Tetrahedron 71 (2015) 2387–2392

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Further study on synthesis of the cyclobakuchiols

Hidehisa Kawashima, Masahiro Sakai, Yuki Kaneko, Yuichi Kobayashi *

Department of Bioengineering, Tokyo Institute of Technology, Box B-52, Nagatsuta-cho 4259, Midori-ku, Yokohama 226-8501, Japan

ARTICLE INFO

Article history:
Received 5 January 2015
Received in revised form 25 February 2015
Accepted 27 February 2015
Available online 5 March 2015

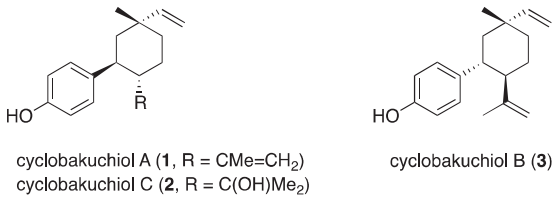
Keywords:
Cyclobakuchiol
Quinic acid
Beta-pinene
Allylic substitution
Quaternary carbon

ABSTRACT

Two results are described. First, quinic acid was transformed into the monoacetate of 2-cyclohexene-1,4-diol. The Ni-catalyzed allylic substitution of the monoacetate with CH_2=C(Me)MgBr/$ZnCl_2$/TMEDA followed by oxidation of the resulting S_N2-type product afforded the 4-(CH_2=C(Me))-substituted 2-cyclohexenone. $BF_3{\cdot}OEt_2$-assisted 1,4-addition of the enone with $(4\text{-}MeOC_6H_4)_2Cu(MgBr){\cdot}MgBr_2$ furnished the ketone, which is the key intermediate for the synthesis of cyclobakuchiols A and C. Second, the allylic picolinate with CMe_2(OTES) and 4-$MeOC_6H_4$ groups at 3 and 4 positions of the cyclohexane ring was synthesized through 1,4-addition of $(4\text{-}MeOC_6H_4)_2Cu(MgBr){\cdot}MgBr_2$ to 4-(CMe_2(OTES))-2-cyclohexenone. Allylic substitution of this picolinate followed by deprotection furnished cyclobakuchiol C. Furthermore, the methyl ether of cyclobakuchiol C was transformed to cyclobakuchiol A.

1. Introduction

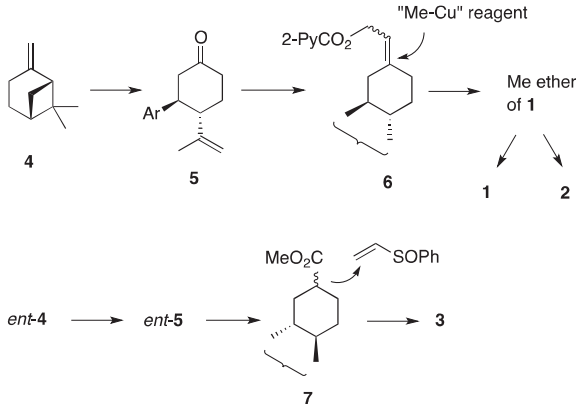
Cyclobakuchiols A and B (**1**, **3**), isolated as a mixture from *Psoralea glandulosa* L. in 1995, exhibit antipyretic and *anti*-inflammatory properties.[1,2] The structurally related cyclobakuchiol C (**2**) was isolated in 2007 from *Psoralea coryllfolia*,[3] although its biological properties have not yet been revealed (Fig. 1). One of the structural feature common to the cyclobakuchiols is a quaternary carbon on the ring possessing vinyl and methyl groups. We recently reported[4] synthesis of cyclobakuchiols A–C (**1**–**3**), and elucidated the absolute configuration for each by comparing their specific rotations with those reported. Ketone **5**, which is the intermediate for the synthesis of **1** and **2**, was synthesized from (+)-β-pinene (**4**) and subsequently transformed into allylic picolinate **6**, which upon allylic substitution[5] with $Me_2Cu(MgBr){\cdot}MgBr_2/ZnI_2$ gave the methyl ether of **1** (Scheme 1). Furthermore, this ether was converted into **2** through epoxidation. On the other hand, the addition of the cyclohexane ester **7**, derived from *ent*-**5**, to CH_2=CHSOPh followed by elimination of the SOPh moiety furnished **3**. Afterward, we have continued synthetic study to develop another approach to the intermediates and/or cyclobakuchiols in connection with biological investigation. Herein, we report alternative synthesis of ketone **5** from quinic acid (**8**) and that of cyclobakuchiol C (**2**) through the cyclohexenone **11**, which is available from *ent*-**4**[4] (Scheme 2). Furthermore, conversion of a cyclobakuchiol C derivative to cyclobakuchiol A (**1**) is presented as well.



cyclobakuchiol A (**1**, R = $CMe{=}CH_2$)
cyclobakuchiol C (**2**, R = $C(OH)Me_2$)

cyclobakuchiol B (**3**)

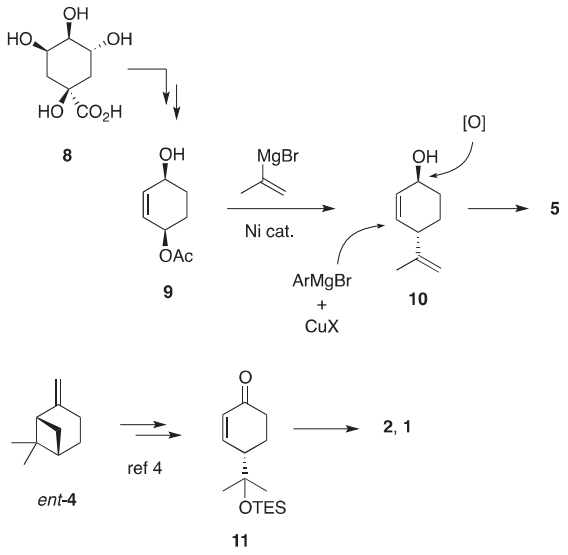
Fig. 1. Cyclobakuchiols A, B, and C.



Scheme 1. The previous synthesis of cyclobakuchiols A–C. Ar: 4-$(MeO)C_6H_4$.

