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PII: S0040-4020(19)30696-9

DOI: https://doi.org/10.1016/j.tet.2019.06.034

Reference: TET 30426

To appear in: *Tetrahedron*

Received Date: 16 May 2019

Revised Date: 17 June 2019

Accepted Date: 20 June 2019

Please cite this article as: Yan O, Peng Y, Li W-DZ, Nickel-mediated reductive coupling of *neo*pentyl bromides with activated alkenes at room temperature and its synthetic application, *Tetrahedron* (2019), doi: https://doi.org/10.1016/j.tet.2019.06.034.

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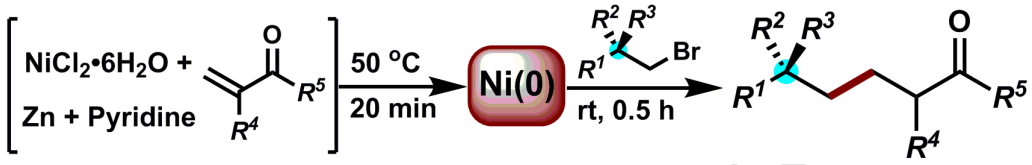

Tetrahedron
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Nickel-mediated reductive coupling of *neo*pentyl bromides with activated alkenes at room temperature and its synthetic application

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
*Neo*pentyl bromide
Nickel
Reductive coupling
Radical
Synthesis

ABSTRACT

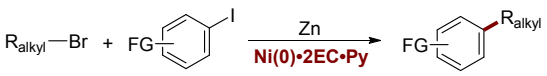
Reductive coupling of sterically hindered *neo*pentyl bromides with activated alkenes mediated by the *in situ* generated Ni(0) complexes along with some feedstock is achieved in good yield under the mild conditions. This practically useful method of C(sp^3)–C(sp^3) bond formation provides a complementary approach to the traditional conjugate addition of preformed organometallic reagents to electrophilic olefins, which often requires cryogenic temperature and rigorous exclusion of air and moisture. The robust application of this reductive coupling reaction was demonstrated in a formal synthesis of stereodivergent (–)-copacamphor and (–)-ylangocamphor, which are valuable intermediates for a class of tricyclo[5.3.0.0^{3,8}]decane sesquiterpenes. Moreover, this convenient protocol resulted in a facile access to the homolog of Corey aldehyde en route to prostaglandins, implying the possible involvement of radical-like species.

1. Introduction

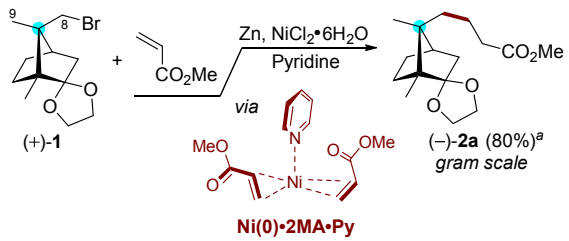
The notorious steric hindrance of *neo*pentyl halides is typically demonstrated in bimolecular nucleophilic substitution reactions (S_N2).[1] The extreme difficulty resulting from 'backside attack' of the electrophilic carbon in this kind of halides by the nucleophile, had been demonstrated by Ingold and co-workers in a series of seminal papers about kinetic studies,[2,3] and further approved by computational studies later.[2f,4] The limited successful examples mainly focused on the cases with hetero-[2b–d,5] rather than carbon nucleophiles. An alternative nucleophilic displacement reactions via unimolecular process (S_N1) also could give corresponding products; however, more favourable carbocation rearrangement[2e,6] always accompanied in most of cases.

In a synthetic project, we needed to realize homologation of (+)-8-bromocamphor ethylene ketal **1**. Many attempts such as enolate alkylation and direct cross–coupling failed,[7] which should be attributed to the remarkable steric encumbrance embedded this *neo*pentyl structure. We then turned to conjugate addition reaction promoted by *n*-Bu_3SnH or Zn/Cu couple,[8] but both of them still cannot effectively work on this unique substrate since competitive reduction of the bromide **1** was predominant. Although Money and co-workers[9] had realized a cross–coupling between (–)-8-iodocamphor and an π-allyl Ni complex[10] [generated from prenyl bromide and 8 equiv of $Ni(CO)_4$] in 40% yield at 60 °C after 36 h, the inherent danger and inconveniency of this protocol (e.g., $Ni(CO)_4$ is a volatile, flammable, highly toxic liquid,[11] and its preparation and subsequent reaction is needed to run in nonpolar and polar solvents respectively) limited its practical utilization. Even in their hands, the yield of this transformation was poor and irreproducible, hence they abandoned this procedure eventually and utilized an umpolung route involving cyanation, alkylation and decyanation[12a] in the total synthesis of (+)-longifolene.[12b] Consequently, an effective alkylation approach of *neo*pentyl halides is still in high demand.

a) **Prior study:** reductive coupling of alkyl bromides with ***Ar*I** (ref. 16)



b) **This work:** radical addition of *neo*pentyl bromide



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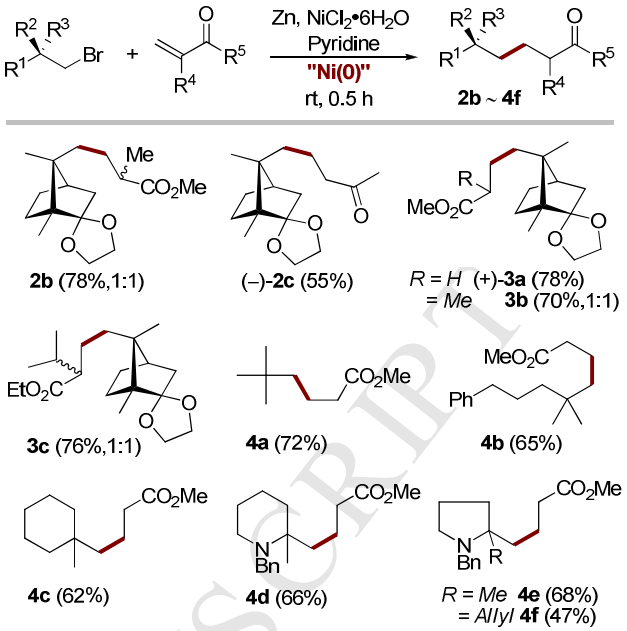
Scheme 1. A transferable ligand enables reductive coupling of *neo*pentyl bromide. [a] A yield of 73% was obtained under 10 mol % Ni condition.

Direct cross-electrophile coupling has already emerged as an advantageous method for the formation of C–C bonds. It can avoid some problems associated with preformed organometallic reagents which are inevitable in conventional cross-coupling of a nucleophile with an electrophile, therefore leading to generally excellent functional-group compatibility. A noteworthy advance is Ni-catalyzed reductive coupling of the challenging unactivated alkyl halides.[13–16] Recently, Weix[13a] and Gong[14a,d,f] developed bi- or tridentate amine ligated Ni complex-catalyzed reactions toward C(sp^3)–C(sp^2) and C(sp^3)–C(sp^3) bond construction, and these catalytic systems had been further expanded to couplings of acyl halides[13b,14b,c] and allyl acetates[14d,e] with alkyl halides under reductive conditions. In particular, Ni/(*R*,*R*)-diphenyl-Box-catalyzed asymmetric reductive acyl cross-coupling with secondary benzyl chlorides had been reported by Reisman;[15a] Ni/PCy_3-catalyzed reductive carboxylation of benzyl halides with CO_2 had also been realized by Martin.[15b] More importantly, Weix[13c] provided an elegant mechanism insight to this kind of cross-electrophile couplings, which would enable rational improvement and reliable application of this strategy. Independently, we[16] have disclosed inter- and unprecedented intramolecular reductive coupling reactions catalyzed by Ni(0)•2EC•Py (Scheme 1a: EC = ethyl crotonate; Py = pyridine), where EC act as π-ligands to Ni and plays an important role on those transformations with unactivated alkenes. Herein, switch of this unique ligand (EC) to methyl acrylate (MA) led to a formation of Ni(0)•2MA•Py complex, which eventually solved the problem mentioned above and achieved carbon chain elongation of (+)-**1** (Scheme 1b). The resulting (–)-**2a** could be easily converted to (–)-**11a** and (–)-**11b**, thereby constituting a formal synthesis of tricyclic sesquiterpenoids (–)-copacamphor and (–)-ylangocamphor (*vide infra*). Moreover, several other electron-deficient olefins were suitable as well, and the generated analogous Ni complexes promoted reductive coupling of various *neo*pentyl bromides successfully. The hypotheses involving radical species were supported by the radical clock experiments and an efficient synthesis of Corey aldehyde homolog **8**.

2. Results and discussion

As shown in Scheme 1b and the Experimental Section, once subjection of (+)-**1** to red-brown Ni(0)•2MA•Py complex *in situ* generated from a mixture of regular $Zn/NiCl_2•6H_2O$/pyridine/methyl acrylate,[17] the desired reductive coupling reaction was smoothly completed within 0.5 hour at room temperature, and ester (–)-**2a** was isolated in 80% yield. Notably, the efficiency of this transformation remains to be almost identical on a scale of 30 mmol. The reaction catalyzed by the above complex generated from 10 mol% $NiCl_2$ could also proceed under otherwise identical conditions, and 73% yield of (–)-**2a** can be obtained although the reaction time is very long (4 days) compared with that of the stoichiometric version. To our surprise, this unique Ni(0) complex did not receive much attention, and known utilization focused on the side chain elongation of C-22 steroidal iodide[18] and glycosyl bromides.[19] To the best of our knowledge, reductive coupling of *neo*pentyl bromides with MA has not been reported to date.[20] This fact prompted us to investigate more cases with respect to this kind of challenging substrates and further expand to diverse conjugate additions with other activated alkenes. Given the availability of this Ni(0) complex from benchtop and very cheap materials, the stoichiometric reaction conditions were employed for the following studies.

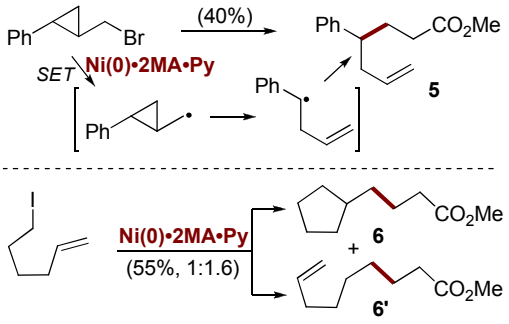


Scheme 2. Reductive couplings of various *neo*pentyl bromides and activated olefins.

