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A Concise Total Synthesis of (–)-Berkelic Acid

Hong-Gang Cheng[1†], Zhenjie Yang[1†], Ruiming Chen[1], Liming Cao[1], Wen-Yan Tong,[3] Qiang Wei[1], Qingqing Wang[1], Chenggui Wu[1], Shuanglin Qu*[3] and Qianghui Zhou*[1,2]

Dedicated to the 70th anniversary of Shanghai Institute of Organic Chemistry

Abstract: Herein, we report a concise total synthesis of (–)-berkelic acid in eight linear steps. This synthesis features a Catellani reaction/oxa-Michael cascade for the construction of the isochroman scaffold, a one-pot deprotection/spiroacetalization operation for the formation of tetracyclic core structure, and a late-stage Ni-catalyzed reductive coupling for the introduction of the lateral chain. Notably, four stereocenters are established from a single existing chiral center with excellent stereocontrol during the deprotection/spiroacetalization process. Stereocontrol of the intriguing deprotection/spiroacetalization process is supported by DFT calculations.

(–)-Berkelic acid (**1**, Figure 1A) was isolated in 2006 by Stierle[1] and co-workers from an extremophilic Penicillium species collected from the Berkeley Pit Lake in Butte, Montana (USA). This compound was reported to display selectivity against the human ovarian cancer cell line OVCAR-3 (GI_{50} 91 nm), as well as a moderate inhibitory activity against the matrix metalloproteinase MMP-3 (1.87 μM) and the cysteine protease caspase-1 (98 μM). The structure of (–)-berkelic acid features a unique tetracyclic isochroman/chroman spiroketal structure, a pentasubstituted phenyl ring with a free hydroxyl group and six stereogenic centers, including one quaternary carbon center. Owing to the distinctive molecular architecture, promising biological activities[8] as well as the limited natural accessibility,[1] (–)-berkelic acid has attracted substantial attention from the synthetic community.[2-7]

In 2008, Fürstner and co-workers completed the synthesis of the methyl ester variant of (+)-berkelic acid, and revised the assignment of the relative stereochemistry at C18 and C19.[2a] Soon after, Snider[3b] and co-workers reported the first total synthesis of (–)-berkelic acid, featuring an oxa-Pictet–Spengler reaction for the construction of the tetracyclic core. In the same year, a bio-inspired approach was developed by De Brabander and co-workers,[4] using a Ag-catalyzed dearomatization/cycloisomerization/cycloaddition cascade sequence as the key step. Both of these reports confirmed the structure reassignments made by the Fürstner group, establishing the absolute configuration of (–)-berkelic acid, including the stereochemistry of C22. In 2010, the Fürstner group also accomplished the total synthesis of (–)-berkelic acid, using a deprotection/Michael addition/spiroacetali-zation cascade to construct the tetracyclic core.[2b] In 2012, Fañanás, Rodríguez and co-workers developed a scalable route involving a Ag-catalyzed double cycloisomerizations/formal [4+2]-cycloaddition sequence to access (–)-berkelic acid. However, the diastereoselectivity of this route was only moderate.[5] Aside from these total synthesis works, several other formal syntheses of (–)-berkelic acid have also been reported by the groups of Pettus[6] and Brimble[7]. While these studies constitute great progress, there is still room for improving the synthetic efficiency, for example, higher diastereoselectivity control[3b,5] and finding more efficient methods to install the lateral chain[2-5].

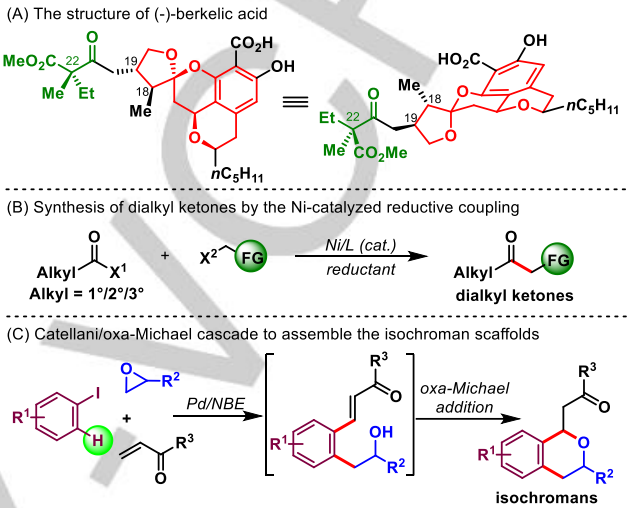

Figure 1. The structure of (–)-berkelic acid and planned synthetic tools for (–)-berkelic acid synthesis.

