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Facile synthesis of isocampholenic acids by the rearrangement of camphor derivatives

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ABSTRACT

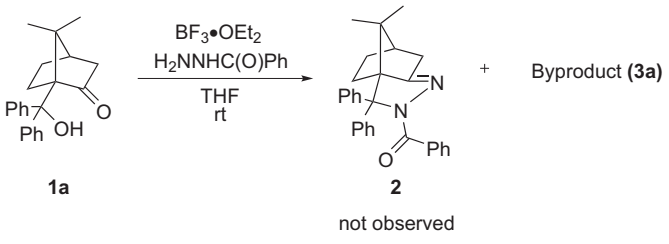
A variety of substituted isocampholenic acid derivatives were prepared by rearrangement of the camphor skeleton of a variety of tertiary alcohols derived from ketopinic acid. The reaction was highly reliable and retained the stereochemical information from the camphor scaffold. This rearrangement represents an efficient way to prepare synthetically useful isocampholenic acids. Mechanistic experiments show that a short-lived carbocation is implicated in the reaction.

1. Introduction

The use of camphor-based starting materials in the synthesis of natural products, chiral auxiliaries, organocatalysts, and ligands is a general strategy to exploit the stereochemical information from nature's chiral pool.[1] Many syntheses of alkaloid natural products employ rearrangements of the camphor skeleton to provide access to complex intermediates while controlling stereochemistry. Rearrangement reactions have been utilized in the synthesis of natural products, such as the zizaane sesquiterpenes,[2] (−)-quadrone,[3] (+)-ophiobolin C,[4] (+)-norpatchoulenol,[5] taxane diterpenes,[6] and the clavularanes.[7] Most of these syntheses involve the conversion of camphor derivatives into cyclopentanoid building blocks. Several methods have been described for such transformations, including those producing campholenic acid derivatives,[8] isocampholenic acids,[9] campholanic acid intermediates,[10] and cyclopentene carboxylic acids.[11] One method of converting camphor-based starting materials into isocampholenic acid derivatives involves the condensation of 9,10-dibromocamphor compounds with KOH.[12,13] This method has been employed in the synthesis of many natural products,[4,7,14] and chiral synthetic intermediates.[15] The value of cyclopentanoid compounds in the synthesis of alkaloid natural products suggests that methods which facilitate access to these derivatives have significant synthetic utility. Herein we disclose a method that provides a three-step synthesis to a variety of substituted isocampholenic acid derivatives.

2. Results and discussion

During the synthesis of a potential organocatalyst, we attempted to condense ketone **1a** with a benzoyl hydrazide to prepare cyclic hydrazone **2** (Scheme 1). When this was done, the desired product was not observed, instead, a significant amount of an unexpected byproduct was obtained. This byproduct was formed when a variety of protic acids were used as catalysts in the reaction, however, it was exclusively obtained in quantitative yield when $BF_3 \cdot OEt_2$ was employed. The structure of the unknown compound was elucidated by INADEQUATE analysis and found to be isocampholenic acid **3a**. This structural assignment was subsequently confirmed by a single crystal X-ray structure (Fig. 1).



Scheme 1.

Because of the efficiency of this process, we decided to investigate if this was a general method for synthesizing cyclopentanoid compounds. Toward this end, several diaryl-substituted

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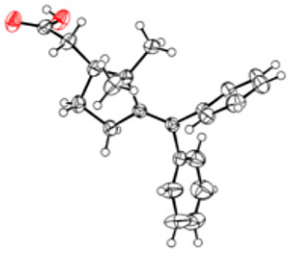
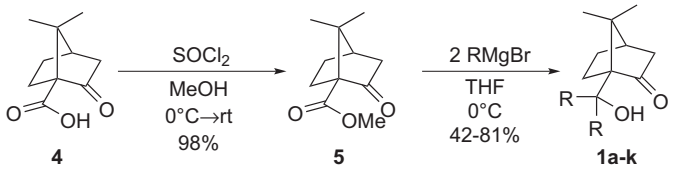


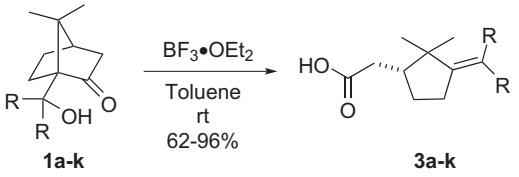
Fig. 1. X-ray ORTEP image of byproduct.

alcohols were prepared. Ketopinic acid[16] **4** was converted into methyl ester **5** by treatment with thionyl chloride in methanol.[17] This derivative was then converted into the alcohols **1a**–**k** by exposure to the appropriate Grignard reagent at 0 °C (Scheme 2).[18] Treatment of the products obtained from these condensations with $BF_3 \cdot OEt_2$ smoothly converted the tertiary alcohols **1** into the rearranged isocampholenic acids **3** in high yields (Table 1).



Scheme 2.

Table 1
$BF_3 \cdot OEt_2$ promoted rearrangements to obtain isocampholenic acid derivatives **3** from camphor derived tertiary alcohols **1**[a]



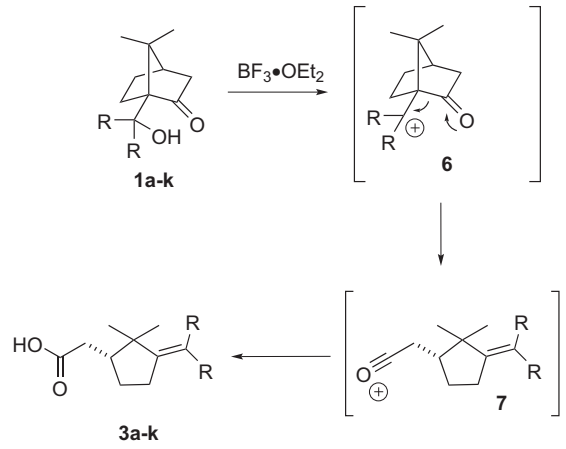
Entry	R	Yield[b] (%)
1	Ph (**a**)	96
2	4-F–C_6H_4 (**b**)	96
3	4-CH_3–C_6H_4 (**c**)	80
4	3-CH_3–C_6H_4 (**d**)	89
5	4-^{t}Bu–C_6H_4 (**e**)	76
6	4-CF_3–C_6H_4 (**f**)	84[c]
7	4-OMe–C_6H_4 (**g**)	80
8	3-OMe–C_6H_4 (**h**)	79
9	2-OMe–C_6H_4 (**i**)	62
10	2-Naphthyl (**j**)	65[d]
11	2-Thiophenyl (**k**)	93

[a] Reaction conditions: $BF_3 \cdot OEt_2$ (1.2 equiv), toluene, room temperature, 15 min.
[b] Isolated yield.
[c] Reaction required 48 h to complete.
[d] Dichloromethane used in place of toluene.

The reactions proceeded in good to excellent yields and occurred very rapidly and cleanly (Table 1). The presence of fluoro-substituted aryl rings (entry 2) was tolerated and resulted in a similar yield to that of the unsubstituted case (entry 1). Alkyl substituents on the aryl rings also did not significantly alter the efficiency of the reaction (entries 3–5). The effect of electronics on the rearrangement reaction was investigated by employing an electron withdrawing *p*-trifluoromethyl substituent (entry 6), and an electron donating *p*-methoxy group (entry 7). Comparable yields were obtained in both cases, however, the presence of the trifluoromethyl substituent significantly slowed the rate of the reaction.

Substituents located on the *meta* or *ortho* position of the aryl ring did not significantly impair the reaction (entries 4, 8 and 9), although the yield diminished slightly in the case of an *ortho*-methoxy substituted derivative. Large aromatic groups, such as naphthyl could also be present (entry 10), and the use of a heteroaromatic-substituted alcohol gave the rearranged product in excellent yield (entry 11).

The rearrangement likely proceeded via carbocationic intermediate **6**, that subsequently rearranged to provide the carboxylic acids **3** via an acylium species (Scheme 3). This was suggested by the fact that a differentially substituted alcohol (**11**) gave a mixture of isomers (**12**) from the reaction (see below).



Scheme 3.

