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Concise syntheses of (+)-maximumins B and C and (+)-ottensinin†

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Maximumin B (**1**), maximumin C (**2**), and ottensinin (**3**) are three rearranged labdane diterpenoids featuring a unique 3-substituted γ -pyrone motif. Herein, we report the first syntheses of (+)-**1** and (+)-**2** and an improved synthesis of (+)-**3** in 4–12 steps. Key features for the syntheses of **1** and **2** include a Pd-catalyzed decarboxylative coupling reaction establishing the 3-substituted γ -pyrone and a Baran decarboxylative coupling reaction enabling ketone formation in the final step. A Ni-catalyzed $C(sp^2)$ – $C(sp^3)$ cross-electrophile coupling reaction was applied to accomplish the synthesis of **3**. Furthermore, in-depth pharmacological screening unveiled ottensinin (**3**) as a potent KCNQ2 agonist exhibiting comparable potency to retigabine, making it a promising lead for the development of a novel class of anti-epileptic drugs.

1. Introduction

Rearranged labdane diterpenoids represent a rare class of natural products that are biogenetically derived *via* the skeletal rearrangement of intact labdane diterpenoid precursors, and often exhibit a diverse range of bioactivities,^{1–6} thereby drawing considerable interest from the synthetic community.^{7–9} Maximumins B (**1**) and C (**2**) are two rearranged labdane diterpenoids with novel carbon skeletons that were isolated from *Amomum maximum* by our group in 2019 (Fig. 1).¹⁰ A co-isolated known 16(13 \rightarrow 12)-*abeo*-labdane diterpenoid ottensinin (**3**),^{11–14} sharing a common 3-substituted γ -pyrone motif, was considered to be their hypothetically bio-synthetic precursor. Compared to **3**, compounds **1** and **2** feature a distinctively modified B-ring. Of note, compounds **1–3** demonstrated significant inhibition against nuclear factor

kappa B (NF- κ B), a promising target in regulating immune and inflammatory dysfunction.^{15,16}

The unusual structural features and promising pharmacological properties of **1–3** attracted our attention. To overcome limited accessibility for further biological studies, chemical synthesis towards this diterpenoid class is highly desired.¹⁷ Previously, the research groups of Katoh,^{18,19} Yang,²⁰ and Li²¹ successfully employed 3-lithio- γ -pyrone as the primary reactant for the syntheses of diterpenoids with a fully substituted γ -pyrone (Scheme 1A). However, there are very few methods^{22,23} available for the synthesis of 3-substituted γ -pyrone as in **1–3**. In particular, Boukouvalas' group reported the structure revision and first synthesis of **3** in 27% overall yield over 9 steps by using 6-*endo-dig* cyclization to construct the 3-substituted γ -pyrone (Scheme 1B),²² whereas the chemical syntheses of maximumins B (**1**) and C (**2**) have not been reported yet.

The Kv7/KCNQ family of voltage-gated K⁺ channels crucially regulates neuronal signaling and human disease states in the brain and peripheral nerves.²⁴ Among the KCNQ subtypes,

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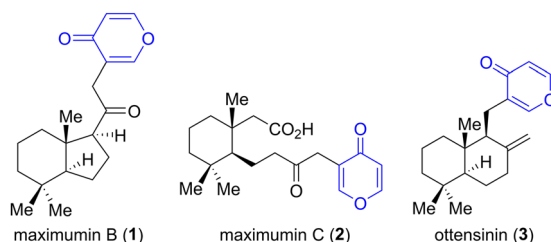
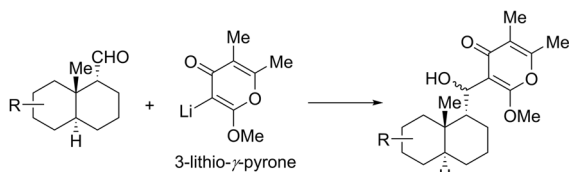
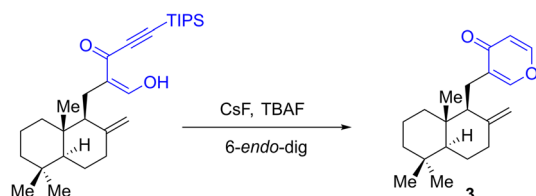


Fig. 1 Structures of maximumins B (**1**) and C (**2**) and ottensinin (**3**).



