ChemPubSoc Europe

DOI: 10.1002/chem.201303538

CHEMISTRY
A European Journal
Full Paper

Stereocontrolled Synthesis

Synthesis of Cyclobakuchiols A, B, and C by Using Conformation-Controlled Stereoselective Reactions

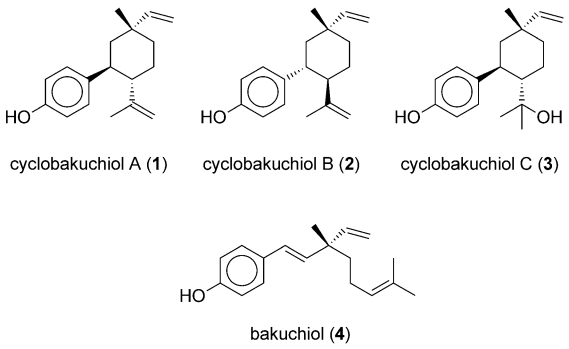
Hidehisa Kawashima, Yuki Kaneko, Masahiro Sakai, and Yuichi Kobayashi*[a]

Abstract: Cyclohexanone with the *p*MeOC$_6$H$_4$ and CH$_2$=C(Me) substituents at the C3 and C4-positions was prepared from (+)-β-pinene and converted to the allylic picolinate by a Masamune–Wittig reaction followed by reduction and esterification. Allylic substitution of this picolinate with Me$_2$CuMgBr·MgBr$_2$ in the presence of ZnI$_2$ proceeded with γ regio- and stereoselectively to afford the quaternary carbon center on the cyclohexane ring with the CH$_2$=CH and Me groups in axial and equatorial positions, respectively. This product was converted to cyclobakuchiol A by demethylation and to cyclobakuchiol C by epoxidation of the CH$_2$=C(Me) group. For the synthesis of cyclobakuchiol B, the enantiomer of the above cyclohexanone derived from (−)-β-pinene was converted to the cyclohexane-carboxylate, and the derived enolate was subjected to the reaction with CH$_2$=CHSOPh followed by sulfoxide elimination to afford the intermediate with the quaternary carbon center with MeOC(=O) and CH$_2$=CH groups in axial and equatorial positions. The MeOC(=O) group was transformed to the Me group to complete the synthesis of cyclobakuchiol B.

Introduction

Cyclobakuchiols A and B are antipyretic and anti-inflammatory compounds isolated as a mixture from *Psoralea glandulosa* L.[1] Recently, cyclobakuchiol C was isolated from *Psoralea coryllfolia*.[2] The structures with the relative stereochemistry have been spectroscopically determined, and the suggested absolute configuration is as depicted in Figure 1 on the basis of the concomitant production of stereodefined bakuchiol (**4**) with an *S* configuration and the probable cyclization of **4** to **1**–**3**. The biological potency of the mixture (**1** and **2**) is higher than that of **4**.[3] However, the potency of each cyclobakuchiol is unexplored, probably because of the difficulty in separating the mixture[1,3] and the lack of a method for the synthesis of **1**–**3**. In this study, we report the synthesis of **1**–**3**, in which the quaternary carbon atoms are constructed in a stereoselective manner. Furthermore, elucidation of the absolute configurations of naturally occurring cyclobakuchiols A–C is presented on the basis of specific rotation analysis.

Recently, we reported the construction of a quaternary carbon center on a cyclohexane ring by using S$_N$2′ selective allylic substitution with alkylcopper reagents.[4] The stereochemistry is controlled by the equatorial attack of reagents to the allylic end (S$_N$2′ position) in the thermodynamically stable chair conformer, which creates a quaternary carbon center with the axial vinyl and equatorial alkyl groups. We supposed that the cyclohexane **I** with Ar (*p*MeOC$_6$H$_4$) and R^1 (Me$_2$C(OH)or CH$_2$=C(Me)) in equatorial positions is the most stable conformer, and that allylation of **I** with a methyl copper reagent would produce **II**, in which the quaternary carbon center in **1** and **3** is correctly furnished (Scheme 1). Furthermore, we realized that the concept of the equatorial attack is applicable to a reaction of enolate **IV** with a vinyl cation equivalent to afford **V** and that conversion of the ester group (CO$_2$R^2) of **V** to Me would produce **2**. Practically, the synthesis of **1**–**3** by this approach was quite successful, as described below. Furthermore, preparation of the key intermediate was improved so as to attain high enantiomeric purity.



cyclobakuchiol A (**1**) cyclobakuchiol B (**2**) cyclobakuchiol C (**3**)

bakuchiol (**4**)

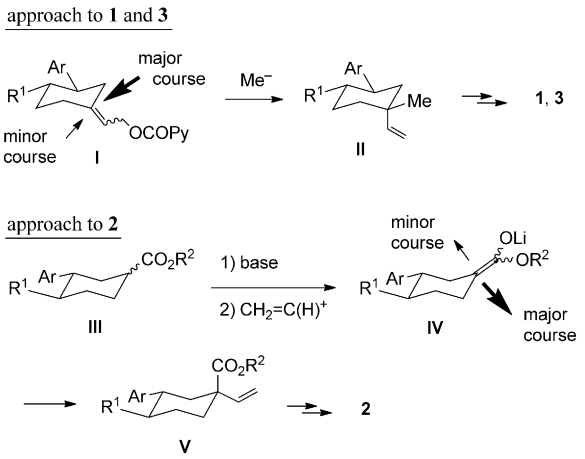
Figure 1. Structures of cyclobakuchiols A–C and bakuchiol.

Results and Discussion

First, the key intermediate **I** was designed as picolinate **10a**, to which we envisaged access through copper-assisted 1,4-addition of *p*MeOC$_6$H$_4$MgBr to enone **8** followed by a Wittig reac-

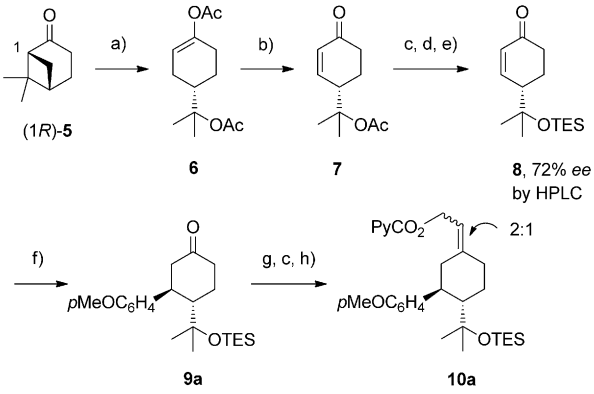
[a] *H. Kawashima, Y. Kaneko, M. Sakai, Prof. Dr. Y. Kobayashi*
Department of Bioengineering
Tokyo Institute of Technology, B52
Nagatsuta-cho 4259, Midori-ku, Yokohama 226-8501 (Japan)
Fax: (+81) 45-924-5789
E-mail: ykobayas@bio.titech.ac.jp

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201303538.



Scheme 1. Key reactions for construction of cyclobakuchiols.