Other Ni(0) complexes can be prepared in analogy to the protocol for Ni(0)•2MA•Py, and therefore provided corresponding addition products in modest to good yields (Scheme 2). For example, the Ni(0) complex derived from methyl α-methyl acrylate (MMA) also promoted the reductive coupling with (+)-**1**, and **2b** as a pair of diastereomers could be obtained in 78% yield. This convergent and high yielding synthesis is advantageous compared to the usual methylation of ester (–)-**2a** because the latter would suffer from over methylation. The Ni(0) complex with MMA as ligands also reductively coupled with (+)-9-bromocamphor ethylene ketal,[21] affording ester **3b** in 70% yield. Especially, the reaction of this bromide mediated by the Ni(0) complex generated from more sterically demanding ethyl α-*iso*propyl acrylate also proceeded smoothly, and the corresponding **3c** was obtained in 76% yield. More reactive enones[20,22] such as methyl vinyl ketone was certainly suitable activated alkene for the reductive coupling of (+)-**1**, thus delivering the expected ketone (–)-**2c** in 55% isolated yield. Besides chiral bromides with a bicyclo[2.2.1] skeleton, other simple *neo*pentyl bromides also could participate the reductive couplings with MA, as exemplified in the cases of **4a**~**4c**. Additionally, the successful syntheses of piperidine **4d** and tetrahydropyrroles (**4e** and **4f**) demonstrated mild nature of the present conditions since none of halides with nitrogen-containing heterocycles was involved in the related previous reactions.[17–20,22] Some features of the present system are noteworthy: the described Ni(0) complexes can be generated from air-stable and moisture-insensitive chemicals including ligands, hence none of glove box and anhydrous operation is necessary; the reductive couplings proceed rapidly at room temperature; the reactions are easily scaled up without significant loss of the efficiency.

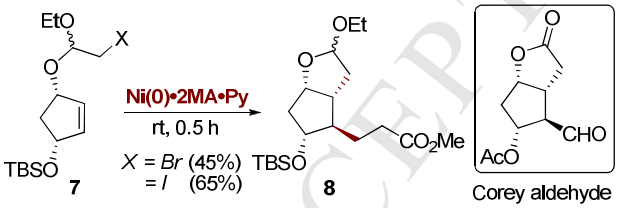
The next radical clock experiments[23] indicated that radical species generated from the bromides by SET process[24] with Ni(0) complexes may be involved in the above reductive couplings. As shown in Scheme 3, subjection of (3-phenylcyclopropyl)methyl bromide[25] to Ni(0)•2MA•Py furnished product **5** in 40% isolated yield via regioselective radical rearrangement and subsequent conjugate addition to MA, accompanying with equal amounts of homocoupling product from favourable dimerization of the resulting benzyl radical. The reaction of 6-iodo-1-hexene[13c,26]

mediated by this Ni complex also worked well, and radical cyclization-coupling product **6** and direct addition product **6′** as an inseparable mixture (1:1.6) were obtained accordingly. Interestingly, when Zn/$NiCl_2$•$6H_2O$/pyridine were mixed and heated at 50 °C for 20 min followed by the addition of (+)-**1** and MA, almost no formation of (–)-**2a** could be observed. This result highlighted the dual critical roles of MA as not only the reactive Michael acceptor but also the efficient η^2 ligand[27] to Ni(0). This mechanism is different from that of allylnickel(II) intermediates, where the enone had been proved to be a η^3 ligand assisted by Et_3SiCl in the investigation by Weix.[22]



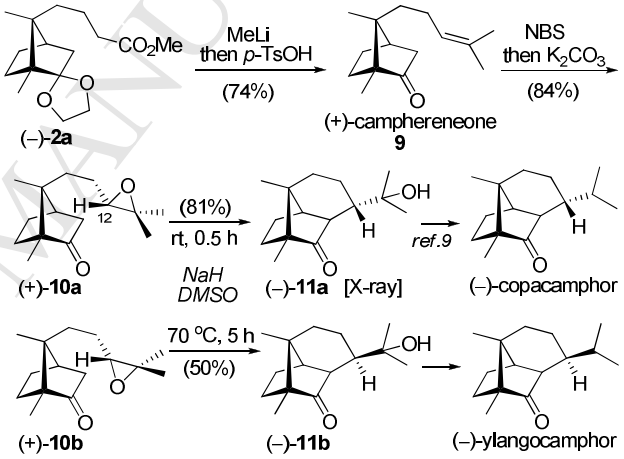
Scheme 3. Radical clock experiments.

Further support for the plausible radical mechanism came from the following tin-free synthesis toward Corey aldehyde analogue for an access to prostaglandins (PGs).[28] Inspired by Stork's classic radical cyclization–trapping strategy featuring stereocontrolled formation of two adjacent carbon centers in PGs,[29a,b] later the modifications by Keck[29c] and Scheffold,[29d] and the recent extension by Oshima,[29e] β-halo acetals **7** that is readily available from *cis*-2-cyclopentene-1,4-diol monosilyl-ether[30] was subjected to Ni(0)•2MA•Py complex (Scheme 4). Two inconsequential epimers **8** (dr = 2:1) were produced in fairly good yields compared to those of previous approaches. It is noteworthy that methyl esters **8** could be viewed as a new two-carbon homologation of well-known Corey aldehyde, and served as another potentially useful precursor to prostaglandins such as $PGF_{2\alpha}$ (Dinoprost™) and analogs such as Latanoprost (Xalatan™).[31]



Scheme 4. Stereoselective synthesis of a potential precursor for $PGF_{2\alpha}$ by tandem cyclization–coupling.

Application of reductive coupling product of *neo*pentyl bromide (+)-**1** was demonstrated in Scheme 5. With sufficient amounts of methyl ester (–)-**2a** in hand, its conversion to (+)-campherenone **9** was straightforward: the addition by MeLi, ketal hydrolysis and dehydration of the resulting tertiary alcohol; the whole protocol needed only one column chromatography purification, and the overall yield of 74% was achieved. Since direct epoxidation of (+)-**9** with *m*-CPBA didn't afford either of the single diastereomer (+)-**10a** or (+)-**10b**, we first utilized NBS to obtain diastereomeric bromohydrins, which can be separated by careful column chromatography (see Experimental Section), and absolute stereochemistry of more polar diastereomer (–)-**9b** was determined by X-ray crystallographic structure.[32] The respective subjection of these two bromohydrins to K_2CO_3 afforded both epoxyketones (+)-**10a** and (+)-**10b** in diastereomerically pure form, which set the stage for intramolecular nucleophilic ring-opening promoted by carbanion[33] and can compare the difference of their cyclization behaviors.[34] Stereospecific cyclization of (+)-**10a** finished rapidly in the methylsulfinyl sodium solution[35] even at room temperature, providing tricyclic keto-alcohol (–)-**11a** in 81% isolated yield, whose stereochemistry was unambiguously confirmed by single-crystal X-ray diffraction analysis (Figure 1).[32] However, the 6-*exo-tet* cyclization of (+)-**10b** needed to raise temperature to 70 °C and prolong reaction time to 5 h, and the corresponding (–)-**11b** was isolated in only 50% yield. It is noteworthy that stereodivergent (–)-**11a** and (–)-**11b** could be easily converted to (–)-copacamphor and (–)-ylangocamphor, two valuable intermediates en route to a class of tricyclo[5.3.0.$0^{3,8}$]decane sesquiterpenes.[9,12b] Not only the stereochemistry but also substituents[36] of the epoxide would exert the influence on cyclization. When H is substituted by Me at C(12), regioselective cyclization of tetrasubstituted epoxide (+)-**12a** could also take place albeit under the rather harsh condition (see Experimental Section), and the desired product (–)-**13**[32] with an all-carbon quaternary stereocenter was obtained in 67% isolated yield.



Scheme 5. Stereospecific synthesis of diastereomeric epoxyketones **10a**,**b** and respective cyclization.

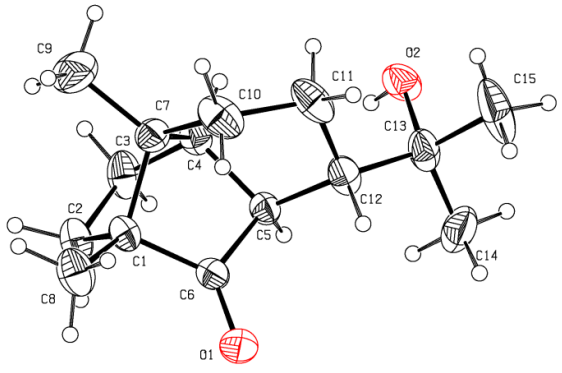


Figure 1. X-ray crystal structure of (–)-**11a**.

3. Conclusion

We have demonstrated in this work a solution on the effective alkylation of various *neo*pentyl bromides with steric bulk by means of Ni(0)•2MA•Py complex and analogues-initiated *reductive conjugate addition* reactions. As an application of this

alternative C–C coupling protocol, three-carbon homologation product (–)-**2a** allowed rapid access to a class of sesquiterpenes with an unique tricyclo[5.3.0.0^{3,8}]decane skeleton. In addition to the radical clock experiments, the realization of a synthesis of a potentially useful precursor **8** to $PGF_{2\alpha}$ provided supportive evidences for the plausible radical-associated mechanism. Extension studies toward the other type of halides[37] and activated alkenes or ligands[38] are currently ongoing, and those results will be reported in due course.

4. Experimental section

4.1. General

For product purification by flash column chromatography, silica gel (200~300 mesh) and petroleum ether (bp 60~90 °C) were used. All solvents were purified and dried by standard techniques, and distilled prior to use. Organic extracts were dried over $MgSO_4$ or Na_2SO_4, unless otherwise specified. Experiments were conducted under an argon or nitrogen atmosphere in oven-dried or flame-dried glassware with magnetic stirring, unless otherwise noted. NMR spectra were measured on 200, 300 and 400 MHz instruments at room temperature. EI–MS was obtained on GC/MS QP-2010 SE. High-resolution mass spectral data were measured with electrospray ionization (ESI), atmosphere pressure chemical ionization (APCI) and secondary ion mass spectroscopy (SIMS). Infrared spectra were recorded on an FT-IR spectrophotometer. The X-ray diffraction studies were carried out on a Bruker SMART Apex CCD area detector diffractometer equipped with graphite-monochromated Mo-Kα radiation source. Melting points were measured on *Kofler* hot stage and are uncorrected.

4.2. General procedure for the reductive cross-coupling reaction promoted by the Ni(0) complex

To a stirred slurry of Zn (390 mg, 6 mmol) in regular pyridine (3 mL) was added the electron-deficient alkene (6 mmol) at room temperature. Under vigorous stirring, $NiCl_2$•$6H_2O$ (475 mg, 2 mmol) was added to the above mixture. The temperature then rose to 50 °C, and stirring was continued for 20 min. The resulting red-brown Ni(0) complex was cooled to room temperature, and a solution of the alkyl bromide (2 mmol) in pyridine (1 mL) was added dropwise. The mixture was stirred for 0.5 h, and then filtered with a short plug (elution with 50 mL of Et_2O) and washed with HCl (1N), water and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography on silica gel to afford desired ester products.