Recently, nickel-catalyzed reductive coupling has become a versatile strategy in organic synthesis for forging new carbon-carbon bonds.[9] For example, in 2012, the Weix group[9f] reported the direct synthesis of functionalized dialkyl ketones via a nickel-catalyzed reductive coupling of carboxylic acid chlorides with alkyl iodides (Figure 1B). We imagined this may be an ideal method for the lage-stage installation of the lateral chain of (–)-berkelic acid. In 2018, our group developed an efficient three-component one-pot procedure for the assembly of isochroman scaffolds,[10] which is enabled by a Catellani reaction[11] followed by an oxa-Michael addition. Readily available aryl iodides, epoxides and electron-poor olefins are utilized as the reactants (Figure 1C). As such, we envisioned this method would enable a highly convergent strategy for the construction of the highly functionalized isochroman core structure of berkelic acid. Inspired by these two synthetic methodologies, we herein report a concise total synthesis of (–)-berkelic acid, featuring the formation of the key isochroman scaffold through the Catellani reaction/oxa-Michael cascade, the

[*] Prof. Dr. H.-G. Cheng, Z. Yang, R. Chen, L. Cao, Q. Wei, Q. Wang, C. Wu, Prof. Dr. Q. Zhou
Sauvage Center for Molecular Sciences, Engineering Research Center of Organosilicon Compounds & Materials (Ministry of Education), College of Chemistry and Molecular Sciences, Wuhan University, Wuhan, 430072 (China), E-mail: qhzhou@whu.edu.cn
Prof. Dr. Q. Zhou
The Institute for Advanced Studies, Wuhan University, Wuhan, 430072 (China)
W.-Y. Tong, Prof. Dr. S. Qu
College of Chemistry and Chemical Engineering, Hunan University, Changsha 410082, China. E-mail: squ@hnu.edu.cn
[†] These authors contributed equally to this work.
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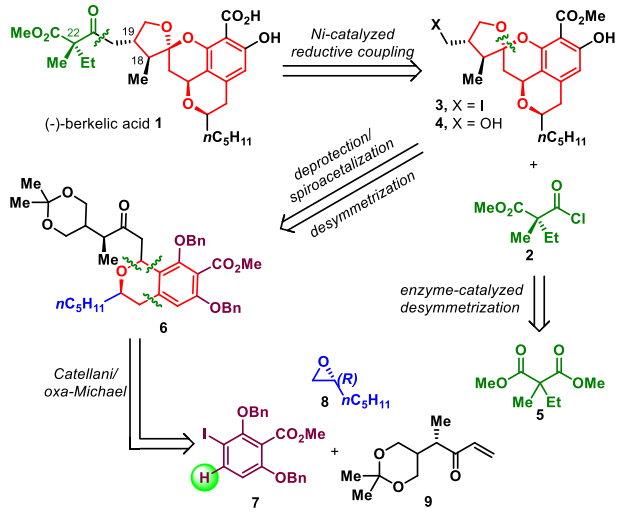
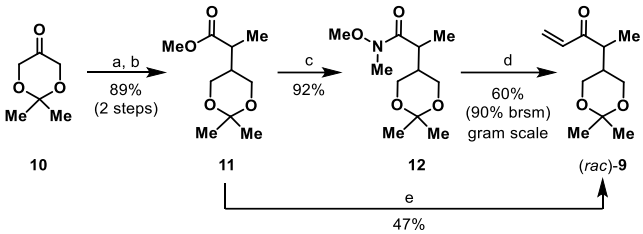
construction of tetracyclic core structure via a one-pot deprotection/spiroacetalization operation, and introduction of the lateral chain by a late-stage Ni-catalyzed reductive coupling.



Scheme 1. Retrosynthetic analysis of (–)-berkelic acid (**1**).

