyaura coupling between our trifluoroborate salt **3** and ketone **8**. Unfortunately, we could not access **18** directly (Path A, Scheme 6). Ketones are apparently not compatible with those conditions. Hence, we then attempted the coupling with **9** bearing the free hydroxy group instead, which afforded **17** in order to get by its further oxidation the corresponding ketone **18**. In this way, **17** was obtained in low yield (Path B, Scheme 6). Based on these results, we further proceeded to a three-step sequence using **4** (THP-protected **9** derivative) that was coupled with **3** to obtain biaryl **2** in excellent 86% yield. Finally, removal of THP group and oxidation using MnO₂ followed smoothly (Path C, Scheme 6).



Further RCM attempts on **17** gave us unexpected results: we

obtained two regioisomers **19** and **19'**. Allylic alcohol isomerized into the corresponding ethyl ketone,²¹ and terminal double bond isomerized once, but also twice to be conjugated with the aromatic core (both compounds were obtained in a 1:1 ratio).²² The failure of the RCM of **17** could be explained by the free rotation of the biaryl axis which increase the difficulty of the two terminal alkenes to cross path. The presence of a Csp³ leads also to a more strained chain compared to the presence of a Csp².²³ As for RCM attempts on **18**, we were quite pleased to see by ¹H NMR that we obtained the expected cyclized compound. Nonetheless, we realized we formed the head-to-tail dimer **20** thus involving a C₂ symmetry as evidenced from HR mass spectrum.²⁴ Changing the solvent, the catalyst, lowering the concentration or adding the starting material *via* a syringe pump over a long period unfortunately did not circumvent our issue. (Table 1)

Table 1 Unexpected results in the course of RCM attempts on **19** and **20**

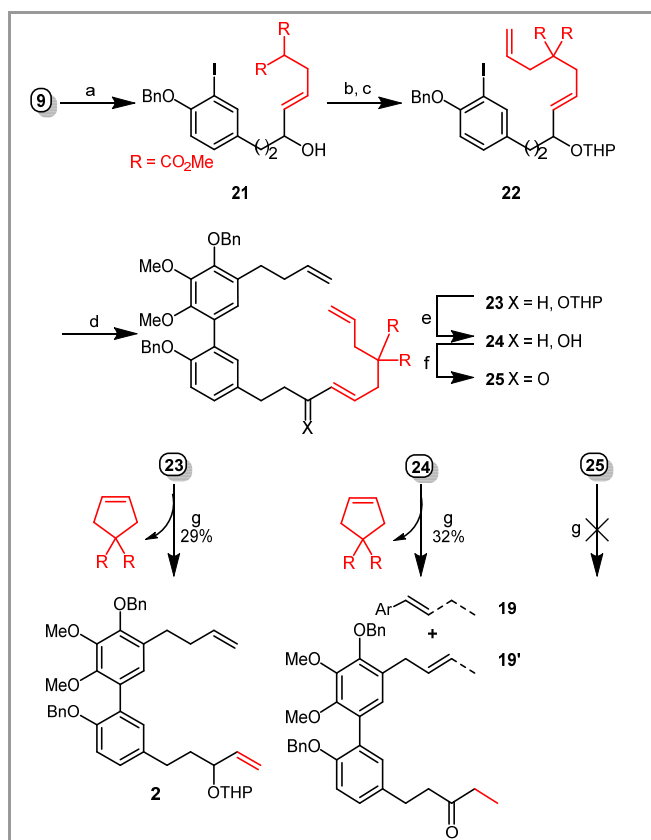
Entry	Catalyst	Solvent	Concentration	Dimer yield
1	GII	CH ₂ Cl ₂	2 mM	20%
2	GII	PhMe	2 mM	30%
3	GII	PhMe	0.5 mM	39%
4	M71	PhMe	0.5 mM	37%
5	GI	PhMe	0.5 mM	n.o.
6	nG-I₂	PhMe	1 mM	17%

Reagents and conditions (a) **GII**, PhMe (2 mM), 110 °C, 16 h, 35%.

