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Stereoselective [2+2]-Cycloadditions of chiral allenic ketones and alkenes: Applications towards the synthesis of benzocyclobutenes and endiandric acids

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ABSTRACT

Cyclobutanes are important motifs that have found utility in many contexts. Prior work has demonstrated an enantioselective isomerization/stereoselective [2 + 2] as a means to access bicyclo [4.2.0] octanes. Herein, the utility of this method is demonstrated towards the synthesis of benzocyclobutenes and a key intermediate towards the endiandric acids.

1. Introduction

The synthesis of cyclobutanes has attracted the attention of synthetic chemists because they are versatile intermediates for diversification, found in numerous natural products, and are useful synthons in medicinal chemistry [1]. As such, many strategies have been developed that target the synthesis of cyclobutanes [1]. Of the known methods, [2 + 2] cycloaddition has emerged as an effective process because it enables the convergent assembly of the cyclobutanes from simple alkene precursors [2]. Many elegant strategies such as photochemical processes, reactions of polarized π-components, and reactions involving ketenes have been reported. While the translation of these approaches to enantioselective synthesis has also been achieved in many situations, substantial gaps remain in our ability to assemble cyclobutanes with control of enantioselectivity [2].

Our lab has taken an interest in [2 + 2] cycloadditions of alkenes with electron deficient allenes [3]. Our interest with these cycloadditions stems from the fact that unactivated alkenes are competent substrates. This stands in contrast to most other methods for intermolecular [2 + 2] cycloaddition. This is due to the likely concerted, yet asynchronous mechanism of these reactions such that carbocation, carbanion, or radical intermediates do not need to be supported. Along these lines, we have reported the development of a catalytic and enantioselective cycloaddition of allenoates with unactivated alkenes [3]. In connection with these efforts, we investigated related cycloadditions of allenic ketones (**5**). We identified a process in which a chiral allene could be generated with control of enantioselectivity by an isomerization with thiourea catalyst **4** [4]. The subsequent diastereoselective cycloaddition [5] with a tethered alkene upon treatment with $Bi(OTf)_3$ (via concerted asynchronous transition state (**6**)) generates bicyclo [4.2.0]octanes **7** [6]. The scope of this method was evaluated, and the application towards the synthesis of *ent*-[3]-ladderanol (**8**) was demonstrated. In a more recent study, this method was utilized in the synthesis of (−)-cajanusine (**9**) [7] and (+)-hippolide J (**10**) [8]. The broad scope of this reaction was enabled by the straightforward synthesis of the alkyne precursors to the allene from lithium acetylides (**1**) and epoxy alkenes (**2**) [6].

In this manuscript, we further establish the generality of this approach towards the synthesis of disparate bicyclo [4.2.0]octane scaffolds (Scheme 1B). In particular, we showcase: 1) an unconventional enantioselective synthesis of benzocyclobutenes (**11**) and, 2) an attempted enantioselective synthesis of a key

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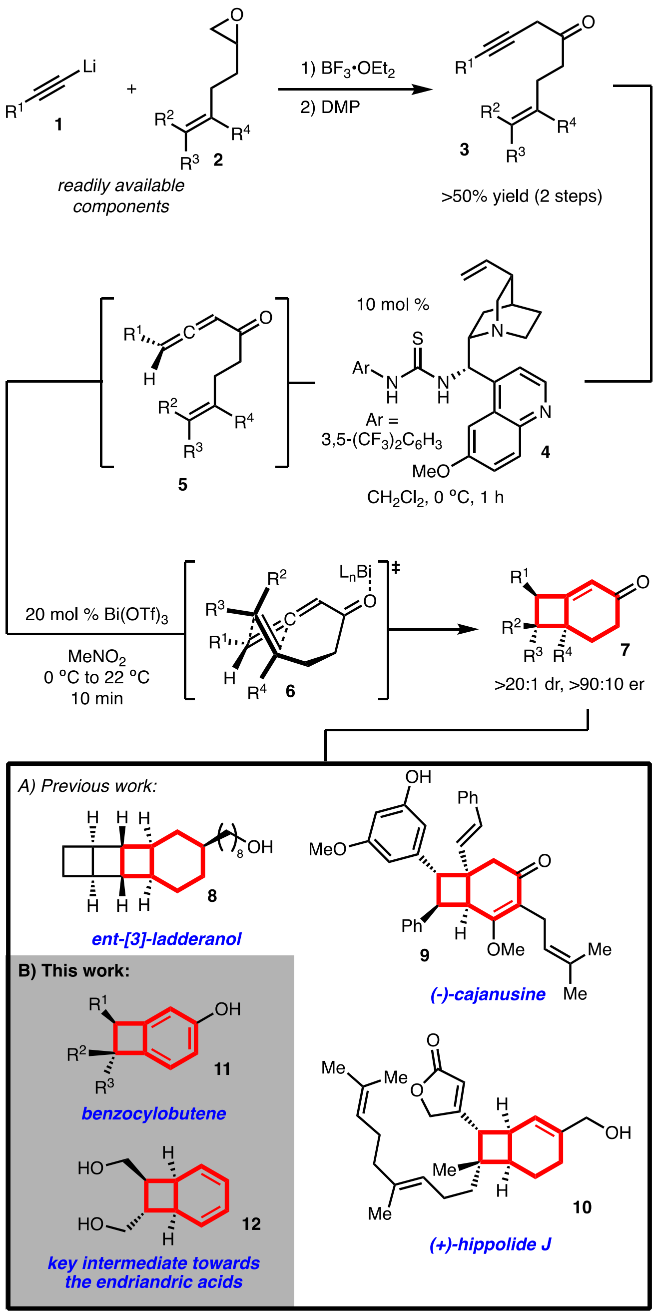


Scheme 1. Stereoselective Allenic Ketone-Alkene [2 + 2] Cycloaddition.

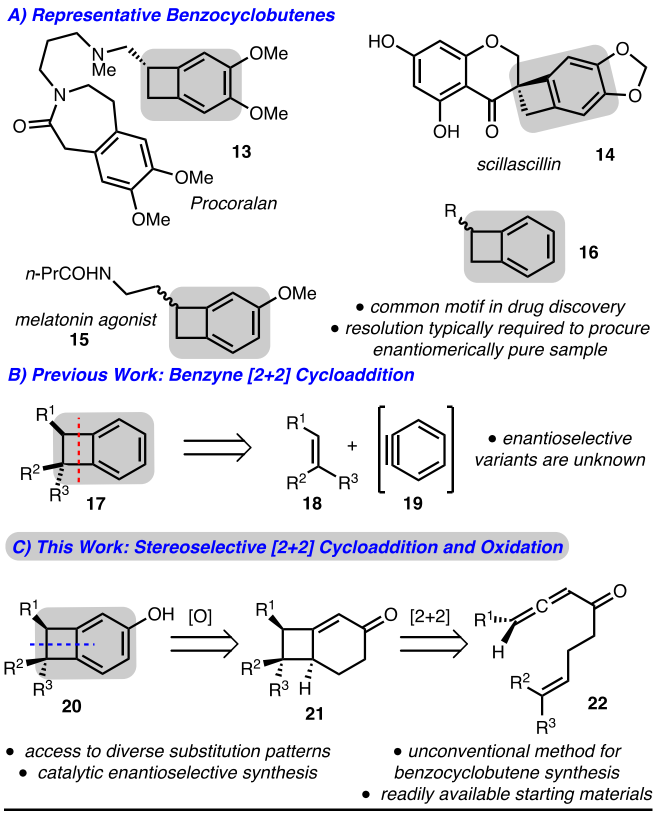
intermediate towards the endiandric acid natural products (**12**).

2. Results and discussion

Enantioselective Synthesis of Benzocyclobutenes: The benzocyclobutene [9] motif has emerged as a valuable scaffold in chemistry since its discovery in 1909 from the doctoral work of Finkelstein [10]. For the next 46 years, benzocyclobutene research remained inactive until Cava and coworkers confirmed the earlier reports of Finkelstein and synthesized scillascillin (**14**), a naturally occurring benzocyclobutene [11]. Since the early discoveries, benzocyclobutenes have frequently appeared in the literature due to their versatile applications [12]. For example, benzocyclobutenes are prevalent in biologically active molecules (e.g., **13** and **15**, Scheme 2A) [13], and the conformational rigidity of benzocyclobutene derivatives makes them interesting candidates for biological evaluation [12c,d]. Furthermore, the parent mono-substituted benzocyclobutene **16** has become a prevalent scaffold in drug discovery [14]. Consequently, these characteristics make benzocyclobutenes attractive targets for chemical synthesis. A key component in a number of these biologically active benzocyclobutene derivatives is a substituted cyclobutane unit. Therefore, methods to access a diverse range of chiral substituted benzocyclobutene derivatives, preferably with control of enantioselectivity, would be valuable.

Despite their manifestation as versatile entities, general methods to access a variety of enantiomerically enriched, substituted benzocyclobutene derivatives are limited. Current approaches, for example, require enantioselective modification of prochiral benzocyclobutene derivatives or, more commonly, resolution of racemic starting materials [15,16]. More recent strategies include the C—H activation of substituted aryl bromides from Baudoin and coworkers [17], the zirconium-mediated cross-coupling of aryllithium compounds with alkenyl bromides from Barluenga and coworkers [18], and a cross coupling approach from Procter [19]. However, the translation to enantioselective synthesis has yet to be established for these processes.

