Enantioselective para-Claisen Rearrangement for the Synthesis of Illicium-Derived Prenylated Phenylpropanoids

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Letter

Enantioselective *para*-Claisen Rearrangement for the Synthesis of *Illicium*-Derived Prenylated Phenylpropanoids

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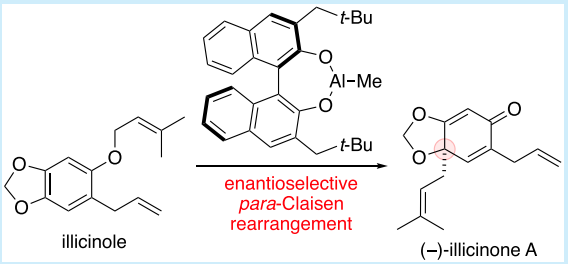
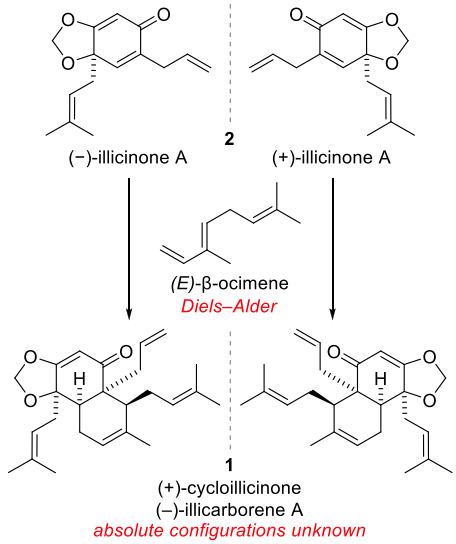
ABSTRACT: The development of the first enantioselective *para*-Claisen rearrangement has been achieved. Using a chiral aluminum Lewis acid, illicinole is rearranged to give (−)-illicinone A (er 87:13), which can then be converted into more complex *Illicium*-derived prenylated phenylpropanoids. The absolute configurations of the natural products (+)-cycloillicinone and (−)-illicarborene A have been determined, and our results cast doubt on the enantiopurity of the natural samples.



(+)-Cycloillicinone (**1**) was isolated from the twigs of Japanese Star Anise, *Illicium anisatum*, by Fukuyama and co-workers in 2011 (Scheme 1).[1] In 2013, Shen and co-workers reported the isolation of the opposite enantiomer, from *Illicium arborescens*, and named it (−)-illicarborene A.[2] The absolute configurations of (+)-cycloillicinone/(−)-illicarborene A (**1**) have not yet been determined.[1,2]

Scheme 1. Diels–Alder Biosynthetic Pathway to (+)-Cycloillicinone/(−)-Illicarborene (1)[1]



Fukuyama and co-workers proposed a biosynthetic pathway toward (+)-cycloillicinone (**1**) involving an intermolecular Diels–Alder cycloaddition between (*E*)-*β*-ocimene and illicinone A (**2**),[1] a known natural product which has been isolated in both enantiomeric forms from *Illicium* plants (Scheme 1).[3] In an attempt to probe the chemical feasibility of this proposed biosynthetic Diels–Alder reaction and to determine the absolute configurations of these natural products, we decided to embark upon efforts toward achieving an enantioselective biomimetic total synthesis.

We planned to follow an approach reported by Danishefsky and co-workers to access illicinone A (**2**),[4] which relies on a remarkably selective *para*-Claisen rearrangement using Yamamoto's bulky Lewis acid, MABR (methylaluminum bis(4-bromo-2,6-di-*tert*-butyl-phenoxide)) (Scheme 2).[5] To access enantioenriched (+)-cycloillicinone/(−)-illicarborene A (**1**), we envisioned pursuing two different strategies: (1) Diels–Alder kinetic resolution of racemic illicinone A (**2**); (2) development of an enantioselective *para*-Claisen rearrangement.

During our early work on this project, Rahman and co-workers reported an elegant biomimetic total synthesis of (±)-cycloillicinone (**1**) (Scheme 2).[6] In their studies, they found a number of acid catalysts promoted a highly regio- and diastereoselective Diels–Alder cycloaddition between (±)-illicinone A (**2**) and (*E*)-*β*-ocimene to give (±)-cycloillicinone (**1**). Regrettably, however, Rahman and co-workers observed no kinetic resolution when using Corey's oxazaborolidinium catalyst (Scheme 2).[6] We, therefore, decided to focus our attention on pursuing an enantioselective *para*-Claisen strategy.