To overcome this synthesis drawback, we next sought to solicit the concept of Relay RCM (RRCM).²⁵ RRCM involves the incorporation of a temporary pentenyl tether containing a terminal olefin to initiate the catalytic process. Once you add the catalyst, the ruthenium carbene can be formed on the terminal olefin, a 5-membered ring is extruded which leads to the desired metal carbene that can undergo further cyclization. Porco *et al* reported in 2004 the synthesis by RRCM of oximidine III, a 12-membered macrocycle.²⁶ They managed to obtain a yield of 71% for the macrocyclization step whereas with a classical RCM they could not get any traces of the expected compound. In our case, we chose to put a malonate group onto the temporary tether to improve the efficiency of our RRCM by dint of the Thorpe-Ingold effect.²⁵

Starting from **9**, we performed the cross-metathesis with dimethyl allylmalonate in the conditions described by Lipshutz *et al*, with a surfactant and copper iodide as an additive thus affording **21**.²⁷ Subsequently, both deprotonation of the

methylene-active malonate motif followed by the trapping with allyl bromide and protection of the allylic alcohol with a THP group were quantitative. THP was a protecting group of choice given that it is easily accessible and easy to orthogonally deprotect. Afterwards, the Suzuki-coupling between **22** and **3** was implemented in a great yield and RRCM assays were attempted. RRCM assay on **23** was not conclusive: we extruded the 5-membered ring but the formed carbene did not react further, we therefore ended up with **2**. We proceeded to the RRCM on free allylic alcohol **24**, but we obtained the same results as with the RCM: isomerization of allylic alcohol into ethyl ketone and isomerization of the terminal double bond. **25** bearing the carbonyl function ended up degraded in the RRCM conditions (Scheme 7).

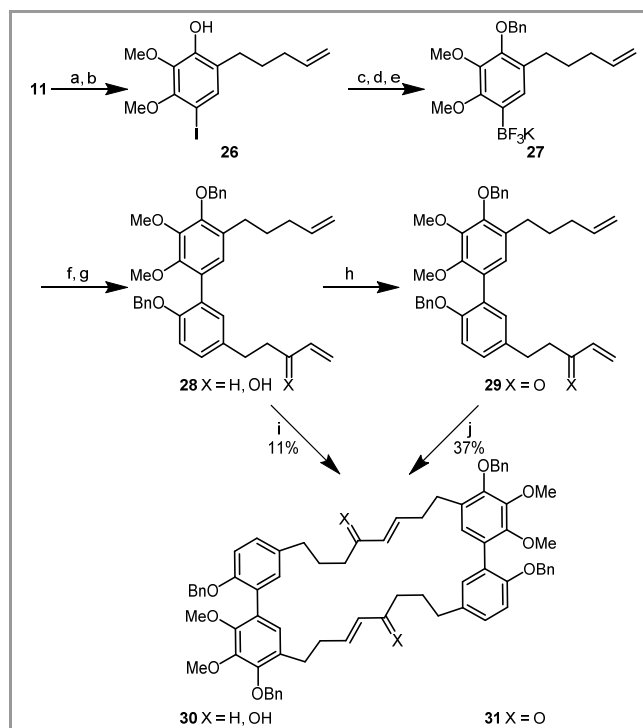


Scheme 7 Synthesis of RRCM precursor and subsequent RRCM attempts *Reagents and conditions* (a) dimethyl allylmalonate, **GII**, CuI, TPGS-750-M, H₂O, 40 °C, 16 h, 55%; (b) DHP, PPTS, DCM, r.t., 16 h, 99%; (c) NaH, allylbromide, THF, 60 °C, 1.5 h, 99%; (d) **3**, Pd(PPh₃)₄, K₂CO₃, TBAB, H₂O, 100 °C, 16 h, 74%; (e) PPTS, MeOH, CH₂Cl₂, 60 °C, 3 h, 99%; (f) MnO₂, CH₂Cl₂, 40 °C, 3 h, 64%; (g) **GII**, PhMe (1 mM), 110 °C, 16 h.