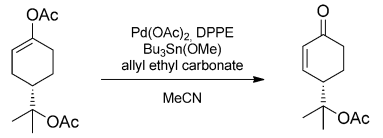
tion of the resulting ketone **9a** (Scheme 2). In accordance with the literature procedure,[5] the cyclobutane ring of nopinone (1*R*)-**5**[6] was opened with $Zn(OAc)_2$ and $BF_3{\cdot}Et_2O$ in Ac_2O, and



Scheme 2. Synthesis of the key picolinate: a) $Zn(OAc)_2$, $BF_3{\cdot}OEt_2$, Ac_2O, 46%; b) $Pd(OAc)_2$, DPPE, $Bu_3Sn(OMe)$, $CH_2{=}CHCH_2OCO_2Et$, MeCN, 80 °C, 10 h, 51%; c) DIBAL; d) PCC; e) TESCl, imidazole, 60% (3 steps); f) *p*$MeOC_6H_4MgBr$ (3 equiv), $CuBr{\cdot}Me_2S$ (1.5 equiv); g) $(EtO)_2P(O)CH_2CO_2Et$, LiCl, DBU, 72% (2 steps); h) 2-$PyCO_2H$, [2-Cl-*N*-Me-Py]$^+$ I^-, DMAP, Et_3N, 86% (2 steps). DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DIBAL = *i*Bu_2AlH; DMAP = 4-(dimethylamino)pyridine; DPPE = ethylenebis(diphenylphosphine); PCC = pyridinium chlorochromate.

subsequent Pd-catalyzed olefination[7] of the resulting enol acetate **6** with $Pd(OAc)_2$, DPPE, $Bu_3Sn(OMe)$, and $CH_2{=}CHCH_2OCO_2Et$ at 80 °C gave enone **7**, which was transformed to the TES (Et_3Si) ether **8** in three steps. Although this method is reported to be stereoselective on the basis of specific rotation analysis, the *ee* of **8** synthesized herein was 72% as determined by sure chiral HPLC analysis. Reinvestigation of the Pd-catalyzed step under various conditions is summarized in Table 1. The enantiomeric purity of **7** was 81% *ee* when the reaction was quenched before completion (3 h) (Table 1, entry 4), whereas higher loading of the catalyst and a longer reaction time resulted in 62–66% *ee*.[8] At a lower temperature (50 °C), the reaction did not proceed. To recover high *ee* by recrystallization of any advanced intermediate(s), enone **8** was converted to **10a** through ketone **9a**. Unfortunately, the intermediates and **10a** were oily compounds.

Table 1. Pd-catalyzed enone formation.

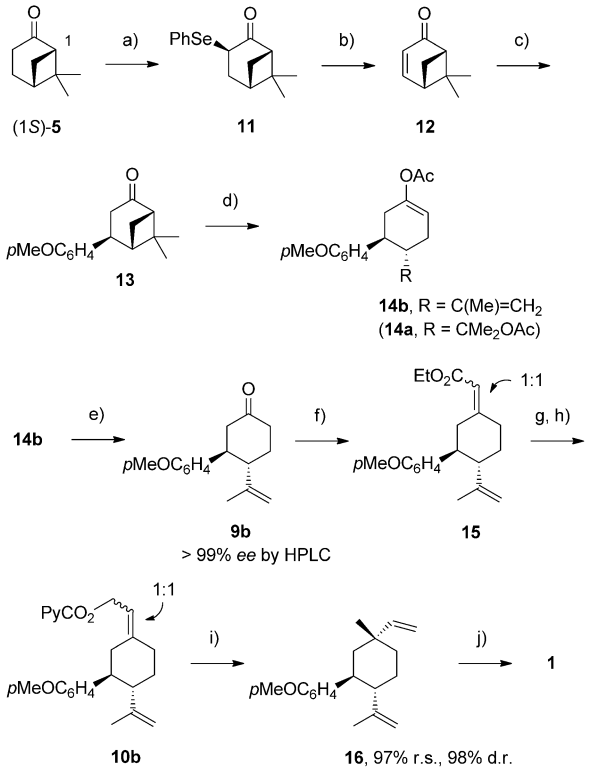


6 7

Entry	$Pd(OAc)_2$ [mol%]	DPPE [mol%]	*T* [°C]	*t* [h]	Yield [%]	*ee* [%]
1	5	5	80	10	51	72
2	10	10	80	18	73	66
3	5	5	80	40	n.d.[a]	62
4	5	5	80	3	38	81
5	5	5	50	3	0[b]	–

[a] n.d. = not determined. [b] Enol acetate **6** was recovered unchanged.

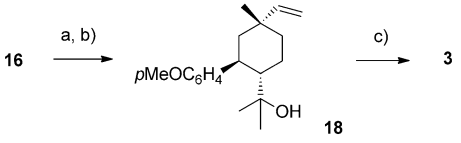
Although the racemization was found to occur in the Pd-catalyzed step, the low *ee* observed even at the beginning of the reaction suggested that the BF_3-assisted cyclobutane ring opening of (1*R*)-**5** is another likely step responsible for the racemization through cation interchange between ring-CH-CMe_2^+ and ring-C^+-$CHMe_2$. Because of the expected difficulty in improving these steps, an altered synthesis shown in Scheme 3 was envisaged with the expectation that a similar cation interchange in the ring opening of **13** would be suppressed by conformation of the ring-opening product, which is stabilized by the *p*$MeOC_6H_4$ anchor. Furthermore, even when it was produced, the isomerization product, which is the diastereomer with the two substituents in a *cis* relationship, was expected to be removed by routine purification. Because the enone olefin is furnished to the opposite side of the molecule, we converted (1*S*)-**5**[6] to enone **12** by bromination followed by dehydrobromination at 140 °C with DBU or with Li_2CO_3/LiBr.[9] However, the yields of **12** in both cases were only 30% over two steps, whereas elimination of the sulfoxide, synthesized in 32% yield from (1*S*)-**5** (LDA, $(PhS)_2$; MMPP = Magnesium Monoperoxyphthalate Hexahydrate), with K_2CO_3 in toluene at 120 °C gave a mixture of products.[10] We then attempted to follow the literature method by α-phenylselenenylation[11] using $(PhSe)_2$, MsOH, and SeO_2 in CH_2Cl_2, wherein SeO_2 is added in three parts after every 15 h of reaction and isolation.[10a] However, our attempt gave a mixture of products. Fortunately, the substitution of H_2SO_4 and MeOH for MsOH and CH_2Cl_2, respectively, accelerated the reaction substantially to afford **11** (diastereomeric ratio (d.r.) > 99:< 1 by ^1H NMR spectroscopy) in 90% yield after only 5 h. Oxidation of **11** with H_2O_2 gave enone **12**, which upon reaction with *p*$MeOC_6H_4MgBr$/CuI furnished ketone **13** in 83% yield from **11**. Cyclobutane ring opening of **13** under the conditions used for (1*R*)-**5** proceeded cleanly as analyzed by TLC analysis. The product isolated was, however, olefin **14b** and not the AcO adduct **14a**. The enol acetate **14b** was exposed to NaOMe in MeOH to afford **9b**, which was > 99% *ee* by chiral HPLC analysis. Masamune–Wittig reaction of **9b** afforded ester **15** as a 1:1 olefin mixture, which was