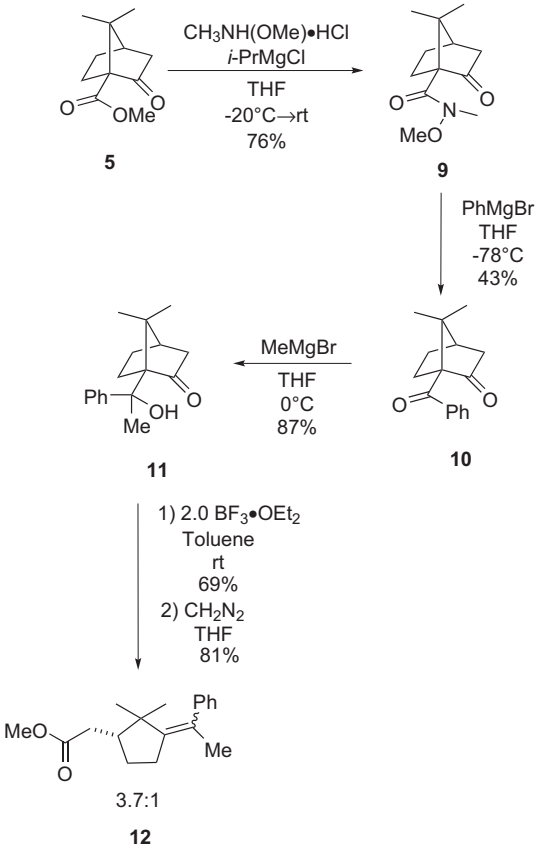
To test this, a toluene solution of alcohol **1e** and methanol (5 equiv) was treated with $BF_3 \cdot OEt_2$. This resulted in the production of the corresponding methyl ester in 91% yield, suggesting that the process involved an intermolecular reaction.[19] We also prepared methyl ether **8**, and performed a crossover experiment using a 1:1 mixture of **8** and **1d**. This experiment gave an 81% combined yield of a 1.1:1 mixture of the corresponding acids and esters. These results are consistent with the reaction proceeding by the rearrangement of a carbocationic intermediate, which then opens to form an acylium.

Dialkyl substituted derivatives did not cleanly rearrange under the reaction conditions. Although dimethyl alcohol **1l** was completely consumed when treated with $BF_3 \cdot OEt_2$, an inseparable mixture of products was obtained. The NMR spectrum of the material obtained indicated that the desired product was present, but the compound could not be satisfactorily purified.

8 : R = 4-^{t}BuC$_6$H$_4$ **1l**

To try to recover reactivity for alkyl-substituted derivatives, we prepared and tested an alkyl, aryl substituted alcohol and subjected it to the reaction conditions (Scheme 4). The required precursor, **11**, was prepared by converting methyl ester **5** into the corresponding Weinreb amide **9**.[20] Treatment with excess PhMgBr in THF at −78 °C resulted in clean conversion to phenyl ketone **10**. When this substance was exposed to MeMgBr, alcohol **11** was obtained as a single isomer.[21] Exposing this material to $BF_3 \cdot OEt_2$ caused rapid conversion to the carboxylic acid, which was immediately treated with diazomethane to provide methyl ester **12**,[22] a material that was obtained as a 3.7:1 mixture of isomers.[23] This result was

consistent with the stepwise mechanism involving carbocationic intermediates, such as **6** (Scheme 3).



Scheme 4.

3. Conclusions

The rearrangement of tertiary alcohols **1** to afford isocampholenic acids **3** is an efficient way to prepare these synthetically useful intermediates. The rearrangement was highly reliable and most products required no further purification. The products retained the stereochemical information of the starting camphor derivatives, and possessed a tetrasubstituted olefin. Functionality suitable for further elaboration is also a key feature of these products. Mechanistic experiments were consistent with ring opening of a keto carbocation, such as **6** to give an acylium ion.

4. Experimental

4.1. General methods

Reactions were performed under nitrogen in oven-dried glassware equipped with a magnetic stir bar and a rubber septum. Solvents were freshly distilled prior to use as follows: THF over sodium/benzophenone and toluene over calcium hydride. $BF_3 \cdot OEt_2$ was freshly distilled before each use. All other reagents were used without further purification unless otherwise indicated. Reactions were monitored by TLC analysis using aluminum plates (250 μm thickness) precoated with silica gel 60 F_{254}. TLC plates were visualized using ultraviolet light and potassium permanganate. Flash chromatography was carried out on 230–400 mesh silica gel 60, or preparatory TLC glass plates precoated with silica gel (Si250F). ^1H and ^{13}C NMR spectra were acquired on a 300 MHz, 400 MHz, or 500 MHz spectrometer in the specified solvent. Infrared spectra were acquired on a FTIR spectrometer. High resolution mass spectra were obtained using an Analytical Concept spectrometer. Melting points were determined using an Electrothermal Meltemp apparatus and are uncorrected.

*4.1.1. Methyl 7,7-dimethyl-2-oxobicyclo[2.2.1]heptane-1-carboxylate (**5**).* Methanol (30 mL) was stirred in a 100 mL round bottom flask and cooled to 0 °C using an ice bath. Thionyl chloride (4 mL, 54.9 mmol) was then slowly added via syringe. To this solution was introduced (*S*)-(+)-ketopinic acid[16] in four portions, waiting 5 min between additions. The resulting reaction mixture was stirred at 0 °C for 4 h, allowed to warm to room temperature over 18 h, and then concentrated under reduced pressure using a rotary evaporator. The resulting residue was diluted with ethyl acetate (50 mL). Water (50 mL) was added and the phases were separated. The aqueous phase was extracted once more with ethyl acetate (2×50 mL). The combined organic extracts were washed with saturated sodium bicarbonate solution (100 mL), and brine (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by silica gel chromatography (5–20% EtOAc in hexanes) to afford **4** as white needles (2.09 g, 98%). ^1H NMR (300 MHz, $CDCl_3$) δ 3.73 (s, 3H), 2.51 (ddd, J=18.3, 3.9, 3.9 Hz, 1H), 2.40–2.27 (m, 1H), 2.09 (dd, J=4.2, 4.2 Hz, 1H), 2.07–1.95 (m, 1H), 1.93 (d, J=18.3 Hz, 1H), 1.77 (ddd, J=13.8, 9.6, 5.1 Hz, 1H), 1.39 (ddd, J=12.3, 9.3, 4.2 Hz, 1H), 1.13 (s, 3H), 1.06 (s, 3H). Spectral data matched those previously reported.[17]

*4.1.2. N-Methoxy-N-7,7-trimethyl-2-oxobicyclo[2.2.1]heptane-1-carboxamide (**9**).* To a solution of **5** (200 mg, 1.02 mmol) in dry THF (10 mL) was added $CH_3NH(OMe) \cdot HCl$ (160 mg, 1.63 mmol). The resulting mixture was cooled to −20 °C and ^{i}PrMgCl (2.6 mL, 5.10 mmol) was added via syringe. After warming to 0 °C over 5 h, the reaction was quenched by the addition of saturated ammonium chloride (5 mL). The aqueous phase was then extracted twice with methyl *tert*-butyl ether (20 mL portions), and the organic extracts combined, dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator. Column chromatography (15–30% EtOAc/hexanes) provided pure **9** as a white powder (153 mg, 67%). Mp 46–48 °C; $[\alpha]_D$ +26.5 (*c* 0.62, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 3.67 (s, 3H), 3.23 (s, 3H), 2.51 (ddd, J=18.4, 5.2, 3.6 Hz, 1H), 2.38–2.28 (m, 1H), 2.15–1.98 (m, 3H), 1.94 (d, J=18.0 Hz, 1H), 1.46–1.39 (m, 1H), 1.21 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.1 (C), 169.9 (C), 67.5 (C), 60.6 (CH_3), 50.1 (C), 43.8 (CH_3), 43.7 (CH_2), 32.6 (CH), 27.1 (CH_2), 26.7 (CH_2), 21.6 (CH_3), 20.4 (CH_3); IR (neat) 1741, 1623 cm^{-1}. MS (EI) 225.1 (M^+); HRMS (EI) calcd for $C_{12}H_{19}NO_3$ (M^+) 225.1365, found 225.1342.