A retrosynthetic analysis of (–)-berkelic acid is depicted in Scheme 1. Inspired by the emerging field of Ni-catalyzed reductive coupling as a powerful tool for the assembly of ketones,[9f-k,9o-q] we envisaged a late-stage Ni-catalyzed reductive coupling of Fürstner's iodide **3**[2,5] with non-racemic acid chloride **2** for the installation of the lateral chain. For the synthesis of **2**, an enzyme-catalyzed hydrolysis of the prochiral diester **5**, referring to Björkling's work[12] could be adopted. Iodide **3** can be derived from the corresponding alcohol **4**,[2,5] which can be obtained via an acid-catalyzed deprotection/spiroacetalization[2,7] of isochroman **6**. For construction of the key isochroman intermediate **6**, we imagined combining the known aryl iodide **7**,[10] optically pure epoxide **8**[13] and a single enantiomer of enone **9** in a Catellani reaction/oxa-Michael addition sequence.[10] Though promising as it seemed, we were aware that this synthetic strategy may encounter several challenges: (i) the late-stage Ni-catalyzed reductive coupling might be problematic, owing to the highly functionalized coupling partner **3**; (ii) two new chiral centers will be generated during the deprotection/spiroacetalization procedure through desymmetrization, and control of the stereochemistry throughout this process will be a difficult task; (iii) the Catellani reaction/oxa-Michael cascade could prove difficult to achieve since the stereogenic centre of enone **9** is theoretically labile under the basic reaction conditions.

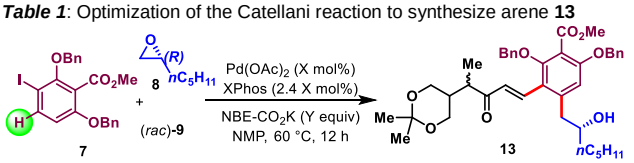
We began our synthesis with the preparation of building blocks **7**, **8** and (rac)-**9** to test the key three-component Catellani reaction. **7**[10] and **8**[13] are known compounds and were prepared on gram scales according to reported procedures.[14] As shown in Scheme 2, the synthesis of (rac)-**9** was achieved on a gram scale in four conventional steps, from commercially available 2,2-dimethyl-1,3-dioxan-5-one (**10**). First, a Horner–Wadsworth–Emmons (HWE) reaction with **10** followed by a catalytic hydrogenation provided ester **11** in 89% overall yield. Treatment of **11** with *N*-methoxymethylamine hydrochloride in the presence of *i*PrMgCl at room temperature gave Weinreb amide **12** in 92% yield. Finally, addition of vinylmagnesium bromide to **12** afforded the desired racemic enone **9** in 60% yield (1.19 g, 90% yield brsm). Alternatively, **9** could be directly obtained from ester **11** in 47% yield, via a tandem procedure involving β-keto phosphonate formation and in situ HWE olefination.[15]



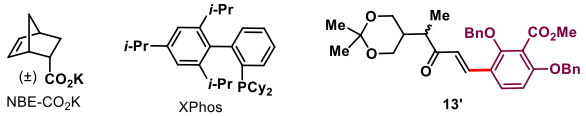
Scheme 2. Retrosynthetic analysis of (–)-berkelic acid (**1**). Reagents and conditions: a) methyl 2-(diethoxyphosphoryl)propanoate, *n*BuLi, THF, -78 °C to 0 °C; b) H_2, Pd/C, MeOH, RT; c) *i*PrMgCl, *N*-methoxymethylamine hydrochloride, THF, RT; d) vinyl-magnesium bromide, THF, 0 °C; e) LDA, $MePO(OMe)_2$, $(CH_2O)_n$, THF, 0 °C. brsm: based on recovered starting material. THF = tetrahydrofuran. RT = room temperature. LDA = lithium diisopropylamide.

With substantial quantities of building blocks **7**, **8** and (rac)-**9** in hand, we then turned our attention to examine the key Catellani reaction to access the pentasubstituted aromatic intermediate **13**. First, **7**, **8** and **9** were subjected to our previously developed reaction conditions: 10 mol% of $Pd(OAc)_2$, 24 mol% of XPhos and 0.5 equivalent of NBE-CO_2K in NMP at 60 °C under an argon atmosphere.[10] The desired product **13** was obtained as an inseparable diastereoisomeric mixture in 26% yield, along with substantial quantities of direct Heck coupling side-product (**13′**) of **7** and **9** (Table 1, entry 1). Increasing the loading of NBE-CO_2K to 1.0 equivalent could effectively reduce the direct Heck coupling side product and improve the yield of **13** to 38% yield (Table 1, entry 2). However, further increasing the loading of NBE-CO_2K (to 1.5 equivalent) had a deleterious effect (Table 1, entry 3). Therefore, we sought to increase the loading of the Pd catalyst. Gratifyingly, the yield of **13** could be significantly improved to 70% when 15 mol% of $Pd(OAc)_2$ and 36 mol% of XPhos were used in