(–)-**2a** was prepared as a colorless oil (80% yield) according to the general procedure. R_f = 0.51 (petroleum ether/EtOAc = 6 : 1); $[\alpha]_D^{15}$ = –11 (*c* = 0.7, $CHCl_3$); IR (film): ν_{max} = 2951, 2877, 1740, 1439, 1264, 1174, 1042, 952 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.93–3.67 (m, 4H), 3.64 (s, 3H), 2.28 (t, J = 7.5 Hz, 2H), 1.92–1.83 (m, 3H), 1.76–1.53 (m, 2H), 1.51–1.42 (m, 1H), 1.40–1.30 (m, 2H), 1.22–0.96 (m, 3H), 0.83 (s, 3H), 0.76 (s, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.3, 117.0, 64.9, 64.5, 53.3, 51.4, 51.0, 44.2, 41.6, 35.0, 32.5, 29.6, 26.6, 21.0, 16.5, 9.8 ppm; EI–MS (70 eV): *m/z* (% relative intensity) 282 (M^+, 11), 251 (5.4), 194 (8), 181 (17), 149 (10), 125 (100), 95 (85); HRMS (SIMS): calcd. for $C_{16}H_{27}O_4^+$ $[M+H]^+$: 283.1904, found: 283.1910.

2b was prepared as a colorless oil (78% yield, d.r. = 1:1) according to the general procedure. R_f = 0.47 (petroleum ether/EtOAc = 6 : 1); IR (film): ν_{max} = 2950, 2877, 1737, 1456, 1380, 1320, 1305, 1268, 1247, 1196, 1171, 1152, 1121, 1046, 1023, 971, 843 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.97–3.71 (m, 4H), 3.70 (s, 3H), 2.41–2.36 (m, 1H), 2.00–1.82 (m, 4H), 1.80–1.60 (m, 1H), 1.58–1.42 (m, 1H), 1.40–1.38 (m, 2H), 1.37–1.15 (m, 2H), 1.16 (d, *J* = 7.2 Hz, 3H), 1.09–0.95 (m, 1H), 0.83 (s, 3H), 0.78 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.4, 116.9, 64.8, 63.5, 53.3, 51.3, 50.8, 44.2, 41.5, 40.0, 30.4, 30.1, 29.7, 26.6, 17.1, 16.4, 9.8 ppm; (*the other isomer*) δ = 177.5, 64.9, 44.1, 41.6, 40.2, 29.5 ppm, other signals are inseparable; HRMS (ESI): calcd. for $C_{17}H_{29}O_4^+$ $[M+H]^+$: 297.2060, found: 297.2057.

(–)-**2c** was prepared as a colorless oil (55% yield) according to the general procedure. R_f = 0.41 (petroleum ether/EtOAc = 6 : 1); $[\alpha]_D^{16}$ = –10 (*c* = 1.5, $CHCl_3$); IR (film): ν_{max} = 2950, 2877, 1715, 1450, 1362, 1112, 1044, 951 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.94–3.72 (m, 4H), 2.43 (t, *J* = 6.9 Hz, 2H), 2.14 (s, 3H), 1.95–1.81 (m, 4H), 1.72–1.59 (m, 2H), 1.52–1.35 (m, 3H), 1.25–1.15 (m, 1H), 1.08–0.95 (m, 1H), 0.86 (s, 3H), 0.78 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 209.7, 117.3, 65.2, 64.8, 53.6, 51.4, 45.0, 44.6, 41.9, 32.7, 30.2, 29.9, 26.9, 20.0, 16.7, 10.1 ppm; EI–MS (70 eV): *m/z* (% relative intensity) 266 (M^+, 14.3), 251 (1.1), 181 (10), 155 (17), 147 (16), 125 (100), 113 (27), 95 (69); HRMS (ESI): calcd. for $C_{16}H_{27}O_3^+$ $[M+H]^+$: 267.1955, found: 267.1963.

(+)-**3a** was prepared as a colorless oil (78% yield) according to the general procedure. R_f = 0.51 (petroleum ether/EtOAc = 6 : 1); $[\alpha]_D^{20}$ = +3 (*c* = 1.6, $CHCl_3$); IR (film): ν_{max} = 2952, 2877, 1739, 1455, 1438, 1259, 1119, 1047 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.94–3.90 (m, 1H), 3.88–3.76 (m, 2H), 3.73–3.69 (m, 1H), 3.67 (s, 3H), 2.30 (t, *J* = 7.2 Hz, 2H), 2.01–1.82 (m, 2H), 1.78–1.48 (m, 2H), 1.44–1.30 (m, 3H), 1.25–1.16 (m, 3H), 1.06–0.95 (m, 1H), 1.03 (s, 3H), 0.78 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.2, 117.3, 65.0, 63.6, 53.2, 50.8, 44.4, 42.0, 34.9, 32.6, 29.7, 29.5, 26.5, 20.1, 16.7, 9.8 ppm; HRMS (APCI): calcd. for $C_{16}H_{27}O_4^+$ $[M+H]^+$: 283.1904, found: 283.1903.

3b was prepared as a colorless oil (70% yield, d.r. = 1:1) according to the general procedure. R_f = 0.55 (petroleum ether/EtOAc = 6 : 1); IR (film): ν_{max} = 2951, 2877, 1737, 1458, 1379, 1319, 1198, 1121, 1048, 967, 845 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.95–3.90 (m, 1H), 3.88–3.78 (m, 2H), 3.75–3.71 (m, 1H), 3.68 (s, 3H), 2.43–2.34 (m, 1H), 2.02–1.90 (m, 2H), 1.88–1.83 (m, 1H), 1.80–1.67 (m, 1H), 1.65–1.49 (m, 2H), 1.47–1.25 (m, 3H), 1.23–1.15 (m, 1H), 1.15 (d, *J* = 7.2 Hz, 3H), 1.04–0.94 (m, 1H), 1.01 (s, 3H), 0.78 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.2, 117.3, 64.9, 63.6, 53.2, 51.5, 50.7, 44.3, 41.8, 40.1, 30.1, 29.5, 28.7, 26.5, 17.0, 16.6, 9.8 ppm; (*the other isomer*) δ = 40.3, 30.4, 28.8, 17.3 ppm, other signals are inseparable; HRMS (ESI): calcd. for $C_{17}H_{29}O_4^+$ $[M+H]^+$: 297.2060, found: 297.2057.

3c was prepared as a colorless oil (76% yield, d.r. = 1:1) according to the general procedure. R_f = 0.67 (petroleum ether/EtOAc = 6 : 1); IR (film): ν_{max} = 2960, 2876, 1730, 1452, 1375, 1318, 1121, 1046, 967 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 4.20–4.10 (m, 2H), 3.94–3.91 (m, 1H), 3.88–3.80 (m, 2H), 3.78–3.72 (m, 1H), 2.05–1.92 (m, 2H), 1.88–1.80 (m, 2H), 1.74–1.50 (m, 2H), 1.48–1.33 (m, 4H), 1.29–1.14 (m, 3H), 1.26 (d, *J* = 6.9 Hz, 3H), 1.01 (s, 3H), 0.94 (d, *J* = 7.8 Hz, 3H), 0.92 (d, *J* = 6.3 Hz, 3H), 0.77 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.7, 117.3, 64.9, 63.6, 59.8, 53.6, 53.2, 50.8, 44.3, 41.8, 30.9, 30.7, 30.5, 29.5, 26.6, 24.6, 20.5, 16.7, 14.4, 9.8 ppm; (*the other isomer*) δ = 175.8, 29.4, 26.3, 20.3, 16.6 ppm, other signals are inseparable; HRMS (SIMS): calcd. for $C_{20}H_{35}O_4^+$ $[M+H]^+$: 339.2530, found: 339.2540.

4a[39] was prepared as a colorless oil (72% yield) according to the general procedure. R_f = 0.55 (petroleum ether/EtOAc = 8 : 1); IR (film): ν_{max} = 2956, 2870, 1743, 1470, 1437, 1364, 1253, 1207, 1173, 1069, 1014 cm^{-1}; ^1H NMR (300

MHz, $CDCl_3$): δ = 3.68 (s, 3H), 2.28 (t, J = 7.5 Hz, 2H), 1.63–1.57 (m, 2H), 1.21–1.16 (m, 2H), 0.89 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.3, 51.4, 43.6, 34.8, 30.3, 29.2 (3C), 20.2 ppm.

4b was prepared as a colorless oil (65% yield) according to the general procedure. R_f = 0.69 (petroleum ether/EtOAc = 6 : 1); IR (film): ν_{max} = 2928, 2853, 1740, 1603, 1494, 1457, 1364, 1170, 1033, 747, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.25 (m, 3H), 7.19–7.17 (m, 2H), 3.66 (s, 3H), 2.58 (t, J = 6.6 Hz, 2H), 2.28 (t, J = 7.2 Hz, 2H), 1.71–1.52 (m, 3H), 1.48–1.10 (m, 5H), 0.88 (s, 3H), 0.84 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.3, 142.8, 128.4 (2C), 128.2 (2C), 125.6, 51.4, 36.5, 36.4, 36.2, 34.4, 32.5, 29.3, 27.1, 22.5, 19.5 ppm; EI–MS (70 eV): *m/z* (% relative intensity) 262 (M^+, 1.4), 248 (4), 216 (3), 147 (5), 143 (7), 104 (22), 91 (100), 74 (31).

4c[40] was prepared as a colorless oil (62% yield) according to the general procedure. R_f = 0.55 (petroleum ether/EtOAc = 6 : 1); IR (film): ν_{max} = 2924, 2851, 1742, 1442, 1257, 1199, 1168 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.66 (s, 3H), 2.27 (t, J = 7.5 Hz, 2H), 1.70–1.51 (m, 6H), 1.43–1.38 (m, 1H), 1.31–1.16 (m, 7H), 0.84 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.6, 51.7, 37.9, 37.6, 37.2, 34.6, 33.5 (2C), 26.8, 26.6 (2C), 22.6 ppm; EI–MS (70 eV): *m/z* (% relative intensity) 198 (M^+, 0.2), 184 (3), 167 (4), 153 (4), 141 (49), 97 (19), 74 (100), 55 (98), 41 (91).

