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Communication

Regioselective Rearrangement

Unknown Camphor: Regioselective Rearrangement under Acylation in a $CF_3SO_3H/(CF_3CO)_2O$ System

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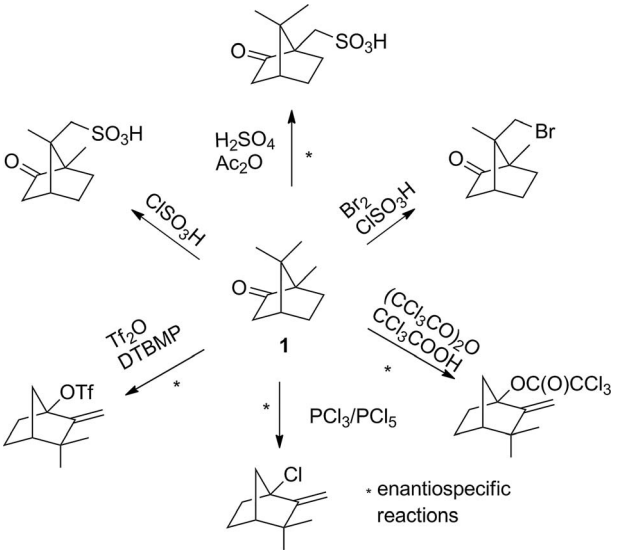
Abstract: The utility of camphor in the chemical sciences is vast and well documented, yet the creation of camphor-derived potentially useful bicyclo[2.2.1]heptane scaffolds still remains one of the great challenges of synthetic organic chemistry. Herein, we show that $CF_3SO_3H/(CF_3CO)_2O$-mediated acylation of camphor with benzoic acids is accompanied by a cascade of alkyl and hydride shifts and opens access to a new type of polyfunctional isoborneol. In case of salicylic acids, camphor feels the presence of the *ortho*-hydroxy group in the aryl moiety, the influence of which provokes cleavage of the bicycloheptane skeleton to lead to monocyclic carvenone.

Introduction

Camphor is a natural compound that exerts a significant influence on the development of synthetic and theoretical organic chemistry. Owing to its unique chemical properties, a wide range of synthetic methods for the regiospecific and stereospecific functionalization of the different carbon atoms of camphor and its derivatives, various bond-cleavage reactions, and rearrangements have been reported.[1] So, camphor has been proven to be an attractive starting material for the preparation of numerous natural and synthetic biologically active compounds,[1,2] as well as for the construction of chiral catalysts,[3] chiral auxiliaries,[4] NMR shift reagents, and others.[5]

The ability of camphor to undergo easy carbocationic transformations is one of its unique features.[1] As far back as 1902 the English chemists Armstrong and Lowry wrote: "No substance known to us suffers rearrangement of its parts and undergoes a complete change of type more readily than does camphor".[6] Its chemical modification is often accompanied by fascinating Wagner–Meerwein and Nametkin rearrangements, as well as by 2,6-hydride shifts, and leads to unpredictable products. Therefore, camphor and its derivatives, relative to other simple organic molecules, have considerable potential for the creation of new molecular scaffolds.[7] However, synthetically useful methods for the stereo- and regioselective modification of camphor on the basis of skeletal rearrangements are limited to C9 and C10 sulfonation,[8,9] C9 bromination,[10] and transformation into 1-substituted camphenes under the action of phosphorus chlorides (e.g., PCl_3/PCl_5),[11] trichloroacetic anhydride or trifluoromethanesulfonic anhydride (Scheme 1).[12,13]



Scheme 1. Known methods for the chemical modification of camphor on the basis of rearrangements. DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine.

The last of these methods, the stereoselective synthesis of 1-camphenyl triflate,[13] was discovered almost three decades ago. Evidently, to create new synthetic applications of camphor, the development of new methods for its regio- and stereoselective modification is undoubtedly interesting for synthetic organic chemistry.

In the present work, the unexpected transformation of camphor (**1**) under $CF_3SO_3H/(CF_3CO)_2O$-mediated acylation with benzoic acids is disclosed. Our recent synthesis of β-diketones by the selective α-acylation of alkyl aryl ketones with carboxylic acids in trifluoromethanesulfonic acid (TfOH)/trifluoroacetic anhydride (TFAA) was the motivation for this research.[14] TFAA, which was used as a medium and an activating agent, eagerly formed acyl trifluoroacetates from the carboxylic acids. The presence of TfOH promoted enolization and increased the acylating ability of the acyl trifluoroacetates.