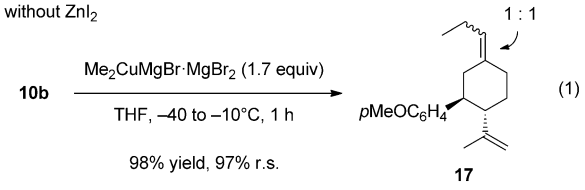
Scheme 3. Synthesis of cyclobakuchiol A: a) $(PhSe)_2$ (0.6 equiv), SeO_2 (1.2 equiv), H_2SO_4 (0.9 equiv), MeOH, RT, 5 h, 90%; b) 7% H_2O_2, pyridine; c) $pMeOC_6H_4MgBr$ (2.5 equiv), CuI (0.6 equiv), 83% (2 steps); d) $Zn(OAc)_2$, $BF_3{\cdot}OEt_2$, Ac_2O. e) NaH, MeOH, 91% (2 steps); f) $(EtO)_2P(O)CH_2CO_2Et$, LiCl, DBU, 81%; g) DIBAL. h) 2-$PyCO_2H$, [2-Cl-*N*-Me-Py]$^+I^-$, DMAP, Et_3N, 100% (2 steps); i) $Me_2CuMgBr{\cdot}MgBr_2$ (1.5 equiv), ZnI_2 (1.7 equiv), THF, −78 °C, 1 h, 92%; j) PhSH, K_2CO_3, NMP, 220 °C, 99%. NMP = *N*-methylpyrrolidone.

transformed to the key picolinate **10b** by DIBAL (iBu_2AlH) reduction followed by esterification with $PyCO_2H$.

Without separation, the olefin mixture **10b** was subjected to allylic substitution with $Me_2CuMgBr{\cdot}MgBr_2$ in the presence of ZnI_2 to afford **16** in 92% yield. To determine the regio- and stereoselectivity, we synthesized regioisomer **17** in 98% yield with 97% regioselectivity (r.s.) by allylic substitution of **10b** with $Me_2CuMgBr{\cdot}MgBr_2$ in the absence of ZnI_2 [Eq. (1)] and the diastereoisomer of **16** (i.e., **25**) by the method delineated in Scheme 5. With the ^1H NMR spectra of the isomers in hand, we calculated the regio- and diastereoselectivity of the allylation to give **16** to be 97% r.s. and 98% d.r. We emphasize that the stereochemistry is controlled by the conformation of the cyclohexane ring and is little affected by the geometry of the allylic moiety, which makes the synthesis highly convenient. Finally, demethylation of **16** with PhSH and K_2CO_3 afforded cyclobakuchiol A (**1**) in quantitative yield. The ^1H and ^{13}C NMR spectra of **1** thus synthesized were consistent with those previously reported.[1]

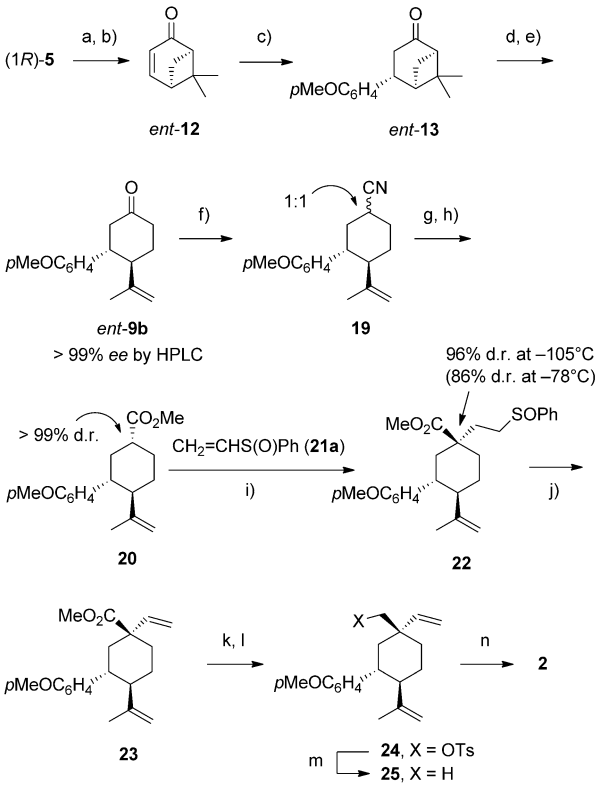


Scheme 4. Synthesis of cyclobakuchiol C: a) *m*CPBA, $NaHCO_3$; b) $LiAlH_4$, THF, 66% (2 steps); c) PhSH, K_2CO_3, NMP, 220 °C, 88%. *m*CPBA = 3-chloroperoxybenzoic acid.



Next, the synthesis of cyclobakuchiol C (**3**) was undertaken by starting from **16**, which upon epoxidation with *m*CPBA followed by hydride reduction with $LiAlH_4$ produced **18** in 66% yield (Scheme 4). Finally, demethylation with $PhSH/K_2CO_3$ produced **3** as solids in 88% yield. The ^1H and ^{13}C NMR spectra of **3** were consistent with those reported for gummy **3**.[2]

To establish access to cyclobakuchiol B (**2**) through enolate capture by a vinyl cation equivalent (Scheme 1, approach to **2**), we applied the method developed for the synthesis of ketone

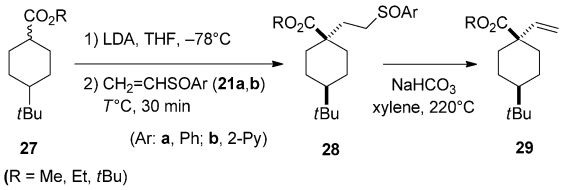


Scheme 5. Synthesis of cyclobakuchiol B: a) $(PhSe)_2$ (0.6 equiv), SeO_2 (1.2 equiv), H_2SO_4 (0.9 equiv), MeOH, 89%; b) H_2O_2, pyridine; c) $pMeOC_6H_4MgBr$ (2.5 equiv), CuI (0.6 equiv), 85% (2 steps); d) $Zn(OAc)_2$, $BF_3{\cdot}OEt_2$, Ac_2O; e) NaH, MeOH, 93% (2 steps); f) $TsCH_2NC$, *t*BuOK, THF; g) KOH, PrOH; h) CH_2N_2, 88% (3 steps); i) LDA, THF, −78 °C then **21a**, −105 °C; j) $NaHCO_3$, xylene, reflux, 85% (2 steps); k) $LiAlH_4$, THF; l) TsCl, Et_3N, DMAP, 91% (2 steps); m) $NaBH_4$, DMF, 80 °C, 12 h, 82%; n) PhSH, K_2CO_3, NMP, 220 °C, 93%. LDA = lithium diisopropylamide.