The free rotation of the biaryl axis combined with the high congestion of the desired compound could undeniably explain the uncompletion of the reaction. Accordingly, we attempted to make the less strained 14-membered cycle analogue, more prompt to undergo cyclization, as a proof of concept. Instead of using commercially available allyl Grignard reagent to prepare the RCM precursors, chain was introduced *via* an *in situ* homoallylic Grignard reagent on **11**. Successive reduction, protection of **26**, lithium-iodine exchange, trifluoroboration, Suzuki-Miyaura coupling on **27** and **4**, deprotection and oxidation proceeded smoothly to procure **29**. Unfortunately, RCM attempts on **28** gave us notably a 28-membered

macrocycle **30** among a myriad of isomerized products (adding benzoquinone to prevent isomerization did not succeed).²⁸ **29** with the ketone gave us also a head-to-tail dimer **31** in 37% yield (Scheme 8).

In conclusion, a 26-membered macrocycle and two 28-membered macrocycles have been successfully synthesized using RCM in high dilution conditions. No traces of 13- or 14-membered cyclized products were spotted even with RRCM. We can infer that the strain outpaces the reactivity, even in our attempts to prepare the 14-membered macrocycle.



Scheme 8 Synthesis of corresponding 14-membered macrocycle precursor and subsequent RCM attempts *Reagents and conditions* (a) butenylbromide, Mg, THF, 0 °C, 0.5 h, 98%; (b) i. TES, TFAA, CH₂Cl₂, 0 °C, 1.5 h; ii. TBAF, THF, 80%; (c) BnBr, NaH, NaI, DMF, 1.5 h, 0 °C to r.t., 47%; (d) i. *t*-BuLi, hexane, -78 °C; ii. *i*-PrOBpin, -78 °C to r.t., 2.5 h; (e) KHF₂, H₂O, MeOH, r.t., 1.5 h, 93% (over 2 steps); (f) **4**, Pd(PPh₃)₄, K₂CO₃, TBAB, H₂O, 100 °C, 16 h; (g) PPTS, MeOH, CH₂Cl₂, 60 °C, 3 h, 35% (over 2 steps); (h) MnO₂, CH₂Cl₂, 40 °C, 3 h, 37%. (i) **GII**, CH₂Cl₂ (1 mM), 16 h, 11% (j) **GII**, PhMe (1 mM), 16 h, 37%.

Acknowledgment

We thank the CNRS France (Centre National de la Recherche Scientifique) as well as the University of Strasbourg, and Paul Massé is grateful to the French ministry of research and development for financial support. We are also really grateful to Marc Mauduit who provided us his catalyzt.

Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

References and Notes

- (1) Begley, M. J.; Campbell, R. V.; Crombie, L.; Whiting, D. A. *J. Chem Soc.* **1971**, 3634.