Table 1: Optimization of the Catellani reaction to synthesize arene **13**



Entry[a]	X (mol%)	Y (equiv)	Yield of **13** (%)[b]
1	10	0.5	26
2	10	1.0	38
3	10	1.5	27
4	15	1.0	70
5[c]	15	1.0	70
6[d]	15	1.0	69



[a] Reactions were performed on a 0.1 mmol scale. [b] Isolated yield. [c] Reaction was performed on a 1.2 mmol scale. [d] Reaction was performed on a 5.4 mmol scale. NMP = *N*-methyl-2-pyrrolidinone.

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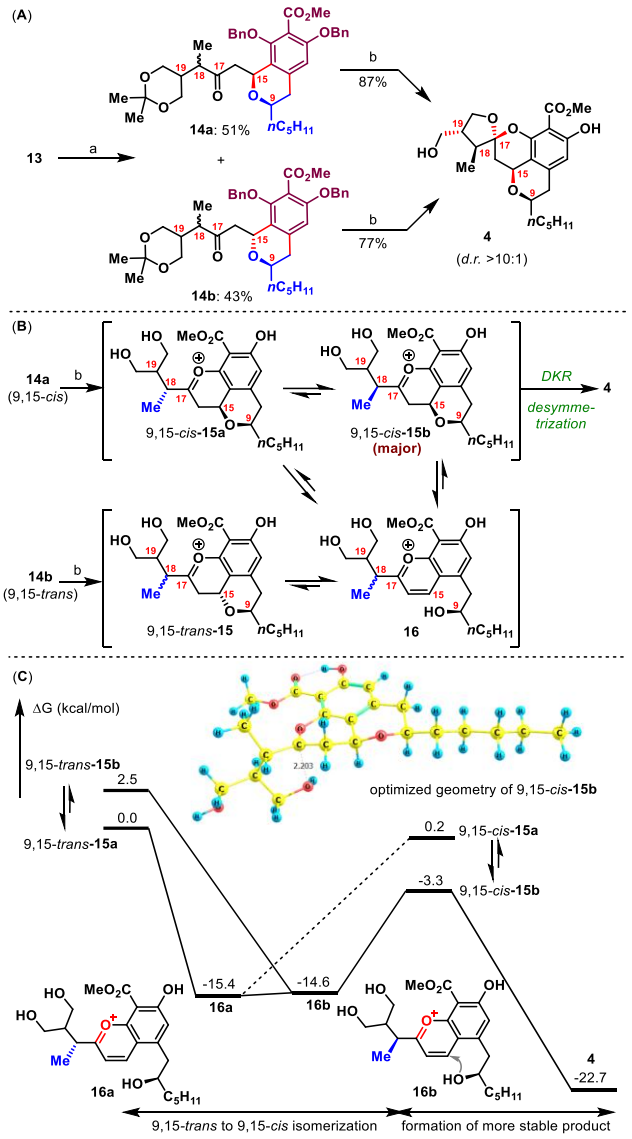
the presence of 1.0 equivalent of NBE-CO_2K (Table 1, entry 4). Notably, this reaction is scalable, the reaction efficiency remained good on 1.2 mmol and 5.4 mmol scale operations (Table 1, entries 5-6), and the latter was able to afford 2.46 grams of **13** (Table 1, entry 6).



Scheme 3. (A) Synthesis of key tetracyclic intermediate **4**: a) Cs_2CO_3, CH_3CN, 60 °C, 1 h; b) Pd/C, H_2, MeOH, 0.5 h; $TsOH{\cdot}H_2O$, 12 h. (B) Proposed reaction mechanism. (C) Computational study. Energies refer to Gibbs free energy activation barriers (in kcal/mol) calculated using M06-2X/def2-TZVPP-SMD(MeOH)//B3LYP-D3(BJ)/def2-SVP. DKR = dynamic kinetic resolution. $TsOH{\cdot}H_2O$ = *p*-Toluenesulfonic acid monohydrate.