* Corresponding author. Tel./fax: +81 45 924 5789; e-mail address: ykobayas@bio.titech.ac.jp (Y. Kobayashi).

http://dx.doi.org/10.1016/j.tet.2015.02.092
0040-4020/

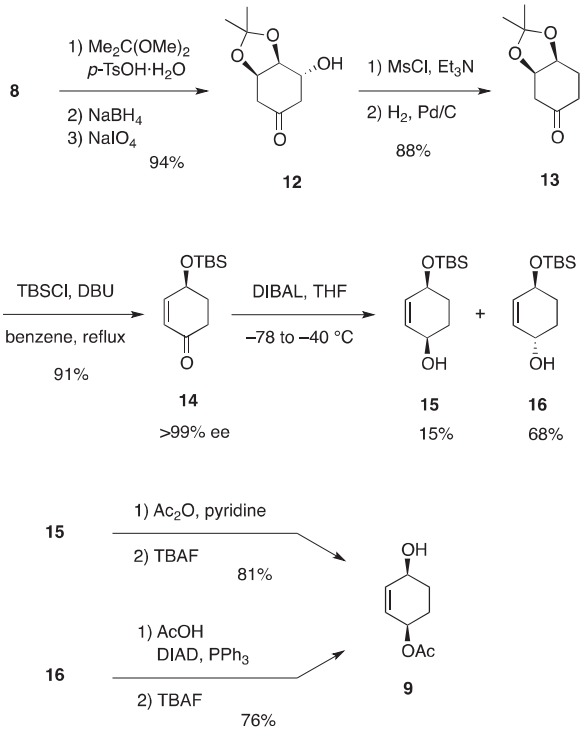


Scheme 2. The present study. Ar: 4-(MeO)C_6H_4.

2. Results and discussion

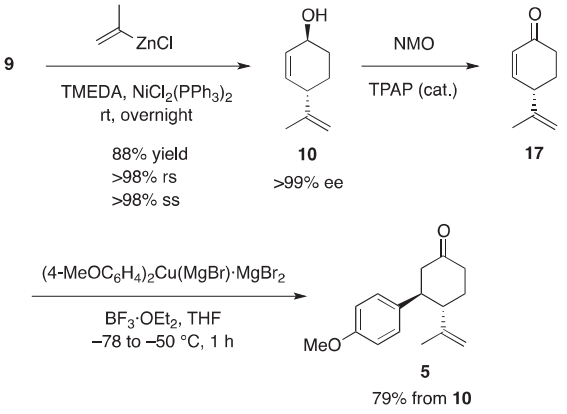
The key step in the previous synthesis of cannabidiol was the nickel-catalyzed allylic substitution of monoacetate **9** with CH_2=C(Me)MgBr/$ZnCl_2$/TMEDA, which proceeds with rarely attainable S_N2-type selectivity giving **10** (Scheme 2).[6] We envisioned that oxidation of **10** and subsequent 1,4-addition of the resulting enone with a 4-$MeOC_6H_4$ reagent would afford the key intermediate **5**.

Monoacetate **9** has been synthesized from cyclohexa-1,3-diene in a racemic form[7] and in an optically active form by enzymatic hydrolysis.[8] In the latter hydrolysis, the use of the enzymes that are somewhat uncommon in organic laboratories is inevitable to attain high enantiomeric purity. We envisioned a method using enone **14**, which can be prepared from quinic acid (**8**)[9] (Scheme 3). In practice, enone **14** was obtained with >99% ee as determined by chiral HPLC in yields compatible to those reported.[9] DIBAL reduction of **14** afforded a diastereomeric mixture of **15** and **16**.[10] The products were separated by chromatography on silica gel, and both were subsequently transformed into monoacetate **9** by reactions indicated in the scheme. The combined yield of **9** from enone **14** through **15** and **16** was 64%.



Scheme 3. Synthesis of the monoacetate.

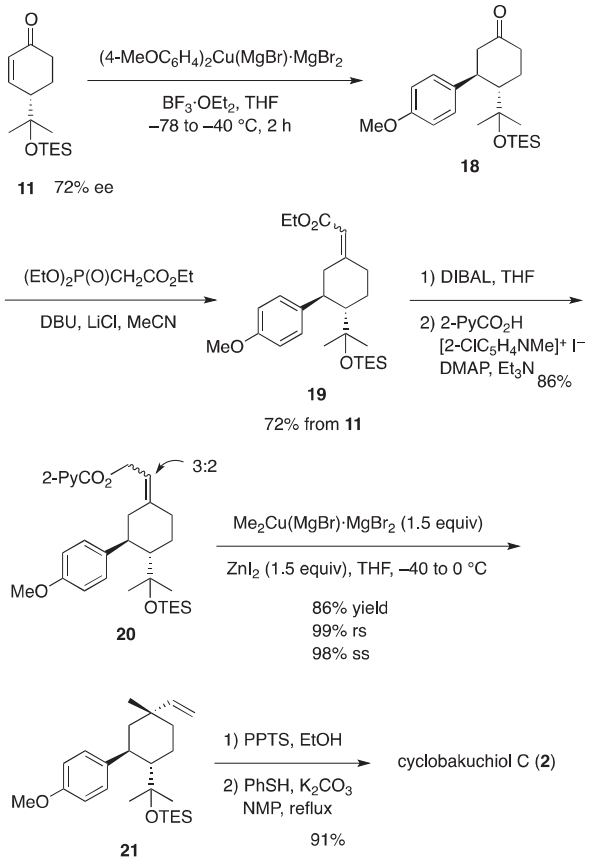
According to our procedure,[6] monoacetate **9** was subjected to Ni-catalyzed allylic substitution with CH_2=C(Me)ZnCl derived from CH_2=C(Me)MgBr and $ZnCl_2$ in the presence of TMEDA to furnish the S_N2 product **10** in 88% yield (Scheme 4).[11] The high regioselectivity (rs) and stereoselectivity (ss) were determined by ^{1}H NMR spectroscopy. Oxidation of **10** with NMO/TPAP (cat.) proceeded well to afford enone **17**, which was somewhat volatile. Consequently, without further purification, crude enone **17** was subjected to a BF_3·OEt_2-assisted 1,4-addition reaction with (4-$MeOC_6H_4)_2$Cu(MgBr)·$MgBr_2$ (prepared from 4-$MeOC_6H_4$MgBr and CuBr·Me_2S in a 2:1 ratio) to produce ketone **5** in 79% yield from **10** after chromatography. The total yield of **5** from quinic acid (**8**) was 33%.



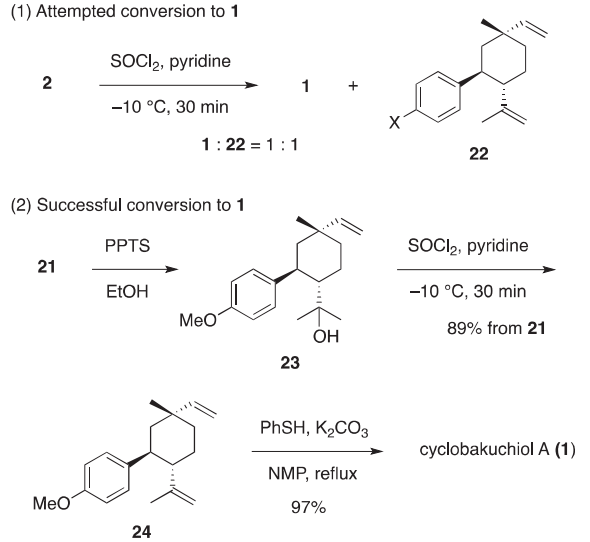
Scheme 4. Synthesis of the ketone intermediate **5**.