A Syntheses of diterpenoids bearing a fully substituted γ -pyroneB Boukouvalas' synthesis of **3** bearing a 3-substituted γ -pyrone

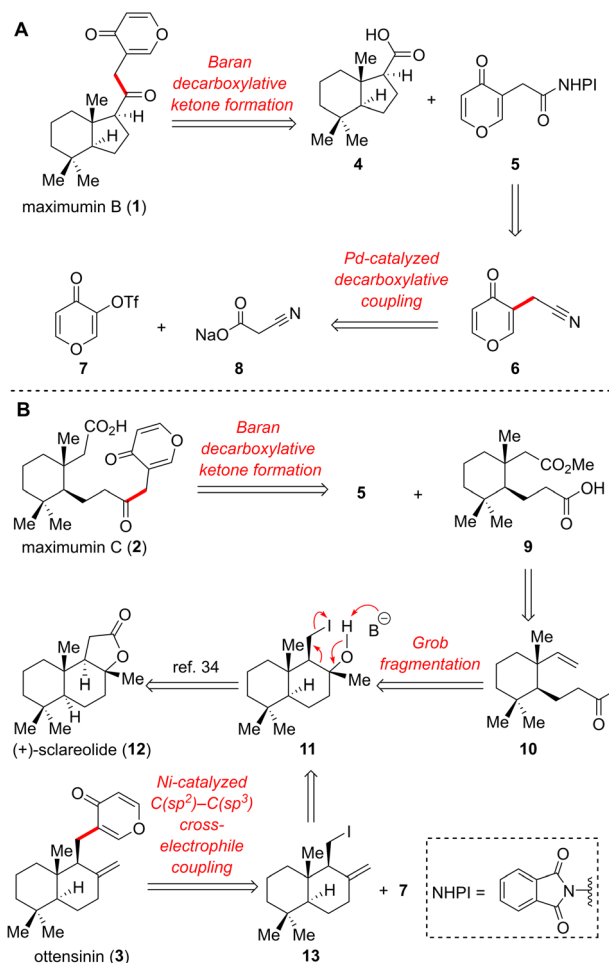
Scheme 1 Previous synthetic efforts toward diterpenoid pyrones.

KCNQ2 is an important drug target for treating epilepsy and a range of other neurological disorders associated with neuronal hyper-excitability.²⁵ Its significance has garnered immense interest, culminating in the approval by the FDA of retigabine (RTG),²⁶ a KCNQ2-targeting medication approved for use as an adjunctive treatment for partial-onset seizures in adults with epilepsy. However, RTG had been withdrawn from the market in 2017 due to concerns regarding its poor stability and potential toxicity,²⁷ prompting the search for new drugs targeted on KCNQ2. In the present study, a screening program to identify KCNQ2 activators led to the identification of ottensinin (**3**) as a potent agonist. As part of our continuing synthetic efforts towards bioactive natural products,^{28–30} we report herein the first syntheses of (+)-maximumins B and C, and a more concise synthesis of (+)-ottensinin, as well as their biological evaluation.

2. Results and discussion

2.1 Retrosynthetic analyses of maximumin B, maximumin C, and ottensinin

Our retrosynthetic analyses for **1–3** are outlined in Scheme 2. We envisioned that maximumin B (**1**) could be prepared by assembly of the known bicyclic carboxylic acid **4**³¹ and redox-active ester (RAE) **5** via the Baran decarboxylative ketone formation (Scheme 2A).³² RAE **5** could be readily made from nitrile **6**, which could be accessed through Pd-catalyzed decarboxylative coupling of triflate **7** with cyanoacetate salt **8** developed by the Liu group.³³ Likewise, maximumin C (**2**) could be synthesized via the Baran decarboxylative ketone formation³² from RAE **5** and acid **9** followed by ester hydrolysis, and the latter could be obtained from methyl ketone **10** via multistep functional group manipulation (Scheme 2B). Ketone **10** could be conveniently prepared from iodide **11** via Grob fragmentation. Compound **11** could be obtained from commercially available (+)-sclareolide (**12**) through a known ring-opening process.³⁴ For the preparation of ottensinin (**3**), we envisaged

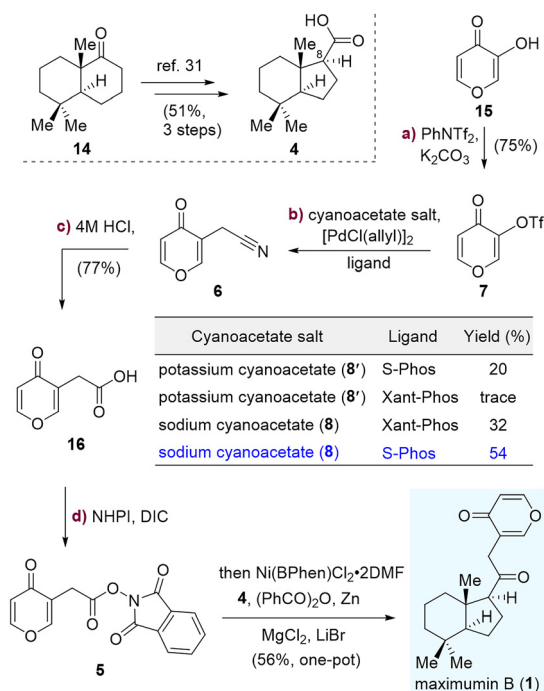
Scheme 2 Retrosynthetic analysis of compounds **1–3**.