With an efficient approach to the pentasubstituted arene **13** established, we next focused on the synthesis of tetracyclic core intermediate **4** (Scheme 3A). To better understand the details of this process, a stepwise operation was initially conducted. Treatment of **13** with Cs_2CO_3 in CH_3CN at 60 °C triggered the oxa-Michael reaction to generate two diastereomers of **14**: 9,15-*cis*-isochroman **14a** and 9,15-*trans*-isochroman **14b**, which can be readily separated on silica gel chromatography. To our surprise, subjecting **14a** to sequential deprotection of the benzyl group through catalytic hydrogenation and the acetonide group in an acidic media (*p*-toluenesulfonic acid in methanol) in a "one pot" operation, triggered the *in situ* spiroacetalization and afforded the key tetracyclic intermediate **4** as the major diastereomer (87% yield, d.r. > 10:1). It is noteworthy that, in this transformation, the three new chiral centers (C17, C18, and C19) were established through spiroacetalization (C17), dynamic kinetic resolution (C18) and desymmetrization (C19). More importantly, when the 1,3-*trans* diastereomer **14b** was subjected to identical reaction conditions, the same diastereomer of **4** was obtained as the major product (77%, d.r. > 10:1). Notably, in this case, four new chiral centers (C15, C17, C18 and C19) were established through isomerization (*trans* to *cis*), spiroacetalization, dynamic kinetic resolution and desymmetrization. It is noteworthy that the above spiroacetalization step was finished alongside a desymmetrization process, and two new chiral centers were generated. The observed experimental results demonstrate excellent diastereocontrol of this challenging process. Additionally, the observed dynamic kinetic resolution of the C18 stereocenter in **14a** and **14b** evidently indicates that the preparation of enantiopure enone **9** (Scheme 1) is not necessary, since the stereo-information of the four newly established chiral centers in **4** are all generated from the C9 stereocenter.

To rationalize this intriguing transformation, we propose the reaction mechanism depicted in Scheme 3B. After global deprotection of **14a** and **14b**, the free phenol groups condense with the C17 carbonyl group to form the tricyclic cationic intermediates 9,15-*cis*-**15a**, 9,15-*cis*-**15b** and 9,15-*trans*-**15**, respectively. Epimerization of the alpha position of the ketone in 9,15-*cis*-**15a** results in an equilibrium with 9,15-*cis*-**15b**. Then, these rigid tricyclic intermediates undergo a facile retro-oxa-Michael addition reaction to form the thermodynamically favored chromenylium intermediate **16**. This intermediate links 9,15-*cis*- and 9,15-*trans*-**15** and constitutes the equilibriums among them. We assume that 9,15-*cis*-**15b** is the most stable tricyclic intermediate, since it corresponds to the major product **4**. Thus, 9,15-*cis*-**15b** undergoes a desymmetrization process involving the nucleophilic attack by one of the two hydroxy groups to the C17 cationic carbonyl to form the stable and isolable tetracyclic product **4** (Scheme 3B). We believe the stereochemistry of this desymmetrization process is controlled by the preferential conformation of 9,15-*cis*-**15b**, and the two newly generated chiral centers were established in a stereospecific manner. Remarkably, the common intermediate **16** enables good relay of stereo information from the C9 stereocenter to the four new chiral centers.

In order to support this assumption, we carried out density functional theory (DFT) calculations (Scheme 3C).[16] As expected, 9,15-*cis*-**15b** is the most thermodynamically stable among these four tricyclic isomers. For instance, 9,15-*cis*-**15b** is more stable than 9,15-*cis*-**15a** and 9,15-*trans*-**15b** by 3.5 and 5.8 kcal/mol, respectively. Thus, 9,15-*cis*-**15b** is the predominant isomer which can lead to product and can be accumulated from 9,15-*cis*-**15a** through epimerization or from 9,15-*trans*-**15** through a retro-oxa-Michael addition and oxa-Michael addition reactions via **16a** and **16b** (The conversion of **15** to **16** may undergo through an enol ether intermediate[17]). The equilibrium towards 9,15-*cis*-**15b** could be driven by the following reaction to form the more stable product **4**. According to the optimized geometry of 9,15-*cis*-**15b** (Scheme 3C), the hydroxyl group on the bottom face is very close