Perhaps one of the most common strategies to access the benzocyclobutene core is through a [2 + 2] cycloaddition of benzyne intermediates (**19**) and alkenes (**18**) (Scheme 2B) [20].Although it is convergent and permits access to a variety of benzocyclobutene derivatives (**17**), this method lacks an enantioselective variant, which is largely due to the difficulty of controlling the reactive benzyne intermediates. The alternative [2 + 2] cycloaddition, which would originate from the disconnection of the benzocyclobutene as outlined in Scheme 1C, has yet to be explored. Therefore,



Scheme 2. Utility and Synthesis of Benzocyclobutenes.

we have taken interest in this unconventional approach with cyclohexenones (**21**) as suitable precursors.

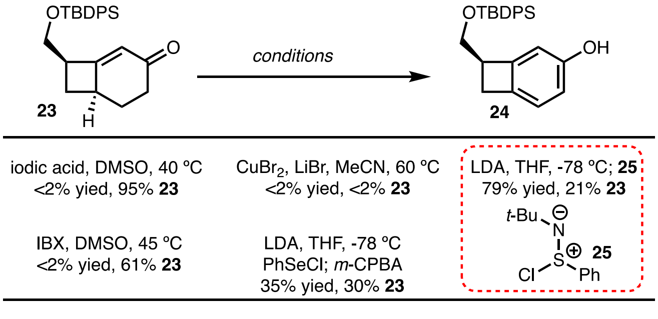
To affect the conversion of cyclohexenone **21** to benzocyclobutene **20**, an oxidation is required. Despite the conversion of cyclohexenones to phenol being a well-established process [21], the extension of these methods to the formation of benzocyclobutenes is not known. After surveying a variety of strategies for the synthesis of benzocyclobutenes (Scheme 3), we ultimately found success with treatment of the cycloadducts with LDA followed by addition of *N*-*tert*-butylbenzenesulfinimidoyl chloride **25**. Originally discovered by Mukaiyama and coworkers, this reagent (**25**) has been shown to convert carbonyl compounds to their corresponding α,β-unsaturated products [22].

As shown in Scheme 4, this process was compatible with a variety of substrates (products **26**–**31**) to provide substituted benzocyclobutene derivatives (Scheme 4). A highlight of the method is that it provides access to highly substituted benzocyclobutenes as demonstrated with synthesis of **27**, **29**, **30**, and **31**.

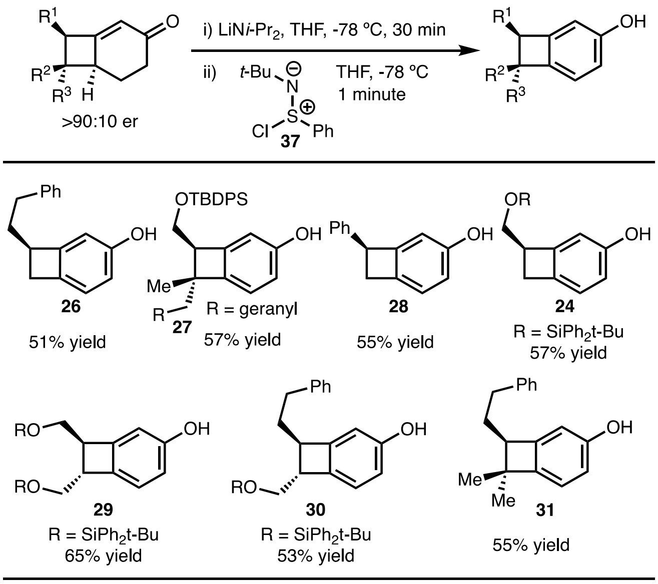
To further demonstrate the utility of the strategy, gram-scale synthesis of **24** was achieved (Scheme 5). Additionally, the presence of the phenol permitted access to cross coupling precursor **32** or carbamate **35** to obtain elaborated benzocyclobutenes **34** and **36**, respectively.

Attempted Enantioselective Synthesis of a Key Intermediate Towards the Endiandric Acids: The endiandric acid family of natural products is an intriguing class not only because of their caged molecular architectures, but also because of their proposed biogenesis [23]. Particularly, Black proposed a provocative biosynthesis in 1979 that involved a series of pericyclic reactions [24]. A year later, Nicolaou reported a landmark synthesis of endiandric acids A-D, which validated this biosynthetic proposal [25] (Scheme 6). The sequence followed an 8-π-electrocyclization followed by a 6-π-electrocyclization of tetraene **37** to arrive at diene **11**. This intermediate could then be advanced to various endiandric acids (e.g., **38**) by use of a Diels-Alder cycloaddition to assemble the tetracycle. At the time we initiated our studies, only one other synthesis of these molecules was reported by Serburn in 2014 and utilized a similar pericyclic cascade sequence [26]. However, more recently Fallon has also described synthesis [27,28]. Despite the fact that these molecules are isolated as racemates, by virtue of their non-enzymatic, spontaneous pericyclic reaction cascade, we envisioned that enantioselective entry would be an interesting challenge to test our method.

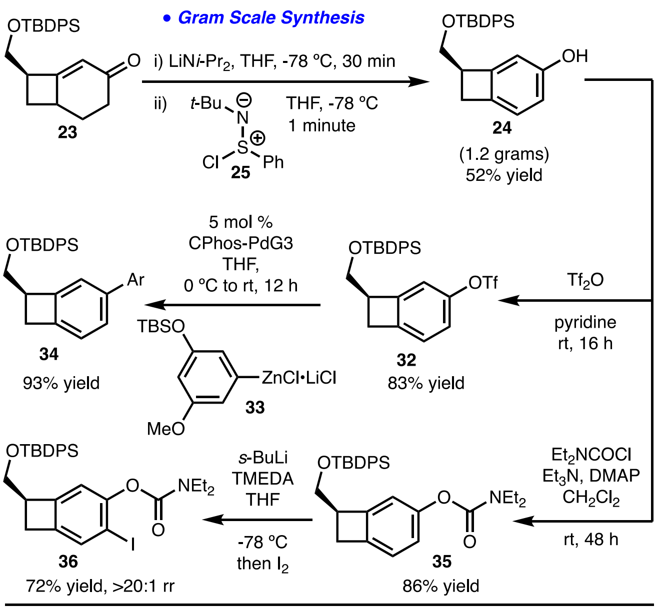
The strategy explored for synthesis of key intermediate **11** involves the conversion of the bridgehead C1−C2-unsaturated carbonyl (**39**) into C4−C5-alkene **40**. It was envisioned that enone **40** could be converted to diene **11** by common approaches. Synthesis of the key intermediate commenced with preparation of β,γ-unsaturated alkynyl ketone **41** from 1,5-hexadiene oxide in four steps (Scheme 7). Stereoselective [2 + 2]-cycloaddition proceeded to generate **42** in good yield, diastereoselectivity and enantioselectivity. Conjugate reduction with Stryker's reagent provided access to **43**. However, enolization of ketone **43** (an important step towards installation of the C4–C5 alkene) resulted in formation of



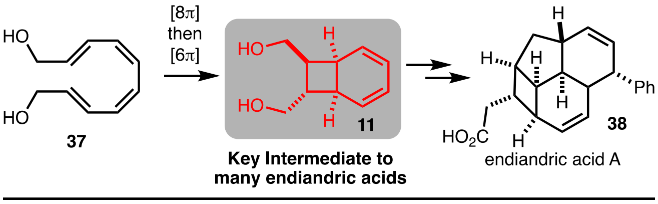
Scheme 3. Synthesis of Benzocyclobutenes.



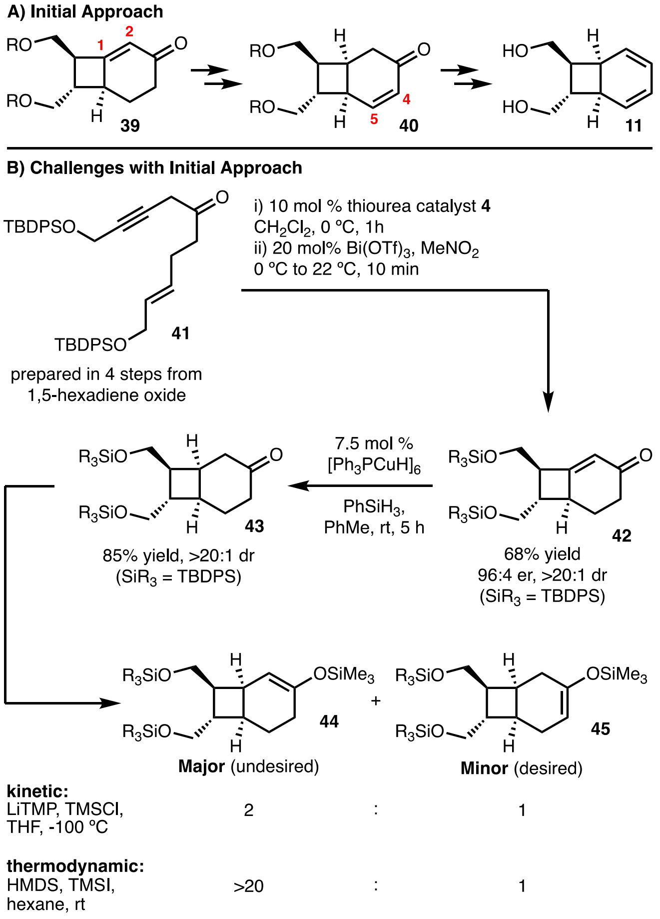
Scheme 4. Oxidation to Benzocyclobutene.



