Asymmetric Syntheses of (+)- and (−)-Collybolide Enable Reevaluation of kappa-Opioid Receptor Agonism

Sophia L. Shevick, Stephan M. Freeman, Guanghu Tong, Robin J. Russo, Laura M. Bohn, and Ryan A. Shenvi*

ABSTRACT: The fungal metabolite collybolide has attracted attention as a non-nitrogenous, potent, and biased agonist of the kappa-opioid receptor (KOR). Here, we report a 10-step asymmetric synthesis of this complex sesquiterpene that enables facile access to either enantiomer. The synthesis relies on a diastereoselective α-benzoyloxylation to install the buried C6 benzoate and avoid irreversible translactonization of the congested, functionally dense core. Neither enantiomer, however, exhibited KOR agonism, indicating that collybolide has been mischaracterized as a KOR agonist. Given the pharmaceutical, medical, and societal interest in collybolide as a next-generation antipruritic and analgesic, this refutation of KOR activity has important ramifications for ongoing studies. Classification of collybolide as a new non-nitrogenous, KOR-selective, potent agonist with the same clinical potential as salvinorin A seems to have been premature.

INTRODUCTION

The freckled mushroom Collybia maculata (nom. alt. Rhodocollybia maculata) clusters in lignan-rich soils of conifer forests of Europe and North America. Bitter and tough to the point of inedibility, no references mention its use in traditional medicine nor its activity in mammals. In 2016, however, a metabolite of C. maculata was reported to exhibit potent and biased agonism of the kappa-opioid receptor (KOR). This sesquiterpene, collybolide, had been singled out for testing due to the similarity of its furano-δ-lactone motif to that of the potent KOR agonist diterpene salvinorin A (SalA). In side-by-side assays with SalA, collybolide exhibited typical agonist behavior selective for the KOR. In the GTPγS binding assay, the collybolide-induced response was submaximal compared to SalA, while in the ERK1/2 MAP kinase and Akt phosphorylation studies, collybolide produced more stimulation than SalA. This change in relative rank-order efficacy led the authors to conclude that collybolide displays biased agonism at KOR. Collybolide also exhibited antipruritic activity in mice, a known consequence of KOR agonism.

The translational potential of collybolide attracted attention across the biomedical community due to indications for the KOR as a target in next-generation analgesics, antipruritics, and antidepressants. However, many questions remained: the unusual concentration—response curves and the lack of a β-arrestin recruitment assay, specifically, required greater pharmacological scrutiny, and structural homology with SalA was nonobvious in three dimensions (Figure 1). Synthetic access to collybolide might address these questions, clarify the absolute stereochemistry of 1, provide material with a different impurity profile than C. maculata isolates, and establish a means for deep-seated modifications of the scaffold. Here, we report the first synthesis of collybolide (1) and the biochemical profiles of the pure enantiomers, (+)-1 and (−)-1. In contrast to a previous report, our data does not support collybolide as a KOR agonist.

Degradation studies of collybolide revealed the synthetic challenges that lay ahead. Like SalA, collybolide (1) epimerized under acidic conditions, scrambling C7 stereochemistry. Treatment of 1 with alkali caused benzoate solvolysis and lactone cleavage. The nucleophilic oxygen (O5) of 1 is positioned 3.1 Å from C15, and the isomer, neocollybolide (3), is calculated (MM2) to be 1.2 kcal/mol more stable than 1, resulting in kinetic and thermodynamic preferences for the formation of 2 and 3.

Treatment of 2 with benzoyl chloride delivered neo-collybolide (3); rearrangement to the collybolide scaffold with SalA was nonobvious in three dimensions (Figure 1). Synthetic access to collybolide might address these questions, clarify the absolute stereochemistry of 1, provide material with a different impurity profile than C. maculata isolates, and establish a means for deep-seated modifications of the scaffold. Here, we report the first synthesis of collybolide (1) and the biochemical profiles of the pure enantiomers, (+)-1 and (−)-1. In contrast to a previous report, our data does not support collybolide as a KOR agonist.