Previously, the (−)-isomer of β-pinene (*ent*-**4**), the inexpensive enantiomer, was transformed into enone **11**.[4] Although the ee was somewhat low,[12] conversion of **11** to cyclobakuchiols A and C would provide an opportunity to synthesize a certain set of analogs as well for biological investigation. Toward the end, the 1,4-addition of BF_3·OEt_2-activated enone **11** with (4-$MeOC_6H_4)_2$Cu(MgBr)·$MgBr_2$ afforded ketone **18**, which was converted to ester **19** as a mixture of the olefinic isomers in 72% yield from enone **11** (Scheme 5). This ester was transformed to allylic picolinate **20** (ca. 3:2 mixture) in 86% yield. Without separation of the olefinic isomers, this picolinate was subjected to ZnI_2-assisted allylic substitution with Me_2Cu(MgBr)·$MgBr_2$ (derived from MeMgBr and CuBr·Me_2S in the 2:1 ratio) to afford **21** in 86% yield with high regio- and stereoselectivity, as determined by ^{1}H NMR spectroscopy.[13] Finally, the TES and the Me protecting groups in **21** were removed by the reactions indicated in the scheme, thus furnishing **2** in 91% yield.

To synthesize cyclobakuchiol A (**1**), we first attempted dehydration of **2** with $SOCl_2$ in pyridine at −10 °C for 30 min (Scheme 6). However, the product was a mixture of **1** and **22**[14] in a 1:1 ratio. By analogy of the substitution of phenol with PCl_5 to chlorobenzene,[15] X is likely chlorine. We then focused on dehydration of the methyl ether of **2** (i.e., **23**) derived from **21** by desilylation with PPTS in EtOH (Scheme 6). In practice, dehydration with $SOCl_2$ gave **24** cleanly in 89% yield over two steps. Finally, exposure of **24** to PhSH and K_2CO_3 in refluxing NMP furnished **1**.



Scheme 5. Synthesis of cyclobakuchiol C.



Scheme 6. Synthesis of cyclobakuchiol A.

3. Conclusion

In conclusion, we developed a synthesis of the ketone intermediate **5** starting from quinic acid (**8**) and a transformation of enone **11** to **2** and **1**. These methods in combination with the previous synthesis of cyclobakuchiols A–C would provide analogs as well for biological study of cyclobakuchiols.

4. Experimental

4.1. General

The ^{1}H NMR (300 or 400 MHz) and ^{13}C NMR (75 or 100 MHz) spectra were measured in $CDCl_3$ using $SiMe_4$ (δ=0 ppm), residual $CHCl_3$ (δ=7.26 ppm), and the center line of $CDCl_3$ triplet (δ=77.1 ppm) as internal standards, respectively. 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 carbons are accompanied by minus (for C and CH_2) and plus (for CH and CH_3) signs of the attached proton test (APT) experiments.

4.2. Synthesis of the key intermediate

*4.2.1. (3aR,7R,7aS)-7-Hydroxy-2,2-dimethyltetrahydrobenzo[d][1,3]dioxol-5(6H)-one (**12**).* A suspension of D-(−)-quinic acid (**8**) (1.52 g, 7.89 mmol), 2,2-dimethoxypropane (3.50 mL, 28.6 mmol), and *p*-TsOH·H_2O (151.7 mg, 0.80 mmol) in acetone (78 mL) was stirred for 1 h under reflux, and Et_3N (0.3 mL, 2.2 mmol) was added to the mixture. The resulting mixture was concentrated and the residual oil was purified by chromatography on silica gel (hexane/EtOAc) to afford the corresponding lactone (1.64 g, 98%) as solids: $[\alpha]_D^{19}$ −36 (*c* 0.80, $CHCl_3$); lit.[9a] $[\alpha]_{586}^{25}$ −34.46 (*c* 1.625, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.52 (s, 3H), 2.21 (dd, J=15, 3 Hz, 1H), 2.29–2.45 (m, 2H), 2.63 (d, J=12 Hz, 1H), 3.45 (s, 1H), 4.31 (dq, J=6, 2 Hz, 1H), 4.45–4.53 (m, 1H), 4.72 (dd, J=6, 2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3, 27.0, 34.3, 38.1, 71.5, 71.6, 72.1, 75.9, 109.8, 179.0. The ^{1}H and ^{13}C NMR spectra were consistent with those reported.[9a,9d]

To an ice-cold solution of the above lactone (1.59 g, 7.42 mmol) in EtOH (60 mL) was added $NaBH_4$ (755 mg, 20.0 mmol) portionwise. The mixture was stirred at 0 °C for 2.5 h and diluted with acetone (6.0 mL, 81.4 mmol). The mixture was concentrated, and the residue was dried for 2 days under reduced pressure for the next reaction.

To an ice-cold solution of the above triol in phosphate buffer (pH 7, 50 mL) was added sodium periodate (1.87 g, 8.74 mmol) in portions. After the addition, the mixture was stirred at room temperature for 1 h and extracted with CH_2Cl_2 repeatedly. The combined extracts were dried over $MgSO_4$ and concentrated. The crude product was purified by chromatography on silica gel (hexane/EtOAc) to afford hydroxy ketone **12** (1.32 g, 96%): $[\alpha]_D^{19}$ +135 (*c* 0.92, $CHCl_3$); lit.[9b] $[\alpha]_D$ +141.24 (*c* 0.89, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (s, 3H), 1.45 (s, 3H), 1.99 (br s, 1H), 2.47 (dm, J=18 Hz, 1H), 2.66 (d, J=3 Hz, 1H), 2.71 (d, J=3 Hz, 1H), 2.82 (dd, J=18, 4 Hz, 1H), 4.25 (br s, 1H), 4.32 (dt, J=7, 2 Hz, 1H), 4.72 (dt, J=7, 3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9, 26.4, 40.2, 41.6, 67.9, 72.2, 74.9, 108.8, 208.9. The ^{1}H spectrum was consistent with that reported.[9b]