*4.1.3. 1-Benzoyl-7,7-dimethylbicyclo[2.2.1]heptan-2-one (**10**).* To a solution of amide **9** (128 mg, 0.57 mmol) in dry THF (5 mL) at −78 °C was added a freshly prepared solution of PhMgBr in THF (0.61 mL, 0.85 mmol). The resulting mixture was allowed to warm to room temperature over 12 h, and then quenched by the addition of saturated ammonium chloride (5 mL). The mixture was then diluted with EtOAc (20 mL), washed with 10% HCl (10 mL), saturated $NaHCO_3$ (10 mL), and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator. Column chromatography (5% EtOAc/hexanes) provided pure **10** as a white powder (59.3 mg, 43%). Mp 60–62 °C; $[\alpha]_D$ −23.1 (*c* 0.62, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.80–7.75 (m, 2H), 7.52–7.36 (m, 3H), 2.63 (ddd, J=18.6, 4.8, 3.3 Hz, 1H), 2.32–1.98 (m, 4H), 2.06 (d, J=18.3 Hz, 1H), 1.55–1.43 (m, 1H), 1.24 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.1 (C), 200.2 (C), 139.1 (C), 131.9 (CH), 128.9 (CH), 128.0 (CH), 73.2 (C), 50.0 (C), 44.4 (CH_2), 44.3 (CH), 28.9 (CH_2), 26.8 (CH_2), 21.8 (CH_3), 20.1 (CH_3); IR (neat) 1733, 1658 cm^{-1}; MS (EI) 242.1 (M^+); HRMS (EI) calcd for $C_{16}H_{18}O_2$ (M^+) 242.1307, found 242.1308.

*4.1.4. 1-(1-Hydroxy-1-phenylethyl)-7,7-dimethylbicyclo[2.2.1] heptan-2-one (**11**).* To a solution of ketone **10** (59 mg, 0.24 mmol) in dry

THF (5 mL) at 0 °C was added a solution of 3.0 M MeMgBr in Et_2O (0.24 mL, 0.73 mmol). The reaction mixture was allowed to warm to room temperature, and stirred at this temperature for 2 h. The reaction was then quenched with saturated ammonium chloride (5 mL), and the aqueous phase extracted twice with EtOAc (20 mL portions). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator. Column chromatography (3% EtOAc/hexanes) provided **11** as fine white needles (53.8 mg, 87%). Mp 79–81 °C; $[\alpha]_D$ −98.9 (*c* 0.74, CH_2Cl_2); ^{1}H NMR (300 MHz, C_6D_6) δ 7.62–7.55 (m, 2H), 7.19–7.05 (m, 3H), 4.07 (s, 1H), 2.14–2.03 (m, 1H), 1.89–1.77 (m, 1H), 1.71 (s, 3H), 1.45 (d, *J*=18.3 Hz, 1H), 1.45–1.33 (m, 1H), 1.25–1.14 (m, 2H), 0.95 (s, 3H), 0.77 (ddd, *J*=17.7, 9.0, 3.6 Hz, 1H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 145.3 (C), 127.5 (CH), 126.9 (CH), 126.8 (CH), 74.6 (C), 67.3 (C), 48.1 (C), 44.7 (CH), 43.4 (CH_2), 28.2 (CH_3), 26.6 (CH_2), 25.7 (CH_2), 21.8 (CH_3), 20.9 (CH_3); IR (neat) 3393, 1717 cm^{-1}; MS (EI) 258.2 (M^+); HRMS (EI) calcd for $C_{17}H_{22}O_2$ (M^+) 258.1620, found 258.1617.

*4.1.5. Methyl-2-((R)-2,2-dimethyl-3-(1-phenylethylidene)cyclopentyl)acetate (**12**).* To a solution of **11** (97 mg, 0.38 mmol) in dry toluene (4 mL) was added a solution of 0.65 M $BF_3{\cdot}OEt_2$ (0.10 mL, 0.76 mmol) under nitrogen. The mixture was stirred at room temperature for 15 min, and the reaction was then quenched by the addition of water (10 mL). The resulting mixture was extracted twice with EtOAc (20 mL portions). The combined organic extracts were washed with brine (20 mL) dried over $MgSO_4$, filtered, and concentrated in vacuo to provide compound the isocampholenic acid without need for further purification (3.7:1 mixture of isomers, 67.6 mg, 69%) as a clear syrup. This product was immediately dissolved in dry THF (2 mL), and a solution of freshly prepared diazomethane in Et_2O (2.6 mL, 1.77 mmol) was added dropwise until the yellow color persisted. The solvent was then evaporated, and the resulting residue purified by column chromatography (3–6% EtOAc/hexanes) to obtain the title compound as a 3.7:1 mixture of isomers (57 mg, 81%). ^{1}H NMR (300 MHz, C_6D_6) δ 7.20–7.01 (m, 5.4H), 3.37 (s, 0.9H), 3.35 (s, 2.1H), 2.38–1.89 (m, 6.9H), 1.79 (dd, *J*=1.5, 1.5 Hz, 2.4H), 1.36–1.21 (m, 0.6H), 1.23 (s, 0.6H), 0.89 (s, 0.6H), 0.71 (s, 2.2H), 0.68 (s, 2.3H); ^{13}C NMR (100 MHz, C_6D_6) δ 173.2 (C), 145.0 (C), 144.7 (C), 128.8 (CH), 127.7 (CH), 126.0 (CH), 50.7 (CH_3), 50.6 (CH_3), 49.3 (CH), 48.5 (CH), 44.3 (C), 44.2 (C), 34.5 (CH_2), 34.3 (CH_2), 32.5 (CH_2), 30.3 (CH_2), 29.0 (CH_2), 27.8 (CH_2), 26.7 (CH_3), 26.3 (CH_3), 24.4 (CH_3), 22.6 (CH_3), 20.7 (CH_3), 20.5 (CH_3); IR (neat) 1735 cm^{-1}; MS (EI) 272.2 (M^+); HRMS (EI) calcd for $C_{18}H_{24}O_2$ (M^+) 272.1776, found 272.1773.

4.2. General procedure for the synthesis of diaryl alcohols (Table 1, compounds 1a–l)

*4.2.1. 1-(Hydroxydiphenylmethyl)-7,7-dimethylbicyclo[2.2.1] heptan-2-one (**1a**).* Magnesium turnings (1.2 g, 51.2 mmol) and a few small crystals of I_2 were placed under a nitrogen atmosphere in a 100 mL round bottom flask equipped with a condenser. The flask was then warmed gently using a heat gun to vaporize the iodine, and the apparatus allowed to stand until the color of the iodine vapor disappeared. Into this flask was introduced one half of a solution of bromobenzene (4.5 mL, 42.7 mmol) in dry THF (30 mL). The solution was stirred until an exothermic reaction was observed, bringing it to reflux. As the reflux began to subside, the other half of the bromobenzene solution was added, and the reaction was heated to reflux for 1 h using a heating mantle, and then cooled to 0 °C in an ice bath. Methyl ester **5** (1.37 g, 6.48 mmol) was then introduced in one portion and the resulting mixture stirred at 0 °C for 1 h. The reaction was quenched with a saturated solution of ammonium chloride (20 mL). Water (50 mL) was then added and the resulting mixture was then extracted twice with EtOAc (50 mL portions). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Pure **3a** (924 mg, 60%) was obtained as clear crystals after recrystallization from 1:4 EtOAc/hexanes. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53–7.15 (m, 10H), 3.82 (s, 1H), 2.57–2.45 (m, 2H), 2.29 (ddd, *J*=13.8, 9.6, 5.1 Hz, 1H), 1.99–1.87 (m, 1H), 1.97 (d, *J*=18.6 Hz, 1H), 1.78 (dd, *J*=4.8, 4.8 Hz, 1H), 1.42 (ddd, *J*=12.0, 9.3, 3.9 Hz, 1H), 1.07 (s, 3H), 0.27 (s, 3H). Spectral data matched those previously reported.[18]

*4.2.2. 1-(Bis(4-fluorophenyl)(hydroxy)methyl)-7,7-dimethylbicyclo [2.2.1]heptan-2-one (**1b**).* Prepared from **5** (100 mg, 0.51 mmol) using a procedure similar to that described for **1a**. Column chromatography (5% EtOAc/hexanes) provided the title compound as clear crystals (142 mg, 78%). Mp 138–140 °C; $[\alpha]_D$ −145.7 (*c* 1.03, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48–7.28 (m, 4H), 7.02–6.86 (m, 4H), 3.76 (s, 1H), 2.51 (ddd, *J*=18.6, 5.1, 3.0 Hz, 1H), 2.48–2.37 (m, 1H), 2.21 (ddd, *J*=13.5, 9.3, 4.8 Hz, 1H), 2.02–1.88 (m, 1H), 1.97 (d, *J*=18.6 Hz, 1H), 1.79 (dd, *J*=4.8, 4.8 Hz, 1H), 1.43 (ddd, *J*=12.6, 9.6, 3.9 Hz, 1H), 1.03 (s, 3H), 0.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9 (d, *J*=35 Hz, C), 160.4 (d, *J*=35.4 Hz, C), 142.7 (d, *J*=1.9 Hz, C), 140.3 (d, *J*=2.7 Hz, C), 130.8 (d, *J*=7.8 Hz, CH), 129.8 (d, *J*=7.4 Hz, CH), 114.1 (d, *J*=2.2 Hz, CH), 113.9 (d, *J*=2.2 Hz, CH), 79.2 (C), 68.1 (C), 50.2 (C), 44.5 (CH), 43.5 (CH_2), 26.8 (CH_2), 25.6 (CH_2), 22.7 (CH_3), 21.9 (CH_3); IR (neat) 3548, 1719 cm^{-1}; MS (EI) 260.1 ($M^+-C_6H_5F$); HRMS (EI) calcd for $C_{16}H_{17}FO_2$ ($M^+-C_6H_5F$) 260.1213, found 260.1237.