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did not occur. The preference for 3 over 1 contrasts the reactivity of other sesquiterpenes like bilobalide where benzoylation promotes a kinetically favorable but contra-
reactivity of other sesquiterpenes like bilobalide where benzoylation leads to exclusive arene oxidation by OsO₄ (strategy 1). In the absence of the furan, dihydroxy-
lization favored the [4.3.0] bicycle (strategy 2)—another dead end due to the intractability of this fused lactone, as noted above. A third-generation approach (strategy 3) accessed 8 via internal radical dioxygenation (see Supporting Information) and similarly led to a dead end to transactonization, mirroring observations in the isolation literature.¹⁷

These three unsuccessful strategies called for an alternative approach that avoided the C6 alcohol entirely and resisted the reflexive benzoylation transform (+BzO) suggested by 1. A fourth-generation approach (Figure 2, gray panel) would install the C6 benzoxy group directly (+BzO), averting undesired transactonization and, ultimately, enabling the first chemical synthesis of 1. All four generations proceeded through the same densely functionalized, enantioenriched core 9. Like our second-generation route, furan installation would occur last, subsequent to alkene oxidation, to avoid furan decomposition. Benzoyloxylation, however, would require an electrophilic source of benzoate and its stereoselective addition to one alkene face—a high risk tactic that ultimately paid off.

**RESULTS AND DISCUSSION**

Synthesis commenced with an asymmetric, organocatalyzed cycloaddition, utilizing the Hayashi–Jørgensen diarylpropionitrile, tritylbenzylic and ethyl ammonium catalyst (R)-(−)-10, a more soluble variant of the commercially available trimethylsilyl ether.¹⁸–²⁰ The electron-deficient diene 11 necessitated extended incubation with 12 (4 days at 4 °C) but yielded cycloadduct (−)-13 (72%, i.e., 80% at 9:1 dr, 92% ee) in large quantity (12 g) after careful optimization. In contrast to previous work in which the ammonium salt was formed in situ, we preformed the air-stable triflate salt (−)-10, as small excesses of triflic acid promoted Mukaiyama-aldol side reactions. The exo-adduct (−)-13 was assigned definitively based on the homodecoupled ¹H NMR (homoced) coupling constant of 9.23 Hz between H₅ and H₆.²¹–²³ Attempts to effect the cycloaddition with the C14 methyl in place were unsuccessful and instead favored a Mukaiyama–Michael adduct likely due to a severe syn-pentane interaction in the cycloaddition transition state. Addition of the methyl group at the expense of additional steps was compensated for by the excellent yield and enantiomeric ratio. The incorrect relative stereochemistry of the C4 carboxylate proved inconsequential as it was inverted during this methyl addition step.

Wittig olefination of (−)-13 proceeded smoothly to access terminal alkene (+)-14 (79%). Whereas this alkene served as a substrate for a carbamoyl-directed Heck reaction in earlier routes, it would later serve as a masked, homologated aldehyde (vide infra). Attempts to oxidize silyl enol ether (+)-14 to enone (−)-16 using Saegusa oxidation conditions led to adequate yields but only at stoichiometric palladium loading (40% yield); attempts to render the oxidation catalytic in palladium were unsuccessful. α-Bromination en route to (−)-16 led to unexpected silyl enol ether transposition (15, verified by ¹H NMR and COSY).²⁵–²⁷ Despite the potential for facile aromatization, 15 underwent concomitant deprotection and elimination when treated with tetrabutylammonium fluoride to yield (−)-16 in 94% yield. We did not observe isomerization of the skipped 1,4-diene of (−)-16 to the corresponding conjugated 1,3-diene. Low substrate concentration (0.03 M in 15) proved crucial for clean conversion to (−)-16, potentially to disfavor olefin–olefin bromonium transfer.²⁸