*4.2.2. (3aR,7aS)-2,2-Dimethyltetrahydrobenzo[d][1,3]dioxol-5(6H)-one (**13**).* To an ice-cold solution of alcohol **12** (3.53 g, 19.1 mmol) and Et_3N (8.0 mL, 57.4 mmol) in CH_2Cl_2 (120 mL) was added a solution of MsCl (1.80 mL, 23.0 mmol) in CH_2Cl_2 (15 mL) over a period of 10 min. The mixture was stirred at room temperature for 2 h and diluted with satd $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2 twice. 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 give the corresponding enone (2.95 g, 92%): $[\alpha]_D^{19}$ +138 (*c* 0.54, $CHCl_3$); lit.[9c] $[\alpha]_D$ +147.5 (*c* 0.48, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (s, 3H), 1.39 (s, 3H), 2.69 (dd, J=18, 4 Hz, 1H), 2.93 (dm, J=18 Hz, 2H), 4.65–4.76 (m, 2H), 6.03 (d, J=10 Hz, 1H), 6.45 (ddd, J=10, 3, 2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.9, 28.1, 39.1, 71.4,

73.7, 110.2, 129.2, 146.2, 195.6. The ^{1}H and ^{13}C NMR spectra were consistent with those reported.[9c]

A mixture of the above enone (2.50 g, 14.8 mmol) and 10% Pd/C (321 mg, 3.02 mmol) in EtOAc (150 mL) under hydrogen was stirred at room temperature overnight and filtered through a pad of Celite. The filtrate was concentrated and the residual oil was purified by chromatography on silica gel (hexane/EtOAc) to give ketone **13** (2.41 g, 96%): $[\alpha]_D^{20}$ +128 (*c* 0.97, $CHCl_3$); lit.[9b] $[\alpha]_D$ +154.38 (*c* 0.78, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 3H), 1.44 (s, 3H), 1.88 (tm, *J*=14 Hz, 1H), 2.03–2.15 (m, 1H), 2.25 (dm, *J*=18 Hz, 1H), 2.41–2.54 (m, 2H), 2.67 (dd, *J*=18, 3 Hz, 1H), 4.54–4.60 (m, 1H), 4.64–4.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.1, 25.8, 26.2, 33.7, 42.2, 71.7, 73.1, 107.9, 210.1. The ^{1}H spectrum was consistent with that reported.[9b]

*4.2.3. (S)-4-((tert-Butyldimethylsilyl)oxy)cyclohex-2-enone (**14**).* To a solution of ketone **13** (3.50 g, 20.6 mmol) and DBU (3.50 mL, 22.6 mmol) in benzene (120 mL) was added TBSCl (3.30 g, 21.8 mmol). The solution was stirred at room temperature for 10 min and heated to reflux. After 2 h, DBU (0.90 mL, 5.9 mmol) was added again and the mixture was stirred further for 1.5 h under reflux. The reaction mixture was washed sequentially with water, phosphate buffer (pH 4), satd $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$ and concentrated to give a residue. Chromatography of the residue on silica gel (hexane/EtOAc) afforded enone **14** (4.26 g, 91%): >99% ee by HPLC (Chiralcel OD-H, hexane/*i*-PrOH=99:1, 1 mL/min, 20 °C, t_R/min=7.0 (*S*-isomer, major), 8.3 (*R*-isomer, minor)); $[\alpha]_D^{20}$ −97 (*c* 1.26, $CHCl_3$); lit.[10b] $[\alpha]_D^{20}$ −102.0 (*c* 2.0, $CHCl_3$) for 98% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 3H), 0.09 (s, 3H), 0.88 (s, 9H), 1.96 (ddt, *J*=9, 4, 13 Hz, 1H), 2.17 (ddq, *J*=13, 1, 5 Hz, 2H), 2.30 (ddd, *J*=17, 13, 5 Hz, 1H), 2.53 (dt, *J*=17, 4 Hz, 1H), 4.45–4.52 (m, 1H), 5.88 (dm, *J*=10 Hz, 1H), 6.79 (dt, *J*=10, 2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.8 (+), −4.6 (+), 18.1 (−), 25.7 (+), 32.9 (−), 35.5 (−), 67.0 (+), 128.7 (+), 153.8 (+), 198.7 (−). The ^{1}H and ^{13}C NMR spectra were consistent with those reported.[9b,16]

*4.2.4. (1R,4S)-4-((tert-Butyldimethylsilyl)oxy)cyclohex-2-enol (**15**) and (1S,4S)-4-((tert-butyldimethylsilyl)oxy)cyclohex-2-enol (**16**).* To a solution of enone **14** (4.16 g, 18.4 mmol) in THF (100 mL) was added DIBAL (1.07 M in hexane, 26.0 mL, 27.6 mmol) dropwise at −78 °C, and the solution was allowed to warm to −40 °C over 1 h before addition of MeOH (22 mL, 552 mmol), H_2O (10 mL, 552 mmol), and NaF (23 g, 552 mmol). The resulting mixture was stirred at room temperature overnight and filtered through a pad of Celite. The filtrate was concentrated and the residual oil was purified by chromatography on silica gel (hexane/EtOAc) to afford *cis* alcohol **15** (612 mg, 15%) and *trans* alcohol **16** (2.85 g, 68%) separately. *Cis* alcohol **15**: $[\alpha]_D^{20}$ −23 (*c* 0.67, EtOH); lit.[10a] $[\alpha]_D$ −30 (*c* 0.40, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.068 (s, 3H), 0.071 (s, 3H), 0.89 (s, 9H), 1.61–1.88 (m, 5H), 4.04–4.17 (m, 2H), 5.74 (dd, *J*=10, 2 Hz, 1H), 5.79 (dd, *J*=10, 3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.6 (+), −4.5 (+), 18.3 (−), 25.9 (+), 28.3 (−), 28.6 (−), 64.9 (+), 66.4 (+), 130.7 (+), 134.2 (+). The ^{1}H NMR and ^{13}C NMR spectra were consistent with those reported.[7b] *Trans* alcohol **16**: $[\alpha]_D^{20}$ −99 (*c* 0.77, $CHCl_3$); lit.[10a] $[\alpha]_D$ −96 (*c* 0.96, $CHCl_3$) for 96% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.07 (s, 3H), 0.89 (s, 9H), 1.38–1.57 (m, 2H), 1.76 (br s, 1H), 1.95–2.02 (m, 1H), 2.07–2.14 (m, 1H), 4.25 (t, *J*=6 Hz, 2H), 5.68 (d, *J*=10 Hz, 1H), 5.74 (d, *J*=10 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.6 (+), −4.5 (+), 18.3 (−), 25.9 (+), 30.9 (−), 31.1 (−), 66.6 (+), 67.1 (+), 131.8 (+), 133.8 (+). The ^{1}H NMR and ^{13}C NMR spectra were consistent with those published.[17]

*4.2.5. (1R,4S)-4-Hydroxycyclohex-2-en-1-yl acetate (**9**).* **From 15**: A solution of alcohol **15** (309 mg, 1.35 mmol) and acetic anhydride (0.65 mL, 6.88 mmol) in pyridine (0.85 mL, 10.6 mmol) was stirred at room temperature for 3 h and diluted with Et_2O and satd $NaHCO_3$. The resulting mixture was stirred for 30 min and extracted with Et_2O twice. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to afford the corresponding acetate, which was used for the next reaction without purification.