Scheme 5. Gram Scale Synthesis and Further Transformations.



Scheme 6. Nicolaou's Synthesis of Endiandric Acid A (**39**).



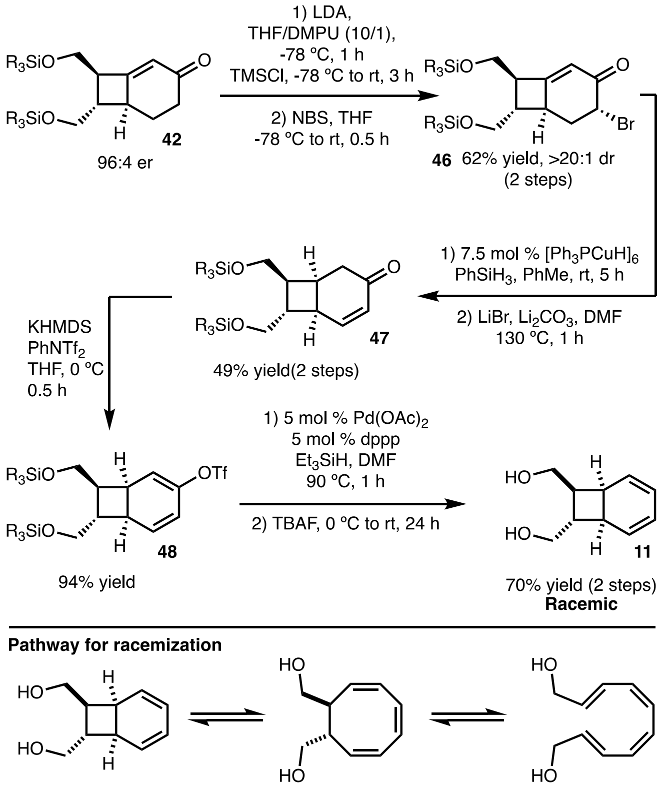
Scheme 7. Initial Efforts Towards Synthesis of Diol **11**.

the undesired enolsilane **44** as the major product. Interestingly, both conditions that would favor kinetic and thermodynamic control led to formation of **44** in preference to **45**. Therefore, an alternative approach was explored in which suitable functionality could be installed at C4 that would enable downstream alkene synthesis.

To allow for later stage alkene synthesis, a bromide was installed at C4 to provide **46** by formation of the enolsilane from **42** and treatment with NBS. Conjugate reduction with Stryker's reagent led to the desired enone, which upon treatment of LiBr and Li_2CO_3, prompted an elimination to generate **47** [29]. Finally, formation of enol triflate **48** and Pd-catalyzed reduction [30] led to synthesis of key intermediate **11** after deprotection [25a]. After the completion of our route, Fallon and coworkers published a study which described the synthesis of several endiandric acids starting from cyclooctatetraene [27]. In addition, computational studies were included that suggested bicyclo [4.2.0]octadienes undergoe facile electrocyclization and would result in racemization of the intermediates. As such, the measured enantiomeric ratio of **11** was found to be 50:50, indicating that the electrocyclic process is rapid [31]. While this does negate an enantioselective synthesis of key intermediate **11**, the studies outlined in Schemes 7 and 8 do demonstrate useful strategies for manipulation of the cycloadducts (e.g., **42**).

3. Summary

Through the development of an enantioselective isomerization/stereoselective [2 + 2]-cycloaddition, the synthesis of disparate bicyclo [4.2.0]octanes was achieved. The core scaffold could be readily functionalized in various ways to arrive at benzocyclobutenes and an intermediate towards the synthesis of the endiandric acids.



Scheme 8. Attempted Enantioselective Synthesis of **11**.

4. Experimental section

^1H NMR and ^{13}C NMR spectra were recorded at room temperature using a Varian I400 (^1H NMR at 400 MHz, ^{13}C NMR at 100 MHz, ^{19}F at 375 MHz), Varian VXR400 (^1H NMR at 400 MHz, ^{13}C NMR at 100 MHz), Varian I500 (^1H NMR at 500 MHz and ^{13}C NMR at 125 MHz) and Varian I600 (^1H NMR at 600 MHz and ^{13}C NMR at 150 MHz). Chemical shifts are reported in ppm from tetramethylsilane with the respective solvent resonance as the internal standard (^1H NMR $CHCl_3$: δ 7.26 ppm ^{13}C NMR $CDCl_3$: δ 77.2 ppm). Data is reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, br = broad, m = multiplet), coupling constants (Hz) and integration. Infrared spectra (IR) were obtained on a Bruker Tensor II FTIR Spectrometer (ATR sampling technique) and recorded in wavenumbers (cm^{-1}). Bands are characterized as broad (br), strong (s), medium (m), and weak (w). Melting points were obtained on a Thomas Hoover capillary melting point apparatus without correction. High Resolution Mass Spectrometry (HRMS) analysis was obtained using Electron Impact Ionization (EI), Chemical Ionization (CI) or Electrospray Ionization (ESI) and reported as *m/z* (relative intensity). GC-MS data was acquired using an Agilent 6890 N Gas Chromatograph and 5973 Inert Mass Selective Detector. ESI was acquired using a Waters/Micromass LCT Classic (ESI-TOF). Optical rotations were measured on a PerkinElmer 241 polarimeter at 589 nm wavelength (sodium D-line) using a standard 10 cm cell (1 mL). Specific rotations, $[\alpha]_D^{20}$, are reported in degree mL/(g•dm) at the specific temperature. Concentrations (c) are given in grams per 100 mL of the specific solvent. Unless otherwise noted, all reactions have been carried out with distilled and degassed solvents under an atmosphere of dry N_2 in oven- (135 °C) and flame-dried glassware with standard vacuum-line techniques. Dichloromethane, diethyl ether and tetrahydrofuran were purified under a positive pressure of dry argon by passage through two columns of activated alumina. Toluene was purified under a positive pressure of dry argon by passage through columns of activated alumina and Q5 (Grubbs apparatus). All work-up and purification procedures were carried out with reagent grade solvents (purchased from Sigma-Aldrich) in air. Standard column chromatography techniques using ZEOprep 60/40–63 μm silica gel were used for purification.

4.1. Benzocyclobutene synthesis

4.1.1. N-tert-butylbenzenesulfinimidoyl chloride [25]

A 250 mL round bottom flask equipped with a stir bar was charged with household bleach (100 mL). The flask was then capped with a septum, wrapped with aluminum foil and placed into an ice/water bath. To the stirring solution was added acetic acid (12.6 mL, 220 mmol, 2.2 eq.) and *tert*-butylamine (10.5 mL, 100 mmol, 1.00 eq.) sequentially at 0 °C. The reaction was stirred at the same temperature for 5 min and diluted with DCM (50 mL). The aqueous layer was extracted with DCM (2 × 50 mL). The combined organic layers were washed with H_2O (100 mL), saturated $NaHCO_3$ solution (100 mL), brine (100 mL) sequentially, dried over anhydrous MgSO4, filtered and concentrated by rotary evaporation (in ice/water bath). The crude *N,N*-dichloro-2-methylpropan-2-amine (~40–60% yield) was directly used in next reaction without further purification.

A 50 mL flame-dried round bottom flask equipped with a stir bar was cooled under vacuum. After evacuated/backfilled with N_2 (x 3) the flask was capped with a septum. The above crude *N*,*N*-dichloro-2-methylpropan-2-amine (1.7 g, assuming 12 mmol, 1.2 eq.) and PhH (10 mL) was then added. Then *S*-phenyl thioacetate (1.3 mL, 10 mmol, 1.0 eq.) was added at room temperature. The septum was quickly replaced with a stopper and the reaction was heated to 80 °C in an oil bath for 1 h (TLC indicated the complete consumption of thioacetate). After allowed to cool room temperature, the solution was directly concentrated by rotary evaporation. The residue was further azeotroped with PhH (2 × 10 mL) by rotary evaporation. Then THF (~8 mL) was added to the flask to make a [1 M] solution of **25**, which was directly used into next reaction without further purification.

4.1.2. General procedure for benzocyclobutene synthesis from bicyclo [4.2.0]oct-1-en-3-one

Freshly made LDA solution: A flame-dried 10 mL round bottom flask equipped with a stir bar was cooled under vacuum. and backfilled with N_2 (x 3). After being evacuated/backfilled with N_2 (x 3) and capped with a septum, diisopropylamine (0.420 mL 3 mmol, 1.05 eq.) and THF (2.83 mL) were added. To the stirring solution was added *n*-butyllithium (2.4 6 M in hexanes, 1.22 mL, 3.00 mmol, 1.00 eq.) slowly (~5 min) at 0 °C (ice/water bath) and allowed to stir for 0.5 h. The resulting LDA solution (0.7–0.9 M) was titrated according to Ireland's procedure [32].