4d was prepared as a colorless oil (66% yield) according to the general procedure. R_f = 0.45 (petroleum ether/EtOAc = 5 : 1); IR (film): ν_{max} = 2923, 2854, 1739, 1597, 1493, 1452, 1258, 1165, 1110, 741, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.19 (m, 5H), 3.64 (s, 3H), 3.58 (s, 2H), 2.62–2.54 (m, 1H), 2.42–2.36 (m, 2H), 2.27–2.10 (m, 2H), 2.08–1.99 (m, 1H), 1.64–1.32 (m, 8H), 0.74 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.9, 140.4, 129.0 (2C), 128.0 (2C), 126.7, 66.4, 65.1, 57.9, 51.4, 40.0, 36.7, 31.3, 29.1, 24.7, 21.9 ppm; EI–MS (70 eV): *m/z* (% relative intensity) 289 (M^+, 2.1), 274 (0.4), 258 (1), 216 (8), 174 (3), 160 (21), 134 (21), 91 (100).

4e was prepared as a colorless oil (68% yield) according to the general procedure. R_f = 0.35 (petroleum ether/EtOAc = 5 : 1); IR (film): ν_{max} = 2934, 2795, 1740, 1603, 1493, 1451, 1309, 1166, 1026, 740, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.20 (m, 5H), 3.66 (s, 3H), 3.41 (q, J = 13.5 Hz, 2H), 2.42–2.23 (m, 2H), 2.21–2.17 (m, 2H), 2.15–2.05 (m, 1H), 2.01–1.95 (m, 1H), 1.68 (t, J = 8.1 Hz, 2H), 1.63–1.58 (m, 2H), 1.35–1.18 (m, 2H), 0.88 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.9, 139.2, 128.7 (2C), 128.1 (2C), 126.7, 64.1, 63.2, 54.6, 51.5, 35.6, 34.1, 33.0, 28.7, 23.8, 22.1 ppm; HRMS (ESI): calcd. for $C_{17}H_{26}NO_2^+$ $[M+H]^+$: 276.1958, found: 276.1958.

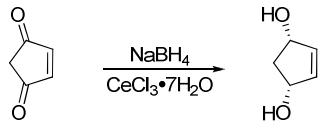
4f was prepared as a colorless oil (47% yield) according to the general procedure. R_f = 0.43 (petroleum ether/EtOAc = 5 : 1); IR (film): ν_{max} = 3067, 3027, 2934, 2795, 1740, 1638, 1603, 1493, 1450, 1439, 1315, 1252, 1171, 996, 914, 740, 670 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.27 (m, 3H), 7.27–7.21 (m, 2H), 5.75–5.66 (m, 1H), 5.01 (d, J = 15.3 Hz, 1H), 5.00 (d, J = 11.1 Hz, 1H), 3.66 (s, 3H), 3.41 (s, 2H), 2.42–2.25 (m, 2H), 2.22–2.15 (m, 2H), 2.10–2.04 (m, 4H), 1.72–1.55 (m, 2H), 1.59 (t, J = 6.0 Hz, 2H), 1.32–1.25 (m, 2H) ppm; ^{13}C/DEPT NMR (50 MHz, $CDCl_3$): δ = 174.6 (s), 139.1 (s), 134.2 (d), 128.7 (d, 2C), 128.0 (d, 2C), 126.7 (d), 117.2 (t), 63.3 (t), 62.2 (t), 54.5 (t), 51.4 (q), 40.0 (t), 35.8 (s), 33.5 (t), 30.9 (t), 28.1 (t), 21.8 (t) ppm; HRMS (ESI): calcd. for $C_{19}H_{28}NO_2^+$ $[M+H]^+$: 302.2115, found: 302.2115.

4.3. Radical clock experiments

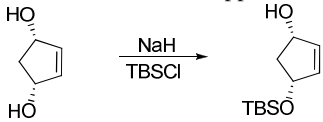
5 was prepared as a colorless oil (40% yield) according to the general procedure. R_f = 0.50 (petroleum ether/EtOAc = 6 : 1); IR (film): ν_{max} = 3027, 2921, 2844, 1737, 1641, 1602, 1493, 1438, 1370, 1204, 1163, 914, 761, 736, 701 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.26 (m, 2H), 7.22–7.19 (m, 1H), 7.17–7.13 (m, 2H), 5.73–5.60 (m, 1H), 4.99 (d, J = 17.1 Hz, 1H), 4.94 (d, J = 9.9 Hz, 1H), 3.61 (s, 3H), 2.68–2.58 (m, 1H), 2.38 (t, J = 6.9 Hz, 2H), 2.16 (q, J = 7.2 Hz, 2H), 2.16–2.02 (m, 1H), 1.91–1.79 (m, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.0, 143.9, 136.5, 128.4 (2C), 127.7 (2C), 126.4, 116.2, 51,4, 45.2, 41.2, 32.1, 30.8 ppm; HRMS (ESI): calcd. for $C_{14}H_{18}O_2Na^+$ $[M+Na]^+$: 241.1199, found: 241.1200.

6[41] and **6′**[42] were prepared as colorless oils (1:1.6, 55% yield) according to the general procedure. R_f = 0.55 (petroleum ether/EtOAc = 8 : 1); IR (film): ν_{max} = 3077, 2929, 2857, 1742, 1640, 1438, 1362, 1251, 1170, 911 cm^{-1}; data for **6′**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.85–5.76 (m, 1H), 4.99 (dd, J = 17.1, 1.8 Hz, 1H), 4.94 (dd, J = 11.7, 1.2 Hz, 1H), 3.67 (s, 3H), 2.31 (t, J = 7.5 Hz, 2H), 2.04 (q, J = 7.2 Hz, 2H), 1.76–1.73 (m, 1H), 1.66–1.42 (m, 3H), 1.41–1.30 (m, 4H) ppm; ^{13}C/DEPT NMR (75 MHz, $CDCl_3$): δ = 174.2 (s), 138.9 (d), 114.2 (t), 51,4 (q), 34.0 (t), 33.6 (t), 28.9 (t), 28.7 (t), 28.6 (t), 24.9 (t) ppm; data for **6**: ^{1}H NMR signals overlap with those of **6′**; ^{13}C/DEPT NMR (75 MHz, $CDCl_3$): δ = 174.3 (s), 51,4 (q), 39.8 (d), 35.6 (t), 34.3 (t), 32.5 (t, 2C), 25.1 (t, 2C), 24.1 (t) ppm.

4.4. Stereoselective synthesis of a precursor for PGF$_{2\alpha}$

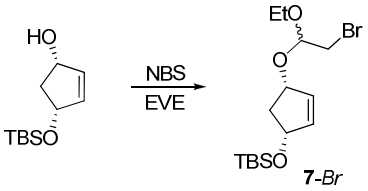


To a solution of $CeCl_3$•$7H_2O$ (3.73 g, 10 mmol) in MeOH (20 mL) was added 2-cyclopentene-1,4-dione[43] (960 mg, 10 mmol) followed by the addition of $NaBH_4$ (380 mg, 10 mmol) portionwise at 0 °C. Once clear solution turned to a milky white, and the resulting reaction mixture was further stirred for 30 min. The mixture was then filtered with a short plug (elution with 100 mL of CH_2Cl_2) and concentrated under reduced pressure. The resulting crude product *cis*-2-cyclopentene-1,4-diol (ca. 1 g) could be used directly without further purification. Colorless solid; mp 59–60 °C (EtOAc); R_f = 0.12 (petroleum ether/EtOAc = 1 : 1); IR (film): ν_{max} = 3304, 3114, 2927, 1643, 1437, 1339, 1179, 1133, 1084, 998, 916, 828, 791, 687 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.01 (s, 2H), 4.63 (brs, 2H), 3.58 (brs, 1H, –O*H*), 3.51 (brs, 1H, –O*H*), 2.70 (dt, J = 14.7, 6.9 Hz, 1H), 1.56 (dt, J = 14.7, 3.3 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.3, 74.9, 43.4 ppm.



NaH (400 mg, 10 mmol, 60% dispersion in mineral oil, washed three times with *n*-hexane distilled from CaH_2) was suspended in THF (20 mL), and a solution of the above diol (1 g) in THF (10 mL) was added dropwise at room temperature. The resulting mixture was stirred for 1 h, and a large amount of opaque white precipitates formed. TBSCl (1.5 g, 10 mmol) was then added portionwise, and vigorous stirring was continued for 2 h. The mixture was poured into Et_2O (100 mL), washed with 10% aqueous $NaHCO_3$ (20

mL) and brine (10 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography on silica gel to afford desired *cis*-4-(*t*-butyldimethylsilanyloxy)-cyclopentene-2-ol[44] (1.62 g, 75%). Colorless oil; R_f = 0.38 (petroleum ether /EtOAc = 5 : 1); IR (film): ν_{max} = 3368, 3179, 2960, 2928, 2872, 1463, 1379, 1239, 1147, 1074, 773, 728 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5.93 (d, *J* = 5.7 Hz, 1H), 5.87 (dd, *J* = 5.4, 1.8 Hz, 1H), 4.64 (t, *J* = 6.3 Hz, 1H), 4.57 (brs, 1H), 2.68 (dt, *J* = 14.7, 7.2 Hz, 1H), 2.22 (brs, 1H, –O*H*), 1.50 (dt, *J* = 14.1, 4.8 Hz, 1H), 0.89 (s, 9H), 0.08 (s, 6H) ppm; ^{13}C/DEPT NMR (75 MHz, $CDCl_3$): δ = 136.8 (d), 135.6 (d), 75.1 (d), 75.0 (d), 44.6 (t), 25.9 (q, 3C), 18.2 (s), –4.68 (q), –4.72 (q) ppm.



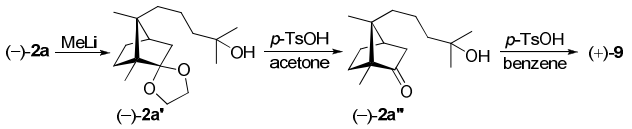
7-*Br*

To an oven-dried round bottom flask were added *N*-bromosuccinimide (2.1 mmol) and dry CH_2Cl_2 (10 mL). The resulting suspension was cooled to –20 °C, and ethyl vinyl ether (2.4 mmol) was added dropwise over a 5 min period followed by the addition of the above *cis*-4- (*t*-butyldimethylsilanyloxy)-cyclopentene-2-ol (2.0 mmol) in CH_2Cl_2 (5 mL) dropwise over a 10 min period. The reaction mixture was slowly warmed to room temperature over a period of 2 h, and was then diluted with Et_2O (30 mL) and poured into a separatory funnel that contained H_2O (10 mL). The aqueous layer was extracted with Et_2O (2 × 30 mL), and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography on silica gel to furnish the desired β-bromo acetal **7**-*Br*[29d] (495 mg, 68%). Colorless oil; R_f = 0.50 (petroleum ether/EtOAc = 20 : 1); ^1H NMR (300 MHz, $CDCl_3$): δ = 5.88 (d, *J* = 3.0 Hz, 2H), 4.77 (q, *J* = 6.0 Hz, 1H), 4.63 (t, *J* = 6.9 Hz, 1H), 4.58 (q, *J* = 5.7 Hz, 1H), 3.66 (dd, *J* = 6.9, 3.0 Hz, 1H), 3.59 (dd, *J* = 9.3, 6.9 Hz, 1H), 3.35 (dd, *J* = 3.9, 1.2 Hz, 1H), 2.71–2.66 (m, 1H), 1.63 (dt, *J* = 12.9, 5.1 Hz, 1H), 1.22 (t, *J* = 6.9 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): (*slightly major isomer*) δ = 137.7, 132.9, 100.7, 79.1, 74.6, 61.4, 41.9, 31.9, 25.8 (3C), 18.1, 15.1, –4.6, –4.7 ppm; (*slightly minor isomer*) δ = 137.5, 132.6, 100.5, 79.3, 74.7, 61.7, 42.3, 32.0, 15.2 ppm, the signals of silyl group are inseparable.