A solution of the above acetate and TBAF (1.0 M in THF, 2.0 mL, 2.0 mmol) in THF (10 mL) was stirred at room temperature for 1 h and diluted with satd NH_4Cl. The resulting mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by chromatography on silica gel (hexane/EtOAc) to give monoacetate **9** (172 mg, 81% from alcohol **15**): $[\alpha]_D^{20}$ +87 (*c* 0.47, $CHCl_3$); lit.[8b] $[\alpha]_D^{25}$ +70.0 ($CHCl_3$) for 79% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.70–1.94 (m, 4H), 2.06 (s, 3H), 2.33 (br s, 1H), 4.14–4.23 (m, 1H), 5.15–5.21 (m, 1H), 5.79 (ddd, *J*=10, 4, 2 Hz, 1H), 5.97 (dd, *J*=10, 4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3 (+), 25.0 (−), 28.2 (−), 65.4 (+), 67.3 (+), 127.9 (+), 134.9 (+), 170.8 (−). The ^{1}H NMR and ^{13}C NMR spectra were consistent with those reported.[16]

From 16: To an ice-cold solution of alcohol **16** (2.85 g, 12.5 mmol) in toluene (120 mL) were added diisopropyl azodicarboxylate (3.70 mL, 19.1 mmol), triphenylphosphine (4.90 g, 18.7 mmol), and acetic acid (1.10 mL, 19.2 mmol). The mixture was stirred at 0 °C for 1.5 h and diluted with satd $NaHCO_3$ 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. Chromatography of the residue on silica gel (hexane/EtOAc) afforded the corresponding acetate, which was used for the next reaction.

A solution of the above acetate and TBAF (25.0 mL, 1.0 M in THF, 25.0 mmol) in THF (100 mL) was stirred at room temperature overnight and diluted with satd 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 **9** (1.48 g, 76% from alcohol **16**). The ^{1}H NMR spectrum was consistent with that obtained from alcohol **15**.

*4.2.6. (1S,4S)-4-(Prop-1-en-2-yl)cyclohex-2-enol (**10**).* To a solution of $ZnCl_2$ (1.67 g, 12.3 mmol) and TMEDA (1.92 mL, 12.9 mmol) in THF (15 mL) was added CH_2=C(Me)MgBr (0.82 M in THF, 12.3 mL, 10.1 mmol). The mixture was stirred at room temperature for 10 min to produce CH_2=C(Me)ZnCl for the reaction with monoacetate **9**. To another ice-cold flask containing $NiCl_2(PPh_3)_2$ (1.00 g, 1.53 mmol) and THF (5 mL) was added CH_2=C(Me)MgBr (0.82 M in THF, 5.61 mL, 4.60 mmol). The mixture was stirred at room temperature for 10 min and cooled to 0 °C. The solution of CH_2=C(Me)ZnCl, prepared above, was transferred to the mixture. The resulting mixture was stirred at room temperature for 20 min, at which time a solution of **9** (479 mg, 3.07 mmol) in THF (5+5 mL) was injected. The reaction was carried out at room temperature overnight, and quenched by addition of satd NH_4Cl. The resulting mixture was extracted with Et_2O four times. The combined organic extracts were washed with brine twice, dried over $MgSO_4$, and concentrated to afford an oil, which was purified by chromatography on silica gel to give **10** (372 mg, 88%): >99% ee by HPLC (Chiralcel OD-H, hexane/*i*-PrOH=99/1, 1 mL/min, 25 °C, t_R/min=18.5 (*S*-isomer, major), 19.3 (*R*-isomer, minor)); $[\alpha]_D^{21}$ −192 (*c* 0.554, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43–1.57 (m, 3H), 1.61 (br s, 1H), 1.72 (s, 3H), 1.86–1.97 (m, 1H), 1.99–2.13 (m, 1H), 2.74–2.81 (m, 1H), 4.19–4.26 (m, 1H), 4.69–4.71 (m, 1H), 4.75–4.78 (m, 1H), 5.69 (dddd, *J*=10, 3, 1.5, 1 Hz, 1H), 5.79 (ddt, *J*=10, 1, 2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9 (+), 25.6 (−), 31.4 (−), 43.0 (+), 66.4 (+), 110.7 (−), 131.1 (+), 132.5 (+), 147.9 (−); HRMS (EI) calcd for $C_9H_{14}O$ [M^+] 138.1045, found 138.1046. The ^{1}H NMR and ^{13}C NMR spectra were consistent with those published.[6] The regioselectivity (>98%) and the stereoselectivity (>98%) of **10** were determined by comparison of the ^{1}H

NMR data of the crude product with those reported for the regioisomer[6] and the stereoisomer[18] (*cis* isomer of **10**).

*4.2.7. (3S,4S)-3-(4-Methoxyphenyl)-4-(prop-1-en-2-yl)cyclohexanone (**5**).* To a suspension of molecular sieves 4A (1.03 g) in CH_2Cl_2 (10 mL) were added 4-methylmorpholine *N*-oxide (479 mg, 4.09 mmol), tetrapropylammonium perruthenate (84.2 mg, 0.240 mmol), and a solution of alcohol **10** (371 mg, 2.67 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at room temperature for 2 h and filtered through a pad of Celite. The filtrate was concentrated to afford enone **17**, which was passed through a pad of silica gel for the next reaction.

To an ice-cold suspension of $CuBr\cdot Me_2S$ (830 mg, 4.04 mmol) in THF (10 mL) was added 4-$MeOC_6H_4MgBr$ (0.91 M in THF, 8.86 mL, 8.06 mmol) dropwise. The mixture was stirred at 0 °C for 30 min and cooled to −78 °C. A solution of the above enone and $BF_3\cdot OEt_2$ (0.51 mL, 4.06 mmol) in THF (10 mL) was added to the mixture. After the addition, the mixture was allowed to warm to −50 °C over 1 h and diluted with satd 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 an oil. Chromatography of the residual oil on silica gel (hexane/EtOAc) afforded ketone **5** (516 mg, 79% from alcohol **10**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (s, 3H), 1.80–1.92 (m, 1H), 2.05–2.14 (m, 1H), 2.46–2.58 (m, 4H), 2.71 (dt, *J*=3, 12 Hz, 1H), 2.93 (dt, *J*=6, 11 Hz, 1H), 3.78 (s, 3H) 4.63 (s, 1H), 4.65 (s, 1H), 6.82 (dm, *J*=9 Hz, 2H), 7.07 (dm, *J*=9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6 (+), 31.8 (−), 41.3 (−), 47.5 (+), 50.0 (−), 50.3 (+), 55.2 (+), 112.7 (−), 113.9 (+), 128.2 (+), 135.3 (−), 146.2 (−), 158.2 (−), 210.5 (−). The ^{1}H and ^{13}C NMR spectra were identical with that reported.[4]