*4.2.3. 1-(Hydroxydi-p-tolylmethyl)-7,7-dimethylbicyclo[2.2.1] heptan-2-one (**1c**).* Prepared from **5** (100 mg, 0.51 mmol) using a procedure similar to that described for **1a**. Column chromatography (3% EtOAc/hexanes) provided the title compound as clear needles (118 mg, 67%). Mp 98–100 °C; $[\alpha]_D$ −180.6 (*c* 0.96, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, *J*=8.1 Hz, 2H), 7.25 (d, *J*=8.4 Hz, 2H), 7.08 (d, *J*=7.8 Hz, 2H), 7.02 (d, *J*=8.4 Hz, 2H), 3.73 (s, 1H), 2.57–2.43 (m, 2H), 2.33 (s, 3H), 2.29 (s, 3H), 2.24 (ddd, *J*=14.1, 9.3, 4.5 Hz, 1H), 1.95 (d, *J*=18.6 Hz, 1H), 1.96–1.86 (m, 1H), 1.76 (dd, *J*=4.8, 4.8 Hz, 1H), 1.40 (ddd, *J*=12.3, 9.3, 3.9 Hz, 1H), 1.05 (s, 3H), 0.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4 (C), 141.7 (C), 136.3 (C), 136.2 (C), 128.9 (CH), 128.1 (CH), 127.9 (CH), 127.7 (CH), 79.5 (C), 68.1 (C), 50.1 (C), 44.5 (CH), 43.5 (CH_2), 26.9 (CH_2), 25.6 (CH_2), 22.7 (CH_3), 21.8 (CH_3), 20.9 (CH_3), 20.8 (CH_3); IR (neat) 3530, 1716 cm^{-1}; MS (EI) 348.2 (M^+); HRMS (EI) calcd for $C_{24}H_{28}O_2$ (M^+) 348.2089, found 348.2070.

*4.2.4. 1-(Hydroxydi-m-tolylmethyl)-7,7-dimethylbicyclo[2.2.1] heptan-2-one (**1d**).* Prepared from **5** (100 mg, 0.51 mmol) using a procedure similar to that described for **1a**. Column chromatography (3% EtOAc/hexanes) provided the title compound as clear crystals (116 mg, 66%). Mp 124–126 °C; $[\alpha]_D$ −188.8 (*c* 0.99, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.00 (m, 8H), 3.86 (s, 1H), 2.61–2.46 (m, 2H), 2.37 (s, 3H), 2.35–2.23 (m, 1H), 2.31 (s, 3H), 1.99 (d, *J*=18.6 Hz, 1H), 1.99–1.89 (m, 1H), 1.79 (dd, *J*=4.5, 4.5 Hz, 1H), 1.44 (ddd, *J*=12.3, 9.3, 3.9 Hz, 1H), 1.09 (s, 3H), 0.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.1 (C), 144.3 (C), 136.7 (C), 136.6 (C), 129.7 (CH), 128.7 (CH), 127.5 (CH), 127.4 (CH), 127.0 (CH), 126.9 (CH), 126.1 (CH), 125.6 (CH), 79.8 (C), 68.1 (C), 50.2 (C), 44.5 (CH), 43.5 (CH_2), 26.9 (CH_2), 25.6 (CH_2), 22.7 (CH_3), 21.8 (CH_3), 21.7 (CH_3), 21.6 (CH_3); IR (neat) 3569, 1719 cm^{-1}; MS (EI) 348.2 (M^+); HRMS (EI) calcd for $C_{24}H_{28}O_2$ (M^+) 348.2089, found 348.2109.

*4.2.5. 1-(Bis(4-tert-butylphenyl)(hydroxy)methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one (**1e**).* Prepared from **5** (100 mg, 0.51 mmol) using a procedure similar to that described for **1a**. Column chromatography (3% EtOAc/hexanes) provided the title compound as white needles (127 mg, 58%). Mp 162–164 °C; $[\alpha]_D$ −116.3 (*c* 1.02, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49–7.21 (m, 8H), 3.82 (s, 1H), 2.58–2.45 (m, 2H), 2.25 (ddd, *J*=13.8, 9.3, 4.5 Hz,

1H), 1.95 (d, *J*=18.6 Hz, 1H), 2.00–1.85 (m, 1H), 1.76 (dd, *J*=4.5, 4.5 Hz, 1H), 1.40 (ddd, *J*=12.9, 9.6, 3.9 Hz, 1H), 1.32 (s, 9H), 1.29 (s, 9H), 1.05 (s, 3H), 0.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7 (C), 149.3 (C), 144.1 (C), 141.4 (C), 128.7 (CH), 127.8 (CH), 124.1 (CH), 123.9 (CH), 79.4 (C), 68.2 (C), 50.1 (C), 44.5 (CH), 43.6 (CH_2), 34.3 (C), 34.2 (C), 31.4 (CH_3), 31.3 (CH_3) 26.9 (CH_2), 25.6 (CH_2), 22.5 (CH_3), 21.4 (CH_3); IR (neat) 3483, 1718 cm^{-1}; MS (EI) 432.3 (M^+); HRMS (EI) calcd for $C_{30}H_{40}O_2$ (M^+) 432.3028, found 432.3075.

*4.2.6. 1-(Bis(4-(trifluoromethyl)phenyl)(hydroxy)methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one (**1f**).* Prepared from **5** (500 mg, 2.55 mmol) using a procedure similar to that described for **1a**. Column chromatography (5% EtOAc/hexanes) provided the title compound as clear crystals (972 mg, 81%). Mp 148–150 °C; $[\alpha]_D$ −137.9 (*c* 1.13, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.54 (m, 4H), 7.49 (s, 4H), 3.86 (s, 1H), 2.53 (ddd, *J*=18.8, 4.8, 2.8 Hz, 1H), 2.49–2.43 (m, 1H), 2.32–2.23 (m, 1H), 2.02–1.92 (m, 1H), 1.99 (d, *J*=18.8 Hz, 1H), 1.83 (dd, *J*=4.8, 4.8 Hz, 1H), 1.47 (ddd, *J*=12.8, 9.2, 3.6 Hz, 1H), 1.07 (s, 3H), 0.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3 (C), 147.7 (C), 129.2 (CH), 128.4 (CH), 124.5 (q, *J*=3.7 Hz, CH), 124.3 (q, *J*=3.7 Hz, CH), 79.5 (C), 67.9 (C), 50.3 (C), 44.4 (CH), 43.3 (CH_2), 26.8 (CH_2), 25.6 (CH_2), 22.8 (CH_3), 21.9 (CH_3); IR (neat) 3542, 1716 cm^{-1}; MS (EI) 456.2 (M^+); HRMS (EI) calcd for $C_{24}H_{22}F_6O_2$ (M^+) 456.1524, found 456.1557.

*4.2.7. 1-(Hydroxybis(4-methoxyphenyl)methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one (**1g**).* Prepared from **5** (500 mg, 2.55 mmol) using a procedure similar to that described for **1a**. Column chromatography (7–10% EtOAc/hexanes) provided the title compound as a clear syrup (614 mg, 63%). $[\alpha]_D$ −155.9 (*c* 1.29, CH_2Cl_2); ^{1}H NMR (400 MHz, C_6D_6) δ 7.62–7.46 (m, 4H), 6.79–6.71 (m, 4H), 3.92 (s, 1H), 3.31 (s, 3H), 3.29 (s, 3H), 2.29–2.17 (m, 1H), 2.21 (ddd, *J*=18.0, 4.8, 2.8 Hz, 1H), 1.99 (ddd, *J*=14.0, 9.6, 4.8 Hz, 1H), 1.58 (d, *J*=18.0 Hz, 1H), 1.60–1.51 (m, 1H), 1.30 (dd, *J*=4.8, 4.8 Hz, 1H), 0.99 (s, 3H), 0.95 (ddd, *J*=12.8, 9.2, 3.6 Hz, 1H), 0.31 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 159.0 (C), 158.8 (C), 140.2 (C), 138.0 (C), 131.0 (CH), 129.9 (CH), 112.8 (CH), 112.7 (CH), 79.6 (C), 68.4 (C), 54.7 (CH_3), 54.6 (CH_3), 50.0 (C), 44.7 (CH), 43.6 (CH_2), 26.9 (CH_2), 25.8 (CH_2), 22.8 (CH_3), 22.2 (CH_3); IR (neat) 3527, 1719 cm^{-1}; MS (EI) 380.2 (M^+); HRMS (EI) calcd for $C_{24}H_{28}O_4$ (M^+) 380.1988, found 380.2008.