9b from (1*S*)-**5** to (1*R*)-**5**, which afforded *ent*-**9b** with >99% *ee* by chiral HPLC analysis (Scheme 5). A methoxycarbonyl moiety was installed on the carbonyl carbon atom of *ent*-**9b** by reductive cyanation[12] with $TsCH_2NC$ and *t*BuOK followed by hydrolysis of the resulting nitrile **19** (diastereomeric mixture) and esterification. The methyl ester **20**, which was isolated in 88% yield, was a single diastereomer, and downward stereochemistry (equatorial in the chair conformation) was tentatively assigned to the CO_2Me group, although the stereochemistry was indecisive to the next reaction.

Amongst the different methods[13–18] for introducing a vinyl group to the α-position of carbonyl compounds, we chose two of them on the basis of operational simplicity: 1) aldol reaction with MeCHO followed by the elimination of H_2O and 2) addition to CH_2=CHSOPh (**21a**) followed by elimination of PhSOH. The former method was examined by using an ester with the Me_2C(OTES) substituent in place of CH_2=C(Me), which gave the corresponding product with 90% d.r. in 61% yield in three steps. To achieve higher d.r. and yield, we changed the focus of our investigation to the latter method, although this method has not been extensively explored.[14] An enolate anion was prepared from **20** with LDA as a 1:1 *E*/*Z* mixture [Eq. (2)], which was determined by ^{1}H NMR spectroscopy of the derived TMS enol ether **26**,[19] and was subjected to reaction with CH_2=CHSOPh (**21a**) at −78 °C in THF. The reaction completed in 30 min to afford the adduct **22**, which upon thermolysis produced ester **23**, but with 86% d.r., as determined by ^{1}H NMR spectroscopy. To optimize the reaction conditions, we studied a model reaction by using esters **27** (R = Me) and **21a** (Ar = Ph) under the conditions used for **20**, whereas we did not examine the other methods, such as $GaCl_3$-mediated addition of a thioester TMS ether to TMS acetylene that proceeds with somewhat low 75% d.r.[15b] In practice, the addition of ester **27** to **21a** proceeded with a level of d.r. (86–87%) similar to that of the real case (Table 2, entry 1). However, no improvement was provided by larger esters **27** (R = Et, *t*Bu) or by 2-pyridyl sulfoxide **21b** (Ar = 2-pyridyl) (entries 2–5). In contrast, a lower reaction temperature of −105 °C (MeOH/liquid nitrogen) resulted in a higher d.r. of 92% without a delay in the reaction (entry 6). This protocol was successful in reacting **20** with **21a**, and subsequent elimination of PhSOH afforded olefin **23** with 96% d.r. in 85% yield (two steps). The methyl ester group in **23** was then converted to the methyl group in three steps. Finally, demethylation of **25** furnished **2** in 93% yield. The ^{1}H and ^{13}C NMR spectra of **2** synthesized were consistent with those reported previously.[1]

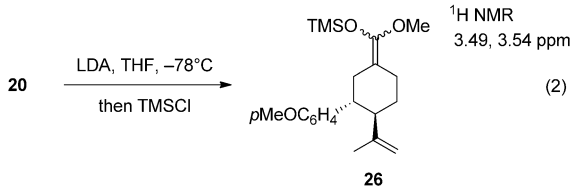
Table 2. Model study.[a,b]



27 (R = Me, Et, *t*Bu) **28** **29**

Entry	R	Ar	*T* [°C]	d.r. **28**	d.r. **29**
1	Me	Ph	−78	86	87
2	Me	2-Py	−78	84	n.d.
3	Et	Ph	−78	84	n.d.
4	Et	2-Py	−78	84	n.d.
5	*t*Bu	Ph	−78	72	73
6	Me	Ph	−105[d]	92	n.d.

[a] LDA (3 equiv), CH_2=CHSOAr (2 equiv). [b] Diastereomeric ratio of **27**: R = Me, 7:3; R = Et, 8:2; R = *t*Bu, 7:3. [c] Determined by ^{1}H NMR spectroscopy. [d] MeOH/N_2 (liq.).



Although a comparison of the specific rotation is one way to establish the absolute configuration of natural cyclobakuchiols A–C, specific rotations have been reported for few of the compounds: cyclobakuchiol C[2] ($[\alpha]_D^{20} = -15.3$ ($c = 0.38$ in MeOH)) and the two methyl ethers of cyclobakuchiols (reported as isomers A and B)[20] derived from bakuchiol (**4**) with an *S* configuration by acid-catalyzed cyclization ($[\alpha]_D = +3.1$ ($c = 0.16$) and −30.6 ($c = 0.18$) in EtOH for isomers A and B, respectively). On the basis of $[\alpha]_D^{28} = -18$ ($c = 0.30$ in MeOH) obtained for synthetic **3**, cyclobakuchiol C is definitely suggested to possess the same absolute configuration as that of **3**. Regarding cyclobakuchiols A and B, **16** and **25** (the methyl ethers of **1** and **2**) showed $[\alpha]_D^{26} = +3.2$ ($c = 0.76$) and $[\alpha]_D^{28} = -32$ ($c = 0.58$) in EtOH. The latter $[\alpha]_D$ value strongly indicates that isomer B should be **25**, and that isomer A should thus be **16**. Consequently, naturally occurring cyclobakuchiols A and B were definitely assigned as **1** and **2**.

Conclusion

The synthesis of **1**–**3** was stereoselectively accomplished by taking advantage of the conformation-controlled reactions, specifically, allylic substitution of picolinate **10b** with $Me_2CuMgBr{\cdot}MgBr_2/ZnI_2$ and the addition of the enolate derived from ester **20** to CH_2=CHSOPh (**21a**). The high stereoselectivity observed in the allylic substitution and the enolate capture by the vinyl sulfoxide was independent of the olefin stereochemistry of allylic picolinate **10b** and the enolate derived from ester **20**, respectively. In addition, we developed a method for the synthesis of enone **12** and its enantiomer *ent*-**12** with high enantiomeric purity. With **1**–**3** in hand for the first time, the absolute configurations of naturally occurring cyclobakuchiols A–C were established as **1**–**3** by $[\alpha]_D$ analysis. Research concerning biological studies of each cyclobakuchiol is ready to start.