that it could be produced by the Ni-catalyzed C(sp²)-C(sp³) cross-electrophile coupling³⁵ of iodide **13** with triflate **7** (Scheme 2B). The former could be synthesized from tertiary alcohol **11** by a dehydration process. Such a modular approach would not only improve overall synthetic efficiency, but also facilitate further structural optimization and structure-activity relationship (SAR) analysis.

2.2 Synthesis of (+)-maximumin B (**1**)

Our synthesis commenced with the preparation of two decarboxylative cross-coupling precursors, acid **4** and RAE **5** (Scheme 3). The former was readily prepared in 51% overall yield over 3 steps from the well-documented Wieland-Miescher ketone derivative **14** according to the known method reported by the Liang group.³¹ The synthesis of RAE **5** initially began with the Pd-catalyzed decarboxylative coupling³³ of triflate **7** (obtained from 3-hydroxy- γ -pyrone **15** in 75% yield) with potassium cyanoacetate **8'**. After carefully screening the reaction conditions, it was observed that employing sodium cyanoacetate **8** as the reactant instead led to an increase in the yield. Furthermore, 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (S-Phos) served as a superior ligand compared to 4,5-





Scheme 3 Synthesis of (+)-maximuin B (1).

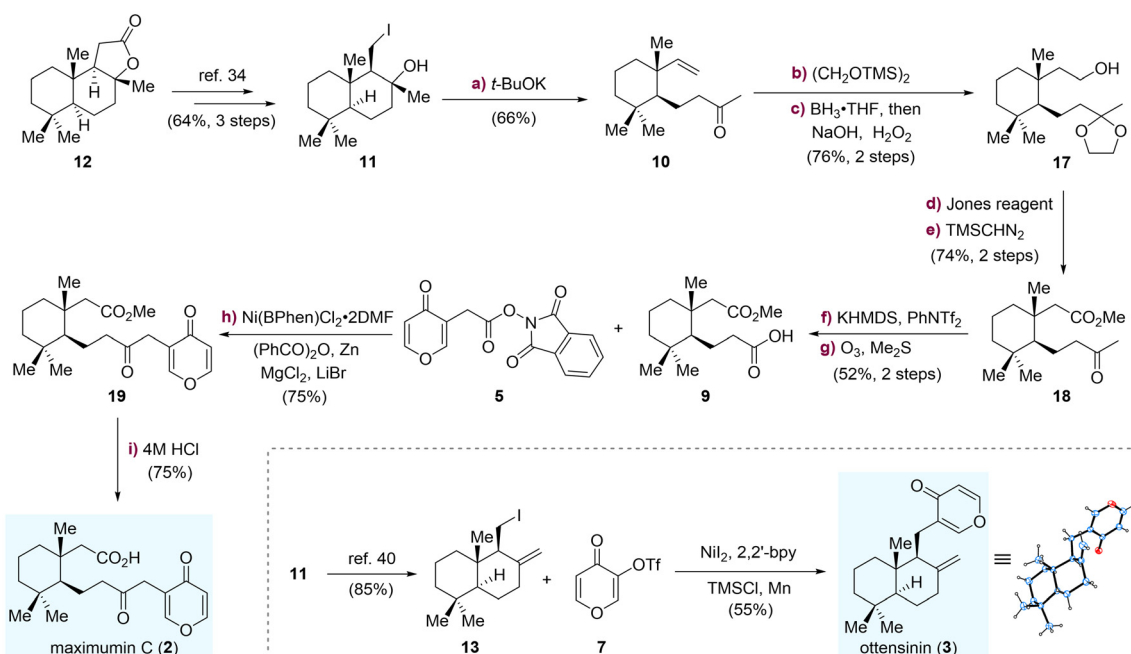
bis(diphenylphosphino)-9,9-dimethylxanthene (Xant-Phos). Under the optimal reaction conditions, the desired nitrile **6** was obtained in 54% yield. Notably, it represents the first successful utilization of pyrone-triflate as a substrate in this Pd-catalyzed decarboxylative coupling reaction. In our attempt to hydrolyze nitrile **6**, we unexpectedly found that various basic

conditions (NaOH, LiOH, KOH) proved fruitless. This could potentially be attributed to the reactive α,β -unsaturated ketone moiety present in **6**. Finally, we achieved the desired γ -pyrone-3-acetic acid **16** under acidic conditions in 77% yield. Interestingly, compound **16** is a natural product exhibiting selective and irreversible inhibition of interleukin-1 β converting enzyme.³⁶