*4.2.8. 1-(Hydroxybis(3-methoxyphenyl)methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one (**1h**).* Prepared from **5** (100 mg, 0.51 mmol) using a procedure similar to that described for **1a**. Column chromatography (5% Et_2O/toluene) provided the title compound as a clear syrup (135 mg, 70%). $[\alpha]_D$ −153.7 (*c* 0.29, CH_2Cl_2); ^{1}H NMR (300 MHz, C_6D_6) δ 7.53 (s, 1H), 7.40 (dd, *J*=2.1, 2.1 Hz, 1H), 7.28–7.22 (m, 1H), 7.09–6.99 (m, 3H), 6.69–6.61 (m, 2H), 3.96 (s, 1H), 3.33 (s, 3H), 3.29 (s, 3H), 2.33 (ddd, *J*=14.4, 12.0, 3.6 Hz, 1H), 2.13 (ddd, *J*=18.6, 5.1, 3.0 Hz, 1H), 2.08–1.99 (m, 1H), 1.58–1.45 (m, 1H), 1.50 (d, *J*=18.3 Hz, 1H), 1.25 (dd, *J*=4.5, 4.5 Hz, 1H), 0.97 (s, 3H), 0.87 (ddd, *J*=12.6, 9.3, 3.6 Hz, 1H), 0.32 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 159.4 (C), 149.4 (C), 146.8 (C), 124.4 (CH), 128.1 (CH), 121.9 (CH), 121.5 (CH), 116.2 (CH), 114.9 (CH), 112.1 (CH), 111.9 (CH), 79.9 (C), 68.4 (C), 54.7 (CH_3), 54.6 (CH_3), 50.1 (C), 44.6 (CH), 43.3 (CH_2), 26.9 (CH_2), 25.9 (CH_2), 22.8 (CH_3), 21.9 (CH_3); IR (neat) 3512, 1719 cm^{-1}; MS (EI) 380.2 (M^+); HRMS (EI) calcd for $C_{24}H_{28}O_4$ (M^+) 380.1988, found 380.1997.

*4.2.9. 1-(Hydroxybis(2-methoxyphenyl)methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one (**1i**).* Prepared from **5** (200 mg, 1.02 mmol) using a procedure similar to that described for **1a**. Recrystallization from 3:1 hexanes/EtOAc provided the title compound as a clear crystals (164 mg, 42%). $[\alpha]_D$ −43.1 (*c* 0.51, CH_2Cl_2); ^{1}H NMR (500 MHz, $(CD_3)_2SO$, 145 °C) δ 7.67–7.63 (m, 1H), 7.52–7.48 (m, 1H), 7.18–7.08 (m, 2H), 6.92–6.75 (m, 4H), 5.00 (s, 1H), 3.40 (s, 3H), 3.25 (s, 3H), 2.66–2.58 (m, 1H), 2.45–2.38 (m, 1H), 2.17 (ddd, *J*=14.0, 9.5, 5.0 Hz, 1H), 1.90–1.83 (m, 1H), 1.89 (d, *J*=18.0 Hz, 1H), 1.72 (dd, *J*=4.5, 4.5 Hz, 1H), 1.36 (ddd, *J*=11.5, 9.5, 4.0 Hz, 1H), 1.04 (s, 3H), 0.70 (s, 3H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$, 145 °C) δ 213.4, 156.5, 156.4, 135.3, 134.9, 129.5, 128.5, 126.8, 126.3, 118.5, 118.1, 113.0, 112.6, 79.8, 68.1, 54.9, 54.7, 49.6, 44.2, 42.9, 25.4, 22.4, 21.7; IR (neat) 3517, 1734 cm^{-1}; MS (EI) 380.2 (M^+); HRMS (EI) calcd for $C_{24}H_{28}O_4$ (M^+) 380.1988, found 380.2011.

*4.2.10. 1-(Hydroxy(naphthalen-2-yl)(naphthalen-3-yl)methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one (**1j**).* Prepared from **5** (100 mg, 0.51 mmol) using a procedure similar to that described for **1a**. Column chromatography (3% EtOAc/hexanes) provided the title compound as a white fluffy powder (111 mg, 52%). Mp 228–230 °C $[\alpha]_D$ −266.8 (*c* 0.40, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18–8.11 (m, 1H), 7.98–7.96 (m, 1H), 7.88–7.58 (m, 7H), 7.51–7.42 (m, 4H), 7.34–7.28 (m, 1H), 4.04 (s, 1H), 2.70–2.47 (m, 3H), 2.08 (d, *J*=18.8 Hz, 1H), 2.01–1.89 (m, 1H), 1.81 (dd, *J*=4.8, 4.8 Hz, 1H), 1.53–1.47 (m, 1H), 1.18 (s, 3H), 0.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8 (C), 141.8 (C), 132.5 (C), 132.3 (C), 132.2 (C), 132.1 (C), 128.6 (CH), 128.5 (CH), 128.2 (CH), 127.4 (CH), 127.3 (CH), 127.2 (CH), 126.9 (CH), 126.7 (CH), 126.5 (CH), 126.0 (CH), 125.9 (CH), 125.7 (CH), 80.3 (C), 68.2 (C), 50.3 (C), 44.6 (CH), 43.5 (CH_2), 26.9 (CH_2), 25.8 (CH_2), 22.9 (CH_3), 22.0 (CH_3); IR (neat) 3513, 1710 cm^{-1}; MS (EI) 420.2 (M^+); HRMS (EI) calcd for $C_{30}H_{28}O_2$ (M^+) 420.2089, found 420.2099.

*4.2.11. 1-(Hydroxydi(thiophen-2-yl)methyl)-7,7-dimethylbicyclo[2.2.1]heptan-2-one (**1k**).* Prepared from **5** (140 mg, 0.71 mmol) using a procedure similar to that described for **1a**. Column chromatography (3% EtOAc/hexanes) provided the title compound as a charcoal powder (160 mg, 68%). Mp 112–114 °C. $[\alpha]_D$ −147.8 (*c* 0.97, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24–7.12 (m, 4H), 6.98–6.91 (m, 2H), 4.33 (s, 1H), 2.63–2.41 (m, 2H), 2.09–1.94 (m, 2H), 1.90 (d, *J*=18.3 Hz, 1H), 1.83 (dd, *J*=4.5, 4.5 Hz, 1H), 1.44–1.33 (m, 1H), 0.98 (s, 3H), 0.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5 (C), 148.2 (C), 126.5 (CH), 126.3 (CH), 125.5 (CH), 124.1 (CH), 124.0 (CH), 68.5 (C), 49.6 (C), 44.7 (CH), 43.3 (CH_2), 26.6 (CH_2), 26.2 (CH_2), 21.5 (CH_3), 21.2 (CH_3); IR (neat) 3448, 1712 cm^{-1}; MS (EI) 332.1 (M^+); HRMS (EI) calcd for $C_{18}H_{20}O_2S_2$ (M^+) 332.0905, found 332.0907.