4.3. Synthesis of cyclobakuchiol C

*4.3.1. Ethyl 2-((3S,4S)-3-(4-methoxyphenyl)-4-(2-((triethylsilyl)oxy)propan-2-yl)cyclohexylidene)acetate (**19**).* To an ice-cold suspension of $CuBr\cdot Me_2S$ (169 mg, 0.824 mmol) in THF (3 mL) was added 4-$MeOC_6H_4MgBr$ (1.87 mL, 0.87 M in THF, 1.63 mmol) dropwise. The mixture was stirred at 0 °C for 30 min and cooled to −78 °C. A solution of enone **11** (146 mg, 0.543 mmol) and $BF_3\cdot OEt_2$ (0.10 mL, 0.810 mmol) in THF (2 mL) was added. The mixture was allowed to warm to −40 °C over 2 h and diluted with satd NH_4Cl. The product was extracted with EtOAc three times. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to give crude ketone **18**, which was passed through a short silica gel column for the next reaction.

To an ice-cold suspension of LiCl (94.2 mg, 2.22 mmol) in MeCN (2 mL) were added DBU (0.32 mL, 2.14 mmol) and triethyl phosphonoacetate (0.44 mL, 2.20 mmol). The mixture was stirred at 0 °C for 30 min, and the above ketone was added. The reaction was carried out at room temperature overnight and quenched by addition of satd 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 ester **19** (162 mg, 72% from enone **11**) as a mixture of the stereoisomers (ca. 7:3): IR (neat) 1714, 1512, 1149, 1038, 741 cm^{-1}; ^{1}H NMR of the olefin mixture (300 MHz, $CDCl_3$) δ 0.52 (q, *J*=8 Hz, 6H), 0.91 (t, *J*=8 Hz, 9H), 0.80, 1.00 and 1.01 (3s, 6H), 1.23 and 1.27 (2t, *J*=7 and 7 Hz, 3H), 1.29–1.48 (m, 1H), 1.74–1.91 (m, 1H), 2.06–2.45 (m, 4H), 2.56–2.82 (m, 1H), 3.52–3.68 (m, 1H), 3.78 (s, 3H), 4.05–4.19 (m, 2H), 5.53 and 5.65 (2s, 0.7H and 0.3H), 6.78–6.84 (m, 2H), 7.03–7.14 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 6.8 (−), 7.2 (+), 14.34 and 14.38 (+), 25.6 (−), 26.9 and 27.5 (+), 28.1 and 29.3 (−), 30.6 and 31.3 (+), 36.6 and 38.7 (−), 44.8 and 45.7 (+), 45.3 (−), 52.5 and 52.8 (+), 55.2 and 55.3 (+), 59.5 (−), 76.1 (−), 112.9 and 113.6 (+), 113.70 and 113.74 (+), 128.5 and 128.6 (+), 139.4 and 139.7 (−), 157.8 (−), 162.3 and 162.5 (−), 166.7 and 166.8 (−); HRMS (FAB) calcd for $C_{26}H_{42}O_4SiNa$ [(M+Na)$^+$] 469.2750, found 469.2753.

*4.3.2. 2-((3S,4S)-3-(4-Methoxyphenyl)-4-(2-((triethylsilyl)oxy)propan-2-yl)cyclohexylidene)ethyl picolinate (**20**).* To a solution of ester **19** (36.2 mg, 0.087 mmol) in THF (1 mL) was added DIBAL (0.18 mL, 1.04 M in hexane, 0.187 mmol) dropwise at −78 °C, and the solution was stirred at −78 °C for 30 min before addition of H_2O (0.10 mL, 5.56 mmol) and NaF (216 mg, 5.14 mmol). The resulting mixture was stirred at room temperature for 30 min and filtered through a pad of Celite. The filtrate was concentrated and the residual oil was purified by chromatography on silica gel (hexane/EtOAc) to give the corresponding alcohol (33.3 mg, 17.2 mmol, 94%): IR (neat) 3342, 1610, 1512, 1246, 1039, 741 cm^{-1}; ^{1}H NMR of the olefin mixture (300 MHz, $CDCl_3$) δ 0.46–0.60 (m, 6H), 0.75–1.14 (m, 15H), 1.20–3.71 (m, 9H), 3.783 and 3.786 (2s, 3H), 4.06 and 4.11 (2d, *J*=7 and 7 Hz, 2H), 5.28–5.35 and 5.37–5.45 (2m, 1H), 6.78–6.85 (m, 2H), 7.04–7.13 (m, 2H).

To an ice-cold solution of the above alcohol (212 mg, 0.524 mmol), picolinic acid (80.3 mg, 0.652 mmol), Et_3N (0.22 mL, 1.58 mmol), and DMAP (62.9 mg, 0.515 mmol) in CH_2Cl_2 (6 mL) was added 2-chloro-1-methylpyridinium iodide (272 mg, 1.07 mmol). The mixture was stirred at room temperature overnight and diluted with satd $NaHCO_3$. 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 furnish picolinate **20** (244 mg, 91%) as a mixture of the stereoisomers (ca. 3:2): IR (neat) 1718, 1512, 1246, 1038, 744 cm^{-1}; ^{1}H NMR of the olefin mixture (300 MHz, $CDCl_3$) δ 0.45–0.57 (m, 6H), 0.76–1.01 (m, 15H), 1.24–2.88 (m, 8H), 3.767 and 3.783 (2s, 3H), 4.75 and 4.97 (2d, *J*=7 and 7 Hz, 0.8H and 1.2H), 5.42 and 5.51 (2t, *J*=7 and 7 Hz, 0.4H and 0.6H), 6.79 and 6.81 (2d, *J*=8.5 and 8.5 Hz, 2H), 7.07 and 7.11 (2d, *J*=8.5 and 8.5 Hz, 2H), 7.43–7.51 (m, 1H), 7.80–7.88 (m, 1H), 8.09–8.18 (m, 1H), 8.74–8.80 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 6.8 (−), 7.2 (+), 26.9 and 27.0 (+), 27.1, 28.2, 28.3, 35.8, 38.8, 45.8 (for 3C, −), 31.3 and 31.5 (+), 46.2 and 46.3 (+), 53.2 and 53.3 (+), 55.2 and 55.3 (+), 62.3 (−), 76.1 and 76.2 (−), 113.65 and 113.73 (+), 114.9 and 115.3 (+), 125.2 (+), 126.8 and 126.9 (+), 128.6 (+), 137.00 and 137.03 (+), 139.6 and 139.8 (−), 145.9 and 146.1 (−), 148.4 (−), 149.90 and 149.93 (+), 157.7 and 157.8 (−), 167.0 (−); HRMS (FAB) calcd for $C_{30}H_{43}O_4SiNa$ [(M+Na)$^+$] 532.2859, found 532.2850.