With the two acid fragments **4** and **16** securely in hand, we attempted to combine them together through the Baran decarboxylative ketone formation.³² Given the likelihood of inversion at the C-8 stereocenter in compound **4**, we opted to transform acid **16** into RAE **5** by using *N,N*-diisopropylcarbodiimide (DIC) as the condensing agent. Unfortunately, RAE **5** decomposed spontaneously during separation by column chromatography. Thus, we decided to use a one-pot method to circumvent the challenging purification of **5**. Pleasingly, the coupling proceeded smoothly under the standard conditions, delivering the target maximuin B (**1**) in 56% yield.

2.3 Synthesis of (+)-maximuin C (2)

Upon successful completion of the concise synthesis of (+)-maximuin B, we then moved forward to synthesize (+)-maximuin C (**2**) starting from commercial (+)-sclareolide (**12**), which was converted to iodide **11** based on a three-step sequence reported by the Baran group (Scheme 4).³⁴ Subsequently, compound **11** was subjected to Grob fragmentation^{37,38} under the basic conditions to achieve the ring-opening product **10**. To avoid Prins cyclization, the keto carbonyl group of **10** was strategically protected with $(\text{CH}_2\text{OTMS})_2$. Then, hydroboration-oxidation of the terminal alkene resulted in the alcohol **17**. Exposure of **17** to Jones

Scheme 4 Syntheses of (+)-maximuin (**2**) and (+)-ottensinin (**3**).

reagent efficiently transformed the hydroxymethyl group into a carboxylic acid, concomitantly eliminating the ketal protecting group. The resulting acid was methylated with trimethylsilyl diazomethane (TMSCHN₂) to afford ester **18**. Since the ester group was incompatible with the harsh basic conditions of the haloform reaction, a two-step approach utilizing ozonolysis of the enol triflate intermediate was developed to transform methyl ketone **18** to acid **9**. This mild alternative approach represents an improved variation of Heathcock's two-step method,³⁹ employing a silyl enol ether as an intermediate and delivering a one-carbon less silyl ester instead. The following one-pot decarboxylative coupling³² of acid **9** with RAE **5** took place smoothly to yield ketone **19**, which underwent acidic hydrolysis to readily achieve the desired maximumin C (2).

2.4 Synthesis of (+)-ottensinin (3)

Henceforward, we began the synthesis of ottensinin (**3**) (Scheme 4). Initially, our attempts to synthesize ottensinin *via* Suzuki cross-coupling of borate ester with vinyl triflate were unsuccessful. Therefore, we opted to employ the Ni-catalyzed C(sp²)-C(sp³) cross-electrophile coupling³⁵ to attach iodide **13** to vinyl triflate **7**, and the former could be easily synthesized from the advanced intermediate **11** using the method previously reported by the Li group.⁴⁰ To our delight, the coupling reaction resulted in the desired ottensinin (**3**) with good conversion.

2.5 Biological evaluation

With adequate quantity of maximumin B (**1**), maximumin C (**2**), and ottensinin (**3**) in hand, we advanced to a broader spectrum of pharmacological screening studies. Epilepsy is a chronic neurological disorder arising from abnormal discharges of brain neurons.⁴¹ The KCNQ2 channel, a pivotal member of potassium voltage-gated channels, is closely related to neuronal excitatory disorders, serving as a significant target for anti-epileptic drugs.⁴² Compounds **1**–**3** and two synthetic intermediates **16** and **19** were evaluated for their activation effects on KCNQ2. It was found that ottensinin (**3**) possesses the ability to efficiently activate KCNQ2 ($I_{\text{drug}}/I_{\text{control}} = 1.77 \pm 0.07$), which is even stronger than RTG ($I_{\text{drug}}/I_{\text{control}} = 1.44 \pm 0.13$) (Table 1). The dose–effect relationship of ottensi-

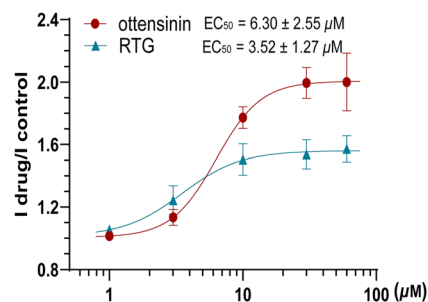


Fig. 2 Dose–response curves of the activation of RTG and ottensinin (**3**) on KCNQ2.