*4.2.12. 1-(Bis(4-tert-butylphenyl)(methoxy)methyl)-7,7-dimethylbicyclo[2.2.1] heptan-2-one (**8**).* To a dry 25 mL round bottom flask containing NaH (103 mg, 2.58 mmol) was added a solution of **1e** (223 mg, 0.52 mmol) in dry DMF (10 mL). Methyl iodide (97 μL, 1.56 mmol) was then added and the resulting mixture stirred at room temperature for 18 h. The reaction was quenched with water (10 mL), and extracted twice with EtOAc (20 mL portions). The combined organic phases were then washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography (2% EtOAc in hexanes) provided the title compound as a clear oil (73.5 mg, 32%). ^{1}H NMR (400 MHz, C_6D_6) δ 7.79 (d, *J*=8.4 Hz, 2H), 7.64 (d, *J*=8.0 Hz, 2H), 7.31–7.24 (m, 4H), 2.95 (s, 3H), 2.24–2.13 (m, 1H), 2.03 (ddd, *J*=13.6, 9.6, 5.2 Hz, 1H), 1.77–1.67 (m, 1H), 1.55 (d, *J*=18.0 Hz, 1H), 1.32 (dd, *J*=3.6, 3.6 Hz, 1H), 1.26 (s, 9H), 1.24 (s, 9H), 1.02–0.88 (m, 1H), 0.93 (s, 3H), 0.29 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 212.7 (C), 150.1 (C), 149.7 (C), 138.5 (C), 131.1 (CH), 130.5 (CH), 124.4 (CH), 124.2 (CH), 86.3 (C), 70.5 (C), 53.0 (CH_3), 50.0 (C), 45.9 (CH), 44.4 (CH_2), 34.4 (C), 34.3 (C), 31.5 (CH_3), 31.4 (CH_3), 27.5 (CH_2), 26.6 (CH_2), 22.2 (CH_3), 22.1 (CH_3); IR (neat) 1740 cm^{-1}; MS (EI) 446.3 (M^+); HRMS (EI) calcd for $C_{31}H_{42}O_2$ (M^+) 446.3185, found 446.3160.

4.3. General procedure for the synthesis of isocampholenic acid derivatives (Table 1, compounds 3a–k)

*4.3.1. 2-((R)-2,2-Dimethyl-3-(diphenylmethylene)cyclopentyl)acetic acid (**3a**).* To a solution of **1a** (1.06 g, 3.31 mmol) in dry toluene

(30 mL) was added $BF_3 \cdot OEt_2$ (0.49 mL, 4.00 mmol). The mixture was stirred at room temperature for 15 min, and the reaction was then quenched by the addition of water (20 mL). The resulting mixture was extracted twice with EtOAc (30 mL portions). The combined organic extracts were washed with brine (20 mL) dried over $MgSO_4$, filtered, and concentrated in vacuo to provide compound **3a** as a white powder (1.02 g, 96%). Mp 138–140 °C; $[\alpha]_D$ −126.3 (*c* 0.51, CH_2Cl_2); ^1H NMR (300 MHz, C_6D_6) δ 7.21–6.96 (m, 10H), 2.31–2.21 (m, 2H), 2.19–2.05 (m, 2H), 1.95 (dd, *J*=14.7, 10.5 Hz, 1H), 1.89–1.76 (m, 1H), 1.24–1.09 (m, 1H), 0.78 (s, 3H), 0.76 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 180.7 (C), 148.3 (C), 145.3 (C), 142.9 (C), 136.3 (C), 129.9 (CH), 128.6 (CH), 128.5 (CH), 126.5 (CH), 126.3 (CH), 48.5 (CH), 44.8 (C), 34.8 (CH_2), 31.9 (CH_2), 28.3 (CH_2), 26.8 (CH_3), 22.9 (CH_3); IR (neat) 1693 cm^{-1}; MS (EI) 320.2 (M^+); HRMS (EI) calcd for $C_{22}H_{24}O_2$ (M^+) 320.1776, found 320.1791.

*4.3.2. 2-((R)-3-(Bis(4-fluorophenyl)methylene)-2,2-dimethylcyclopentyl)acetic acid (**3b**).* Prepared from **1b** (25 mg, 0.07 mmol) using a procedure similar to that described for **3a** to obtain the title compound as a clear syrup (24.6 mg, 96%). $[\alpha]_D$ −108.6 (*c* 0.48, CH_2Cl_2); ^1H NMR (400 MHz, C_6D_6) δ 6.88–6.69 (m, 8H), 2.21 (dd, *J*=14.8, 3.2, 1H), 2.15–2.03 (m, 3H), 1.96 (dd, *J*=14.8, 10.8, 1H), 1.88–1.78 (m, 1H), 1.21–1.08 (m, 1H), 0.69 (s, 3H), 0.67 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 180.3 (C), 163.0 (d, *J*=28.8 Hz, C), 160.6 (d, *J*=28.4 Hz, C), 149.6 (C), 140.8 (d, *J*=3.2 Hz, C), 138.5 (d, *J*=3.3 Hz, C), 133.9 (C), 131.3 (d, *J*=7.6 Hz, CH), 130.0 (d, *J*=7.7 Hz, CH), 115.4 (d, *J*=21.0 Hz, CH), 114.9 (d, *J*=21.0 Hz, CH), 48.5 (CH), 44.7 (C), 34.7 (CH_2), 31.9 (CH_2), 28.2 (CH_2), 26.8 (CH_3), 22.8 (CH_3); IR (neat) 1701 cm^{-1}; MS (EI) 356.2 (M^+); HRMS (EI) calcd for $C_{22}H_{22}F_2O_2$ (M^+) 356.1588, found 356.1583.

*4.3.3. 2-((R)-2,2-Dimethyl-3-(di-p-tolylmethylene)cyclopentyl) acetic acid (**3c**).* Prepared from **1c** (33 mg, 0.10 mmol) using a procedure similar to that described for **3a** to obtain the title compound as a white sticky solid (26.8 mg, 80%). Mp 80–82 °C; $[\alpha]_D$ −86.3 (*c* 0.41, CH_2Cl_2); ^1H NMR (400 MHz, C_6D_6) δ 7.17–7.09 (m, 4H), 6.96 (d, *J*=7.6 Hz, 2H), 6.92 (d, *J*=7.6 Hz, 2H), 2.40–2.33 (m, 2H), 2.22–2.11 (m, 2H), 2.10 (s, 3H), 2.07 (s, 3H), 1.94 (dd, *J*=14.4, 10.4 Hz, 1H), 1.91–1.83 (m, 1H), 1.25–1.13 (m, 1H), 0.85 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 180.6 (C), 148.0 (C), 142.8 (C), 140.4 (C), 136.2 (C), 135.7 (C), 135.4 (C), 129.9 (CH), 129.3 (CH), 128.8 (CH), 128.5 (CH), 48.6 (CH), 44.8 (C), 34.8 (CH_2), 32.0 (CH_2), 28.3 (CH_2), 26.7 (CH_3), 22.7 (CH_3), 20.8 (CH_3), 20.7 (CH_3); IR (neat) 1702 cm^{-1}; MS (EI) 348.2 (M^+); HRMS (EI) calcd for $C_{24}H_{28}O_2$ (M^+) 348.2089, found 348.2140.

*4.3.4. 2-((R)-2,2-Dimethyl-3-(di-m-tolylmethylene)cyclopentyl)acetic acid (**3d**).* Prepared from **1d** (31 mg, 0.09 mmol) using a procedure similar to that described for **3a** to obtain the title compound as clear needles (27.6 mg, 89%). Mp 100–102 °C; $[\alpha]_D$ −94.4 (*c* 0.50, CH_2Cl_2); ^1H NMR (400 MHz, C_6D_6) δ 7.13–7.02 (m, 6H), 6.85 (d, *J*=7.6 Hz, 2H), 2.42–2.28 (m, 2H), 2.25–2.11 (m, 2H), 2.09 (s, 3H), 2.06 (s, 3H), 1.96 (dd, *J*=14.8, 10.8 Hz, 1H), 1.91–1.83 (m, 1H), 1.27–1.14 (m, 1H), 0.85 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 180.6 (C), 147.9 (C), 145.5 (C), 143.1 (C), 137.9 (C), 137.4 (C), 136.5 (C), 130.6 (CH), 129.1 (CH), 128.6 (CH), 127.9 (CH), 127.3 (CH), 127.1 (CH), 127.0 (CH), 125.7 (CH), 48.6 (CH), 44.8 (C), 34.9 (CH_2), 31.9 (CH_2), 28.3 (CH_2), 26.9 (CH_3), 23.0 (CH_3), 21.5 (CH_3), 21.4 (CH_3); IR (neat) 1700 cm^{-1}; MS (EI) 348.2 (M^+); HRMS (EI) calcd for $C_{24}H_{28}O_2$ (M^+) 348.2089, found 348.2083.