Experimental Section

General methods

The ^{1}H (300 or 400 MHz) and ^{13}C NMR (75 or 100 MHz) spectroscopic data were recorded in $CDCl_3$ by using Me_4Si ($\delta = 0$ ppm)

and the centerline of the triplet ($\delta = 77.1$ ppm), respectively, as internal standards. Signal patterns are indicated as br s (broad singlet), s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Coupling constants (*J*) are given in Hertz (Hz). Chemical shifts of carbon atoms are accompanied by minus (for C and CH_2) and plus (for CH and CH_3) signs of the attached proton test (APT) experiments. HRMS was performed with a double-focusing mass spectrometer with an ionization mode of positive FAB or EI as indicated for each compound. The solvents that were distilled prior to use are THF (from Na/benzophenone), Et_2O (from Na/benzophenone), and CH_2Cl_2 (from CaH_2). After the reactions were completed, the organic extracts were concentrated by using an evaporator, and then the residues were purified by chromatography on silica gel (Kanto, spherical silica gel 60N. $[Cu(acac)_2]$ was purchased from TCI, Japan, and used without purification, whereas $CuBr{\cdot}Me_2S$ was prepared as described previously.[21]

Synthetic methods

(1*S*,5*R*)-6,6-Dimethylbicyclo[3.1.1]heptan-2-one ((1*S*)-5): $RuCl_3{\cdot}nH_2O$ (51 mg) was added to a suspension of (+)-β-pinene (1.03 g, 7.54 mmol) and $NaIO_4$ (6.70 g, 31.3 mmol) in CCl_4 (10 mL), MeCN (10 mL), and H_2O (15 mL), and the mixture was stirred at RT for 2 h and then diluted with H_2O. The resulting mixture was extracted with CH_2Cl_2 three times. The combined extracts were dried over $MgSO_4$ and concentrated to afford a residual oil, which was purified by chromatography on silica gel (hexane/EtOAc) to afford ketone (1*S*)-**5** (952 mg, 91%). $[\alpha]_D^{23} = -39.8$ ($c = 1.131$ in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.86$ (s, 3H), 1.33 (s, 3H), 1.59 (d, $J =$ 10 Hz, 1H), 1.90–2.10 (m, 2H), 2.21–2.27 (m, 1H), 2.34 (ddd, $J = 19$, 9, 2 Hz, 1H), 2.49–2.64 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 21.4 (−), 22.1 (+), 25.3 (−), 25.9 (+), 32.8 (−), 40.4 (+), 41.2 (−), 58.0 (+), 215.0 ppm (−); the ^{1}H NMR spectrum was consistent with that reported.[22]

(1*S*,3*R*,5*S*)-6,6-Dimethyl-3-(phenylselanyl)bicyclo[3.1.1]heptan-2-one (11): H_2SO_4 (0.20 mL, 18 M, 3.60 mmol) was added to an ice-cold solution of ketone (1*S*)-**5** (570 mg, 4.12 mmol), $(PhSe)_2$ (708 mg, 2.27 mmol), and SeO_2 (549 mg, 4.95 mmol) in MeOH (8 mL). The mixture was stirred at RT for 5 h and diluted with saturated $NaHCO_3$. The resulting mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to afford a residual oil, which was purified by chromatography on silica gel (hexane/EtOAc) to afford selenide **11** (1.09 g, 90%). $[\alpha]_D^{24} = +32.4$ ($c = 0.888$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.84$ (s, 3H), 1.35 (s, 3H), 1.87 (d, $J =$ 11 Hz, 1H), 2.17–2.28 (m, 2H), 2.49–2.63 (m, 2H), 2.70 (t, $J = 5$ Hz, 1H), 3.86 (dd, $J = 9$, 2 Hz, 1H), 7.28–7.34 (m, 3H), 7.63–7.70 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 22.1$ (+), 25.7 (−), 25.9 (+), 31.6 (−), 40.3 (+), 40.8 (+), 42.2 (−), 57.7 (+), 128.3 (+), 129.2 (+), 130.5 (−), 134.7 (+), 210.1 ppm (−); the ^{1}H NMR spectrum was consistent with that reported.[10]

(1*S*,4*S*,5*S*)-4-(4-Methoxyphenyl)-6,6-dimethylbicyclo-[3.1.1]heptan-2-one (13): 7% H_2O_2 (2.09 mL, 4.24 mmol) was added to an ice-cold solution of selenide **11** (841 mg, 2.87 mmol) and pyridine (0.46 mL, 5.70 mmol) in CH_2Cl_2 (6 mL). The mixture was stirred at RT overnight and diluted with saturated $NaHSO_3$. The resulting mixture was extracted with CH_2Cl_2 three times. The combined extracts were washed with saturated $CuSO_4$ and brine, dried over $MgSO_4$, and concentrated to afford enone **12**, which was used for the next reaction without further purification. Enone **12**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.04$ (s, 3H), 1.52 (s, 3H), 2.14 (d, $J =$ 8 Hz, 1H), 2.60 (q, $J = 6$ Hz, 1H), 2.72 (dt, $J = 2$, 6 Hz, 1H), 2.85 (dt, $J = 9$, 6 Hz, 1H), 5.95 (d, $J = 9$ Hz, 1H), 7.52 ppm (dd, $J = 9$, 6 Hz, 1H); the ^{1}H NMR spectrum was consistent with that reported.[10]

p$MeOC_6H_4MgBr$ (8.0 mL, 0.90 M in THF, 7.20 mmol) was added dropwise to a suspension of CuI (328 mg, 1.72 mmol) in THF (8 mL) at −78 °C and the solution was stirred at −78 °C for 30 min. A solution of the above enone **12** in THF (8 mL) was added dropwise. The mixture was allowed to warm to −50 °C over 2 h and saturated NH_4Cl was added. The resulting mixture was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to afford a residual oil, which was purified by chromatography on silica gel (hexane/EtOAc) to give ketone **13** (581 mg, 83% from **11**). $[\alpha]_D^{24} = -45.3$ ($c =$ 1.13 in $CHCl_3$); IR (neat): $\tilde{\nu} = 1708$, 1513, 1250, 1035, 826 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.98$ (s, 3H), 1.39 (s, 3H), 1.89 (d, $J =$ 11 Hz, 1H), 2.38 (t with fine couplings, $J = 5$ Hz, 1H), 2.55 (dt, $J = 11$, 6 Hz, 1H), 2.62 (t, $J = 5$ Hz, 1H), 2.67 (dd, $J = 19$, 7 Hz, 1H), 2.78 (dd, $J = 19$, 9 Hz, 1H), 3.38 (t, $J = 8$ Hz, 1H), 3.80 (s, 3H), 6.87 (d with fine couplings, $J = 9$ Hz, 2H), 7.17 ppm (d with fine couplings, $J = 9$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 22.0$ (+), 22.8 (−), 26.1 (+), 36.6 (+), 41.1 (−), 41.9 (−), 46.8 (+), 55.3 (+), 57.2 (+), 114.1 (+), 127.8 (+), 136.5 (−), 158.1 (−), 213.4 ppm (−); HRMS (FAB): *m/z*: calcd for $C_{16}H_{20}O_2^+$: 244.1463 [M^+]; found: 244.1464.

(3*S*,4*S*)-3-(4-Methoxyphenyl)-4-(prop-1-en-2-yl)cyclohexanone (9b): $BF_3{\cdot}OEt_2$ (0.25 mL, 1.99 mmol) was added to an ice-cold mixture of ketone **13** (909 mg, 3.72 mmol) and $Zn(OAc)_2$ (722 mg, 3.93 mmol) in Ac_2O (10 mL). The mixture was stirred at RT overnight and diluted with H_2O. The resulting mixture was extracted with EtOAc three times. The combined extracts were washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated to afford acetate **14b**, which was used for the next reaction without further purification.