nin and RTG on KCNQ2 channel was further examined, and the median effective concentration (EC_{50}) was determined by a dose–response curve analysis (Fig. 2). The results revealed that ottensinin could dose-dependently activated KCNQ2 channel, with an EC_{50} value of $6.30 \pm 2.55 \mu\text{M}$, which is comparable to retigabine ($3.52 \pm 1.27 \mu\text{M}$). In order to reveal how ottensinin activates KCNQ2 channel activity, the effect of $10 \mu\text{M}$ ottensinin on channel dynamics was investigated. Activation curves were fitted with the Boltzmann equation and showed that the half-activation voltages of KCNQ2 before and after treatment with $10 \mu\text{M}$ ottensinin were $-9.53 \pm 1.91 \text{ mV}$ and $-12.26 \pm 3.23 \text{ mV}$, respectively (Fig. 3A). Before and after treatment with $10 \mu\text{M}$ ottensinin, the activation constant was 247.75 ± 35.03 and 237.56 ± 30.32 , and the deactivation constant was 12.81 ± 30.32 and 14.92 ± 0.18 , there were no significant change (Fig. 3B). Therefore, we suspect that ottensinin does not generate activity by changing KCNQ2 channel dynamics, and its specific mechanism of action is still under investigation.

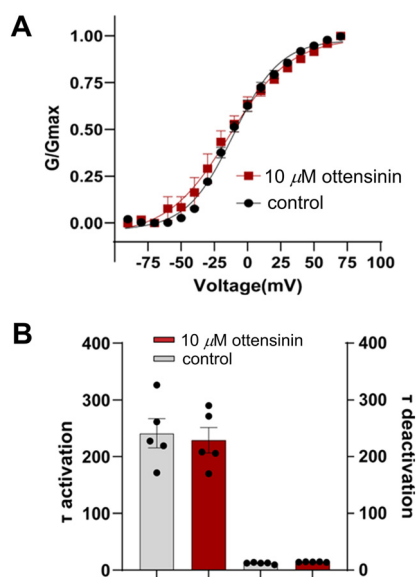


Fig. 3 Effects of ottensinin (**3**) on the electrophysiological properties of KCNQ2. (A) Steady-state activation curve in control (black) and $10 \mu\text{M}$ compound **3** (red). (B) The effects of compound **3** on the activation and deactivation properties of KCNQ2.

Table 1 Effects of compounds **1**–**3**, **16**, and **19** on the KCNQ2 channel

Compound	$I_{\text{drug}}/I_{\text{control}}^a$	<i>n</i>
1	1.01 ± 0.01	3
2	0.98 ± 0.03	3
3	1.77 ± 0.07	3
16	1.14 ± 0.09	3
19	1.03 ± 0.09	3
RTG ^b	1.44 ± 0.13	4

^a The amplitude change of the outward current: I_{control} , amplitude of the outward current without the compound; I_{drug} , amplitude of the outward current with the compound; $I_{\text{drug}}/I_{\text{control}}$, effect of $10 \mu\text{M}$ compound on the amplitude of the outward current of KCNQ2 channel.

^b RTG (retigabine) was used as the positive control.



3. Conclusions

In summary, we have accomplished the first asymmetric total synthesis of maximumin B (**1**) from a well-documented Wieland–Miescher ketone derivative **14** and 3-hydroxy- γ -pyrone **15** in 17% yield over 4 steps. Moreover, starting from commercially available (+)-sclareolide, (+)-maximumin C (**2**) and (+)-ottensinin (**3**) have been effectively synthesized in 12 and 5 linear longest steps with overall yields of 6.6% and 30%, respectively. The prominent features of the present chemical syntheses include Baran decarboxylative ketone formation, Pd-catalyzed decarboxylative coupling, and Ni-catalyzed C(sp²)-C(sp³) cross-electrophile coupling. Of the same importance, our robust synthesis built the foundation for deeper biological studies. The in-depth pharmacological screening revealed ottensinin (**3**) to be a potent KCNQ2 agonist, thereby holding the potential to be further developed into a completely novel class of antiepileptic drug. Further structural optimization of ottensinin is currently underway in our laboratory, and related progress will be disclosed in due course.