Mukaiyama oxidation: A flame dried 13 × 100 mm screw-capped vial equipped with a stir bar was allowed to cool under vacuum. After being evacuated/backfilled with N_2 (x 3) and capped with a septum, cycloadduct (0.3 mmol, 1 eq.) and THF (0.3 mL) was added and the resulting solution was cooled and stirred at −78 °C in a dry ice/acetone bath. Then, LDA (0.74 M, 0.85 mL 0.63 mmol, 2.1 eq.) was added. At this point, the solution turned orange and the resulting reaction was allowed to stir for 30 min at the same temperature. Then, the solution of **25** in THF (1.0 M, 0.45 mL, 0.45 mmol, 1.5 eq.) was quickly added via syringe and stirred vigorously for 1 min at −78 °C. The reaction was quenched with saturated NH_4Cl solution (1.5 mL). After allowing to warm to room temperature, the aqueous layer was extracted with Et_2O (1 mL x 3). The combined organic layers were washed with brine (3 mL) dried over $MgSO_4$, filtered and concentrated by rotary evaporation. The residue was purified by flash column chromatography (FCC) to afford phenol product.

4.1.3. (R)-8-(((tert-butyldiphenylsilyl)oxy)methyl)bicyclo-[4.2.0] octa-1,3,5-trien-3-ol [24]

According to general procedure, phenol **24** (59.5 mg, 51% yield) was prepared from (6*S*,8*R*)-8-(((*tert*-butyldiphenylsilyl)oxy) methyl)bicyclo [4.2.0]oct-1-en-3-one (94:6 er) and purified by FCC (Hex: Et_2O = 19 : 1 to 9 : 1) as yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.72–7.57 (m, 4H), 7.49–7.31 (m, 6H), 6.91 (dd, *J* = 7.9, 0.9 Hz, 1H), 6.68 (ddd, *J* = 7.8, 2.3, 0.7 Hz, 1H), 6.63 (m, 1H), 3.88 (d, *J* = 7.1 Hz, 2H), 3.71–3.55 (m, 1H), 3.15 (ddd, *J* = 13.6, 5.0, 0.7 Hz, 1H), 2.74 (ddd, *J* = 13.7, 2.7, 0.7 Hz, 1H), 1.06 (s, 9H); **^{13}C NMR (100 MHz, $CDCl_3$):** δ 155.1, 148.2, 135.8, 135.7, 134.0, 133.9, 129.7, 129.7, 127.9, 127.8, 124.0, 114.8, 110.3, 66.7, 44.5, 32.1, 27.0, 19.4; **IR**: 3272 (br), 2930 (s), 2857 (s), 1600 (s), 1474 (s), 1205 (m), 1151 (s), 1112 (s). **HRMS** (**ESI**): Calculated for $C_{25}H_{29}O_2Si$ $[M+H]^+$: 389.1931. Found: 389.1928; **Optical Rotation:** $[\alpha]_D^{20}$: 13.6 (*c* = 1.00, CH_2Cl_2) for an enantiomerically enriched sample of 94:6 er.

4.1.4. (R)-8-Phenethylbicyclo [4.2.0]octa-1,3,5-trien-3-ol [26]

According to general procedure, phenol **26** (34.3 mg, 51% yield) was prepared from (6*S*,8*R*)-8-phenethylbicyclo [4.2.0]oct-1-en-3-one (91:9 er) and purified by FCC (Hex: Et_2O = 19 : 1 to 9 : 1) as yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.36–7.26 (m, 2H), 7.25–7.16 (m, 3H), 6.93 (d, *J* = 7.9 Hz, 1H), 6.67 (dd, *J* = 7.9, 2.2 Hz, 1H), 6.60 (d, *J* = 2.3 Hz, 1H), 4.65 (s, 1H), 3.47–3.36 (m, 1H), 3.23 (dd, *J* = 13.6, 5.2 Hz, 1H), 2.87–2.71 (m, 2H), 2.67 (dd, *J* = 13.6, 2.5 Hz, 1H), 2.02 (m, 2H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 154.9, 150.6, 142.3, 135.3, 128.6, 128.5, 125.9, 124.2, 114.5, 109.8, 42.3, 36.2, 35.1, 34.7. **IR:** 3350 (br), 3025 (m), 2919 (s), 1595 (s), 1494 (s), 1471 (s), 1453 (s), 1165 (s). **HRMS (CI):** Calculated for $C_{16}H_{16}O$ $[M]^+$: 224.1196. Found: 224.1203. **Optical Rotation:** $[\alpha]_D^{20}$: 13.5 (c = 1.00, CH_2Cl_2) for an enantiomerically enriched sample of 91:9 er.

4.1.5. (7R,8R)-8-(((tert-butyldiphenylsilyl)oxy)methyl)-7-((E)-4,8-dimethylnona-3,7-dien-1-yl)-7-methylbicyclo [4.2.0]octa-1,3,5-trien-3-ol [27]

According to general procedure, phenol **27** (63.2 mg, 57%) was prepared from (6*S*,7*S*,8*R*)-8-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-7-((*E*)-4,8-dimethylnona-3,7-dien-1-yl)-7-methylbicyclo [4.2.0] oct-1-en-3-one (99:1 er) and purified by FCC (Hex: EtOAc = 19 : 1 to 9 : 1) as yellow oil. **^{1}H NMR (600 MHz, $CDCl_3$)**: δ 7.70 (d, *J* = 7.0 Hz, 4H), 7.45–7.36 (m, 6H), 6.91 (d, *J* = 7.8 Hz, 1H), 6.63 (d, *J* = 7.7 Hz, 1H), 6.57 (s, 1H), 5.14 (t, *J* = 6.5 Hz, 2H), 5.09 (t, *J* = 5.6 Hz, 2H), 4.51 (s, 1H), 3.93 (dd, *J* = 10.0, 7.1 Hz, 1H), 3.87 (t, *J* = 9.5 Hz, 1H), 3.34 (t, *J* = 7.6 Hz, 1H), 2.12–2.05 (m, 4H), 1.98–1.96 (m, 2H), 1.71–1.68 (m, 5H), 1.60 (s, 3H), 1.59 (s, 3H), 1.31 (s, 3H), 1.08 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$):** δ 155.1, 145.3, 144.3, 135.8, 135.8, 135.0, 133.9, 131.4, 129.8, 129.7, 127.8, 127.8, 124.7, 124.5, 121.9, 114.6, 110.8, 63.8, 54.1, 49.8, 41.8, 39.9, 27.0, 26.9, 25.9, 24.7, 19.4, 19.4, 17.8, 16.1. **IR:** 3353 (br), 3025 (m), 2960 (s), 1591 (m), 1471 (m), 1112 (s). **HRMS (CI):** Calculated for $C_{37}H_{48}O_2SiNa$ $[M+Na]^+$: 575.3316. Found: 575.3314. **Optical Rotation:** $[\alpha]_D^{20}$: +5.5 (c = 1.00, CH_2Cl_2) for an enantiomerically enriched sample of 99:1 er.

4.1.6. (S)-8-Phenylbicyclo [4.2.0]octa-1,3,5-trien-3-ol [28]

According to general procedure, phenol **28** (32.3 mg, 55% yield) was prepared from (6*S*,8*S*)-8-phenylbicyclo [4.2.0]oct-1-en-3-one (96:4 er) and purified by FCC (Hex: Et_2O = 19 : 1 to 9 : 1) as yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.39–7.13 (m, 5H), 7.01 (d, J = 7.9 Hz, 1H), 6.74 (dd, J = 7.9, 2.2 Hz, 1H), 6.67 (d, J = 2.2 Hz, 1H), 4.61 (dd, J = 5.7, 2.6 Hz, 1H), 3.63 (dd, J = 13.5, 5.6 Hz, 1H), 2.98 (dd, J = 13.5, 2.6 Hz, 1H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 155.3, 148.6, 142.8, 135.7, 128.6, 127.0, 126.6, 124.5, 115.2, 110.4, 46.8, 39.1. **IR**: 3341 (br), 3024 (w), 2922 (m), 1595 (m), 1451 (s), 1165 (s), 697 (s). **HRMS** (**ESI**): Calculated for $C_{14}H_{13}O$ $[M+H]^+$: 197.0961. Found: 197.0953. **Optical Rotation:** $[\alpha]_D^{20}$: 169.1 (c = 1.00, CH_2Cl_2) for an enantiomerically enriched sample of 96:4 er;

4.1.7. (7R,8R)-7,8-bis(((tert-Butyldiphenylsilyl)oxy)methyl)bicyclo[4.2.0]octa-1,3,5-trien-3-ol [29]

According to general procedure, phenol **29** (84 mg, 65%) was prepared from (6*S*,7*S*,8*R*)-7,8-bis(((*tert*-butyldiphenylsilyl)oxy)methyl)bicyclo [4.2.0]oct-1-en-3-one (96:4 er) and purified by FCC (Hex: EtOAc = 19 : 1 to 9 : 1) as yellow oil. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.66–7.63 (m, 8H), 7.42–7.34 (m, 12H), 6.98 (d, J = 7.8 Hz, 1H), 6.67 (d, J = 7.8 Hz, 1H), 6.64 (s, 1H), 4.58 (s, 1H), 3.97 (dd, J = 9.4, 7.0 Hz, 1H), 3.97–3.87 (m, 3H), 3.35 (dt, J = 16.9, 6.7 Hz, 2H), 1.03 (s, 9H), 1.02 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$):** δ 155.4, 147.0, 137.5, 135.8, 135.7, 135.7, 134.0, 134.0, 133.9, 133.9, 129.7, 129.7, 129.7, 129.7, 127.8, 127.8, 127.8, 124.0, 114.7, 110.5, 66.0, 65.8, 48.3, 47.7, 27.0, 27.0, 19.4, 19.4. **IR**: 3382 (br), 3070 (w), 2929 (m), 1591 (m), 1471 (s), 1112 (s), 791 (s). **HRMS** (**ESI**): Calculated for $C_{42}H_{48}O_3Si_2Na$ $[M+Na]^+$: 679.3034. Found: 679.3034. **Optical Rotation:** $[\alpha]_D^{20}$: +3.5 (c = 1.00, CH_2Cl_2) for an enantiomerically enriched sample of 96:4 er.