*4.3.5. 2-((R)-3-(Bis(4-tert-butylphenyl)methylene)-2,2-dimethylcyclopentyl)acetic acid (**3e**).* Prepared from **1e** (25 mg, 0.06 mmol) using a procedure similar to that described for **3a** to obtain the title compound as a white powder (19 mg, 76%). Mp 176–178 °C; $[\alpha]_D$ −86.1 (*c* 0.53, CH_2Cl_2); ^1H NMR (400 MHz, C_6D_6) δ 7.28–7.21 (m, 8H), 2.49–2.34 (m, 2H), 2.22–2.10 (m, 2H), 2.01–1.92 (m, 1H), 1.91–1.82 (m, 1H), 1.21–1.16 (m, 1H), 1.19 (s, 9H), 1.18 (s, 9H), 0.87 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 180.3 (C), 149.0 (C), 148.6 (C), 148.2 (C), 142.7 (C), 140.3 (C), 136.1 (C), 129.8 (CH), 128.4 (CH), 125.5 (CH), 124.9 (CH), 48.6 (CH), 44.8 (C), 34.8 (CH_2), 34.4 (C), 34.3 (C), 32.2 (CH_2), 31.5 (CH_3), 28.4 (CH_2), 27.0 (CH_3), 23.1 (CH_3); IR (neat) 1701 cm^{-1}; MS (EI) 432.3 (M^+); HRMS (EI) calcd for $C_{30}H_{40}O_2$ (M^+) 432.3028, found 432.3042.

*4.3.6. 2-((R)-3-(Bis(4-(trifluoromethyl)phenyl)methylene)-2,2-dimethylcyclopentyl)acetic acid (**3f**).* Prepared from **1f** (300 mg, 0.64 mmol) using a procedure similar to that described for **3a**. Column chromatography (15–30% EtOAc/hexanes) provided the title compound as a pale yellow powder (253 mg, 84%). Mp 60–62 °C; $[\alpha]_D$ −89.3 (*c* 0.52, CH_2Cl_2); ^1H NMR (400 MHz, C_6D_6) δ 7.35 (d, *J*=8.0 Hz, 2H), 7.29 (d, *J*=8.0 Hz, 2H), 6.92 (d, *J*=8.0 Hz, 2H), 6.83 (d, *J*=8.0 Hz, 2H), 2.18 (dd, *J*=14.8, 3.2 Hz, 1H), 2.11–1.91 (m, 4H), 1.86–1.76 (m, 1H), 1.18–1.05 (m, 1H), 0.61 (s, 3H), 0.59 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 180.7 (C), 150.7 (C), 147.6 (C), 145.5 (C), 133.4 (C), 130.2 (CH), 129.2 (q, *J*=32.2 Hz, C), 128.8 (CH), 128.8 (q, *J*=32.0 Hz, C), 125.8 (q, *J*=3.7 Hz, CH), 125.2 (q, *J*=3.7 Hz, CH), 124.9 (q, *J*=270.1 Hz, C), 124.8 (q, *J*=270.2 Hz, C), 48.3 (CH), 44.9 (C), 34.7 (CH_2), 31.7 (CH_2), 28.1 (CH_2), 26.6 (CH_3), 22.7 (CH_3); IR (neat) 1705 cm^{-1}; MS (EI) 456.2 (M^+); HRMS (EI) calcd for $C_{24}H_{22}F_6O_2$ (M^+) 456.1524, found 456.1523.

*4.3.7. 2-((R)-3-(Bis(4-methoxyphenyl)methylene)-2,2-dimethylcyclopentyl)acetic acid (**3g**).* Prepared from **1g** (26 mg, 0.07 mmol) using a procedure similar to that described for **3a** to obtain the title compound as a pale yellow syrup (22 mg, 80%). $[\alpha]_D$ −104.5 (*c* 1.09, CH_2Cl_2); ^1H NMR (400 MHz, C_6D_6) δ 7.13–7.08 (m, 4H), 6.00–6.72 (m, 4H), 3.30 (s, 3H), 3.28 (s, 3H), 2.47–2.33 (m, 2H), 2.24 (dd, *J*=14.8, 3.2 Hz, 1H), 2.20–2.12 (m, 1H), 1.99 (dd, *J*=14.4, 10.4 Hz, 1H), 1.95–1.86 (m, 1H), 1.28–1.16 (m, 1H), 0.88 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 180.3 (C), 158.6 (C), 158.4 (C), 148.3 (C), 138.2 (C), 135.7 (C), 135.5 (C), 131.0 (CH), 129.7 (CH), 114.0 (CH), 113.6 (CH), 54.7 (CH_3), 54.6 (CH_3), 48.7 (CH), 44.8 (C), 34.9 (CH_2), 32.2 (CH_2), 28.4 (CH_2), 27.0 (CH_3), 23.1 (CH_3); IR (neat) 1701 cm^{-1}; MS (EI) 380.2 (M^+); HRMS (EI) calcd for $C_{24}H_{28}O_4$ (M^+) 380.1988, found 380.1982.

*4.3.8. 2-((R)-3-(Bis(3-methoxyphenyl)methylene)-2,2-dimethylcyclopentyl)acetic acid (**3h**).* Prepared from **1h** (87 mg, 0.23 mmol) using a procedure similar to that described for **3a** to obtain the title compound as a clear syrup (69 mg, 79%). $[\alpha]_D$ −101.8 (*c* 1.20, CH_2Cl_2); ^1H NMR (400 MHz, C_6D_6) δ 7.10–7.01 (m, 2H), 6.99–6.96 (m, 2H), 6.91–6.82 (m, 2H), 6.64–6.58 (m, 2H), 3.28 (s, 3H), 3.26 (s, 3H), 2.43–2.29 (m, 2H), 2.19 (dd, *J*=14.8, 3.6 Hz, 1H), 2.15–2.07 (m, 1H), 1.94 (dd, *J*=14.8, 10.8 Hz, 1H), 1.88–1.80 (m, 1H), 1.23–1.10 (m, 1H), 0.86 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 180.3 (C), 159.7 (C), 148.3 (C), 146.6 (C), 144.2 (C), 136.0 (C), 129.7 (CH), 129.0 (CH), 122.5 (CH), 120.9 (CH), 116.1 (CH), 114.7 (CH), 111.8 (CH), 111.6 (CH), 54.7 (CH_3), 54.6 (CH_3), 48.6 (CH), 34.8 (CH_2), 31.9 (CH_2), 28.2 (CH_2), 26.8 (CH_3), 22.9 (CH_3); IR (neat) 1701 cm^{-1}; MS (EI) 380.2 (M^+); HRMS (EI) calcd for $C_{24}H_{28}O_4$ (M^+) 380.1988, found 380.1967.

*4.3.9. 2-((R)-3-(Bis(2-methoxyphenyl)methylene)-2,2-dimethylcyclopentyl)acetic acid (**3i**).* Prepared from **1i** (30 mg, 0.08 mmol) using a procedure similar to that described for **3a** to obtain the title compound as a white powder (19 mg, 62%). Mp 182–184 °C; $[\alpha]_D$ −24.6 (*c* 0.29, CH_2Cl_2); ^1H NMR (500 MHz, $(CD_3)_2SO$, 145 °C) δ 7.33–7.22 (m, 2H), 7.18–7.07 (m, 2H), 6.94–6.80 (m, 4H), 3.78 (s, 3H), 3.76 (s, 3H), 2.32–2.24 (m, 1H), 2.15–2.06 (m, 2H), 2.03–1.94 (m, 2H), 1.84–1.75 (m, 1H), 1.35–1.24 (m, 1H), 0.82 (s, 6H); ^{13}C NMR (100 MHz, C_6D_6) δ 180.5 (C), 180.4 (C), 157.5 (C), 156.5

(C) 156.3 (C), 149.3 (C), 149.1 (C), 133.7 (C), 132.5 (CH), 132.2 (CH), 130.9 (CH), 130.5 (CH), 120.9 (CH), 120.7 (CH), 119.9 (CH), 119.7 (CH), 111.3 (CH), 110.8 (CH), 110.7 (CH), 55.0 (C), 54.9 (C), 54.6 (C), 54.5 (C), 48.7 (CH), 48.4 (CH), 44.9 (C), 44.6 (C), 35.1 (CH_2), 34.8 (CH_2), 31.5 (CH_2), 31.3 (CH_2), 28.3 (CH_2), 27.9 (CH_2), 24.3 (CH_3), 22.5 (CH_3), 22.4 (CH_3), 21.2 (CH_3), 1.3 (CH_3); IR (neat) 1707 cm^{-1}; MS (EI) 380.2 (M^+); HRMS (EI) calcd for $C_{24}H_{28}O_4$ (M^+) 380.1988, found 380.1975.