Data availability

Data for this article, including experimental procedures, ¹H NMR spectra, ¹³C NMR spectra, physical states, high-resolution mass spectroscopy (HRMS) data of all products, specific rotations of new chiral compounds **9**, **10**, **17–19**, **S4–S6**, the melting point range of compound **3**, representative assay results of compounds **1–3**, **16**, **19**, and effects of compound (**3**) on current of KCNQ2 channel at different concentrations are available in the ESI.†

Crystallographic data for compound **3** has been deposited at the Cambridge Crystallographic Data Centre (deposition number: CCDC 2355511†).

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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References

- Q. Zhao, L.-G. Xiao, L.-S. Bi, Y. Si, X.-M. Zhang, J.-H. Chen and H.-Y. Liu, Hedychins E and F: Labdane-Type Norditerpenoids with Anti-Inflammatory Activity from the Rhizomes of *Hedychium forrestii*, *Org. Lett.*, 2022, **24**, 6936–6939.
- C. Zhang, Y. Li, Z. Chu, S. Yuan, Y. Qiao, J. Zhang, L. Li, Y. Zhang, R. Tian, Y. Tang and H. Lou, Rearranged 19-nor-7,8-*seco*-labdane diterpenoids and Diels–Alder cycloadducts from the Chinese liverwort *Pallavicinia ambigua*: Structural elucidation, photoinduced rearrangement, and cytotoxic activity, *Chin. Chem. Lett.*, 2024, **35**, 108206.
- M. Zhu, Y. Gao, Y. Li, F. Xie, J. Zhou, L. Xu, D. Lv, X. Zhang, Z. Xu, T. Dong, T. Shen, J. Zhang and H. Lou, Novel Diterpenoids Incorporating Rearranged Labdanes from the Chinese Liverwort *Anastrophylllum joergensenii* and Their Anti-inflammatory Activity, *J. Agric. Food Chem.*, 2023, **71**, 19551–19567.
- J. Zhou, J. Zhang, R. Li, J. Liu, P. Fan, Y. Li, M. Ji, Y. Dong, H. Yuan and H. Lou, Hapmnioides A–C, Rearranged Labdane-Type Diterpenoids from the Chinese Liverwort *Haplotrium mnioides*, *Org. Lett.*, 2016, **18**, 4274–4276.
- X.-D. Wu, D. Luo, W.-C. Tu, Z.-T. Deng, X.-J. Chen, J. Su, X. Ji and Q.-S. Zhao, Hypophyllins A–D, Labdane-Type Diterpenoids with Vasorelaxant Activity from *Hypoestes phyllostachya* “Rosea”, *Org. Lett.*, 2016, **18**, 6484–6487.
- H. Yin, J.-G. Luo, S.-M. Shan, X.-B. Wang, J. Luo, M.-H. Yang and L.-Y. Kong, Amomaxins A and B, Two Unprecedented Rearranged Labdane Norditerpenoids with a Nine-Membered Ring from *Amomum maximum*, *Org. Lett.*, 2013, **15**, 1572–1575.
- L. M. T. Frija, R. F. M. Frade and C. A. M. Afonso, Isolation, Chemical, and Biotransformation Routes of Labdane-type Diterpenes, *Chem. Rev.*, 2011, **111**, 4418–4452.
- P. S. Grant and M. A. Brimble, *seco*-Labdanes: A Study of Terpenoid Structural Diversity Resulting from Biosynthetic C–C Bond Cleavage, *Chem. – Eur. J.*, 2021, **27**, 6367–6389.
- S. C. Philkhana and D. S. Reddy, Total synthesis of natural fregenedadiol and its diacetate, rearranged labdanes with aromatized B ring, *Tetrahedron Lett.*, 2017, **58**, 1262–1264.
- K.-L. Ji, Y.-Y. Fan, Z.-P. Ge, L. Sheng, Y.-K. Xu, L.-S. Gan, J.-Y. Li and J.-M. Yue, Maximumins A–D, Rearranged Labdane-Type Diterpenoids with Four Different Carbon Skeletons from *Amomum maximum*, *J. Org. Chem.*, 2019, **84**, 282–288.
- H. Yin, C. Guo and J.-M. Gao, Four new pyrrole alkaloids from the rhizomes of *Amomum koenigii*, *J. Nat. Med.*, 2021, **75**, 173–177.
- K. Akiyama, H. Kikuzaki, T. Aoki, A. Okuda, N. H. Lajis and N. Nakatani, Terpenoids and a Diarylheptanoid from *Zingiber ottensii*, *J. Nat. Prod.*, 2006, **69**, 1637–1640.
- J.-G. Luo, H. Yin, B.-Y. Fan and L.-Y. Kong, Labdane Diterpenoids from the Roots of *Amomum maximum* and Their Cytotoxic Evaluation, *Helv. Chim. Acta*, 2014, **97**, 1140–1145.
- Y. Sivasothy, H. Ibrahim, A. S. Paliany, S. A. Alias, N. R. Md Nor and K. Awang, A New Bis-Labdanic Diterpene from the Rhizomes of *Alpinia pahangensis*, *Planta Med.*, 2013, **79**, 1775–1780.