NaH (80 mg, 60% in mineral oil, 2.01 mmol) was added to a solution of the above acetate in MeOH (10 mL) at RT. The mixture was stirred for 30 min and then diluted with saturated NH_4Cl. The resulting mixture was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to afford a residual oil, which was purified by chromatography on silica gel (hexane/EtOAc) to give ketone **9b** (825 mg, 91% from **13**). >99% *ee* by chiral HPLC analysis (see the Supporting Information); $[\alpha]_D^{23} = +55$ ($c = 0.65$ in $CHCl_3$); m.p. 118–119 °C; IR (neat): $\tilde{\nu} = 1700$, 1517, 1254, 1030 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.52$ (s, 3H), 1.86 (ddt, $J = 13$, 6, 12 Hz, 1H), 2.05–2.14 (m, 1H), 2.45–2.59 (m, 4H), 2.71 (dt, $J = 3$, 12 Hz, 1H), 2.93 (dt, $J = 6$ and 11 Hz, 1H), 3.78 (s, 3H), 4.63 (s, 1H), 4.65 (s, 1H), 6.82 (d with fine couplings, $J = 9$ Hz, 2H), 7.07 ppm (d with fine couplings, $J = 9$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 19.6$ (+), 31.9 (−), 41.3 (−), 47.5 (−), 50.0 (−), 50.3 (+), 55.2 (+), 112.7 (−), 113.9 (+), 129.2 (+), 135.3 (−), 146.2 (−), 158.2 (−), 210.4 ppm (−); HRMS (FAB): *m/z*: calcd for $C_{16}H_{20}O_2^+$: 244.1463 [M^+]; found: 244.1464.

Ethyl 2-[(3*S*,4*S*)-3-(4-methoxyphenyl)-4-(prop-1-en-2-yl)cyclohexylidene]acetate (15): DBU (1.80 mL, 12.1 mmol) and triethyl phosphonoacetate (2.51 mL, 12.5 mmol) were added to a suspension of LiCl (556 mg, 13.1 mmol) in MeCN (6 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min, and then ketone **9b** (725 mg, 2.97 mmol) was added. The reaction was carried out at RT overnight and quenched by addition of saturated NH_4Cl. The resulting mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford the ester **15** (756 mg, 81%) as a mixture of the stereoisomers (1:1 by ^{1}H NMR spectroscopy). IR (neat): $\tilde{\nu} =$ 1713, 1648, 1513, 1249, 1151 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$

1.26, 1.29 (2 t, $J=7$, 7 Hz, 3H), 1.48 (s, 3H), 1.52–1.67 (m, 1H), 1.91–2.07 (m, 2H), 2.28–2.43 (m, 2H), 2.47–2.57 (m, 1H), 2.59–2.69 (m, 1H), 3.770, 3.774 (2s, 1.5, 1.5H), 3.93–4.01 (m, 1H), 4.13, 4.17 (2q, $J=7$, 7 Hz, 2H), 4.56, 4.58 (2s with fine couplings, 2H), 5.65, 5.68 (2s, 0.5, 0.5H), 6.79, 6.81 (2d with fine couplings, $J=9$, 9 Hz, 2H), 7.07, 7.09 ppm (2d with fine couplings, $J=9$, 9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=14.29$, 14.30 (+), 19.55, 19.58 (+), 29.2, 33.0, 33.8, 37.4, 38.3, 46.5 (for 3C, −), 47.9, 48.8 (+), 51.1, 51.3 (+), 55.0 (+), 59.5, 59.6 (−), 111.8, 111.9 (−), 113.5, 113.7 (+), 113.7, 113.8 (+), 128.1, 128.2 (+), 136.3, 136.6 (−), 147.0, 147.1 (−), 157.8, 158.0 (−), 160.9, 161.2 (−), 166.5, 166.7 ppm (−); HRMS (FAB): *m/z*: calcd for $C_{20}H_{26}O_3^+$: 314.1882 [M^+]; found: 314.1881.

2-[(3*S*,4*S*)-3-(4-Methoxyphenyl)-4-{2-[(triethylsilyl)oxy]propan-2-yl}cyclohexylidene]ethyl picolinate (10b): DIBAL (5.1 mL, 1.02 M in hexane, 5.20 mmol) was added dropwise to a solution of ester **15** (646 mg, 2.05 mmol) in THF (20 mL) at −78 °C, and the solution was stirred at −78 °C for 30 min before the addition of H_2O (2 mL, 111 mmol) and NaF (6.03 g, 144 mmol). The resulting mixture was stirred at RT for 30 min and filtered through a pad of Celite. The filtrate was concentrated in vacuo to afford a residual oil, which was purified by chromatography on silica gel (hexane/EtOAc) to afford the alcohol (557 mg, 100%) as a mixture of the stereoisomers (1:1 by ^{1}H NMR spectroscopy). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.41$–1.60 (m, 1H), 1.479 and 1.481 (2s, 1.5 and 1.5H), 1.82–2.02 (m, 2H), 2.14–2.29 (m, 1H), 2.30–2.39 (m, 1H), 2.40–2.64 (m, 2H), 2.70–2.82 (m, 1H), 3.770, 3.774 (2s, 1.5, 1.5H), 4.08–4.23 (m, 2H), 4.52–4.60 (m, 2H), 5.39–5.48 (m, 1H), 6.806, 6.812 (2d with fine couplings, $J=7$, 8 Hz, 2H), 7.06, 7.07 ppm (2d with fine couplings, $J=7$, 8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=19.67$, 19.70 (+), 28.4 (−), 33.3, 33.8 (−), 36.4, 37.7 (−), 45.9 (−), 48.0, 48.6 (+), 51.6, 51.8 (+), 55.1, 55.2 (+), 58.5, 58.6 (−), 111.56, 111.61 (−), 113.62, 113.65 (+), 121.33 (+), 128.22, 128.25 (+), 137.1, 137.2 (−), 142.4, 142.7 (−), 147.6, 147.7 (−), 157.8, 157.9 ppm (−).