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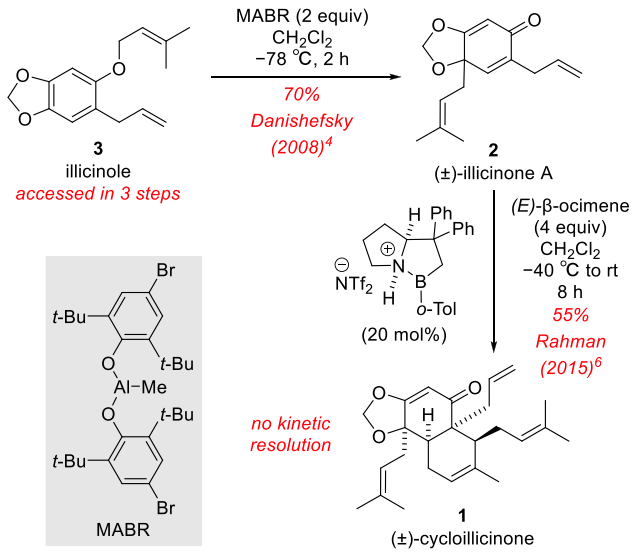
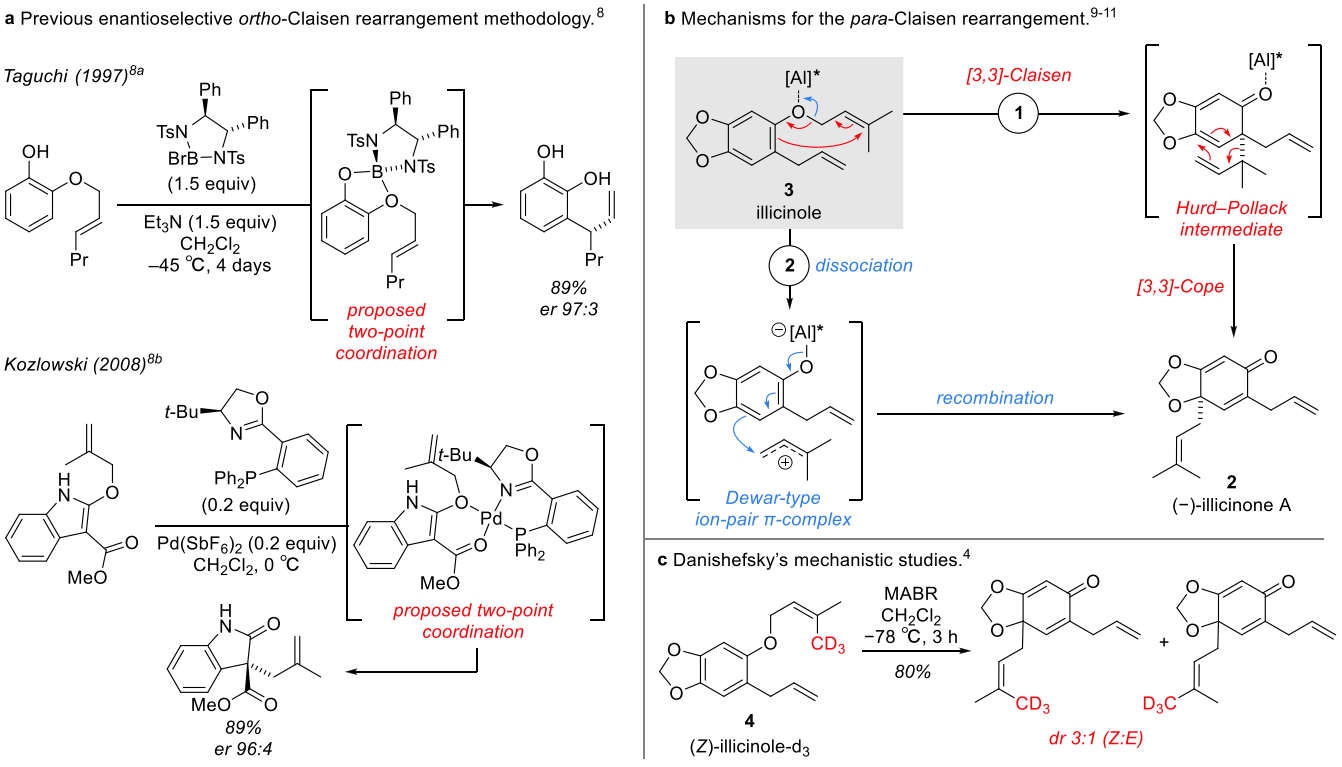
Scheme 2. Previous Non-enantioselective Syntheses of (±)-Illicinone A (2) and (±)-Cycloillicinone (1)[4,6]