The challenging C4 quaternary stereocenter could be accessed via conjugate addition (see Scheme 1) but not using standard approaches (MeLi or MeMgBr in combination with Cu(I) salts), which either failed to convert (−)-16 or formed 1,2-addition products. To lessen the basicity and increase the Lewis acidity of the methyl pro-nucleophile, we turned to AlMe₃⁻⁄⁻ in the presence of (10 mol %) Cu(I)Br·SMe₂ and TMSCl, which furnished the desired conjugate addition product in a modest 1.7:1 dr favoring diastereomer (−)-18 (60% yield, diastereomers assigned by NOE). The
The diastereomeric ratio could be improved to 3.6:1 dr with catalytic Cu(II)(OTf)$_2$ (10 mol %) in favor of the desired diastereomer (64% yield). Diastereoselectivity may depend on copper aggregation or oxidation states, which could perturb steric interactions with the vinyl substituent en route to Cu$_{3+}$ insertion products. Addition of TMSCl prevented further reactivity of the aluminum enolate intermediate; its absence resulted in complex reaction mixtures. Deprotection of the newly formed trimethylsilyl enol ethers occurred upon workup with 2 M HCl. Diastereoselective reduction of cyclohexanone proceeded smoothly with $L$-Selectride, resulting in a single diastereomer, which lactonized under the reaction conditions to form (+)-9 (75% yield, relative and absolute stereochemistry assigned by X-ray crystallography, see Scheme 1).

Prosecution of our fourth-generation strategy required oxidation of the terminal alkene to the corresponding aldehyde. Attempts to effect this transformation directly with nitrite-modified aldehyde-selective Wacker oxidation conditions failed to convert the starting material, while Wacker oxidation of the alkene under substrate control yielded mixtures of aldehyde and methyl ketone. Instead, successful oxidation was achieved via a one-pot hydroboration/oxidation approach (Scheme 2). Efficient hydroboration of (+)-9 was accomplished exclusively with dicyclohexylborane, whereas BH$_3$·SMe$_2$ or Sia$_3$BH did not hydroborate efficiently, and 9-BBN or BH$_3$·THF did not allow efficient oxidation. The intermediate trialkylborane was oxidized directly to (+)-19 by PCC (52% yield). We attribute the difficulties of this alkene oxidation to steric crowding in (+)-9 from both the C14 methyl and the C9 ester that flank the terminal olefin. Given the difficulties of the oxidation of vinylfuran (Figure 2), the steric hindrance of this alkene had proven to be a recurring challenge in this synthesis.

Access to (+)-19 allowed us to skirt this same steric hindrance and probe intramolecular appendage of the benzoyloxy group (Scheme 2). The intramolecularity of $\alpha$-oxidation would thus solve the problems of instability, inaccessibility, and stereoselectivity in a single maneuver. To carry out the benzoyloxilation, we turned to N-tert-butyloxamidinium salt, explored extensively by the Tomkinson group in the chemoselective $\alpha$-oxygenations of aldehydes and ketones. The mechanism proposed for this transformation involves condensation to the iminium, tautomerization to the enamine, and [3,3]-sigmatropic rearrangement to give the $\alpha$-benzoyloxy imine, which hydrolyzes in situ or upon workup. The development of this reagent hinges on literature precedent from House and Cummins on the spontaneous rearrangement of acylated oxime or nitrone intermediates, respectively. A multihetero-Claisen rearrangement proceeding through a chairlike transition state (i.e., (+)-19 to (−)-21) suggests two competing transition state conformers leading to the major and minor diastereomers. Diastereoselectivity was improved.
by variation of acid coreagents, with HCl leading to the highest dr (4.2:1) (see Table in Scheme 2). This dependence of dr on acid suggests that the acid either affects the equilibrium ratio of enamine conformations or changes the activity and oxophilicity but low basicity relative to organolithium acids.