4.1.8. (R)-7,7-dimethyl-8-phenethylbicyclo[4.2.0]octa-1,3,5-trien-3-ol [30]

According to general procedure, phenol **30** (41.6 mg, 55% yield) was prepared from (6*S*,7*R*,8*R*)-7-(((*tert*-butyldiphenylsilyl)oxy)methyl)-8-phenethylbicyclo [4.2.0]oct-1-en-3-one (96:4 er) and purified by FCC (Hex: Et_2O = 19 : 1 to 9 : 1) as yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$):** δ 7.38–7.12 (m, 5H), 6.95–6.85 (d, J = 7.9 Hz, 1H), 6.64 (dd, J = 7.9, 2.2 Hz, 1H), 6.58 (d, J = 2.2 Hz, 1H), 5.93 (s, 1H), 3.05 (dd, J = 9.8, 6.1 Hz, 1H), 2.90–2.67 (m, 4H), 1.39 (s, 3H), 1.25 (s, 3H). **^{13}C NMR (100 MHz, $CDCl_3$):** δ 155.1, 147.3, 145.5, 142.5, 128.6, 128.5, 126.0, 121.2, 114.4, 110.7.53.6, 46.2, 35.2, 32.2, 28.2, 22.5. **IR**: 3340 (br), 3062 (w), 3026 (m), 2948 (s), 2859 (s), 1594 (m), 1453 (s). **HRMS** (**CI**): Calculated for $C_{18}H_{21}O$ $[M+H]^+$: 253.1587. Found: 253.1587. **Optical Rotation:** $[\alpha]_D^{20}$: +27.7 (c = 1.00, CH_2Cl_2) for an enantiomerically enriched sample of 96:4 er;

4.1.9. (R)-7,7-dimethyl-8-phenethylbicyclo [4.2.0]octa-1,3,5-trien-3-ol [31]

According to general procedure, phenol **31** (41.6 mg, 55% yield) was prepared from (6*S*,8*R*)-7,7-dimethyl-8-phenethylbicyclo [4.2.0]oct-1-en-3-one (97:3 er) and purified by FCC (Hex: Et_2O = 19 : 1 to 9 : 1) as yellow oil. **^{1}H NMR (400 MHz, CDCl3):** δ 7.38–7.12 (m, 5H), 6.95–6.85 (d, J = 7.9 Hz, 1H), 6.64 (dd, J = 7.9, 2.2 Hz, 1H), 6.58 (d, J = 2.2 Hz, 1H), 5.93 (s, 1H), 3.05 (dd, J = 9.8, 6.1 Hz, 1H), 2.90–2.67 (m, 4H), 1.39 (s, 3H), 1.25 (s, 3H). **^{13}C NMR (100 MHz, CDCl3):** δ 155.1, 147.3, 145.5, 142.5, 128.6, 128.5, 126.0, 121.2, 114.4, 110.7.53.6, 46.2, 35.2, 32.2, 28.2, 22.5. **IR**: 3340 (br), 3062 (w), 3026 (m), 2948 (s), 2859 (s), 1594 (m), 1453 (s). **HRMS** (**CI**): Calculated for $C_{18}H_{21}O$ $[M+H]^+$: 253.1587. Found: 253.1587. **Optical Rotation:** $[\alpha]_D^{20}$: +27.7 (c = 1.00, CH_2Cl_2) for an enantiomerically enriched sample of 97:3 er;

4.1.10. Gram scale synthesis of 24

A flame dried 50 mL flask equipped with a stir bar was cooled under vacuum. After evacuated/backfilled with N_2 (x 3) and capped with a septum, diisopropylamine (1.85 mL, 13.2 mmol, 2.20 eq.) and THF (20 mL) was added. The stirring was cooled to 0 °C in an ice/water bath and *n*-BuLi (1.93 M in Hex, 6.50 mL, 12.6 mmol, 2.10 eq.) was added dropwise via syringe. After 30 min, the premade LDA solution was cooled to −78 °C in a dry ice/acetone bath and a solution of (6*S*,8*R*)-8-(((*tert*-butyldiphenylsilyl)oxy)methyl)bicyclo [4.2.0]oct-1-en-3-one (95:5 er) (2.34 g, 6.00 mmol, 1.00 eq.) in THF (20 mL) was slowly added via syringe (~5 min). At this point, the solution turned orange and the resulting reaction was allowed to stir for 1 h at the same temperature. Then, freshly made solution of **25** (1.0 M, 9.0 mL, 9.0 mmol, 1.5 eq.) was quickly added via syringe and stirred vigorously for 1 min at −78 °C. The reaction was quenched with saturated NH_4Cl solution (30 mL). After warmed back to room temperature, the aqueous layer was extracted with Et_2O (30 mL x 3). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated by rotary evaporation. The residue was purified by FCC (Hex: EtOAc = 19 : 1 to 9:1) to afford phenol **24** (1.2 g, 52% yield) as dark brown oil.

4.1.11. (R)-8-(((tert-Butyldiphenylsilyl)oxy)methyl)bicyclo[4.2.0]octa-1,3,5-trien-3-yl trifluoromethanesulfonate [32]

A flame dried 10 mL flask equipped with a stir bar was cooled under vacuum. After being evacuated/backfilled with N_2 (x 3) and capped with a septum, phenol **24** (97 mg, 0.25 mmol, 1.0 eq.) and pyridine (2.5 mL) was added. Then trifluoromethanesulfonic anhydride (50 mL, 0.30 mmol, 1.2 eq.) was added at room temperature and the reaction was stirred for 16 h at the same temperature. After that the mixture was diluted with EtOAc (10 mL). The resulting solution was washed with 1 M $CuSO_4$ solution (3 × 2 mL) and brine (5 mL) successively, dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by FCC (Hex: EtOAc = 50 : 1) to afford triflate **32** (108 mg, 83% yield) as colorless oil. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.69–7.66 (m, 4H), 7.52–7.32 (m, 6H), 7.15–7.12 (m, 2H), 7.06 (s, 1H), 4.01 (dd, J = 10.1, 7.1 Hz, 1H), 3.89 (dd, J = 10.1, 7.1 Hz, 1H), 3.73 (q, J = 6.1 Hz, 1H), 3.25 (dd, J = 14.3, 5.3 Hz, 1H), 2.93 (d, J = 14.3 Hz, 1H), 1.06 (s, 9H). **^{13}C NMR (126 MHz, $CDCl_3$):** δ 149.0, 148.9, 144.6, 135.8, 135.7, 133.7, 133.6, 129.9, 129.8, 127.9, 127.8, 124.8, 121.0, 118.9 (q, J = 320.8 Hz), 116.4, 77.4, 77.2, 76.9, 65.5, 44.7, 32.3, 26.9, 19.3. **IR**: 3071 (w), 2957 (m), 2859 (s), 1461 (m), 1424 (s), 1212 (s). **HRMS** (**CI**): Calculated for $C_{26}H_{28}O_4F_3SSi$ $[M+H]^+$: 521.1426. Found: 521.1424. **Optical Rotation:** $[\alpha]_D^{20}$: 10.7 (c = 1.00, CH_2Cl_2) for an enantiomerically enriched sample of 96:4 er.

4.1.12. (R)-tert-Butyl ((4-(3-((tert-butyldimethylsilyl)oxy)-5-methoxyphenyl)bicyclo [4.2.0]-octa-1,3,5-trien-7-yl)methoxy)diphenylsilane [34]

A flame-dried 4 mL vial equipped with a stir bar was cooled under vacuum. After backfilled with N_2 and capped with a septum, the flask was transferred into glovebox and charged with CPhos-Pd-G3 (2.0 mg, 0.0025 mmol, 0.050 eq.). The vial was capped with a septum and removed from the glovebox. A solution of triflate **32** (26 mg, 0.050 mmol, 1.0 eq.) in THF (0.8 mL) was then added. The vial was then placed into an ice/water bath and zinc reagent **33** (0.5 M, 0.2 mL, 0.1 mmol, 2 eq.)[7] was added dropwise via syringe. Then ice/water bath was removed, and the mixture was stirred at room temperature for 12 h. The reaction was quenched with saturated NH_4Cl solution (1 mL). The aqueous layer was extracted with Et_2O (3 × 1 mL). The combined organic layer was washed brine (2 mL), dried over anhydrous $MgSO_4$, filtered and concentrated by rotary evaporation. The residue was purified by FCC (Hex: PhMe = 4 : 1) to afford cross coupling product **34** (28 mg, 93% yield) as colorless oil. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.68–7.66 (m, 4H), 7.41–7.35 (m, 7H), 7.30 (s, 1H), 7.11 (d, J = 7.5 Hz, 1H), 6.68 (s, 1H), 6.63 (s, 1H), 6.37 (s, 1H), 3.94 (d, J = 7.0 Hz, 2H), 3.80 (s, 3H), 3.78–3.72 (m, 1H), 3.28 (dd, J = 14.2, 5.0 Hz, 2H), 2.88 (d, *J* = 14.3 Hz, 1H), 1.06 (s, 9H), 0.99 (s, 9H), 0.22 (s, 5H). **^{13}C NMR (126 MHz, CDCl$_3$):** *δ* 160.9, 157.0, 147.7, 144.5, 143.8, 135.8, 135.8, 134.0, 134.0, 129.8, 129.7, 127.8, 126.8, 123.2, 121.6, 112.0, 106.2, 105.0, 66.6, 55.5, 45.1, 32.9, 27.0, 25.9, 19.4, 18.4, −4.2. **IR**: 3071 (w), 2957 (m), 2859 (s), 1582 (s) 1461 (m), 1158 (s). **HRMS** (**CI**): Calculated for $C_{38}H_{49}O_3Si_2$ $[M+H]^+$: 609.3219. Found: 609.3215. **Optical Rotation:** $[\alpha]_D^{20}$: 37.8 (*c* = 1.00, CH_2Cl_2) for an enantiomerically enriched sample of 96:4 er.