It was clear that achieving enantioselectivity in the *para*-Claisen rearrangement of illicinole (**3**) was going to be very challenging. There are no examples of enantioselective *para*-Claisen rearrangements in the literature.[7] A limited number of enantioselective *ortho*-Claisen rearrangements are known, but these rely on substrates with the potential for two-point binding to a chiral reagent (Scheme 3a).[8] Nevertheless, given the long established [3,3]-Claisen/[3,3]-Cope mechanism for *para*-Claisen rearrangements (Scheme 3b, pathway 1),[9] one might assume that enantioselectivity could be achieved by simple extension of *ortho*-Claisen methodology. That is to say, a point-to-point chirality transfer in the [3,3]-Cope rearrangement reduces the challenge to achieving enantioselectivity in the initial [3,3]-Claisen rearrangement. However, when using an isotopically labeled substrate, **4**, in the MABR-mediated *para*-Claisen rearrangement, Danishefsky and co-workers observed partial retention of prenyl group geometry (Scheme 3c).[4] This was attributed to a "direct prenyl migration" pathway, as opposed to the more common [3,3]-Claisen/[3,3]-Cope mechanism,[9] which would be expected to give a 1:1 (*E*):(*Z*) mixture. No mechanistic speculation was put forward for the direct prenyl migration pathway, although Dewar-type intermediates have been suggested for other *para*-Claisen rearrangements (Scheme 3b, pathway 2).[10,11] Clearly, if this reaction does proceed via a Dewar-type mechanism, this will place a particularly high demand on any catalyst to control enantioselectivity at the remote *para*-position.

We began our studies by conducting the known three-step synthesis of illicinole (**3**), from sesamol, on a multigram scale (Scheme 4; (1) *O*-allylation, (2) *ortho*-Claisen rearrangement, (3) *O*-prenylation).[4] We then repeated Danishefsky's MABR mediated *para*-Claisen rearrangement to access 1.7 g of (±)-illicinone A (**2**).[4] Yamamoto's Lewis acids have been extensively used to promote Diels–Alder reactions,[12] and we envisioned developing a one-pot consecutive *para*-Claisen/Diels–Alder reaction sequence to directly access (±)-cycloillicinone (**1**). This was achieved by first treating illicinole (**3**) with MABR at −78 °C for 2.5 h before a diastereomeric mixture of (*E*)/(*Z*)-*β*-ocimene (dr 3:2, 4.5 equiv) was added and the reaction was warmed to room temperature.[13] This

Scheme 3[a]



[a](a) Examples of enantioselective *ortho*-Claisen rearrangements.[8] (b) Mechanisms for the *para*-Claisen rearrangement.[9−11] (c) Mechanistic studies on the MABR-mediated *para*-Claisen rearrangement by Danishefsky and co-workers.[4].

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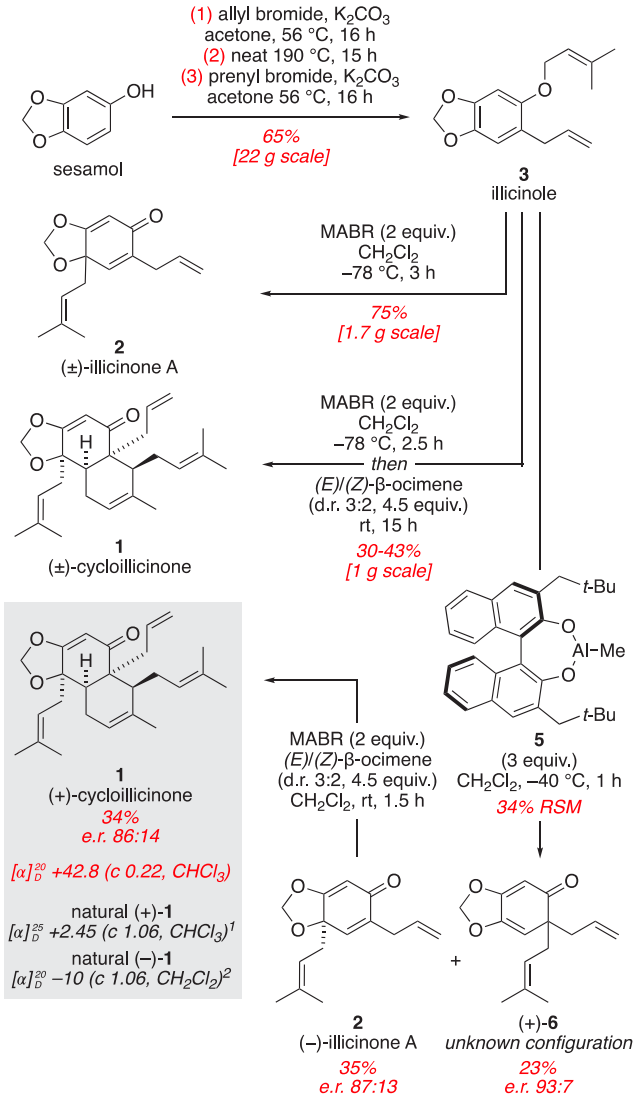
Org. Lett. 2021, 23, 3248−3252