- (2) (a) Jahng, Y.; Park, J. G. *Molecules* **2018**, *23*, 3107. (b) Alberti, Á.; Riethmüller, E.; Béni, S. J. *Pharm. Biomed. Anal.* **2018**, *147*, 13. (c) Zhu, J.; Islas-Gonzalez, G.; Bois-Choussy, M. *Org. Prep. Proced. Int.* **2000**, *32*, 505. (d) Sun, C.; Huang, H.; Xu, C.; Li, X.; Chen, K. *Plant Foods Hum. Nutr.* **2013**, *68*, 97.
- (3) (a) Gulder, T.; Baran, P. S. *Nat. Prod. Rep.* **2012**, *29*, 899. (b) Joshi, B. S.; Pelletier, S. W.; Gary Newton, M.; Lee, D.; McGaughey, G. B.; Puar, M. S. *J. Nat. Prod.* **1996**, *59*, 759.
- (4) (a) Tao, J.; Morikawa, T.; Toguchida, I.; Ando, S.; Matsuda, H.; Yoshikawa, M. *Bioorg. Med. Chem.* **2002**, *10*, 4005. (b) Wang, M.; Liu, Y.; Pan, R. L.; Wang, R. Y.; Ding, S. L.; Dong, W. R.; Sun, G. B.; Ye, J. X.; Sun, X. B. *Int. J. Mol. Med.* **2019**, *43*, 2133. (c) Kubo, M.; Yamazaki, M.; Matsuda, H.; Matsuo, K.; Asanuma, Y. *Biol. Pharm. Bull.* **2002**, *24*, 259.
- (5) (a) Shen, S.; Liao, Q.; Feng, Y.; Liu, J.; Pan, R.; Lee, S. M. Y.; Lin, L. *Food Chem.* **2019**, *270*, 305. (b) Shen, S.; Liao, Q.; Liu, J.; Pan, R.; Lee, S. M. Y.; Lin, L. *J. Cachexia. Sarcopenia Muscle* **2019**, *10*, 429. (c) CN108434127A (issued August 24th 2018).
- (6) Dai, G. H.; Meng, G. M.; Tong, Y. L.; Chen, X.; Ren, Z. M.; Wang, K.; Yang, F. *Phytomedicine* **2014**, *21*, 1490.
- (7) Martin, M. D.; Calcul, L.; Smith, C.; Jinwal, U. K.; Fontaine, S. N.; Darling, A.; Seeley, K.; Wojtas, L.; Narayan, M.; Gestwicki, J. E.; Smith, G. R.; Reitz, A. B.; Baker, B. J.; Dickey, C. A. *ACS Chem. Biol.* **2015**, *10*, 1099.
- (8) Mohamed, S. E. N.; Whiting, D. A. *J. Chem. Soc. Perkin Trans. I* **1983**, 2577.
- (9) Bochicchio, A.; Schiavo, L.; Chiummiento, L.; Lupattelli, P.; Funicello, M.; Hanquet, G.; Choppin, S.; Colobert, F. *Org. Biomol. Chem.* **2018**, *16*, 8859.
- (10) (a) Meidlinger, D.; Marx, L.; Bordeianu, C.; Choppin, S.; Colobert, F.; Speicher, A. *Angew. Chem., Int. Ed.* **2018**, *57*, 9160. (b) Norouzi-Arasi, H.; Salom-Roig, X. J.; Lanners, S.; Hanquet, G. *Curr. Org. Synth.* **2017**, *15*, 105. (c) Bensoussan, C.; Rival, N.; Hanquet, G.; Colobert, F.; Reymond, S.; Cossy, J. *Nat. Prod. Rep.* **2014**, *31*, 468. (d) Chiummiento, L.; Funicello, M.; Lopardo, M. T.; Lupattelli, P.; Choppin, S.; Colobert, F. *Eur. J. Org. Chem.* **2012**, 188. (e) Ferreiro-Mederos, L.; Lanners, S.; Henchiri, H.; Fekih, A.; Hanquet, G. *Nat. Prod. Res.* **2009**, *23*, 256. (f) Bonini, C.; Chiummiento, L.; Pullez, M.; Solladié, G.; Colobert, F. *J. Org. Chem.* **2004**, *69*, 5015.
- (11) (a) Dansou, B.; Pichon, C.; Dhal, R.; Brown, E.; Mille, S. *Eur. J. Org. Chem.* **2000**, 1527. (b) Harrowven, D. C.; Woodcock, T.; Howes, P. D. *Tetrahedron Lett.* **2002**, *43*, 9327.
- (12) (a) Lecourt, C.; Dhambri, S.; Allievi, L.; Sanogo, Y.; Zeghib, N.; Ben Othman, R.; Lannou, M.-I.; Sorin; Ardisson J. *Nat. Prod. Rep.* **2018**, *35*, 105 and references cited therein. (b) Cheng-Sanchez I.; Sarabia, F. *Synthesis* **2018**, *50*, 3749.