- 15 G.-Y. Kim, K.-H. Kim, S.-H. Lee, M.-S. Yoon, H.-J. Lee, D.-O. Moon, C.-M. Lee, S.-C. Ahn, Y. C. Park and Y.-M. Park, Curcumin Inhibits Immunostimulatory Function of Dendritic Cells: MAPKs and Translocation of NF- κ B as Potential Targets¹, *J. Immunol.*, 2005, **174**, 8116–8124.
- 16 E. Pikarsky, R. M. Porat, I. Stein, R. Abramovitch, S. Amit, S. Kasem, E. Gutkovich-Pyest, S. Urieli-Shoval, E. Galun and Y. Ben-Neriah, NF- κ B functions as a tumour promoter in inflammation-associated cancer, *Nature*, 2004, **431**, 461–466.
- 17 J.-X. Zhao and J.-M. Yue, Frontier studies on natural products: moving toward paradigm shifts, *Sci. China: Chem.*, 2023, **66**, 928–942.
- 18 K. Watanabe, K. Iwasaki, T. Abe, M. Inoue, K. Ohkubo, T. Suzuki and T. Katoh, Enantioselective Total Synthesis of (–)-Candelalide A, a Novel Blocker of the Voltage-Gated Potassium Channel Kv1.3 for an Immunosuppressive Agent, *Org. Lett.*, 2005, **7**, 3745–3748.
- 19 T. Abe, K. Iwasaki, M. Inoue, T. Suzuki, K. Watanabe and T. Katoh, Convergent and enantioselective total synthesis of (–)-nalanthalide, a potential Kv1.3 blocking immunosuppressant, *Tetrahedron Lett.*, 2006, **47**, 3251–3255.
- 20 Z. Li and D. Yang, Construction of 9,10-*syn-trans*-decalin skeleton via semipinacol rearrangement: asymmetric synthesis of (+)-*syn*-copalol and a candelalide analog, *Tetrahedron Lett.*, 2015, **56**, 3667–3669.
- 21 Y. Ji, Y. Liu, W. Guan, C. Guo, H. Jia, B. Hong and H. Li, Enantioselective Divergent Syntheses of Diterpenoid Pyrones, *J. Am. Chem. Soc.*, 2024, **146**, 9395–9403.
- 22 J. Boukouvalas and J.-X. Wang, Structure Revision and Synthesis of a Novel Labdane Diterpenoid from *Zingiber ottensii*, *Org. Lett.*, 2008, **10**, 3397–3399.
- 23 L. Klier, T. Bresser, T. A. Nigst, K. Karaghiosoff and P. Knochel, Lewis Acid-Triggered Selective Zincation of Chromones, Quinolones, and Thiochromones: Application to the Preparation of Natural Flavones and Isoflavones, *J. Am. Chem. Soc.*, 2012, **134**, 13584–13587.
- 24 C. M. Carver, S. D. Hastings, M. E. Cook and M. S. Shapiro, Functional responses of the hippocampus to hyperexcitability depend on directed, neuron-specific KCNQ2 K⁺ channel plasticity, *Hippocampus*, 2020, **30**, 435–455.
- 25 X. Li, Q. Zhang, P. Guo, J. Fu, L. Mei, D. Lv, J. Wang, D. Lai, S. Ye, H. Yang and J. Guo, Molecular basis for ligand activation of the human KCNQ2 channel, *Cell Res.*, 2021, **31**, 52–61.
- 26 M. Y. Splinter, Ezogabine (Retigabine) and Its Role in the Treatment of Partial-Onset Seizures: A Review, *Clin. Ther.*, 2012, **34**, 1845–1856.
- 27 M. R. Groseclose and S. Castellino, An Investigation into Retigabine (Ezogabine) Associated Dyspigmentation in Rat Eyes by MALDI Imaging Mass Spectrometry, *Chem. Res. Toxicol.*, 2019, **32**, 294–303.
- 28 J.-X. Zhao, Y.-Y. Yu, S.-S. Wang, S.-L. Huang, Y. Shen, X.-H. Gao, L. Sheng, J.-Y. Li, Y. Leng, J. Li and J.-M. Yue, Structural Elucidation and Bioinspired Total Syntheses of Ascorbylated Diterpenoid Hongkonoids A–D, *J. Am. Chem. Soc.*, 2018, **140**, 2485–2492.