*4.3.3. Triethyl((2-((1S,2S,4R)-2-(4-methoxyphenyl)-4-methyl-4-vinylcyclohexyl)propan-2-yl)oxy)silane (**21**).* To an ice-cold suspension of $CuBr\cdot Me_2S$ (44.2 mg, 0.215 mmol) and ZnI_2 (70.7 mg, 0.221 mmol) in THF (1 mL) was added MeMgBr (0.41 mL, 1.06 M in THF, 0.435 mmol) dropwise. The mixture was stirred at 0 °C for 30 min and cooled to −40 °C. A solution of picolinate **20** (73.0 mg, 0.143 mmol) in THF (2 mL) was added to the mixture dropwise. The resulting mixture was allowed to warm to 0 °C over 3 h and diluted with hexane and satd NH_4Cl with vigorous stirring. The layers were separated and the aqueous layer was extracted with hexane twice. The combined extracts were washed with aqueous $Na_2S_2O_3$ and brine successively, dried over $MgSO_4$, and concentrated. The crude product was purified by chromatography on silica gel (hexane/EtOAc) to give olefin **21** (49.8 mg, 86%): $[\alpha]_D^{22}$ −3 (*c* 0.99, $CHCl_3$); IR (neat) 1512, 1248, 1041, 829 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.48 (q, *J*=8 Hz, 6H), 0.74 (s, 3H), 0.90 (t, *J*=8 Hz, 9H), 0.94 (s, 6H), 1.24–1.46 (m, 4H), 1.58–1.82 (m, 2H), 1.94–2.04 (m, 1H), 2.62 (dt, *J*=3.5, 11.5 Hz, 1H), 3.78 (s, 3H), 5.02 (dd, *J*=18, 1.5 Hz, 1H), 5.09 (dd, *J*=11, 1.5 Hz, 1H), 5.82 (dd, *J*=18, 11 Hz, 1H), 6.79 (d, *J*=8.5 Hz, 2H), 7.05 (d, *J*=8.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 6.9 (−), 7.3 (+), 23.8 (−), 27.2 (+), 31.3 (+), 31.8 (+), 37.5 (−), 38.0 (−), 41.9 (+), 49.4 (−), 53.2 (+), 55.3 (+), 76.3 (−), 112.5 (−), 113.6 (+), 128.6 (+), 140.7

(−), 146.2 (+), 157.6 (−); HRMS (FAB) calcd for $C_{25}H_{42}O_2SiNa$ [(M+Na)$^+$] 425.2852, found 425.2841. The regioselectivity (99%) and the stereoselectivity (98%) were determined by ^{1}H NMR spectroscopy.

*4.3.4. Cyclobakuchiol C (**2**).* A solution of the TES ether **21** (62.2 mg, 0.154 mmol) and PPTS (38.9 mg, 0.154 mmol) in EtOH (1.5 mL) was stirred at room temperature for 22 h and diluted with satd $NaHCO_3$. The resulting mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to afford the corresponding alcohol, which was passed through a short silica gel column for the next reaction.

To a suspension of the above alcohol and K_2CO_3 (10.7 mg, 0.077 mmol) in NMP (1 mL) was added PhSH (0.020 mL, 0.195 mmol). The mixture was stirred under reflux of NMP for 5 h, cooled to room temperature, and diluted with H_2O. The resulting mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated. Chromatography of the residual oil on silica gel (hexane/EtOAc) furnished cyclobakuchiol C (**2**) (38.6 mg, 91% from TES ether **21**): $[\alpha]_D^{22}$ −42 (*c* 0.79, $CHCl_3$); lit.[4] $[\alpha]_D^{26}$ −45 (*c* 0.30, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (s, 3H), 1.15 (s, 6H), 1.18–1.54 (m, 3H), 1.66–1.87 (m, 4H), 2.67 (dt, *J*=3, 11.5 Hz, 1H), 5.02 (dd, *J*=18, 1 Hz, 1H), 5.12 (dd, *J*=11, 1 Hz, 1H), 5.78 (dd, *J*=18, 11 Hz, 1H), 6.52 (d, *J*=8 Hz, 2H), 7.08 (br s, 2H), 7.77 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.7 (+), 25.5 (−), 29.4 (+), 31.4 (+), 37.4 (−), 37.6 (−), 41.4 (+), 48.3 (−), 53.1 (+), 76.3 (−), 112.8 (−), 116.3 (+), 129.1 (+), 136.8 (−), 145.9 (+), 155.4 (−). The ^{1}H and ^{13}C NMR spectra and the $[\alpha]_D$ value were consistent with those reported.[4]

4.4. Synthesis of cyclobakuchiol A

*4.4.1. 1-Methoxy-4-((1S,2S,5R)-5-methyl-2-(prop-1-en-2-yl)-5-vinylcyclohexyl)benzene (**24**).* A solution of TES ether **21** (163.3 mg, 0.406 mmol) and PPTS (122.9 mg, 0.489 mmol) in EtOH (4 mL) was stirred at room temperature for 24 h and diluted with satd $NaHCO_3$. The resulting mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to afford crude alcohol **23**, which was passed through a short silica gel column for the next reaction.

To a suspension of the above alcohol in pyridine (4 mL) was added $SOCl_2$ (0.089 mL, 1.22 mmol) at −10 °C. The mixture was stirred at the same temperature for 30 min and diluted with satd $NaHCO_3$. The resulting mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford olefin **24** (97.5 mg, 89% from TES ether **21**): $[\alpha]_D^{21}$ +2 (*c* 1.19, $CHCl_3$); lit.[4] $[\alpha]_D^{28}$ +2.0 (*c* 0.76, $CHCl_3$); IR (neat) 3074, 1512, 1248, 827 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (s, 3H), 1.48 (s, 3H), 1.33–1.75 (m, 4H), 1.77–1.86 (m, 2H), 2.23 (dt, *J*=4, 11.5 Hz, 1H), 2.68 (dt, *J*=3, 11.5 Hz, 1H), 3.76 (br s, 1H), 4.51 (br s, 1H), 4.54 (br s, 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*=8.5 Hz, 2H), 7.04 (d, *J*=8.5 Hz, 2H); ^{13}C NMR (75 MHz, $CHCl_3$) δ 19.7 (+), 29.0 (−), 31.6 (+), 37.6 (−), 37.8 (−), 42.7 (+), 47.5 (−), 51.4 (+), 55.2 (+), 111.2 (−), 112.6 (−), 113.5 (+), 128.3 (+), 138.1 (−), 146.3 (+), 148.6 (−), 157.6 (−). The ^{1}H and ^{13}C NMR spectra, IR spectrum, and the $[\alpha]_D$ value were consistent with those reported.[4]