2-Chloro-1-methylpyridinium iodide (836 mg, 3.27 mmol) was added to an ice-cold solution of the above alcohol (438 mg, 1.61 mmol), picolinic acid (275 mg, 2.23 mmol), Et_3N (0.66 mL, 4.76 mmol), and DMAP (208 mg, 1.70 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at RT overnight and diluted with saturated $NaHCO_3$. The resulting mixture was extracted with EtOAc three times. The combined extracts were washed with 1 N HCl and brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to picolinate **10b** (607 mg, 100% from **15**) as a mixture of the stereoisomers (1:1 by ^{1}H NMR spectroscopy). IR (neat): $\tilde{\nu}=1738$, 1718, 1512, 1246, 1126 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.48$ (s, 3H), 1.46–1.68 (m, 1H), 1.83–2.07 (m, 2H), 2.19–2.31 (m, 1H), 2.33–2.65 (m, 3H), 2.83–2.94 (m, 1H), 3.77, 3.78 (2s, 1.5, 1.5H), 4.55 (d with fine couplings, $J=10$ Hz, 2H), 4.87–5.05 (m, 2H), 5.49–5.58 (m, 1H), 6.80, 6.81 (2d with fine couplings, $J=9$, 9 Hz, 2H), 7.06, 7.09 (2d with fine couplings, $J=9$, 9 Hz, 2H), 7.43–7.51 (m, 1H), 7.84 (ddt, $J=3$, 2, 8 Hz, 1H), 8.15 (t with fine couplings, $J=8$ Hz, 1H), 8.72–8.84 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=19.6$, 19.7 (+), 28.6, 33.1, 33.6, 36.4, 38.0, 45.8 (for 3C, −), 47.8, 48.4 (+), 51.6 (+), 55.12, 55.14 (+), 62.08, 62.13 (−), 111.60, 111.65 (−), 113.61, 113.64 (+), 116.0, 116.1 (+), 125.15, 125.17 (+), 127.10, 126.82 (+), 128.21, 128.28 (+), 136.95, 136.98 (+), 136.95, 137.00 (−), 145.4, 145.6 (−), 147.5, 147.6 (−), 148.37, 148.39 (−), 149.87, 149.90 (+), 157.8, 157.9 (−), 165.2, 165.3 ppm (−); HRMS (FAB): *m/z*: calcd for $C_{24}H_{27}NO_3+H^+$: 378.2069 [M+H$^+$]; found: 378.2064.

1-Methoxy-4-[(1*S*,2*S*,5*R*)-2-(prop-1-en-2-yl)-5-vinylcyclohexyl]-benzene (16): MeMgBr (3.80 mL, 0.99 M in THF, 3.76 mmol) was added slowly to an ice-cold suspension of CuBr·Me_2S (389 mg, 1.89 mmol) and ZnI_2 (664 mg, 2.08 mmol) in THF (10 mL). The resulting mixture was stirred at 0 °C for 30 min and cooled to −78 °C. A solution of picolinate **10b** (*E*/*Z*=1:1, 471 mg, 1.25 mmol) in THF (15 mL) was added to the mixture dropwise. The resulting mixture was stirred at −78 °C for 1 h and quenched by addition of saturated NH_4Cl with vigorous stirring. The layers were separated and the aqueous layer was extracted with EtOAc twice. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford olefin **16** (310 mg, 92%): 97% regioselectivity, 98% stereoselectivity. $[\alpha]_D^{28}=+2.0$ ($c=0.76$ in $CHCl_3$), $[\alpha]_D^{26}=+3.2$ ($c=0.76$ in EtOH); lit.[20] $[\alpha]_D^{RT}=+3.1$ ($c=0.16$ in EtOH); IR (neat): $\tilde{\nu}=1643$, 1612, 1512, 1247 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.98$ (s, 3H), 1.48 (s, 3H), 1.35–1.72 (m, 4H), 1.77–1.86 (m, 2H), 2.23 (dt, $J=4$, 12 Hz, 1H), 2.68 (dt, $J=3$, 12 Hz, 1H), 3.76 (s, 3H), 4.51 (s with fine coupling, 1H), 4.53 (brs, 1H), 5.07 (dd, $J=18$, 1 Hz, 1H), 5.13 (dd, $J=11$, 1 Hz, 1H), 5.85 (dd, $J=18$, 11 Hz, 1H), 6.79 (d, $J=9$ Hz, 2H), 7.04 ppm (d, $J=9$ Hz, 2H); ^{13}C NMR (100 MHz, $CHCl_3$): $\delta=19.7$ (+), 29.1 (−), 31.6 (+), 37.6 (−), 37.8 (−), 42.8 (+), 47.6 (−), 51.5 (+), 55.2 (+), 111.2 (−), 112.6 (−), 113.6 (+), 128.3 (+), 138.1 (−), 146.3 (+), 148.6 (−), 157.6 ppm (−); HRMS (FAB): *m/z*: calcd for $C_{19}H_{26}O^+$: 270.1984 [M^+]; found: 270.1984; the ^{1}H NMR spectrum was consistent with that reported.[20]

Cyclobakuchiol A (1): PhSH (0.03 mL, 0.29 mmol) was added to a suspension of olefin **16** (51 mg, 0.188 mmol) and K_2CO_3 (20 mg, 0.148 mmol) in NMP (3.5 mL). The reaction was carried out at 220 °C overnight and quenched by addition of 1 N HCl. The resulting mixture was extracted with EtOAc three times. The combined extracts were dried over $MgSO_4$ and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford cyclobakuchiol A (**1**) (48 mg, 99%) as a solid: $[\alpha]_D^{21}=0$ ($c=0.40$ in $CHCl_3$); m.p. 66–69 °C; IR (nujol): $\tilde{\nu}=3260$, 1512, 1456, 1238, 827 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.98$ (s, 3H), 1.34–1.45 (m, 2H), 1.48 (s, 3H), 1.50–1.71 (m, 2H), 1.76–1.85 (m, 2H), 2.21 (dt, $J=4$, 12 Hz, 1H), 2.67 (dt, $J=3$, 12 Hz, 1H), 4.48–4.56 (m, 2H), 4.67 (brs, 1H), 5.07 (dd, $J=18$, 1 Hz, 1H), 5.13 (dd, $J=11$, 1 Hz, 1H), 5.85 (dd, $J=18$, 11 Hz, 1H), 6.71 (d with fine couplings, $J=8$ Hz, 2H), 6.99 ppm (d with fine couplings, $J=8$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=19.7$ (+), 29.0 (−), 31.6 (+), 37.6 (−), 37.8 (−), 42.8 (+), 47.5 (−), 51.5 (+), 111.2 (−), 112.6 (−), 115.1 (+), 128.6 (+), 138.3 (−), 146.3 (+), 148.6 (−), 153.4 ppm (−); HRMS (FAB): *m/z*: calcd for $C_{18}H_{22}O^+$: 256.1827 [M^+]; found: 256.1824; the ^{1}H and ^{13}C NMR spectra were consistent with those reported.[1]

1-Methoxy-4-[(1*S*,2*S*)-2-(prop-1-en-2-yl)-5-propylidenecyclohexyl]benzene (17): MeMgBr (0.44 mL, 0.99 M in THF, 0.43 mmol) was added slowly to an ice-cold suspension of CuBr·Me_2S (40 mg, 0.20 mmol) in THF (1 mL). The resulting mixture was stirred at 0 °C for 30 min and cooled to −40 °C. A solution of picolinate **10b** (*E*/*Z*=1:1, 50 mg, 0.13 mmol) in THF (1 mL) was added to the mixture dropwise. The resulting mixture was allowed to warm to −10 °C over 1 h and diluted with saturated NH_4Cl with vigorous stirring. The layers were separated and the aqueous layer was extracted with EtOAc twice. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford olefin **17** as a 1:1 mixture of the *E* and *Z* isomers (35 mg, 98%). 97% regioselectivity; $[\alpha]_D^{20}=-58$ ($c=0.63$ in $CHCl_3$); IR (neat): $\tilde{\nu}=$ 3070, 1513, 1247, 1039, 826 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$ 0.94 and 0.97 (2t, $J=8$, 8 Hz, 1.5, 1.5H), 1.45–1.47 (m, 1H), 1.48 (s, 3H), 1.79–1.94 (m, 2H), 1.94–2.11 (m, 2H), 2.11–2.23 (m, 1H), 2.23–2.37 (m, 1H), 2.37–2.56 (m, 2H), 2.71 (dd, $J=11$, 2 Hz, 1H), 3.77, 3.78 (2s, 1.5, 1.5H), 4.52 (brs, 1H), 4.55 (brs, 1H), 5.14, 5.18 (2t, $J=$ 7, 7 Hz, 0.5, 0.5H), 6.79, 6.81 (2d, $J=8$, 8 Hz, 1, 1H), 7.06, 7.08 ppm