*4.3.10. 2-((R)-2,2-Dimethyl-3-((naphthalen-2-yl)(naphthalen-3-yl) methylene)cyclopentyl)acetic acid (**3j**).* Prepared from **1j** (35 mg, 0.08 mmol) using a procedure similar to that described for **3a** to obtain the title compound as a clear syrup (23 mg, 65%). $[\alpha]_D$ −143.2 (*c* 0.60, CH_2Cl_2); ^1H NMR (400 MHz, C_6D_6) δ 7.84–7.81 (m, 1H), 7.76–6.73 (m, 1H), 7.68–7.52 (m, 6H), 7.39–7.33 (m, 2H), 7.27–7.18 (m, 4H), 2.50–2.30 (m, 2H), 2.24–2.13 (m, 2H), 1.99 (dd, *J*=11.7, 8.4 Hz, 1H), 1.93–1.84 (m, 1H), 1.29–1.16 (m, 1H), 0.85 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 179.7 (C), 149.5 (C), 142.6 (C), 140.4 (C), 136.0 (C), 134.3 (C), 133.6 (C), 132.6 (C), 132.6 (C), 128.8 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 128.2 (CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127.4 (CH), 127.2 (CH), 126.3 (CH), 126.2 (CH), 125.9 (CH), 125.8 (CH), 48.6 (CH), 45.0 (C), 34.6 (CH_2), 32.1 (CH_2), 28.4 (CH_2), 26.9 (CH_3), 23.1 (CH_3); IR (neat) 1699 cm^{-1}; MS (EI) 420.2 (M^+); HRMS (EI) calcd for $C_{30}H_{28}O_2$ (M^+) 420.2089, found 420.2106.

*4.3.11. 2-((R)-2,2-Dimethyl-3-(di(thiophen-2-yl)methylene)cyclopentyl)acetic acid (**3k**).* Prepared from **1k** (47 mg, 0.14 mmol) using a procedure similar to that described for **3a** to obtain the title compound as a turquoise powder (44 mg, 93%). Mp 76–78 °C; $[\alpha]_D$ −130.5 (*c* 0.57, CH_2Cl_2); ^1H NMR (400 MHz, C_6D_6) δ 6.89 (dd, *J*=4.8, 0.8 Hz, 1H), 6.86 (dd, *J*=5.2, 1.2 Hz, 1H), 6.78 (dd, *J*=3.2, 1.2 Hz, 1H), 6.73 (dd, *J*=4.0, 1.6 Hz, 1H), 6.70 (dd, *J*=4.8 Hz, 2.8 Hz, 1H), 6.69 (dd, *J*=4.8, 2.8 Hz, 1H), 2.70–2.49 (m, 2H), 2.17 (dd, *J*=14.8, 3.2 Hz, 1H), 2.11–2.01 (m, 1H), 1.96–1.85 (m, 2H), 1.28–1.16 (m, 1H), 0.81 (s, 3H), 0.76 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 179.8 (C), 154.2 (C), 147.3 (C), 142.8 (C), 126.4 (CH), 126.3 (CH), 125.9 (CH), 125.5 (CH), 124.8 (CH), 121.2 (CH), 48.1 (CH), 46.2 (C), 34.4 (CH_2), 33.7 (CH_2), 28.1 (CH_2), 25.8 (CH_3), 22.2 (CH_3); IR (neat) 1699 cm^{-1}; MS (EI) 332.1 (M^+); HRMS (EI) calcd for $C_{18}H_{20}O_2S_2$ (M^+) 332.0905, found 332.0925.

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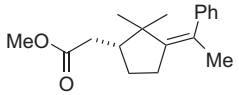
Supplementary data

Detailed experimental procedures and copies of ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 908239. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk). Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2012.12.011.

References and notes

1. (a) Money, T. *Nat. Prod. Rep.* **1985**, *2*, 253; (b) Langlois, Y.; Kouklovsky, C. *Synlett* **2009**, 3065; (c) McGarrigle, E. M.; Myers, E. L.; Illa, O.; Shaw, M. A.; Riches, S. L.; Aggarwal, V. K. *Chem. Rev.* **2007**, *107*, 5841; (d) Boobalan, R.; Chen, C.; Lee, G. H. *Org. Biomol. Chem.* **2012**, *10*, 1625; (e) Komarov, I. V.; Monsees, A.; Spannenberg, A.; Baumann, W.; Schmidt, U.; Fischer, C.; Börner, A. *Eur. J. Org. Chem.* **2003**, 138; (f) Lemay, M.; Ogilvie, W. W. *Org. Lett.* **2005**, *7*, 4141.
2. Liu, H. J.; Chan, W. H. *Can. J. Chem.* **1982**, *60*, 1081.
3. Liu, H. J.; Llinas-Brunet, M. *Can. J. Chem.* **1988**, *66*, 528.
4. Rowley, M.; Tsukamoto, M.; Kishi, Y. *J. Am. Chem. Soc.* **1989**, *111*, 2735.
5. Liu, H. J.; Ralitsch, M. *J. Chem. Soc., Chem. Commun.* **1990**, 997.
6. (a) Paquette, L. A.; Zhao, M. *J. Am. Chem. Soc.* **1998**, *120*, 5203; (b) Paquette, L. A.; Wang, H. L.; Su, Z.; Zhao, M. *J. Am. Chem. Soc.* **1998**, *120*, 5213.
7. Williams, D. R.; Coleman, P. J.; Henry, S. S. *J. Am. Chem. Soc.* **1993**, *115*, 11654.
8. (a) Stevens, R. V.; Gaeta, F. C. A.; Lawrence, D. S. *J. Am. Chem. Soc.* **1983**, *105*, 7713; (b) Lansbury, P. T.; Mazur, D. J.; Springer, J. P. *J. Org. Chem.* **1985**, *50*, 1632.
9. Knizhnikov, V. O.; Voitenko, Z. V.; Golovko, V. B.; Gorichko, M. V. *Tetrahedron* **2012**, *68*, 1972.
10. (a) Rüedi, G.; Nagel, M.; Hansen, H. J. *Org. Lett.* **2003**, *5*, 2691; (b) Grošelj, U.; Bevk, D.; Jakše, R.; Meden, A.; Stanovnik, B.; Svete, J. *Tetrahedron: Asymmetry* **2005**, *16*, 2187.
11. Martínez, A. G.; Vilar, E. T.; Fraile, A. G.; de la Moya Cerero, S.; Maroto, B. L. *Tetrahedron: Asymmetry* **2001**, *12*, 189.
12. Hutchinson, J. H.; Money, T.; Piper, S. E. *Can. J. Chem.* **1986**, *64*, 854.
13. Ferguson, C. G.; Money, T.; Pontillo, J.; Whitelaw, P. D. M.; Wong, M. K. C. *Tetrahedron* **1996**, *52*, 14661.
14. (a) Hutchinson, J. H.; Money, T. *Can. J. Chem.* **1985**, *63*, 3182; (b) Money, T.; Wong, M. K. C. *Tetrahedron* **1996**, *52*, 6307; (c) Mermet-Mouttet, M. P.; Gabriel, K.; Heissler, D. *Tetrahedron Lett.* **1999**, *40*, 843; (d) Hiersemann, M.; Helmboldt, H. *Top. Curr. Chem.* **2005**, *243*, 73.
15. (a) Clase, J. A.; Money, T. *Can. J. Chem.* **1992**, *70*, 1537; (b) Money, T.; Richardson, S. R.; Wong, M. K. C. *Chem. Commun.* **1996**, 667; (c) Clase, J. A.; Money, T. *Synthesis* **1989**, 934.
16. Bartlett, P. P.; Knox, L. H. *Organic Syntheses*; Wiley & Sons: New York, NY, 1973; Collect. Vol. 5; 1965; *689; Vol. 45*, p 55.
17. Gilbertson, S. R.; Fu, Z. *Org. Lett.* **2001**, *3*, 161.
18. Chu, Y. Y.; Yu, C. S.; Chen, C. J.; Yang, K. S.; Lain, J. C.; Lin, C. H.; Chen, K. *J. Org. Chem.* **1999**, *64*, 6993.
19. Acid **3e** was recovered intact when exposed to the same conditions, indicating that the ester was not formed by the action of Lewis acid on the product.
20. Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U. H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461.
21. Compound **11** was isolated as a single isomer, but the relative configuration of the exocyclic alcohol could not be established.
22. The methyl ester was synthesized in an attempt to separate the isomers.
23. Comparison of some characteristic resonances in the ^1H NMR of the isocampholenic acid derivatives **3a**–**k** suggested that the major isomer was **13**.



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