7-*I*[29b,c] was prepared similarly according to the above procedure for **7**-*Br*. Colorless oil; R_f = 0.52 (petroleum ether/EtOAc = 20 : 1); IR (film): ν_{max} = 3065, 2955, 2932, 2889, 2858, 1635, 1611, 1468, 1370, 1254, 1196, 1103, 1077, 1043, 906, 837, 777, 670 cm^{-1}; (*slightly major isomer*) ^1H NMR (300 MHz, $CDCl_3$): δ = 5.92–5.87 (m, 1H), 4.73 (q, *J* = 6.0 Hz, 1H), 4.64 (t, *J* = 6.9 Hz, 1H), 4.57 (q, *J* = 5.7 Hz, 1H), 3.66 (dd, *J* = 3.6, 2.4 Hz, 1H), 3.59 (dd, *J* = 6.9, 1.8 Hz, 1H), 3.21 (dd, *J* = 5.4, 1.5 Hz, 1H), 2.68 (dt, *J* = 15.6, 7.2 Hz, 1H), 1.65 (dt, *J* = 13.5, 5.7 Hz, 1H), 1.22 (t, *J* = 7.2 Hz, 3H), 0.87 (s, 9H), 0.06 (s, 6H) ppm; ^{13}C/DEPT NMR (75 MHz, $CDCl_3$): δ = 137.5 (d), 132.6 (d), 100.9 (d), 78.9 (d), 74.6 (d), 61.1 (d), 41.8 (t), 25.8 (q, 3C), 18.1 (s), 15.07 (q), 5.8 (t), –4.6 (q), –4.7 (q) ppm; (*slightly minor isomer*) ^1H NMR (300 MHz, $CDCl_3$): δ = 4.57 (q, *J* = 6.0 Hz, 1H), 3.68 (dd, *J* = 3.3, 2.4 Hz, 1H), 3.53 (dd, *J* = 7.2, 2.4 Hz, 1H), 2.70 (dt, *J* = 11.4, 6.9 Hz, 1H), 1.63 (dt, *J* = 12.9, 5.7 Hz, 1H), 1.23 (t, *J* = 7.2 Hz, 3H) ppm, other signals are inseparable; ^{13}C/DEPT NMR (75 MHz, $CDCl_3$): δ = 137.6 (d), 133.0 (d), 101.1 (d), 78.9 (d), 74.7 (d), 61.4 (d), 42.4 (t), 15.12 (q), 5.9 (t) ppm, the signals of silyl group are inseparable.

To a stirred slurry of Zn (195 mg, 3 mmol) in regular pyridine (2 mL) was added methyl acrylate (0.27 mL, 3 mmol) at room temperature. Under vigorous stirring, $NiCl_2$•$6H_2O$ (238 mg, 1 mmol) was added to the above mixture. The temperature then rose to 50 °C, and stirring was continued for 20 min. The resulting red-brown Ni(0)•2MA•Py complex was cooled to room temperature, and a solution of the β-iodo acetal **7**-*I* (412 mg, 1 mmol) in pyridine (2 mL) was added dropwise over a 10-min period. After 0.5 h, the mixture was filtered with a short plug (elution with 50 mL of Et_2O), and washed with water (3 × 10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography (petroleum ether/EtOAc = 30 : 1→15 : 1) on silica gel to afford desired **8** (*less polar*) and **8** (*more polar*) (2:1, 242 mg, 65%) as colorless oils. Data for **8** (*less polar*): R_f = 0.58 (petroleum ether/EtOAc = 3 : 1); IR (film): ν_{max} = 2953, 2931, 2858, 1742, 1461, 1440, 1370, 1335, 1254, 1172, 1115, 1056, 1006, 938, 882, 837, 776, 667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5.17 (d, *J* = 4.8 Hz, 1H), 4.41 (dt, *J* = 7.5, 5.4 Hz, 1H), 3.71 (q, *J* = 8.1 Hz, 1H), 3.69–3.61 (m, 1H), 3.64 (s, 3H), 3.37 (dt, *J* = 14.1, 6.9 Hz, 1H), 2.36 (t, *J* = 7.2 Hz, 2H), 2.29–2.20 (m, 2H), 2.07 (dd, *J* = 12.9, 10.2 Hz, 1H), 1.88 (t, *J* = 6.0 Hz, 1H), 1.86–1.75 (m, 1H), 1.68–1.59 (m, 1H), 1.56–1.47 (m, 2H), 1.15 (t, *J* = 7.2 Hz, 3H), 0.86 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H) ppm; ^{13}C/DEPT NMR (75 MHz, $CDCl_3$): δ = 174.0 (s), 105.5 (d), 79.8 (d), 78.9 (d), 62.3 (t), 53.0 (d), 51.5 (q), 44.5 (d), 41.0 (t), 39.7 (t), 32.3 (t), 27.9 (t), 25.7 (q, 3C), 17.9 (s), 15.2 (q), –4.4 (q), –4.9 (q) ppm; HRMS (ESI): calcd. for $C_{19}H_{36}O_5SiNa^+$ $[M+Na]^+$: 395.2224, found: 395.2222. Data for **8** (*more polar*): R_f = 0.52 (petroleum ether/EtOAc = 3 : 1); IR (film): ν_{max} = 2933, 2858, 1741, 1468, 1440, 1369, 1254, 1171, 1115, 1058, 1024, 952, 884, 836, 776 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.12 (d, *J* = 4.8 Hz, 1H), 4.43 (q, *J* = 7.6 Hz, 1H), 3.72 (dt, *J* = 16.8, 6.8 Hz, 1H), 3.64 (s, 3H), 3.53 (td, *J* = 9.6, 6.4 Hz, 1H), 3.36 (dt, *J* = 16.4, 6.8 Hz, 1H), 2.41 (ddd, *J* = 18.8, 10.4, 5.6 Hz, 2H), 2.31 (dt, *J* = 12.4, 7.2 Hz, 1H), 2.04 (t, *J* = 8.0 Hz, 2H), 2.00–1.93 (m, 1H), 1.91–1.81 (m, 2H), 1.68 (td, *J* = 11.2, 7.2 Hz, 1H), 1.60–1.51 (m, 1H), 1.15 (t, *J* = 7.2 Hz, 3H), 0.84 (s, 9H), 0.01 (s, 3H), –0.001 (s, 3H) ppm; ^{13}C/DEPT NMR (50 MHz, $CDCl_3$): δ = 174.3 (s), 105.6 (d), 81.1 (d), 77.6 (d), 62.3 (t), 51.5 (q), 51.3 (d), 44.2 (d), 43.2 (t), 38.3 (t), 32.5 (t), 28.2 (t), 25.7 (q, 3C), 17.9 (s), 15.0 (q), –4.2 (q), –4.8 (q) ppm; HRMS (ESI): calcd. for $C_{19}H_{36}O_5SiNa^+$ $[M+Na]^+$: 395.2224, found: 395.2222.

*4.5. An effective approach to (+)-campherenone (**9**)*



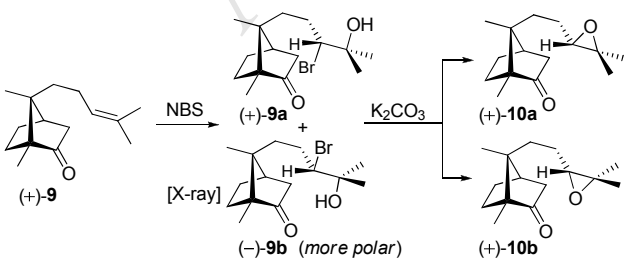
To a stirred solution of methyl ester (–)-**2a** (2 g, 7.1 mmol) in Et_2O (20 mL) was added MeLi (1.0 M in Et_2O, 15.6 mL) dropwise at –40 °C under Ar. The resulting mixture was stirred for 30 min, and quenched with water (5 mL) and extracted with Et_2O (3 × 50 ml). The combined organic phases were washed with water (20 mL), brine (20 mL), and dried over $MgSO_4$. After the solvent was evaporated in *vacuo*, the crude residue was

purified by flash column chromatography (petroleum ether/AcOEt = 5 : 1) on silica gel to afford 1.9 g (95%) of tertiary alcohol (–)-**2a′** as a colorless oil. R_f = 0.27 (petroleum ether/AcOEt = 3 : 1); $[\alpha]_D^{16}$ = –17 (*c* = 1.0, $CHCl_3$); IR (film): ν_{max} = 3383, 2960, 2875, 1473, 1378, 1178, 1125, 1049, 947 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.90–3.69 (m, 4H), 2.00–1.78 (m, 4H), 1.70–1.55 (m, 1H), 1.50–1.28 (m, 6H), 1.25–1.10 (m, 1H), 1.18 (s, 6H), 1.08–0.95 (m, 1H), 0.82 (s, 3H), 0.76 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 117.1, 71.0, 64.9, 63.5, 53.3, 51.2, 45.1, 44.4, 41.7, 33.3, 29.6, 29.2, 29.1, 26.6, 20.0, 16.6, 9.9 ppm; EI–MS (70 eV): *m/z* (% relative intensity) 282 (M^+, 7.3), 267 (7), 223 (5), 181 (15), 153 (6.2), 125 (100), 95 (100); HRMS (ESI): calcd. for $C_{17}H_{31}O_3^+$ $[M+H]^+$: 283.2268, found: 283.2261.