4.1.13. (R)-8-(((tert-Butyldiphenylsilyl)oxy)methyl)bicyclo [4.2.0] octa-1,3,5-trien-3-yl diethylcarbamate ***[35]***

A flame dried 10 mL flask equipped with a stir bar was cooled under vacuum. After evacuated/backfilled with N_2 (x 3) and capped with a septum, phenol **24** (97 mg, 0.25 mmol, 1.0 eq.) and DCM (2.5 mL) was added. To the stirring solution was added Et_3N (70 mL, 0.50 mmol, 2.0 eq.), diethylcarbamoyl chloride (50.0 mL, 0.375 mmol, 1.50 eq.) and DMAP (3.0 mg, 0.025 mmol, 0.1 eq.) sequentially at room temperature and the mixture was stirred for 48 h at the same temperature. The reaction was quenched with saturated NH_4Cl solution (1 mL). The aqueous layer was extracted with DCM (3 × 1 mL). The combined organic layer was washed brine (2 mL), dried over anhydrous $MgSO_4$, filtered and concentrated by rotary evaporation. The residue was purified by FCC (Hex: EtOAc = 9 : 1) to afford carbamate **35** (104 mg, 86% yield) as pale yellow oil. **^{1}H NMR (500 MHz, CDCl$_3$)**: *δ* 7.72−7.54 (m, 4H), 7.47−7.33 (m, 6H), 7.02 (d, *J* = 7.9 Hz, 1H), 6.92 (d, *J* = 7.9 Hz, 1H), 6.86 (s, 1H), 3.94 (dd, *J* = 10.0, 7.0 Hz, 1H), 3.86 (dd, *J* = 9.9, 7.6 Hz, 1H), 3.66 (q, *J* = 5.0 Hz, 1H), 3.49−3.29 (m, 4H, br), 3.21 (dd, *J* = 14.0, 5.2 Hz, 1H), 2.81 (d, *J* = 14.0 Hz, 1H), 1.22 (dd, *J* = 11.1, 6.8 Hz, 6H, br), 1.06 (s, 9H). **^{13}C NMR (126 MHz, CDCl$_3$):** *δ* 154.8, 150.8, 147.3, 140.8, 135.8, 135.7, 134.0, 133.9, 129.7, 129.7, 127.8, 123.9, 121.4, 116.8, 66.6, 44.7, 42.3, 42.0, 32.7, 27.0, 19.4, 14.4, 13.6. **IR**: 3070 (w), 2960 (m), 2857 (s), 1718 (s), 1466 (m), 1155 (s). **HRMS** (**CI**): Calculated for $C_{30}H_{37}O_3NSi$ $[M+H]^+$: 488.2615. Found: 488.2619. **Optical Rotation:** $[\alpha]_D^{20}$: 15.6 (*c* = 1.00, CH_2Cl_2) for an enantiomerically enriched sample of 96:4 er.

4.1.14. (R)-8-(((tert-butyldiphenylsilyl)oxy)methyl)-4-iodobicyclo [4.2.0]octa-1,3,5-trien-3-yl diethylcarbamate ***[36]***

A flame-dried 4 mL vial equipped with a stir bar was cooled under vacuum. After evacuated/backfilled with N_2 (x 3) and capped with a septum, carbamate **35** (25 mg, 0.050 mmol, 1.0 eq.) and THF (0.5 mL) was added. The solution was cooled to −78 °C in a dry ice/acetone bath and *s*-BuLi (0.87 M, 0.12 mL, 0.10 mmol, 2.0 eq.) was added followed by TMEDA (15 mL, 0.10 mmol, 2.0 eq.). The reaction was stirred for 1 h at the same temperature and a solution of iodine (38 mg, 0.15 mmol, 3.0 eq.) in THF (0.5 mL) was added dropwise. The reaction was stirred for another 1 h at −78 °C and quenched with 4 : 1 saturated NH_4Cl and NaS_2O_3 solution (1 mL). The aqueous layer was extracted with Et_2O (3 × 1 mL). The combined organic layer was washed brine (2 mL), dried over anhydrous $MgSO_4$, filtered and concentrated by rotary evaporation. The residue was purified by FCC (Hex: EtOAc = 19 : 1) to afford iodide **36** (22 mg, 72% yield, >20:1 rr) as pale yellow oil. **^{1}H NMR (600 MHz, CDCl$_3$)** *δ* 7.67−7.64 (m, 4H), 7.43−7.35 (m, 6H), 6.97 (s, 2H), 4.24 (dd, *J* = 10.5, 3.9 Hz, 1H), 3.91 (dd, *J* = 10.4, 7.6 Hz, 1H), 3.61−3.54 (m, 1H), 3.50 (q, *J* = 6.1, 5.7 Hz, 2H), 3.39 (q, *J* = 6.0 Hz, 2H), 3.20 (dd, *J* = 13.9, 5.2 Hz, 1H), 2.93 (dd, *J* = 13.9, 2.0 Hz, 1H), 1.31 (t, *J* = 6.9 Hz, 3H), 1.21 (t, *J* = 6.9 Hz, 3H), 1.03 (s, 9H). **^{13}C NMR (126 MHz, CDCl$_3$)** *δ* 153.6, 151.6, 150.5, 142.6, 135.8, 135.8, 134.0, 133.9, 129.7, 129.7, 127.8, 123.4, 123.1, 84.3, 63.8, 46.4, 42.4, 42.1, 32.2, 27.0, 19.5, 14.5, 13.5. **IR**: 3070 (w), 2960 (m), 2857 (s), 1725 (s), 1415 (s), 1152 (s). **HRMS** (**CI**): Calculated for $C_{30}H_{37}O_3NISi$ $[M+H]^+$: 614.1582. Found: 614.1582. **Optical Rotation:** $[\alpha]_D^{20}$: 28.5 (*c* = 1.00, CH_2Cl_2) for an enantiomerically enriched sample of 96:4 er.

4.2. Formal synthesis of endiandric acids

4.2.1. (6S,7S,8R)-7,8-bis(((tert-Butyldiphenylsilyl)oxy)methyl) bicyclo [4.2.0]oct-1-en-3-one ***[42]***

A flame-dried round bottom flask equipped with a stir bar was cooled under vacuum. After evacuated/backfilled with N_2 (x 3) and capped with a septum, ketone **41** (1.97 g, 3.00 mmol, 1.00 eq.) was added followed by DCM (6 mL). To the stirring solution was added thiourea catalyst (178 mg, 0.300 mmol, 0.100 eq.) at 0 °C in an ice/water bath and the reaction was stirred for 1 h at the same temperature. Then the mixture was diluted with $MeNO_2$ (15 mL) and bismuth triflate (393 mg, 0.600 mmol, 0.200 eq.) was added also at 0 °C. After addition, the ice bath was immediately replaced with a room temperature water bath and the reaction was stirred vigorously for 10 min before it was quenched with saturated NH_4Cl solution (20 mL). The aqueous layer was extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine 30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated by rotary evaporation. The residue was purified by FCC (Hex: EtOAc = 9 : 1 to 4 : 1) to afford enone **42** (1.34 g, 68% yield, >20 : 1 dr) as a yellow oil. **^{1}H NMR (600 MHz, CDCl$_3$):** *δ* 7.65−7.61 (m, 8H), 7.46−7.32 (m, 12H), 5.83 (s, 1H) 3.82−3.70 (m, 4H), 3.33 (q, *J* = 5.9 Hz, 1H), 2.92 (dt, *J* = 11.3, 6.3 Hz, 1H), 2.43 (d, *J* = 16.7 Hz, 1H), 2.28 (td, *J* = 16.7, 15.7, 4.6 Hz, 1H), 2.16−2.06 (m, 2H), 1.77−1.69 (m, 1H), 1.06 (s, 9H), 1.02 (s, 9H). **^{13}C NMR (101 MHz, CDCl$_3$):** *δ* 199.6, 171.7, 135.7, 135.7, 133.6, 133.6, 133.4, 133.4, 129.9, 129.9, 127.9, 127.9, 118.3, 65.0, 63.3, 48.6, 45.0, 42.4, 38.0, 30.4, 27.1, 27.0, 19.4, 19.3. **IR:** 3070 (w), 2857 (m), 1670 (s), 1427 (m), 1110 (s), 701 (s). **HRMS (ESI):** Calculated for $C_{42}H_{51}O_3Si_2$ $[M+H]^+$: 659.3382. Found: 659.3378. **Optical rotation:** $[\alpha]_D^{20}$: +18.4 (*c* = 1.00, $CHCl_3$) for an enantiomerically enriched sample of 96 : 4 er. The enantiomeric purity was established by HPLC analysis using a chiral column (Lux 3μ Cellulose-1, 0.5 mL/min, 98.5 : 1.5 Hexane:Isopropanol, 254 nm, t_{major} = 18.647 min, t_{minor} = 20.955 min). Absolute stereochemistry was determined according to published literature. Relative stereochemistry was determined by analysis of relevant NOE interactions.