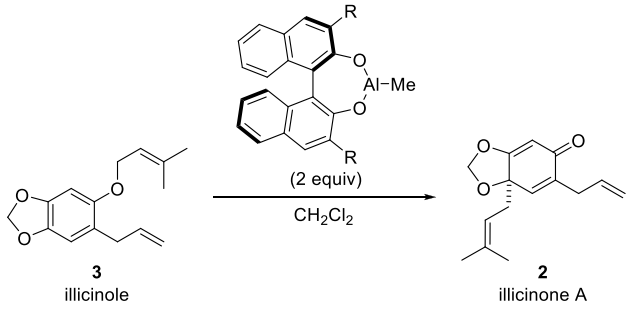
Scheme 4. Gram-Scale, Streamlined Syntheses of Racemic Illicinone A (2) and Cycloillicinone (1), and the First Enantioselective Synthesis of (−)-Illicinone A (2) and (+)-Cycloillicinone (1)



one-pot reaction gave (±)-cycloillicinone (**1**) in 30−43% yield, depending on the scale (up to gram scale), which is in line with the yields achieved by Rahman and co-workers over two-steps.[6]

Our attention then turned to developing the first enantioselective *para*-Claisen rearrangement, for which we decided to focus on chiral aluminum Lewis acids. This decision was driven by the fact MABR works well in the non-enantioselective *para*-Claisen rearrangement of illicinole (**3**) and Yamamoto and co-workers have shown that chiral aluminum Lewis acids can mediate enantioselective aliphatic-Claisen rearrangements with substrates where two-point coordination is not involved.[14] An initial screen of various chiral ligands, including quinine, TADDOL, and salen-type ligands, identified (*R*)-BINOL as a preliminary hit, giving illicinone A (**2**) in an er of 46:54 (Table 1, entry 1). From this very modest result, an extensive investigation into ligand structure was conducted (30 ligands screened; see the Supporting Information for full details). Most of the BINOL-type ligands that we screened did not provide any significant

Table 1. Screen of 3,3′-Substituted BINOL Ligands for the Enantioselective *para*-Claisen Rearrangement of Illicinole (3)



entry	R	temperature	er of **2**
1	H	rt	46:54
2	Me	rt	45:55
3	Ph	rt	40:60
4	$SiPh_3$	rt	57:43
5	2,6-dimethylphenyl	rt	40:60
6	1-naphthyl	rt	40:60
7	9-anthracenyl	rt	30:70
8	9-anthracenyl	−40 °C	26:74
9	9-anthracenyl	−60 °C	nr
10	neopentyl	rt	76:24
11	neopentyl	−40 °C	87:13
12	neopentyl	−60 °C	nr
13	methylene-1-adamantyl	−20 °C	84:16
14	methylene-1-adamantyl	−40 °C	nr