In our hands, 3-furyltitanium reagents failed to deliver 1, however, resulting instead in titanium alkoxide addition to the aldehyde. Furfyllithium and magnesium halides demonstrated no increase in [35S]GTPγS binding over basal activity (Figure 3c), in contrast to the low nanomolar potency previously described. To further investigate the pharmacological properties of (+)-1, we also tested whether agonism could be revealed in other assays; however, there was no evidence that (+)-1 activated hKOR in assays measuring inhibition of adenylyl cyclase or the recruitment of β-arrestin2 (Figure 3c). Moreover, to ensure that we were not missing low efficacy partial agonism, we tested whether (+)-1 could antagonize β-arrestin2 recruitment induced by U69,593; however, again no efficacy for this system was observed. The lack of efficacy associated with synthetic (+)-1 might have been caused by synthesis of the incorrect unnatural enantiomer of collybolide (1) or 7-epi-1 activates or inhibits kappa-opioid receptor signaling. (a) The 1H NMR data report of synth-(+)-1 matches nat-(+)-1, and its 600 MHz data can be simulated at 100 MHz to produce aligned spectra for visual comparison. (b) The rapidity of complexity increase, depicted on a Gantt chart, allowed the synthesis of (−)-1 in 12 days. (c) Stimulation of hKOR using (+)-1, (−)-1, (−)-7-epi-1, and (+)-7-epi-1 (10−10−10−5 M) relative to the control agonist U69,593 in (left) a [35S]GTPγS binding assay performed in hKOR-CHO cell membranes; (center) inhibition of forskolin-stimulated cAMP accumulation in CHO-hKOR cells; (right) β-arrestin2 recruitment assay (U2OS hKOR DiscoveRx PathHunter). (d) Antagonism of 1 µM U69,593 stimulated β-arrestin2 recruitment with the KOR antagonist, norBNI; collybolide does not antagonize the response. Experimental details can be found in ref 51.

Figure 3. Neither enantiomer of collybolide (1) or 7-epi-1 activates or inhibits kappa-opioid receptor signaling. (a) The 1H NMR data report of synth-(+)-1 matches nat-(+)-1, and its 600 MHz data can be simulated at 100 MHz to produce aligned spectra for visual comparison. (b) The rapidity of complexity increase, depicted on a Gantt chart, allowed the synthesis of (−)-1 in 12 days. (c) Stimulation of hKOR using (+)-1, (−)-1, (−)-7-epi-1, and (+)-7-epi-1 (10−10−10−5 M) relative to the control agonist U69,593 in (left) a [35S]GTPγS binding assay performed in hKOR-CHO cell membranes; (center) inhibition of forskolin-stimulated cAMP accumulation in CHO-hKOR cells; (right) β-arrestin2 recruitment assay (U2OS hKOR DiscoveRx PathHunter). (d) Antagonism of 1 µM U69,593 stimulated β-arrestin2 recruitment with the KOR antagonist, norBNI; collybolide does not antagonize the response. Experimental details can be found in ref 51.
enantiomer. Although the optical rotation and CD spectra of synth-(+)-1 agreed with isolated nat-(+)-1, values in either sample might be overridden by an impurity with large circular birefringence of the opposite rotation as 1. Existing X-ray crystal structures of 1 and 9-epi-1 reported inconclusive Flack parameters that prevent confidence in the assignment. In contrast, the structure parameters of (+)-9 (X-ray) and others (see Supporting Information) allowed conclusive assignment of absolute stereochemistry in the series from (R)-(−)-10.

Given the brevity of our synthesis and the unexpected inactivity of synth-(+)-1, we decided to synthesize the opposite enantiomer, (−)-1. Normally a major undertaking, the entire synthesis from (S)-10-HOTf and 11 was performed in only 12 days. The Gantt chart (Figure 3b) depicts the ease with which the route attains the 443 molecular bits (mcbits) of 1 from low complexity building blocks 11 and 12 (95 and 171 mcbits, respectively). Access to ent-(−)-1, the enantiomer of the absolute configuration assigned to nat-1, allowed parallel assays of (+)-1 and (−)-1 to identify which antipode might be responsible for KOR agonism. To our dismay, neither enantiomer of 1 or 7-epi-1 indicated KOR agonism as evident through [35S]GTPγS functional assay or inhibition of cAMP accumulation. These data significantly affect ongoing research and expectations from multiple laboratories involved in opioid research related to the collybolides.