4.2.2. (1S,6R,7S,8S)-7,8-bis(((tert-Butyldiphenylsilyl)oxy)methyl) bicyclo[4.2.0]octan-3-one ***[43]***

[Cu−H] solution: A flame-dried 25 mL round bottom flask equipped with a stir bar was cooled under vacuum. After backfilled with N_2 and capped with a septum, the flask was transferred into glovebox and charged with Stryker's reagent (30 mg, 0.015 mmol, 0.050 eq.). The flask was sealed with a septum and removed from the glovebox. Toluene (3 mL) followed by Phenylsilane (0.15 mL, 1.2 mmol, 4.0 eq.) were sequentially added at room temperature. The mixture was stirred for 10 min at the same temperature to afford the premade [Cu−H] catalyst solution. [Reduction]: A flame-dried 25 mL round bottom flask equipped with a stir bar was cooled under vacuum. After evacuated/backfilled with N_2 (x 3) and capped with a septum, enone **42** (191 mg, 0.300 mmol, 1.00 eq.) and PhMe (3 mL) were added. To the stirring solution was added premade [Cu−H] catalyst solution at room temperature via syringe. The mixture was stirred at the same temperature for 5 h and then diluted with Hex (5 mL). The suspension was filtered through a pad of Celite and silica followed by wash was EtOAc (15 mL). The filtrate was concentrated and purified by FCC (Hex: EtOAc = 15 : 1 to 9 : 1) to afford ketone **43** (158 mg, 83% yield, >20:1 dr) as pale yellow oil. **^{1}H NMR (600 MHz, CDCl$_3$):** *δ* 7.69−7.53 (m, 8H), 7.43−7.31 (m, 12H), 3.70−3.62 (m, 3H), 3.59 (dd, *J* = 10.1, 6.4 Hz, 1H), 2.70−2.64 (m, 2H), 2.54 (p, *J* = 8.0 Hz, 1H), 2.40−2.34 (m, 3H), 2.16−1.95 (m, 3H), 1.72 (dq, *J* = 13.9, 9.0, 6.6 Hz, 1H), 1.02 (s, 9H), 1.01 (s, 9H). **^{13}C NMR (101 MHz, CDCl$_3$):** *δ* 214.2, 135.7, 135.6, 133.8, 133.8, 133.7, 129.7, 127.8, 127.8, 66.4, 63.6, 44.3, 38.7, 38.2, 37.5, 31.5, 30.6, 27.0, 25.4, 19.3, 19.3. **IR**: 3070 (w), 2930 (m), 1714 (s), 1427 (s), 1111 (s). **HRMS**

(**ESI**): Calculated for $C_{42}H_{52}O_2Si_2Na$ $[M+Na]^+$: 683.3347. Found: 683.3343. **Optical Rotation:** $[\alpha]_D^{20}$: +16.8 (c = 1.00, $CHCl_3$) for an enantiomerically enriched sample of 96:4 er.

*4.2.3. (4R,6S,7S,8R)-4-bromo-7,8-bis(((tert-butyldiphenylsilyl)oxy) methyl)bicyclo [4.2.0] oct-1-en-3-one **[46]***

A flame-dried 250 mL round bottom flask equipped with a stir bar was cooled under vacuum. After evacuated/backfilled with N_2 (x 3) and capped with a septum, diisopropylamine (1.80 mL, 12.6 mmol, 1.50 eq.) and THF (60 mL) were added. To the stirring solution was added *n*-butyllithium (2.50 M in hexanes, 5.00 mL, 12.6 mmol, 1.50 eq.) slowly (~5 min) at 0 °C in an ice/water bath and stirred for 0.5 h. Then the premade LDA solution was cooled to −78 °C in a dry ice/acetone bath and a solution of a solution of enone **42** (5.6 g, 8.5 mmol, 1 eq) in THF (25 mL) was added slowly to the solution via syringe followed by addition of DMPU (8.5 mL). After stirred for another 0.5 h at the same temperature, TMSCl (2.7 mL, 21 mmol, 2.5 eq.) was added. Then the dry ice/acetone bath was removed. The mixture was naturally warmed to room temperature over 12 h and quenched with saturated $NaHCO_3$ solution (40 mL). The aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous MgSO4, filtered and concentrated by rotary evaporation. The crude enolsilylether was directly used to next reaction without further purification.

A flame-dried 250 mL round bottom flask equipped with a stir bar was cooled under vacuum. After evacuated/backfilled with N_2 (x 3) and capped with a septum, above crude enolsilylether (assuming 8.5 mmol, 1.0 eq.) and THF (85 mL) were added. The solution was cooled to −78 °C in a dry ice/acetone bath and NBS (1.5 g, 8.5 mmol, 1.0 eq.) was added. Then the dry ice/acetone bath was removed. The mixture was naturally warmed to room temperature over 0.5 h and quenched with saturated $NaHCO_3$ solution (30 mL). The aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous MgSO4, filtered and concentrated by rotary evaporation. The residue was purified by FCC (Hex: EtOAc = 9 : 1) to afford bromide **46** (3.8 g, 62% for 2 steps, >20:1 dr) as pale yellow oil. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.68−7.54 (m, 8H), 7.44−7.33 (m, 12H), 5.83 (s, 1H), 4.35 (s, 1H), 3.80−3.75 (m, 2H), 3.73 (dd, J = 10.7, 5.8 Hz, 1H), 3.39 (q, J = 6.3 Hz, 1H), 3.31 (q, J = 7.3 Hz, 1H), 2.41 (dd, J = 5.7, 2.5 Hz, 1H), 2.39 (dd, J = 5.6, 2.3 Hz, 1H), 2.15−2.06 (m, 2H), 1.06 (s, 9H), 1.02 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 191.2, 171.9, 135.7, 135.6, 133.4, 133.3, 133.3, 133.2, 130.0, 129.9, 128.0, 127.9, 127.9, 115.4, 64.7, 63.0, 49.1, 48.9, 43.3, 39.1, 38.4, 27.0, 27.0, 19.4, 19.3. **IR (neat):** 3071 (w), 2857 (m), 1674 (s), 1471 (m), 1111 (s), 701(s). **HRMS (ESI):** Calculated for $C_{42}H_{49}O_3BrSi_2Na$ $[M+Na]^+$: 759.2296. Found: 759.2296. **Optical rotation:** $[\alpha]_D^{20}$: +34.7 (c = 1.00, $CHCl_3$) for an enantiomerically enriched sample of 96 : 4 er.

4.2.4. (1S,4R,6R,7S,8S)-4-bromo-7,8-bis(((tert-butyldiphenylsilyl) oxy)methyl)bicyclo [4.2.0]octan-3-one

[Cu−H] solution: A flame-dried 10 mL round bottom flask equipped with a stir bar was cooled under vacuum. After backfilled with N_2 and capped with a septum, the flask was transferred into glovebox and charged with Stryker's reagent (300 mg, 0.150 mmol, 0.0750 eq.). The flask was sealed with a septum and removed from the glovebox. Toluene (10 mL) followed by Phenylsilane (1 mL, 8 mmol, 4 eq.) were sequentially added at room temperature. The mixture was stirred for 10 min at the same temperature to afford the premade [Cu−H] catalyst solution. [Reduction]: A flame-dried 25 mL round bottom flask equipped with a stir bar was cooled under vacuum. After evacuated/backfilled with N_2 (x 3) and capped with a septum, enone **46** (1.5 g, 2.0 mmol, 1.0 eq.) and PhMe (10 mL) were added. To the stirring solution was added premade [Cu−H] catalyst solution at room temperature via syringe. The mixture was stirred at the same temperature for 5 h and then diluted with Hex (20 mL). The suspension was filtered through a pad of Celite and silica followed by wash was EtOAc (5 mL x 3). The filtrate was concentrated and purified by FCC (Hex: EtOAc = 15 : 1 to 9 : 1) to afford ketone (754 mg, 51%, >20:1 dr) as pale yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ 7.62−7.60 (m, 8H), 7.43−7.33 (m, 12H), 4.35 (t, J = 4.1 Hz, 1H), 3.67 (dt, J = 9.8, 4.6 Hz, 2H), 3.63−3.55 (m, 2H), 2.87 (dt, J = 18.2, 8.0 Hz, 1H), 2.69 (dd, J = 16.2, 11.1 Hz, 1H), 2.61 (d, J = 6.7 Hz, 1H), 2.60−2.47 (m, 3H), 2.39 (dt, J = 11.8, 6.7 Hz, 1H), 2.23−2.14 (m, 2H), 1.02 (s, 9H), 1.01 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 205.1, 135.7, 135.7, 135.6, 133.7, 133.7, 133.6, 133.5, 129.8, 127.9, 127.8, 66.2, 63.2, 47.8, 44.3, 38.7, 36.4, 34.9, 30.5, 29.8, 27.0, 27.0, 19.4, 19.3. **IR (neat):** 3070 (w), 2857 (m), 1724 (s), 1427 (m), 1111 (s), 701(s). **HRMS (ESI):** Calculated for $C_{42}H_{51}O_3BrSi_2Na$ $[M+Na]^+$: 761.2452. Found: 761.2454. **Optical rotation:** $[\alpha]_D^{20}$: +23.4 (c = 1.00, $CHCl_3$) for an enantiomerically enriched sample of 96 : 4 er.