improvement (e.g., Table 1, entries 2−6). It was not until we tried 3,3′-9-anthracenyl substituted BINOL that we observed our first promising increase in er to 30:70 (Table 1, entry 7).[15] When this reaction was conducted at −40 °C, we observed a slight improvement in the er to 26:74 (Table 1, entry 8), but the reaction failed to proceed at lower temperatures (Table 1, entry 9). We postulated that if a Dewar-type mechanism was operating (Scheme 3b, Pathway 2), maximizing the distance over which the chiral environment might extend from the aluminum center should be beneficial to enantioselectivity. Thus, we investigated 3,3′-neopentyl substituted BINOL,[16] which gave (−)-illicinone A (**2**) in an er of 76:24 at room temperature (Table 1, entry 10) and 87:13 at −40 °C (Table 1, entry 11), with no reaction occurring at −60 °C (Table 1, entry 12). The 3,3′-methylene-1-adamantyl substituted BINOL gave a promising er of 84:16 at −20 °C (Table 1, entry 13), but attempts to improve this by lowering the temperature failed (Table 1, entry 14). We took our best performing ligand (Table 1, entry 11) and further optimized the reaction by screening Lewis acid loading, solvent, and reaction time (see the Supporting Information for full details). Our best result was achieved when using 3 equiv of chiral Lewis acid **5** in CH_2Cl_2 at −40 °C for 1 h,[16] which resulted in a 35% isolated yield of (−)-illicinone A (**2**) in an er of 87:13 (Scheme 4).[17,18] The diminished yield in this enantioselective reaction, compared to the MABR-mediated reaction, is attributable to the formation of an unexpected side product (+)-**6** in 23% yield (er 93:7) and recovery of 34% unreacted illicinole (**3**).[19,20] Fortuitously, compound (+)-**6** is a known natural product isolated from various *Illicium* species,[21] which has previously only been synthesized in racemic form.[22]

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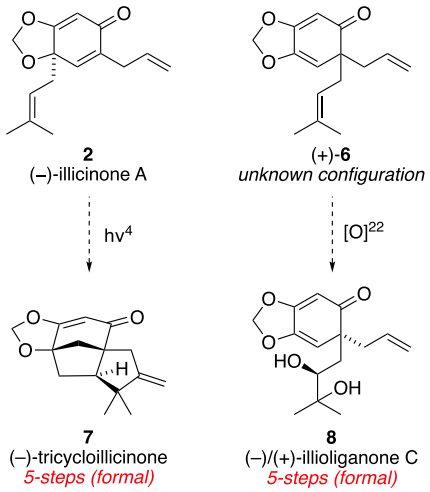
Org. Lett. 2021, 23, 3248−3252

The formation of (+)-**6** can fit with a Dewar-type mechanism (Scheme 3b, pathway 2), with the higher enantioselectivity compared to the formation of (−)-illicinone A (**2**) (er 93:7 vs 87:13), perhaps a result of the C−C bond formation occurring closer to the chiral Lewis acid. However, a concerted [1,3]-sigmatropic rearrangement [$_{\pi}2_{s}+_{\sigma}2_{a}$] mechanism could also be proposed.[23] More detailed studies will be required to probe the mechanism of this reaction further.

A Diels−Alder reaction between (−)-illicinone A (**2**, er 87:13) and (*E*)/(*Z*)-*β*-ocimene gave (+)-cycloillicinone (**1**) in 34% yield (Scheme 4).[24] Analysis of the product by chiral-HPLC confirmed the expected retention of enantiopurity during this reaction (er 86:14). The specific rotation of our synthetic (+)-cycloillicinone (**1**, er 86:14) was much larger than that reported for the natural products (Scheme 4).[1,2] Therefore, it is likely that natural (+)-cycloillicinone[1] and (−)-illicarborene A[2] are isolated in a nonenantiopure form. Although confirmation of this proposal will require interrogation of authentic samples of the natural products,[25] it is interesting to note that Terashima and Furuya have provided evidence that (−)-tricycloillicinone (**7**), a biosynthetically related natural product,[26] is isolated from *Illicium tashiroi* in an er of ∼60:40.[27]

In summary, we have achieved the first enantioselective total syntheses of (−)-illicinone A (**2**) (4 steps, 23% yield, er 87:13), (+)-**6** (4 steps, 15% yield, er 93:7), and (+)-cycloillicinone (**1**) (5 steps, 8% yield, er 86:14). Our synthetic access to enantioenriched samples of (−)-illicinone A (**2**) and (+)-**6** also constitutes formal enantioselective syntheses of (−)-tricycloillicinone (**7**) (5 steps cf. Terashima's previous 12-step enantioselective synthesis)[27] and illioliganone C (**8**) (5 steps),[22] respectively (Scheme 5). Development of the first enantioselective *para*-Claisen rearrangement to access (−)-illicinone A (**2**) is certainly noteworthy, and efforts are now underway in our laboratory to probe the mechanism of this process and to develop more broadly useful methodology.

Scheme 5. Formal Enantioselective Syntheses of (−)-Tricycloillicinone (7) and (−)/(+)-Illioliganone C (8)



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00620.

Experimental procedures and analytical data for all compounds (PDF)

FAIR data, including the primary NMR FID files, for compounds **1**, **2**, **3**, **6**, **S1**, **S3**, and **S4** (ZIP)

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Notes

The authors declare no competing financial interest.

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