- (13) Chausset-Boissarie, L.; Arvai, R.; Cumming, G. R.; Besnard C. E.; Peter Kundig, E. P. *Chem. Commun.*, **2010**, *46*, 6264.
- (14) (a) Clavier, H.; Caijo, F.; Borré, E.; Rix, D.; Boeda, F.; Nolan, S. P.; Mauduit, M. *Eur. J. Org. Chem.* **2009**, 4254. (b) Tracz, A.; Matczak, M.; Urbaniak, K.; Skowerski, K. *Beilstein J. Org. Chem.* **2015**, *11*, 1823. (c) Boeda, F.; Clavier, H.; Nolan, S. P. *Chem. Comm.* **2008**, 2726.
- (15) Christiansen, E.; Due-Hansen, M. E.; Urban, C.; Merten, N.; Pfeleiderer, M.; Karlsen, K. K.; Rasmussen, S. S.; Steensgaard, M.; Hamacher, A.; Schmidt, J.; Drewke, C.; Petersen, R. K.; Kristiansen, K.; Ullrich, S.; Kostenis, E.; Kassack, M. U.; Ulven, T. *ACS Med. Chem. Lett.* **2010**, *1*, 345.
- (16) Gomtsyan, A. *Org. Lett.* **2000**, *2*, 11.
- (17) Lalic, G.; Corey, E. J. *Org. Lett.* **2007**, *9*, 4921.
- (18) Yuen, A. K. L.; Hutton, C. A. *Tetrahedron Lett.* **2005**, *46*, 7899.
- (19) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302.
- (20) Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.
- (21) Bäckvall, J.-E.; Andreasson, U. *Tetrahedron Lett.* **1993**, *34*, 5459.
- (22) Jun Yue, C.; Liu, Y.; He, R. *J. Mol. Catal. A Chem.* **2006**, *259*, 17.
- (23) Whiting, D. A.; Wood, A. F. *Tetrahedron Lett.* **1978**, *19*, 2335
- (24) Preparation of **20**
A solution of **18** (1 equiv., 51 mg, 0.091 mmol) in toluene (180 mL) was degassed for 30 minutes under a flow of argon. The reaction mixture was heated at reflux. Then, Grubbs 2nd generation (20 mol%, 15 mg, 0.018 mmol) was added in one portion. The reaction mixture was stirred at reflux for 16 h. The reaction mixture was filtered through a pad of both activated charcoal and silica gel and solvent was evaporated under reduced pressure to afford **20** (20 mg, 35 mmol, 39%) as an oil. ¹H NMR (500 MHz, Chloroform-*d*) δ 7.50 – 7.44 (m, 4H), 7.43 – 7.34 (m, 6H), 7.27 – 7.20 (m, 10H), 7.14 – 7.00 (m, 2H), 6.98 (d, *J* = 2.3 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 6.70 – 6.65 (m, 4H), 5.97 (d, *J* = 16.0 Hz, 2H), 5.13 – 5.08 (m, 4H), 5.05 – 4.90 (m, 4H), 3.99 – 3.82 (m, 6H), 3.64 (s, 6H), 2.94 – 2.71 (m, 8H), 2.57 – 2.48 (m, 4H), 2.46 – 2.35 (m, 4H). ¹³C NMR (125 MHz, Chloroform-*d*) δ 203.21, 154.64, 150.68, 150.13, 146.32, 138.01, 137.64, 133.60, 131.36, 131.31, 128.82, 128.72, 128.65, 128.36, 128.16, 128.13, 127.62, 127.08, 126.66, 113.24, 75.29, 70.76, 61.00, 60.97, 41.91, 33.25, 29.84, 29.02. HRMS (ESI+): C₇₀H₆₈NaO₁₀ ([M+Na]⁺): calcd 1091.4705, found 1091.4700.
- (25) Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004**, *126*, 10210.
- (26) (a) Wallace, D. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 1912. (b) Wang, X.; Bowman, E. J.; Bowman, B. J.; Porco, J. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3601.
- (27) Lipshutz, B. H.; Petersen, T. B.; Abela, A. R. *Org. Lett.* **2008**, *10*, 1333.
- (28) Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160.