(2d, $J=8$, 8 Hz, 1, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=14.9$ (+), 19.8 (+), 20.5, 20.6 (−), 28.1 (−), 33.5, 34.2 (−), 36.5, 37.7 (−), 46.1 (−), 48.2, 48.9 (−), 51.96, 52.01 (+), 55.20 (+), 111.4 (−), 113.59, 113.63 (+), 124.25, 124.34 (+), 128.31, 128.34 (+), 137.6, 137.7 (−), 137.8 (−), 148.14, 148.17 (−), 157.75, 157.82 ppm (−); HRMS (FAB): *m/z*: calcd for $C_{19}H_{26}O+Na^+$: 293.1881 [*M*+Na^+]; found: 293.1888.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan.

Keywords: allylic substitution · asymmetric synthesis · copper · magnesium · synthesis design

[1] C. N. Backhouse, C. L. Delporte, R. E. Negrete, B. K. Cassels, C. Schneider, E. Breitmaier, A. S. Feliciano, *Phytochemistry* **1995**, *40*, 325–327.
[2] S. Yin, C.-Q. Fan, J.-M. Yue, *J. Asian Nat. Prod. Res.* **2007**, *9*, 29–33.
[3] C. N. Backhouse, C. L. Delporte, R. E. Negrete, S. Erazo, A. Zuñiga, A. Pinto, B. K. Cassels, *J. Ethnopharmacol.* **2001**, *78*, 27–31.
[4] Y. Kaneko, Y. Kiyotsuka, H. P. Acharya, Y. Kobayashi, *Chem. Commun.* **2010**, *46*, 5482–5484.
[5] a) M. Kato, M. Watanabe, B. Vogler, Y. Tooyama, A. Yoshikoshi, *J. Chem. Soc. Chem. Commun.* **1990**, 1706–1707; b) C. Siegel, P. M. Gordon, D. B. Uliss, G. R. Handrick, H. C. Dalzell, R. K. Razdan, *J. Org. Chem.* **1991**, *56*, 6865–6872.
[6] We used (1*R*)-**5** with $[\alpha]_D^{20}=-19$ to -23 (neat) and (1*S*)-**5** with $[\alpha]_D^{20}=+21$ to $+23$ (neat), purchased from Tokyo Chemical Industry and Aldrich, respectively. Note that the *ee* of (1*R*)-**5** ($[\alpha]_D^{21}=-22$ (neat)) available from Aldrich is 97%.
[7] J. Tsuji, I. Minami, I. Shimizu, *Tetrahedron Lett.* **1983**, *24*, 5639–5640.
[8] Formation of π-allyl Pd-H species from enone **7** might be involved.
[9] J. Grimshaw, J. T. Grimshaw, H. R. Juneja, *J. Chem. Soc. Perkin Trans. 1* **1972**, 50–52.
[10] a) M. Watanabe, B. Z. Awen, M. Kato, *J. Org. Chem.* **1993**, *58*, 3923–3927; b) H. Kosugi, J. Ku, M. Kato, *J. Org. Chem.* **1998**, *63*, 6939–6946.
[11] N. Miyoshi, T. Yamamoto, N. Kambe, S. Murai, N. Sonoda, *Tetrahedron Lett.* **1982**, *23*, 4813–4816.
[12] O. H. Oldenziel, D. van Leusen, A. M. van Leusen, *J. Org. Chem.* **1977**, *42*, 3114–3118.
[13] Aldol with MeCHO followed by elimination: a) Y. Hayashi, S. Orikasa, K. Tanaka, K. Kanoh, Y. Kiso, *J. Org. Chem.* **2000**, *65*, 8402–8405; b) A. Kuramochi, H. Usuda, K. Yamatsugu, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, *127*, 14200–14201; c) I. L. Jones, F. K. Moore, C. L. L. Chai, *Org. Lett.* **2009**, *11*, 5526–5529.
[14] Addition to vinyl sulfoxide followed by elimination: a) R. H. van der Veen, C. Kruk, H. Cerfontain, *J. Am. Chem. Soc.* **1983**, *105*, 4367–4374; b) R. H. van der Veen, H. Cerfontain, *J. Chem. Soc. Perkin Trans. 1* **1985**, 661–668.
[15] Addition to TMS acetylene/$GaCl_3$: a) M. Yamaguchi, T. Tsukagoshi, M. Arisawa, *J. Am. Chem. Soc.* **1999**, *121*, 4074–4075; b) M. Arisawa, C. Miyagawa, S. Yoshimura, Y. Kido, M. Yamaguchi, *Chem. Lett.* **2001**, 1080–1081.
[16] Addition to $PhSeCH_2CHO$ followed by elimination: a) D. L. J. Clive, C. G. Russell, *J. Chem. Soc. Chem. Commun.* **1981**, 434–436; b) R. Tanaka, K. Ohishi, N. Takanashi, T. Nagano, H. Suizu, T. Suzuki, S. Kobayashi, *Org. Lett.* **2012**, *14*, 4886–4889.
[17] Reaction with CH_2=CHBr/Pd cat.: A. Chieffi, K. Kamikawa, J. Åhman, J. M. Fox, S. L. Buchwald, *Org. Lett.* **2001**, *3*, 1897–1900.
[18] Reaction with vinyl ether–iron complex followed by elimination: a) T. C. T. Chang, M. Rosenblum, S. B. Samuels, *J. Am. Chem. Soc.* **1980**, *102*, 5930–5931; b) T. C. T. Chang, M. Rosenblum, N. Simms, *Org. Synth.* **1993**, *66*, 95–107.
[19] The enol ether (crude) as the 1:1 *E/Z* mixture was characterized by ^1H and ^{13}C NMR spectroscopy (see the Supporting Information). Since the ether was chemically unstable, purification was unsuccessful.
[20] A. S. C. P. Rao, U. R. Nayak, S. Dev, *Tetrahedron* **1974**, *30*, 1107–1114.
[21] Y. Kiyotsuka, H. P. Acharya, Y. Katayama, T. Hyodo, Y. Kobayashi, *Org. Lett.* **2008**, *10*, 1719–1722.
[22] A. D. William, Y. Kobayashi, *J. Org. Chem.* **2002**, *67*, 8771–8782.

Received: September 7, 2013
Published online on November 22, 2013