To a stirred solution of (–)-**2a′** (1.9 g, 6.7 mmol) in acetone (20 mL) was added *p*-TsOH (100 mg, 0.53 mmol). The resulting mixture was stirred for 2 h at reflux temperature. Acetone was evaporated, and the residue was extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with water (20 mL), brine (20 mL), and dried over $MgSO_4$. After the solvent was evaporated in *vacuo*, the crude residue was purified by flash column chromatography (petroleum ether/AcOEt = 3 : 1) on silica gel to afford 1.4 g (87%) of keto-alcohol (–)-**2a″** as a colorless oil. R_f = 0.11 (petroleum ether/AcOEt = 3 : 1); $[\alpha]_D^{18}$ = +24 (*c* = 0.9, $CHCl_3$); IR (film): ν_{max} = 3432, 2961, 1741, 1468, 1378, 1184, 1047 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.28–2.18 (m, 2H), 1.95–1.80 (m, 2H), 1.78–1.65 (m, 1H), 1.59–1.20 (m, 7H), 1.22 (s, 6H), 1.20–1.05 (m, 1H), 0.96 (s, 3H), 0.91 (s, 3H) ppm; EI–MS (70 eV): *m/z* (% relative intensity) 238 (M^+, 3.7), 223 (13), 220 (15.8), 205 (5.3), 149 (13), 109 (8), 81 (71), 41 (100); HRMS (SIMS): calcd. for $C_{15}H_{27}O_2^+$ $[M+H]^+$: 239.2006, found: 239.2001.

To a stirred solution of keto-alcohol (–)-**2a″** (1.4 g, 5.9 mmol) in benzene (15 mL) was added *p*-TsOH (50 mg, 0.26 mmol). The resulting mixture was stirred for 4 h at reflux temperature and the reaction was quenched with saturated $NaHCO_3$ (5 mL) and extracted with Et_2O (2 × 50 mL). The combined organic phases were washed with water (15 mL), brine (15 mL), and dried over $MgSO_4$. After the solvent was evaporated in *vacuo*, the crude residue was purified by flash column chromatography (petroleum ether/AcOEt = 100 : 1) on silica gel to afford 1.16 g (90%) of (+)-camphereneone **9** as a colorless oil, R_f = 0.74 (petroleum ether/AcOEt = 10 : 1); $[\alpha]_D^{18}$ = +32 (*c* = 1.0, $CHCl_3$), lit.[12b] $[\alpha]_D^{25}$ +30.77 (*c* = 2.78, $CHCl_3$); IR (film): ν_{max} = 2960, 1744, 1649, 1457, 1364, 1152, 1071 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5.06 (t, 1H, *J* = 6.9 Hz), 2.30–2.24 (m, 2H), 2.13–2.03 (m, 1H), 1.94–1.81 (m, 3H), 1.78–1.59 (m, 2H), 1.66 (s, 3H), 1.59 (s, 3H), 1.43–1.25 (m, 2H), 1.20–1.07 (m, 1H), 0.97 (s, 3H), 0.90 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 219.7, 131.6, 124.3, 58.7, 49.6, 42.8, 39.7, 34.0, 30.0, 27.0, 25.6, 23.9, 17.5, 15.9, 9.2 ppm; EI–MS (70 eV): *m/z* (% relative intensity) 220 (M^+, 34), 177 (10), 135 (31), 109 (96), 81 (46), 69 (100).

*4.6. Syntheses of diastereomeric epoxyketones **10a** and **10b***



To a stirred solution of (+)-camphereneone **9** (860 mg, 3.9 mmol) in THF/H_2O (15 mL, v/v = 2:1) was added NBS (765 mg, 4.3 mmol) portionwise at room temperature. The resulting mixture was stirred for 10 min, and quenched with saturated $NaHCO_3$ (5 mL) and extracted with Et_2O (3 × 30 mL). The combined organic phases were washed with water (10 mL), brine (10 mL), and dried over $MgSO_4$. After the solvent was evaporated in *vacuo*, the crude residue was purified by flash column chromatography (petroleum ether/AcOEt = 12 : 1 → 9 : 1) on silica gel to afford 510 mg (41%) of bromohydrin (+)-**9a** and 630 mg (51%) of bromohydrin (–)-**9b** as colorless crystals. Data for (+)-**9a**: R_f = 0.26 (petroleum ether/AcOEt = 6 : 1); mp 63–64 °C (*n*-hexane); $[\alpha]_D^{18}$ = +46 (*c* = 0.75, $CHCl_3$); IR (film): ν_{max} = 3446, 2959, 2880, 1739, 1448, 1378, 1126, 1045, 955 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.87 (dd, *J* =11.4, 1.8Hz, 1H), 2.35 (dt, *J* = 15.0, 4.2 Hz, 1H), 2.19 (t, *J* = 4.2 Hz, 1H), 2.14–2.04 (m, 1H), 2.07 (s, 1H, –O*H*), 1.92–1.83 (m, 2H), 1.75–1.55 (m, 2H), 1.49–1.37 (m, 2H), 1.36 (s, 3H), 1.34 (s, 3H), 1.18–1.08 (m, 1H), 0.96 (s, 3H), 0.93 (s, 3H), 0.88–0.78 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 219.5, 72.8, 71.8, 58.9, 49.6, 42.8, 39.9, 33.5, 30.3, 30.3, 27.1, 27.1, 26.3, 16.6, 9.5 ppm; EI–MS (70 eV): *m/z* (% relative intensity) 318 (M^+, 5.3), 316 (M^+, 5.2), 303 (3), 301 (3), 219 (25), 179 (53), 137 (32), 109 (98), 81 (100); HRMS (SIMS): calcd. for $C_{15}H_{26}O_2{}^{79}Br^+$ $[M+H]^+$: 317.1111, found: 317.1108. Data for (–)-**9b**: R_f = 0.22 (petroleum ether/AcOEt = 6 : 1); mp 58–59 °C (*n*-hexane); $[\alpha]_D^{18}$ = –32 (*c* = 0.9, $CHCl_3$); IR (film): ν_{max} = 3450, 2960, 2879, 1738, 1449, 1379, 1128, 1043, 968 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.85 (dd, *J* = 9.6, 3.3 Hz, 1H), 2.21 (dt, *J* = 15.0, 3.6 Hz, 1H), 2.18 (d, *J* = 3.6 Hz, 1H), 2.06 (s, 1H, –O*H*), 1.94–1.81 (m, 4H), 1.75–1.54 (m, 2H), 1.46–1.33 (m, 2H), 1.34 (s, 6H), 1.04–0.82 (m, 1H), 0.96 (s, 3H), 0.93 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 219.5, 72.8, 71.2, 59.0, 49.6, 42.9, 40.1, 33.1, 30.11, 30.12, 27.1, 27.0, 26.5, 16.0, 9.5 ppm; EI–MS (70 eV): *m/z* (% relative intensity) 318 (M^+, 6), 316 (M^+, 5.8), 303 (2.8), 301 (3.1), 219 (18.3), 179 (48), 137 (33), 109 (92), 81 (100). This bromohydrin was dissolved in hexane/EtOAc (5 : 1). After 2 days, colorless single crystals were obtained by slow evaporation of the solvent at room temperature.

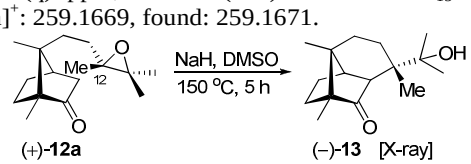
To a stirred solution of (+)-**9a** or (–)-**9b** (100 mg, 0.32 mmol) in MeOH (3 mL) was added K_2CO_3 (44 mg, 0.32 mmol) one portion at room temperature. The resulting mixture was stirred for 5 min, and quenched with water (2 mL) and extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with water (5 mL), brine (5 mL), and dried over $MgSO_4$. After the solvent was evaporated in *vacuo*, the crude residue was purified by flash column chromatography (petroleum ether/AcOEt = 16 : 1) on silica gel to afford 70 mg (95%) of epoxide (+)-**10a** or (+)-**10b** as a colorless oil. Data for (+)-**10a**[9]: R_f = 0.33 (petroleum ether/AcOEt = 6 : 1); $[\alpha]_D^{18}$ = +20 (*c* = 1.0, $CHCl_3$); IR (film): ν_{max} = 2960, 2880, 1743, 1452, 1380, 1324, 1123, 1046 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.61 (t, *J* = 6.0 Hz, 1H), 2.22–2.14 (m, 2H), 1.92–1.79 (m, 2H), 1.73–1.62 (m, 2H), 1.44–1.26 (m, 3H), 1.26 (s, 3H), 1.22 (s, 3H), 1.04–0.84 (m, 2H), 0.94 (s, 3H), 0.89 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 219.3, 64.1, 58.6, 58.4, 49.3, 42.6, 39.6, 30.2, 29.9, 26.8, 24.9, 24.8, 18.5, 15.8, 9.1 ppm; EI–MS (70 eV): *m/z* (% relative intensity) 236 (M^+, 4.4), 221 (7.3), 193 (6), 163 (7.2), 135 (38), 109 (87), 95 (97), 41 (100); Data for (+)-**10b**: R_f = 0.33 (petroleum ether/AcOEt = 6 : 1); $[\alpha]_D^{18}$ = +25 (*c* = 1.0, $CHCl_3$); IR (film): ν_{max} = 2960, 2879, 1743, 1452, 1380, 1324, 1123, 1047 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.60 (t, *J* = 6.0 Hz, 1H), 2.28–2.16 (m, 2H), 1.91–1.79 (m, 2H), 1.72–1.35 (m, 4H), 1.32–1.22 (m, 1H), 1.25 (s, 3H), 1.22 (s, 3H), 1.16–1.10 (m, 2H), 0.92 (s, 3H), 0.88 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 219.1, 64.1, 58.5,

58.2, 49.3, 42.5, 39.6, 30.2, 29.9, 26.8, 24.9, 24.8, 18.5, 15.8, 9.2 ppm; HRMS (SIMS): calcd. for $C_{15}H_{25}O_2^+$ $[M+H]^+$: 237.1849, found: 237.1842.