- 29 G.-Z. Yang, L. Wang, Y.-Y. Fan, Z.-W. Lai, X.-N. Yu, L.-G. Lou, K. Gao and J.-M. Yue, Concise Total Synthesis of Dysoxylactam A and a Simplified Analog, *Chin. J. Chem.*, 2022, **40**, 2027–2034.
- 30 C.-Y. Zheng, J.-X. Zhao, C.-H. Yuan, X. Peng, M. Geng, J. Ai, Y.-Y. Fan and J.-M. Yue, Unprecedented sesterterpenoids orientanoids A–C: Discovery, bioinspired total synthesis and antitumor immunity, *Chem. Sci.*, 2023, **14**, 13410–13418.
- 31 T. Qiao, Y. Wang, S. Zheng, H. Kang and G. Liang, Total Syntheses of Norrisolide-Type Spongian Diterpenes Cheloviolene C, Seconorrisolide B, and Seconorrisolide C, *Angew. Chem., Int. Ed.*, 2020, **59**, 14111–14114.
- 32 S. Ni, N. M. Padial, C. Kingston, J. C. Vantourout, D. C. Schmitt, J. T. Edwards, M. M. Kruszyk, R. R. Merchant, P. K. Mykhailiuk, B. B. Sanchez, S. Yang, M. A. Perry, G. M. Gallego, J. J. Mousseau, M. R. Collins, R. J. Cherney, P. S. Lebed, J. S. Chen, T. Qin and P. S. Baran, A Radical Approach to Anionic Chemistry: Synthesis of Ketones, Alcohols, and Amines, *J. Am. Chem. Soc.*, 2019, **141**, 6726–6739.
- 33 R. Shang, D.-S. Ji, L. Chu, Y. Fu and L. Liu, Synthesis of α -Aryl Nitriles through Palladium-Catalyzed Decarboxylative Coupling of Cyanoacetate Salts with Aryl Halides and Triflates, *Angew. Chem., Int. Ed.*, 2011, **50**, 4470–4474.
- 34 D. D. Dixon, J. W. Lockner, Q. Zhou and P. S. Baran, Scalable, Divergent Synthesis of Meroterpenoids via “Borono-sclareolide”, *J. Am. Chem. Soc.*, 2012, **134**, 8432–8435.
- 35 K. A. Johnson, S. Biswas and D. J. Weix, Cross-Electrophile Coupling of Vinyl Halides with Alkyl Halides, *Chem. – Eur. J.*, 2016, **22**, 7399–7402.
- 36 M. J. Salvatore, O. D. Hensens, D. L. Zink, J. Liesch, C. Dufresne, J. G. Ondeyka, T. M. Jürgens, R. P. Borris, S. Raghoobar, E. McCauley, L. Kong, S. E. Gartner, G. E. Koch, F. Pelaéz, M. T. Diez, C. Cascales, I. Martin, J. D. Polishook, M. J. Balick, H. T. Beck, S. R. King, A. Hsu and R. B. Lingham, L-741,494, a Fungal Metabolite That Is an Inhibitor of Interleukin-1 β Converting Enzyme, *J. Nat. Prod.*, 1994, **57**, 755–760.
- 37 A. F. Barrero, E. J. Alvarez-Manzaneda, R. Chahboun and M. C. Páiz, A new enantiospecific route toward monocarbocyclic terpenoids: Synthesis of (–)- caparrapi oxide, *Tetrahedron Lett.*, 1998, **39**, 9543–9544.
- 38 S.-K. Li and X. Wang, *China Pat*, CN114751814, 2022.
- 39 R. D. Clark and C. H. Heathcock, Synthesis of a cytotoxic vernolepin prototype. Ozonization of silyloxyalkenes, *J. Org. Chem.*, 1976, **41**, 1396–1403.
- 40 Y. Sun, R. Li, W. Zhang and A. Li, Total Synthesis of Indotertine A and Drimentines A, F, and G, *Angew. Chem., Int. Ed.*, 2013, **52**, 9201–9204.



- 41 T. Hu, J. Zhang, J. Wang, L. Sha, Y. Xia, T. C. Ortyl, X. Tian and L. Chen, Advances in Epilepsy: Mechanisms, Clinical Trials, and Drug Therapies, *J. Med. Chem.*, 2023, **66**, 4434–4467.
- 42 S. Shi, J. Li, F. Sun, Y. Chen, C. Pang, Y. Geng, J. Qi, S. Guo, X. Wang, H. Zhang, Y. Zhan and H. An, Molecular Mechanisms and Structural Basis of Retigabine Analogues in Regulating KCNQ2 Channel, *J. Membr. Biol.*, 2020, **253**, 167–181.