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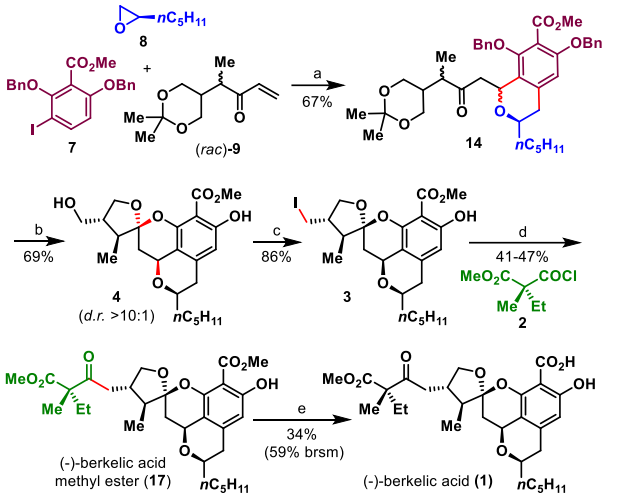
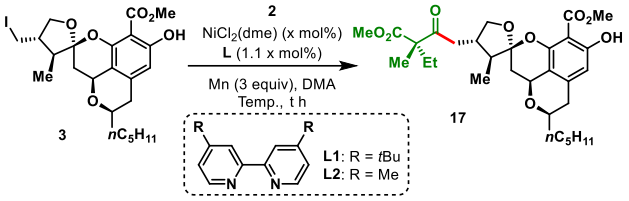
to the C17 cationic carbonyl group (the C-O distance is 2.203 Å, indicating a favorable electrostatic interaction), which took the exclusive role for the nucleophilic attack. Therefore, the stereo-configurations of the two new chiral centers were established as 18*S*/19*R*. These calculations agree with the experimental results.



Scheme 4. Total synthesis of (–)-berkelic acid (**1**). Reagents and conditions: a) $Pd(OAc)_2$, XPhos, NBE-CO_2K, NMP, 60 °C, 12 h; Cs_2CO_3, 11 h; b) Pd/C, H_2, MeOH, 0.5 h; TsOH·H_2O, 12 h; c) I_2, PPh_3, imidazole, DCM, 3 h; d) **2**, $NiCl_2$(dme), dmbpy, Mn, DMA, 0 °C, 5-10 h; e) $(Bu_3Sn)_2O$, toluene, 115 °C, 8 h. DCM = dichloromehane. dme = dimethoxyethane. dmbpy = 4,4'-dimethyl-2,2'-bipyridine. DMA = *N,N*-dimethylacetamide.

Having demonstrated the feasibility of the stepwise synthesis of isochroman scaffold, we then attempted the one-pot procedure. As shown in Scheme 4, after the completion of the three-component Catellani reaction (monitored by TLC), Cs_2CO_3 was directly added into the reaction mixture and stirred at the same temperature for an additional 11 hours. Consistent with the stepwise experiments, the desired isochroman intermediate **14** was obtained as a 1.2:1 diastereo mixture of 9,15-*cis*-**14a** and 9,15-*trans*-**14b** in 67% combined yield. The isochroman mixture of **14** was then subjected to the deprotection/spiroacetalization protocol to provide **4** in a good yield and excellent diastereoselectivity (69%, d.r. > 10:1). Treatment of **4** with PPh_3 and I_2 in DCM gave Fürstner's iodide **3**[2] in 86% yield. At this stage, we focused on the late-stage reductive coupling to introduce the lateral chain. Initially, **3** reacted with acyl chloride **2** (70% *ee*)[12,18] under Weix's conditions ($NiCl_2$(dme) and dtbpy (**L1**) in the presence of Mn in DMA at 0 °C)[9f]. The desired coupling product, (–)-berkelic acid methyl ester **17** was obtained in 25% yield, along with the de-iodination side product **S6** and an unidentified byproduct (Table 2, entry 1). When dmbpy (**L2**) was used as the ligand, the yield of **17** was significantly improved to 47% (Table 2, entry 2). Optimization by increasing the catalyst loading to 15 mol% proved ineffective (Table 2, entry 3). Further optimization by performing the reaction at room temperature or -5 °C and -10 °C all led to unsatisfactory results (Table 2, entries 4-6). Thus, the reaction conditions of entry 2 (Table 2) was fixed as the best conditions for synthesizing **17**, and about 50 mg of the pure sample can be obtained in one operation.[19] The extremely mild reaction conditions and excellent function group tolerance ensured the success of this impressive late-stage Ni-catalyzed reductive coupling. Finally, (–)-berkelic acid (**1**) was accessed through the selective saponification of the methyl benzoate of **17** in the presence of $(Bu_3Sn)_2O$, following reported procedures.[4-5] The NMR spectra and optical rotation of both (–)-berkelic acid methyl ester **17** and (–)-berkelic acid are in agreement with those previously reported (see SI for the corresponding comparisons).