4.7. Comparison of 6-exo-tet cyclization behaviors

NaH (8 mg, 60% dispersion in mineral oil, washed three times with *n*-hexane distilled from CaH_2) was placed in round-bottomed flask, and DMSO (1 mL) was introduced under Ar. The resulting mixture was heated with stirring to 70–75 °C. Half an hour later, the pale yellow solution was cooled to room temperature, and a solution of the epoxide (+)-**10a** (24 mg, 0.1 mmol) in DMSO (1 mL) was added dropwise. The stirring was continued for 0.5 h, the mixture was then quenched with water (1 mL) and extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with water (5 mL), brine (5 mL), and dried over $MgSO_4$. After the solvent was evaporated in *vacuo*, the crude residue was purified by flash column chromatography (petroleum ether/AcOEt = 8 : 1) on silica gel to afford 19.5 mg (81%) of keto-alcohol (–)-**11a**[9] as a colorless crystal. R_f = 0.15 (petroleum ether/AcOEt = 6 : 1); mp 76–77 °C (*n*-hexane); $[\alpha]_D^{16}$ = –20 (*c* = 2.3, $CHCl_3$); IR (film): ν_{max} = 3430, 2961, 2874, 1735, 1472, 1449, 1378, 1194, 1143, 1038, 938 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.31 (d, *J* = 4.8 Hz, 1H), 2.24 (s, 1H, O*H*), 2.03–1.84 (m, 1H), 1.74–1.62 (m, 2H), 1.58–1.28 (m, 6H), 1.24 (s, 3H), 1.19 (s, 3H), 1.02–0.82 (m, 1H), 0.944 (s, 3H), 0.936 (s, 3H) ppm; ^{13}C/DEPT NMR (75 MHz, $CDCl_3$): δ = 224.7 (s), 73.2 (s), 58.4 (s), 53.6 (d), 49.6 (d), 43.4 (s), 42.0 (d), 30.2 (t), 29.9 (t), 28.7 (q), 26.2 (q), 24.3 (t), 21.1 (t), 18.7 (q), 9.6 (q) ppm; EI–MS (70 eV): *m/z* (% relative intensity) 236 (M^+, 18.6), 221 (18), 175 (20), 149 (23), 95 (34), 59 (37), 40 (100). This compound was dissolved in hexane/EtOAc (4 : 1). After 2 days, colorless single crystals were obtained by slow evaporation of the solvent at room temperature.

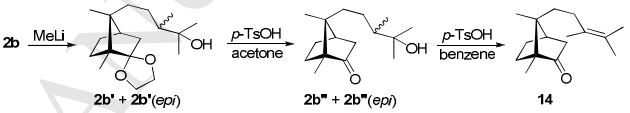
Methylsulfinyl sodium solution was prepared according to the above procedure for (–)-**11a**. Half an hour later, a solution of epoxide (+)-**10b** (24 mg, 0.1 mmol) in DMSO (1 mL) was added to the resulting solution dropwise. The stirring was continued for 5 h at 70 °C, then quenched with water (1 mL) and extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with water (5 mL), brine (5 mL), and dried over $MgSO_4$. After the solvent was evaporated in *vacuo*, the crude residue was purified by flash column chromatography (petroleum ether/AcOEt = 15 : 1) on silica gel to afford 12 mg (50%) of keto-alcohol (–)-**11b** as a colorless crystal. R_f = 0.33 (petroleum ether/AcOEt = 6 : 1); mp 38–39 °C (*n*-hexane); $[\alpha]_D^{20}$ = –7 (*c* = 0.5, $CHCl_3$); IR (film): ν_{max} = 3477, 2954, 2878, 1723, 1471, 1445, 1380, 1265, 1156, 1109, 1009, 945 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.44 (s, 1H, –O*H*), 2.52 (s, 1H), 1.94–1.89 (m, 1H), 1.80 (d, *J* = 3.9 Hz, 1H), 1.81–1.77 (m, 1H), 1.73–1.56 (m, 4H), 1.40–1.25 (m, 3H), 1.34 (s, 3H), 1.14 (s, 3H), 0.93 (s, 6H) ppm; ^{13}C/DEPT NMR (75 MHz, $CDCl_3$): δ = 225.9 (s), 71.6 (s), 57.6 (s), 54.0 (d), 50.4 (d), 49.0 (s), 48.9 (d), 32.0 (t), 31.6 (t), 30.2 (q), 27.6 (q), 25.2 (t), 21.1 (t), 18.2 (q), 8.5 (q) ppm; HRMS (ESI): calcd. for $C_{15}H_{24}O_2Na^+$ $[M+Na]^+$: 259.1669, found: 259.1671.



(+)-**12a** (–)-**13** [X-ray]

Methylsulfinyl sodium solution was prepared according to the above procedure for (–)-**11a**. Half an hour later, a solution of epoxide (+)-**12a** (30 mg, 0.12 mmol) in DMSO (1 mL) was added to the resulting solution dropwise. The stirring was continued for 5 h at 150 °C and quenched with water (1 mL) and extracted with Et_2O (3 × 10 mL). The combined organic phases were washed with water (5 mL), brine (5 mL), and dried over $MgSO_4$. After the solvent was evaporated in *vacuo*, the crude residue was purified by flash column chromatography (petroleum ether/AcOEt = 14 : 1 → 8 : 1) on silica gel to afford 20 mg (67%) of keto-alcohol (–)-**13** as a colorless crystal. R_f = 0.31 (petroleum ether/AcOEt = 5 : 1); mp 95–96 °C (*n*-hexane); $[\alpha]_D^{20}$ = –103 (*c* = 0.6, $CHCl_3$); IR (film): ν_{max} = 3524, 3437, 2955, 2876, 1722, 1463, 1375, 1122, 1038, 948 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.77 (d, *J* = 4.8 Hz, 1H), 1.97 (s, 1H, –O*H*), 1.89–1.78 (m, 2H), 1.75–1.62 (m, 2H), 1.43–1.28 (m, 2H), 1.26–1.16 (m, 1H), 1.24 (s, 3H), 1.20 (s, 3H), 0.99–0.83 (m, 2H), 0.93 (s, 3H), 0.91 (s, 3H), 0.88 (s, 3H) ppm; ^{13}C/DEPT NMR (50 MHz, $CDCl_3$): δ = 224.0 (s), 77.3 (s), 59.6 (d), 58.2 (s), 47.5 (s), 44.7 (d), 43.6 (s), 32.2 (t), 30.2 (t), 28.7 (t), 27.2 (q), 26.0 (q), 24.5 (t), 21.5 (q), 18.6 (q), 9.4 (q) ppm; HRMS (ESI): calcd. for $C_{16}H_{30}O_2N^+$ $[M+NH_4]^+$: 268.2272, found: 268.2275. This compound was dissolved in hexane/EtOAc (4 : 1). After 2 days, colorless single crystals were obtained by slow evaporation of the solvent at room temperature.

*4.8. Synthesis of 12-methyl-camphereneone (**14**)*



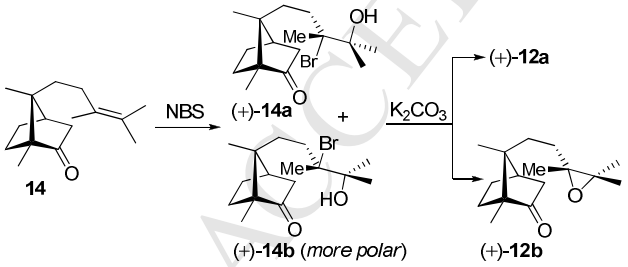
To a stirred solution of methyl ester **2b** (1.1 g, 3.7 mmol) in Et_2O (10 mL) was added MeLi (1.0 M in Et_2O, 9.3 mL) dropwise at –40 °C under Ar. The resulting mixture was stirred for 30 min, and quenched with water (5 mL) and extracted with Et_2O (3 × 50 ml). The combined organic phases were washed with water (20 mL), brine (20 mL), and dried over $MgSO_4$. After the solvent was evaporated in *vacuo*, the crude residue was purified by flash column chromatography (petroleum ether/AcOEt = 10 : 1) on silica gel to afford 451 mg (41%) of alcohol (+)-**2b′** and 528 mg (48%) of alcohol (–)-**2b′** (*epi*) as colorless oils. Data for (+)-**2b′**: R_f = 0.55 (petroleum ether/AcOEt = 3 : 1); $[\alpha]_D^{20}$ = +13 (*c* = 3.0, $CHCl_3$); IR (film): ν_{max} = 3404, 2964, 2875, 1473, 1453, 1379, 1267, 1124, 1046, 948 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.95–3.72 (m, 4H), 2.10–1.99 (m, 1H), 1.95–1.82 (m, 3H), 1.72–1.64 (m, 2H), 1.43–1.24 (m, 3H), 1.23–1.20 (m, 1H), 1.19 (s, 3H), 1.17 (s, 3H), 1.00–0.75 (m, 2H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.84 (s, 3H), 0.80 (s, 3H) ppm; ^{13}C/DEPT NMR (75 MHz, $CDCl_3$): δ = 117.1 (s), 73.6 (s), 64.9 (t), 63.5 (t), 53.3 (s), 51.2 (s), 45.4 (d), 44.4 (t), 41.8 (d), 31.8 (t), 29.8 (t), 27.2 (q and t, 2C), 26.7 (t), 26.1 (q), 16.6 (q), 15.0 (q), 9.9 (q) ppm; HRMS (ESI): calcd. for $C_{18}H_{33}O_3^+$ $[M+H]^+$: 297.2424, found: 297.2422. Data for (–)-**2b′** (*epi*): R_f = 0.42 (petroleum ether/AcOEt = 3 : 1); $[\alpha]_D^{20}$ = –34 (*c* = 1.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 3.96–3.70 (m, 4H), 1.95–1.86 (m, 3H), 1.82–1.43(m, 3H), 1.42–1.31 (m, 3H), 1.24–1.19 (m, 2H), 1.17 (s, 3H), 1.15 (s, 3H), 1.05–0.95 (m, 1H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.83 (s, 3H), 0.80 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 117.1, 73.6, 64.9, 63.5, 53.4, 51.3, 45.4, 44.4, 41.7, 31.6, 29.7, 27.3, 27.0, 26.6, 26.0, 16.6, 14.6, 9.9 ppm; HRMS (ESI): calcd. for $C_{18}H_{33}O_3^+$ $[M+H]^+$: 297.2424, found: 297.2422.