**CONCLUSION**

Whereas biological activity has been wrongly ascribed to natural products when assay readouts are uncertain or impurities are present, the conflict described here represents an unusual case in which multiple, well-established biochemical assays are incorrectly assigned. The explanations we favor for mischaracterization are errors in the assays themselves or misinterpretations of the data. At first, we had entertained the possibilities that collybolide degradation products or unidentified isolate impurities had caused KOR activation. However, correspondence with the authors of ref 3 and others in the community made these possibilities seem unlikely: the sample of 1 used in ref 3 was crystallized to high purity (verified by 1H NMR), and crude extracts of C. maculata containing 1 were also found to lack KOR agonist activity (see email correspondences in Supporting Information).

Unlike the data for U69,593 in Figure 3, the concentration–response data in ref 3 did not fit a standard sigmoidal curve, both for 1 and the positive control, salvinorin A. Furthermore, the maximum % stimulation over basal in the [35S]GTPγS binding assays of ref 3 was only 30–40%, whereas our data for the positive control (U69,593) reached 300% (Figure 4). Low stimulation may have led to the interpretation of background noise as signal.

The authors of ref 3 continue to interrogate the assays used for the characterization of collybolide. Surface-modifying reagents were deemed necessary for their assay due to a “stickiness” ascribed to 1, whereas we did not observe any heterogeneity or adhesion during dilution or sample preparation. Spectroscopic and chromatographic measurements of turbidity and lipophilicity undertaken by our lab indicated no precipitation or aggregation in serial buffer dilutions at a broad range of assay concentrations (see Supporting Information).

The in vivo activity of collybolide observed by the authors of ref 3 in mouse studies raises the possibility that 1 may be an antipruritic, but its target has been incorrectly assigned. Classification of collybolide as a new non-nitrogenous, KOR-selective agonist with the same clinical potential as SalA seems to have been premature. The independent syntheses and assays reported here have excluded collybolide as a KOR agonist and have begun a search for the true potential of this unusual fungal metabolite.

**ASSOCIATED CONTENT**

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscentsci.2c00442.

Experimental procedures, characterization data, structural assignments, biological assay information, NIMH PDSP radioligand displacement and functional assays, and personal correspondences (PDF)

Crystallographic information for (+)-9 (CIF)

Crystallographic information for (R)-(−)-10 (CIF)

Crystallographic information for SI-6 (CIF)

**AUTHOR INFORMATION**

**Corresponding Author**

Ryan A. Shenvi – Department of Chemistry, Scripps Research, La Jolla, California 92037, United States; orcid.org/0000-0001-8353-6449; Email: rshenvi@scripps.edu

**Authors**

Sophia L. Shevick – Department of Chemistry, Scripps Research, La Jolla, California 92037, United States; Skaggs Graduate School of Chemical and Biological Sciences, Scripps Research, La Jolla, California 92037, United States; orcid.org/0000-0003-1703-5448

Stephan M. Freeman – Department of Chemistry, Scripps Research, La Jolla, California 92037, United States; Skaggs Graduate School of Chemical and Biological Sciences, Scripps Research, La Jolla, California 92037, United States

Guanghu Tong – Department of Chemistry, Scripps Research, La Jolla, California 92037, United States

Robin J. Russo – Department of Molecular Medicine and Skaggs Graduate School of Chemical and Biological Sciences, Scripps Research, Jupiter, Florida 33458, United States

Laura M. Bohn – Department of Molecular Medicine, Scripps Research, Jupiter, Florida 33458, United States; orcid.org/0000-0002-6474-8179

Complete contact information is available at: https://pubs.acs.org/doi/10.1021/acscentsci.2c00442

**Notes**

The authors declare no competing financial interest.
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