Table 2. Optimization of Ni-catalyzed reductive coupling of iodide **3** and acyl chloride **2**.



Entry	x	L	Temp. (°C)	Time (h)	Yield (%)[a]
1	10.0	**L1**	0	19	25
2	10.0	**L2**	0	10	47
3	15.0	**L2**	0	10	40
4	10.0	**L2**	25	5	33
5	10.0	**L2**	-5	12	23 (34)[b]
6	10.0	**L2**	-10	20	17 (30)[b]

[a] Isolated yield. [b] Based on recovered **3**.

In conclusion, we have accomplished a concise total synthesis of (–)-berkelic acid (**1**) in eight linear steps starting from commercially available reagents. This synthesis features a three-component Catellani reaction/oxa-Michael cascade for the assembly of isochroman scaffold, a one-pot deprotection/spiroacetalization to construct the tetracyclic core structure, and a late-stage Ni-catalyzed reductive coupling to introduce the lateral chain. Notably, four stereocenters are established from one existing chiral center with excellent stereocontrol during the deprotection/spiroacetalization process. Initial DFT calculations support our proposed mechanism to rationalize the intriguing stereocontrol of the deprotection/spiroacetalization process. We believe this highly efficient stereochemical-relay strategy may have broader implications for asymmetric syntheses.

Acknowledgements

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Keywords: (–)-berkelic acid • Catellani reaction • spiroacetalization • reductive coupling • total synthesis

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[8] The recent bioactivity studies of (–)-berkelic acid (see refs. 3c, 4b and 5c) are inconsistent with the originally reported ones (see ref. 1), which deserves further systematic studies.

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[17] For related calculation results, please see SI for details.

[18] Chiral acyl chloride **2** is readily prepared through the enzymatic hydrolysis of the known prochiral diester **5** (referring to Björkling's work (ref. 11)) and a following reaction with $SOCl_2$. See SI for experimental details.

[19] The 22*R*-diastereomer of (–)-bekelic acid methyl ester **17** and other diastereoisomers were also formed through this reductive coupling protocol (detected by crude ^{1}H NMR and HRMS). However, we failed to obtain the pure sample for characterization owing to the contamination of some unidentified impurities with a similar polarity.

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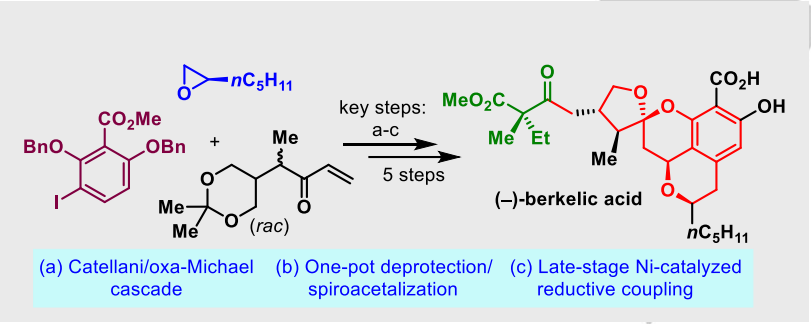

Hong-Gang Cheng[1†], Zhenjie Yang[1†], Ruiming Chen[1], Liming Cao[1], Wen-Yan Tong,[3] Qiang Wei[1], Qingqing Wang[1], Chenggui Wu[1], Shuanglin Qu[3] and Qianghui Zhou*[1,2]*

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A Concise Total Synthesis of (–)-Berkelic Acid

A concise total synthesis of (–)-berkelic acid in eight linear steps was developed. This synthesis features a Catellani reaction/oxa-Michael cascade for the construction of the isochroman scaffold, a one-pot deprotection/spiroacetalization operation for the formation of tetracyclic core structure, and a late-stage Ni-catalyzed reductive coupling for the introduction of the lateral chain.