To a stirred solution of alcohol (+)-**2b′** and (–)-**2b′** (*epi*) (800 mg, 2.7 mmol) in acetone (10 mL) was added *p*-TsOH (51 mg, 0.27 mmol). The resulting mixture was stirred for 2 h at reflux temperature. Acetone was evaporated, and the residue was extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with water (15 mL), brine (15 mL), and dried over

$MgSO_4$. After the solvent was evaporated in *vacuo*, the crude residue was purified by flash column chromatography on silica gel (petroleum ether/AcOEt = 4 : 1) to afford 544 mg (80%) of alcohol (+)-**2b′′** and (+)-**2b′′** (*epi*) as colorless oils. Data for (+)-**2b′′**: R_f = 0.56 (petroleum ether/AcOEt = 2 : 1); $[\alpha]_D^{20}$ = +55 (*c* = 2.4, $CHCl_3$); IR (film): ν_{max} = 3459, 2962, 2876, 1741, 1466, 1449, 1379, 1175, 1088, 945 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.27–2.18 (m, 2H), 1.93–1.79 (m, 3H), 1.75–1.67 (m, 1H), 1.45–1.24 (m, 4H), 1.18 (s, 3H), 1.15 (s, 3H), 1.12–1.01 (m, 1H), 0.97 (s, 3H), 0.96–0.82 (m, 1H), 0.92 (s, 3H), 0.82 (d, *J* = 6.3 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 219.8, 73.3, 58.7, 49.6, 45.1, 42.6, 39.6, 32.8, 30.0, 27.6, 26.8 (2C), 25.8, 15.9, 14.7, 9.2 ppm; HRMS (ESI): calcd. for $C_{16}H_{32}O_2N^+$ $[M+NH_4]^+$: 270.2428, found: 270.2431. Data for (+)-**2b′′** (*epi*): R_f = 0.50 (petroleum ether/AcOEt = 2 : 1); $[\alpha]_D^{20}$ = +2 (*c* = 2.2, $CHCl_3$); IR (film): ν_{max} = 3463, 2962, 2876, 1741, 1466, 1449, 1379, 1173, 1053, 949 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.27–2.22 (m, 2H), 1.93–1.81 (m, 2H), 1.75–1.58 (m, 2H), 1.45–1.20 (m, 4H), 1.17 (s, 3H), 1.14 (s, 3H), 1.11–1.00 (m, 1H), 0.94 (s, 3H), 0.92 (s, 3H), 0.92–0.79 (m, 1H), 0.87 (d, *J* = 6.3 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 219.8, 73.2, 58.7, 49.7, 45.0, 42.7, 39.6, 32.7, 30.0, 27.6, 26.8 (2C), 25.8, 15.9, 14.6, 9.2 ppm; HRMS (ESI): calcd. for $C_{16}H_{32}O_2N^+$ $[M+NH_4]^+$: 270.2428, found: 270.2431.

To a stirred solution of keto-alcohol (+)-**2b′′** and (+)-**2b′′** (*epi*) (360 mg, 1.43 mmol) in benzene (5 mL) was added *p*-TsOH (50 mg, 0.26 mmol). The resulting mixture was stirred for 1.5 h at reflux temperature and the reaction was quenched with saturated $NaHCO_3$ (3 mL) and extracted with Et_2O (2 × 40 mL). The combined organic phases were washed with water (10 mL), brine (10 mL), and dried over $MgSO_4$. After the solvent was evaporated in *vacuo*, the crude residue was purified by flash column chromatography on silica gel (petroleum ether/AcOEt = 100 : 1) to afford 284 mg (85%, 1 : 1) of internal alkene **14** and inseparable terminal alkene as colorless oils. Data for **14**: R_f = 0.50 (petroleum ether/AcOEt = 2 : 1); IR (film): ν_{max} = 3059, 2958, 2926, 2867, 1744, 1646, 1450, 1377, 1045 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.32–2.03 (m, 4H), 1.93–1.84 (m, 2H), 1.83–1.65 (m, 2H), 1.61 (s, 6H), 1.59 (s, 3H), 1.45–1.38 (m, 2H), 1.17–1.08 (m, 1H), 0.98 (s, 3H), 0.88 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 219.6, 127.3, 124.0, 58.7, 49.6, 42.8, 39.8, 32.3, 31.5, 30.2, 30.0 (2C), 26.9, 21.5, 15.8, 9.3 ppm; HRMS (ESI): calcd. for $C_{16}H_{27}O^+$ $[M+H]^+$: 235.2057, found: 235.2060.

*4.9. Syntheses of 12-methyl epoxyketones **12a** and **12b***



To a stirred solution of the mixture of **14** and terminal alkene (500 mg, 2.1 mmol) in THF/H_2O (6 mL, v/v = 2 : 1) was added NBS (394 mg, 2.2 mmol) portionwise at room temperature. The resulting mixture was stirred for 10 min and quenched with saturated $NaHCO_3$ (3 mL) and extracted with Et_2O (3 × 30 mL). The organic layer was washed with water (10 mL), brine (10 mL), and dried over $MgSO_4$. After the solvent was evaporated in *vacuo*, the crude residue was purified by flash column chromatography on silica gel (petroleum ether/AcOEt = 12 : 1 → 8 : 1) to afford 278 mg (40%) of regioisomeric bromohydrin from terminal alkene and 125 mg (18%) of bromohydrin (+)-**14a** and 138 mg (20%) of bromohydrin (+)-**14b** successively as colorless crystals. Data for (+)-**14a**: R_f = 0.19 (petroleum ether/AcOEt = 6 : 1); mp 94–96 °C (*n*-hexane); $[\alpha]_D^{20}$ = +20 (*c* = 0.5, $CHCl_3$); IR (film): ν_{max} = 3464, 2959, 2871, 1739, 1449, 1377, 1049, 950, 862 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.45 (dt, *J* = 4.5, 17.4 Hz, 1H), 2.28–2.21 (m, 2H), 2.16–2.02 (m, 2H), 1.94–1.81 (m, 2H), 1.78–1.68 (m, 1H), 1.66 (s, 3H), 1.49–1.22 (m, 2H), 1.38 (s, 6H), 0.98–0.80 (m, 2H), 0.96 (s, 6H) ppm; ^{13}C/DEPT NMR (75 MHz, $CDCl_3$): δ = 219.2 (s), 87.5 (s), 75.9 (s), 58.6 (s), 49.4 (s), 42.6 (t), 39.5 (d), 35.3 (t), 30.5 (t), 30.1 (t), 26.8 (t), 25.5 (q), 16.3 (q, 2C), 9.2 (q, 2C) ppm; HRMS (ESI): calcd. for $C_{16}H_{31}O_2N^{79}Br^+$ $[M+NH_4]^+$: 348.1533, found: 348.1529. Data for (+)-**14b**: R_f = 0.10 (petroleum ether/AcOEt = 6 : 1); mp 108–110 °C (*n*-hexane); $[\alpha]_D^{20}$ = +2 (*c* = 3.0, $CHCl_3$); IR (film): ν_{max} = 3471, 2961, 2880, 1740, 1449, 1377, 1325, 1051, 952, 862 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.28–2.21 (m, 2H), 2.18 (d, *J* = 3.6 Hz, 1H), 1.93–1.84 (m, 2H), 1.77–1.69 (m, 1H), 1.65 (s, 3H), 1.58–1.52 (m, 1H), 1.47–1.33 (m, 2H), 1.38 (s, 3H), 1.37 (s, 3H), 1.21–1.14 (m, 1H), 0.99 (s, 3H), 0.97 (s, 3H), 0.95–0.84 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 219.2, 87.1, 75.9, 58.8, 49.3, 42.6, 39.7, 35.3, 30.5, 30.0, 26.9, 26.0, 15.6 (2C), 9.3 (2C) ppm; HRMS (ESI): calcd. for $C_{16}H_{31}O_2N^{79}Br^+$ $[M+NH_4]^+$: 348.1533, found: 348.1529.

To a stirred solution of (+)-**14a** or (+)-**14b** (90 mg, 0.27 mmol) in MeOH (2 mL) was added K_2CO_3 (41 mg, 0.30 mmol) one portion at room temperature. The resulting mixture was stirred for 5 min. and quenched with water (2 mL) and extracted with Et_2O (3 × 10 mL). The organic layer was washed with water, brine, and dried over $MgSO_4$. After the solvent was evaporated in *vacuo*, the crude residue was purified by flash column chromatography on silica gel (petroleum ether/AcOEt = 14 : 1) to afford 68 mg (90%) of epoxide (+)-**12a** or (+)-**12b** as a colorless crystal. Data for (+)-**12a**: R_f = 0.30 (petroleum ether/AcOEt = 5 : 1); mp 43–44 °C (*n*-hexane); $[\alpha]_D^{20}$ = +18 (*c* = 1.4, $CHCl_3$); IR (film): ν_{max} = 2958, 2929, 1743, 1469, 1449, 1379, 1203, 1078, 1045, 1021, 854 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.20 (dt, *J* = 4.8, 17.4 Hz, 1H), 2.18 (t, *J* = 3.6 Hz, 1H), 1.95–1.68 (m, 3H), 1.47–1.32 (m, 3H), 1.29 (s, 6H), 1.26 (s, 3H), 1.24–1.17 (m, 1H), 1.08–0.90 (m, 2H), 0.94 (s, 3H), 0.92 (s, 3H) ppm; ^{13}C/DEPT NMR (75 MHz, $CDCl_3$): δ = 219.2 (s), 64.3 (s), 62.2 (s), 58.6 (s), 49.4 (s), 42.7 (t), 39.6 (d), 31.1 (t), 30.0 (t), 29.4 (t), 26.9 (t), 21.3 (q), 20.9 (q), 18.6 (q), 15.8 (q), 9.2 (q) ppm; HRMS (ESI): calcd. for $C_{16}H_{30}O_2N^+$ $[M+NH_4]^+$: 268.2271, found: 268.2268. Data for (+)-**12b**: R_f = 0.27 (petroleum ether/AcOEt = 5 : 1); mp 69–71 °C (*n*-hexane); $[\alpha]_D^{20}$ = +26 (*c* = 1.7, $CHCl_3$); IR (film): ν_{max} = 2960, 2929, 1738, 1470, 1448, 1381, 1201, 1077, 1047, 1020, 858 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.24 (dt, *J* = 4.5, 17.4 Hz, 1H), 2.23–2.19 (m, 1H), 1.92–1.85 (m, 2H), 1.76–1.68 (m, 1H), 1.63–1.60 (m, 1H), 1.47–1.39 (m, 1H), 1.36–1.32 (m, 1H), 1.32 (s, 3H), 1.30 (s, 3H), 1.24 (s, 3H), 1.14–1.07 (m, 2H), 0.94 (s, 3H), 0.93 (s, 3H), 0.88–0.82 (m, 1H) ppm; ^{13}C/DEPT NMR (75 MHz, $CDCl_3$): δ = 219.1 (s), 64.4 (s), 62.0 (s), 58.6 (s), 49.4 (s), 42.6 (t), 39.6 (d), 31.4 (t), 30.1 (t), 29.6 (t), 26.8 (t), 21.3 (q), 20.8 (q), 18.7 (q), 15.9 (q), 9.2 (q) ppm; HRMS (ESI): calcd. for $C_{16}H_{30}O_2N^+$ $[M+NH_4]^+$: 268.2271, found: 268.2268.

Acknowledgments

We thank Dr. Shou-Jie Shen and Dr. Yu-Rong Yang for their assistance. Y. Peng thanks the National Natural Science Foundation of China (No. 21772078), and the Fundamental Research Funds for the Central Universities by Ministry of Education of China (2682019CX70 and 2682019CX71). W.-D. Z. Li thanks the National Natural Science Foundation of China (No. 21672030), and the scholars program of Southwest Jiaotong University for financial support.

Supplementary data

Supplementary data related to this article can be found online at doi:

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