*4.4.2. Cyclobakuchiol A (**1**).* To a suspension of olefin **24** (19.4 mg, 0.072 mmol) and K_2CO_3 (3.7 mg, 0.027 mmol) in NMP (1 mL) was added PhSH (0.008 mL, 0.079 mmol). The mixture was stirred under reflux for 4 h, cooled to room temperature, and diluted with H_2O. The resulting mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated. Chromatography of the crude product on silica gel (hexane/EtOAc) furnished cyclobakuchiol A (**1**) (17.8 mg, 97%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (s, 3H), 1.48 (s, 3H), 1.33–1.72 (m, 4H), 1.77–1.86 (m, 2H), 2.21 (dt, *J*=4, 11.5 Hz, 1H), 2.66 (dt, *J*=3, 11.5 Hz, 1H), 4.49–4.56 (m, 2H), 4.86 (br s, 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, *J*=8.5 Hz, 2H), 6.99 (d, *J*=8.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.7 (+), 29.0 (−), 31.6 (+), 37.5 (−), 37.8 (−), 42.7 (+), 47.4 (−), 51.5 (+), 111.2 (−), 112.7 (−), 115.0 (+), 128.5 (+), 138.3 (−), 146.3 (+), 148.6 (−), 153.4 (−). The ^{1}H and ^{13}C NMR spectra were consistent with those reported.[4]

Acknowledgements

This study was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan (25116709).

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2015.02.092.

References and notes

1. Backhouse, C. N.; Delporte, C. L.; Negrete, R. E.; Cassels, B. K.; Schneider, C.; Breitmaier, E.; Feliciano, A. S. *Phytochem.* **1995**, *40*, 325–327.
2. Backhouse, C. N.; Delporte, C. L.; Negrete, R. E.; Erazo, S.; Zuñiga, A.; Pinto, A.; Cassels, B. K. *J. Ethnopharmacol.* **2001**, *78*, 27–31.
3. Yin, S.; Fan, C.-Q.; Yue, J.-M. *J. Asian Nat. Prod. Res.* **2007**, *9*, 29–33.
4. Kawashima, H.; Kaneko, Y.; Sakai, M.; Kobayashi, Y. *Chem.—Eur. J.* **2014**, *20*, 272–278.
5. Kaneko, Y.; Kiyotsuka, Y.; Acharya, H. P.; Kobayashi, Y. *Chem. Commun.* **2010**, *46*, 5482–5484.
6. Kobayashi, Y.; Takeuchi, A.; Wang, Y.-G. *Org. Lett.* **2006**, *8*, 2699–2702.
7. (a) Bäckvall, J.-E.; Byström, S. E.; Nordberg, R. E. *J. Org. Chem.* **1984**, *49*, 4619–4631; (b) Gatti, R. G. P.; Larsson, A. L. E.; Bäckvall, J.-E. *J. Chem. Soc., Perkin Trans. 1* **1997**, 577–583.
8. (a) Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656–2665; (b) Harris, K. J.; Gu, Q.-M.; Shih, Y.-E.; Girdaukas, G.; Sih, C. J. *Tetrahedron Lett.* **1991**, *32*, 3941–3944; (c) Bäckvall, J.-E.; Gatti, R.; Schink, H. E. *Synthesis* **1993**, 343–348; (d) López-Pelegrín, J. A.; Janda, K. D. *Chem.—Eur. J.* **2000**, *6*, 1917–1922; (e) Suzuki, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **2001**, *66*, 1494–1496; (f) Hua, Z.; Yu, W.; Su, M.; Jin, Z. *Org. Lett.* **2005**, *7*, 1939–1942.
9. (a) Trost, B. M.; Romero, A. G. *J. Org. Chem.* **1986**, *51*, 2332–2342; (b) Audia, J. E.; Boisvert, L.; Patten, A. D.; Villalobos, A.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 3738–3740; (c) Barros, M. T.; Maycock, C. D.; Ventura, M. R. *J. Org. Chem.* **1997**, *62*, 3984–3988; (d) Rohloff, J. C.; Kent, K. M.; Postich, M. J.; Becker, M. W.; Chapman, H. H.; Kelly, D. E.; Lew, W.; Louie, M. S.; McGee, L. R.; Prisbe, E. J.; Schultze, L. M.; Yu, R. H.; Zhang, L. *J. Org. Chem.* **1998**, *63*, 4545–4550; (e) Schwardt, O.; Koliwer-Brandl, H.; Zimmerli, R.; Mesch, S.; Rossato, G.; Spreafico, M.; Vedani, A.; Kelm, S.; Ernst, B. *Bioorg. Med. Chem.* **2010**, *18*, 7239–7251.
10. (a) Bayón, P.; Marjanet, G.; Toribio, G.; Alibés, R.; de March, P.; Figueredo, M.; Font, J. *J. Org. Chem.* **2008**, *73*, 3486–3491; (b) O'Byrne, A.; Murray, C.; Keegan, D.; Palacio, C.; Evans, P.; Morgan, B. S. *Org. Biomol. Chem.* **2010**, *8*, 539–545.
11. An attempted allylic substitution of 4-acetoxy-2-cyclohexen-1-one with CH2=C(Me)ZnCl under similar conditions gave a mixture of unidentified products.
12. Further racemization during the conversion of **11** to **18** was not observed.
13. Without ZnI^2, **21** was obtained with 75% regio- and 98% stereoselectivity in 78% isolated yield.
14. ^{1}H NMR ($CDCl^3$): **22** δ 7.03 (d, *J*=8.5 Hz, 2H), 7.12 (d, *J*=8.5 Hz, 2H); cf. 1 δ 6.71 (d, *J*=8.5 Hz, 2H), 6.99 (d, *J*=8.5 Hz, 2H).
15. Bunnett, J. F.; Zahlerz, R. E. *Chem. Rev.* **1951**, *49*, 273–412 (especially, page 293).
16. Arthurs, C. L.; Morris, G. A.; Piacenti, A.; Pritchard, R. G.; Stratford, I. J.; Tatic, T.; Whitehead, R. C.; Williams, K. F.; Wind, N. S. *Tetrahedron* **2010**, *66*, 9049–9060.
17. Alibés, R.; de March, P.; Figueredo, M.; Font, J.; Marjanet, G. *Tetrahedron: Asymmetry* **2004**, *15*, 1151–1155.
18. Robertson, J.; Fowler, T. G. *Org. Biomol. Chem.* **2006**, *4*, 4307–4318.