*4.2.5. (1S,6R,7S,8S)-7,8-bis(((tert-butyldiphenylsilyl)oxy)methyl) bicyclo [4.2.0]oct-4-en-3-one **[47]***

A flame-dried 25 mL round bottom flask equipped with a stir bar was cooled under vacuum. After evacuated/backfilled with N_2 (x 3) and capped with a septum, above bromide (660 mg, 0.890 mmol, 1.00 eq) and DMF (9 mL) were added. To the stirring solution was added lithium bromide (231 mg, 3.00 eq, 2.67 mmol) and Li_2CO_3 (328 mg, 4.45 mmol, 5.00 eq). The septum was quickly replaced with a glass stopper and the mixture was heated to 130 °C for 1 h in an oil bath. After cooled down to room temperature, the reaction was quenched with 1 M HCl solution (5 mL) dropwise. The aqueous layer was extracted with Et_2O (10 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous MgSO4, filtered and concentrated by rotary evaporation. The residue was purified by FCC (Hex: EtOAc = 9 : 1) to afford enone **47** (561 mg, 96%) as pale yellow oil. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 7.65−7.56 (m, 8H), 7.49−7.33 (m, 12H), 6.75 (dd, J = 10.0, 4.6 Hz, 1H), 5.97 (d, J = 10.2 Hz, 1H), 3.80−3.57 (m, 4H), 3.06−2.95 (m, 1H), 2.82 (td, J = 7.9, 4.2 Hz, 1H), 2.73 (ddd, J = 16.8, 8.5, 5.6 Hz, 1H), 2.59−2.51 (m, 1H), 2.48 (ddd, J = 16.6, 8.4, 5.1 Hz, 1H), 2.23 (p, J = 6.8 Hz, 1H), 1.06 (s, 9H), 1.01 (s, 9H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 199.8, 150.0, 135.7, 135.6, 133.7, 133.6, 133.5, 129.9, 129.9, 129.8, 129.8, 128.8, 127.9, 127.9, 127.8, 65.7, 63.6, 46.0, 38.6, 35.6, 33.7, 30.5, 27.0, 27.0, 19.4, 19.3. **IR:** 3070 (w), 2855 (m), 1674 (m), 1427 (m), 1107 (s), 699(s). **HRMS (ESI):** Calculated for $C_{42}H_{50}O_3Si_2Na$ $[M+Na]^+$: 681.3191. Found: 681.3188. **Optical rotation:** $[\alpha]_D^{20}$: 36.8 (c = 1.00, $CHCl_3$) for an enantiomerically enriched sample of 96 : 4 er.

*4.2.6. (1S,6R,7S,8S)-7,8-bis(((tert-butyldiphenylsilyl)oxy)methyl) bicyclo [4.2.0]octa-2,4-dien-3-yl trifluoromethanesulfonate **[48]***

A flame-dried 25 mL round bottom flask equipped with a stir bar was cooled under vacuum. After evacuated/backfilled with N_2 (x 3) and capped with a septum**,** enone **47** (330 mg, 0.500 mmol, 1.00 eq.) and THF (5 mL) were added. To the stirring solution was added $PhNTf_2$ (268 mg, 0.750 mmol, 1.50 eq.) at room temperature. Then the flask was placed in a ice/water bath and KHMDS (1.0 M in THF, 0.75 mL, 0.75 mmol, 1.5 eq.) was added dropwise. The reaction was stirred for 0.5 h at the same temperature and then was quenched with H_2O (2 mL). The aqueous layer was extracted with Et_2O (3 mL x 3). The combined organic layers were washed with 1 M KOH solution (5 mL), brine (5 mL), dried over anhydrous MgSO4, filtered and concentrated by rotary evaporation. The residue was purified by FCC (Hex: EtOAc = 30 : 1) to afford triflate **48** (372 mg, 94%) as colorless oil. **^{1}H NMR (600 MHz, CDCl3):** δ 7.72−7.53 (m, 8H), 7.45–7.31 (m, 12H), 5.72 (dd, J = 10.0, 5.6 Hz, 1H), 5.63 (d, J = 3.9 Hz, 1H), 5.59 (d, J = 10.1 Hz, 1H), 3.79 (d, J = 8.0 Hz, 2H), 3.59 (dd, J = 10.6, 4.7 Hz, 1H), 3.52 (dd, J = 10.6, 5.6 Hz, 1H), 3.41–3.32 (m, 1H), 3.01 (p, J = 8.3 Hz, 1H), 2.91 (ddd, J = 10.8, 8.5, 5.7 Hz, 1H), 2.50 (tt, J = 8.8, 5.4 Hz, 1H), 1.03 (s, 9H), 1.01 (s, 9H). **^{13}C NMR (126 MHz, CDCl3):** δ 146.4, 135.7, 135.7, 135.6, 133.8, 133.7, 133.7, 132.4, 129.8, 129.8, 129.8, 127.9, 127.8, 119.1, 118.6 (q, J = 320.4 Hz), 115.5, 65.3, 64.0, 50.7, 47.7, 33.6, 32.3, 27.0, 27.0, 26.9, 19.4, 19.3. **IR:** 3072 (w), 2858 (m), 1425 (m), 1112(s), 701(s). **HRMS (ESI):** Calculated for $C_{43}H_{49}O_5F_3SSi_2Na$ $[M+Na]^+$: 813.2684. Found: 813.2689. **Optical rotation:** $[\alpha]_D^{20}$: +2.9 (c = 1.00, $CHCl_3$) for an enantiomerically enriched sample of 96 : 4 er.

4.2.7. ((1R,6S,7S,8S)-Bicyclo [4.2.0]octa-2,4-diene-7,8-diyl) dimethanol [11]

A flame-dried 10 mL round bottom flask equipped with a stir bar was cooled under vacuum. After backfilled with N_2 and capped with a septum, the flask was transferred into glovebox and charged with palladium (II) acetate (10 mg, 0.045 mmol, 0.050 eq.) and dpp (19 mg, 0.045 mmol, 0.050 eq.). Then the flask was sealed with a septum and removed from the glovebox. A solution of triflate **48** (712 mg, 0.900 mmol, 1.00 eq.) in DMF (5 mL) was added followed by triethylsilane (0.29 mL, 1.8 mmol, 2.0 eq). The mixture was heated to 90 °C for 1 h in an oil bath. After allowing to cool to room temperature, the reaction was diluted with H_2O (5 mL). The aqueous layer was extracted with Et_2O (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous MgSO4, filtered and concentrated by rotary evaporation. The crude diene was directly used to next reaction without further purification.

A 25 mL round bottom flask equipped with a stir bar was charged with above crude diene (assuming 0.9 mmol, 1.0 eq.). After evacuated/backfilled with N_2 (x 3) and capped with a septum, THF (5 mL) was added followed by TBAF (1.0 M in THF, 3.6 mL, 3.6 mmol, 4.0 eq.) at 0 °C in an ice bath. Then ice bath was removed, and the mixture was stirred at room temperature for 24 h. The reaction was quenched with saturated NH_4Cl solution (5 mL). The aqueous layer was extracted with Et_2O (5 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous $MgSO_4$, filtered and concentrated by rotary evaporation. The residue was purified by FCC (Hex: EtOAc = 4 : 1 to 1 : 1) to afford diol **11** (103 mg, 70% for 2 steps) as colorless oil. **^{1}H NMR (600 MHz, $CDCl_3$):** δ 5.87 (dd, J = 9.0, 5.9 Hz, 1H), 5.72 (dd, J = 9.5, 5.5 Hz, 1H), 5.61 (dd, J = 9.3, 4.0 Hz, 1H), 5.53 (dd, J = 9.6, 3.4 Hz, 1H), 3.82 (d, J = 6.6 Hz, 2H), 3.76 (d, J = 8.2 Hz, 1H), 3.54–3.45 (m, 1H), 3.17 (s, 1H) 2.80–2.65 (m, 2H), 2.09 (s, 2H). **^{13}C NMR (101 MHz, $CDCl_3$):** δ 126.3, 125.7, 124.4, 122.4, 65.4, 62.8, 52.7, 51.3, 33.1, 32.6. **IR:** 3329 (br, s), 3029 (m), 2922 (s), 1581 (m), 1028 (s). **HRMS (EI):** Calculated for $C_{10}H_{14}O_2$ $[M]^+$: 166.0987. Found: 166.0987. **Optical rotation:** The enantiomeric purity was established by HPLC analysis using a chiral column (Lux 3μ Amylose-2, 0.4 mL/min, 95 : 5 Hexane:Isopropanol, 254 nm, t_1 = 40.609 min, t_2 = 42.902 min) in comparison with authentic racemic standard prepared as previously described [25a].

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

An SI has been uploaded

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2022.132932.

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