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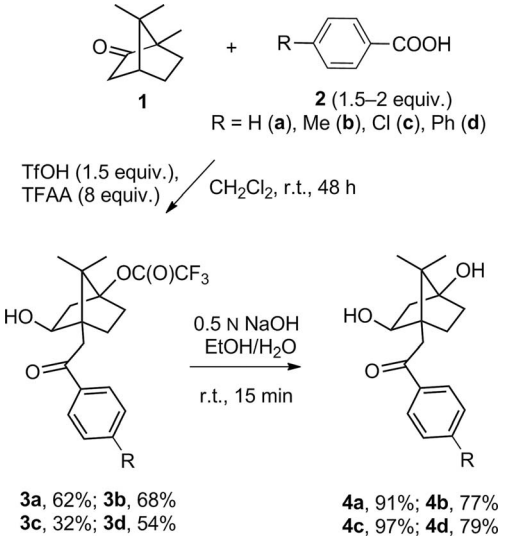
Results and Discussion

Our aim was to synthesize camphor-derived β-diketones by using benzoic acids **2** [ArCOOH; Ar = Ph (**a**), 4-MeC_6H_4 (**b**), 4-ClC_6H_4 (**c**), 4-PhC_6H_4 (**d**), 2-HOC_6H_4 (**e**), 2-HO-5-BrC_6H_3 (**f**), 4-HOC_6H_4 (**g**)] as acylating agents by this method. Taking into consideration the ease with which bornyl cation rearrangements occur, we expected that the TfOH/TFAA-mediated acylation of enantiomerically pure camphor would occur with racemization; therefore, substantially cheaper racemic camphor was used.

Surprisingly, we found that acylation of camphor with benzoic acids **2a**–**d** was followed by rearrangement of the bicyclic skeleton to give **3a**–**d** as previously unknown functional derivatives of isoborneol, e.g., *exo*-4-(2-aryl-2-oxoethyl)-3-hydroxy-7,7-dimethyl-1-(trifluoroacetoxy)bicyclo[2.2.1]heptanes (Scheme 2). Notably, under classic conditions of the Claisen condensation, the reaction of camphor with acyl halides and acid esters gives 1,3-diketones and is not accompanied by rearrangement.[15] Our reactions were performed with a camphor (**1**)/acid **2**/TfOH/TFAA molar ratio of 1:2:1.5:8 in dichloromethane at room temperature for 48 h. One molecule of benzoic acid is involved in the reaction, and the utilization of a smaller excess (1.5 equiv.) of **2** did not reduce the yields of isoborneols **3**. By using 1 equiv. of benzoic acids **2** and/or 0.5 equiv. of TfOH, under the conditions used to synthesize diketones from alkyl aryl ketones and carboxylic acids,[14] the yields of **3a**–**d** were considerably reduced. In the absence of the carboxylic acids, camphor was returned from the reactions, practically without change. Hydrolysis of the obtained trifluoroacetates under very mild conditions gave dihydroxy ketones **4a**–**d** in excellent yields.



Scheme 2. Acylation of camphor (**1**) with benzoic acids **2a**–**d**.

The structures of bicyclo[2.2.1]heptanes **3** and **4**, previously unknown, were determined by a combination of conventional 1D and 2D NMR spectroscopy experiments (^{1}H NMR and ^{13}C NMR, DEPT90, 135COSY, HSQC, and HMBC) and elemental analyses, in addition to X-ray structure analysis data for **3a**, **3b**, **4b**, and **4c**.[16] To gain patterns for the assignment of the ^{1}H and ^{13}C signals in the NMR spectra of compounds **3** and **4**, full assignment of the ^{1}H and ^{13}C signals for compound **3a** as a representative example was accomplished (see the Supporting Information for the ^{1}H and ^{13}C NMR spectroscopy data).

The *exo* configuration of the secondary hydroxy group of 3-hydroxy-7,7-dimethyl-4-phenacyl-1-(trifluoroacetoxy)bicyclo-[2.2.1]heptane (**3a**) was determined on the basis of the magnitudes of the vicinal $^3J_{H2n\text{-}H3n}$ and $^3J_{H2x\text{-}H3n}$ coupling constants and the long-rang $^4J_{H2x\text{-}H6x}$ coupling constant. Generally, the magnitude of the $^3J_{H,H}$ coupling constant for protons with a *cis* configuration is much larger (7–12 Hz) than that for protons with a *trans* orientation (2–6 Hz), and the presence of the appreciable long-range $^4J_{H,H}$ coupling constant is specific for W-arranged protons.[17] The observed magnitudes of $^3J_{H2n\text{-}H3n}$ = 8.6 Hz, $^3J_{H2x\text{-}H3n}$ = 4.0 Hz, and $^4J_{H2x\text{-}H6x}$ = 4.1 Hz allowed the *exo* configuration for the hydroxy group at C3 to be unambiguously ascribed and allowed assignment of the methylene protons at C2 (Figure 1).

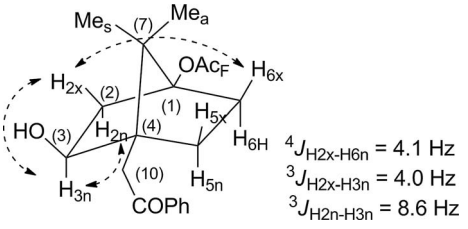


Figure 1. ^{1}H–^{1}H COSY correlations to determine the position of the OH group in **3a**.

Luckily, we were able to grow crystals of bicycloheptanes **3a**, **3b**, **4b**, and **4c** that were suitable for X-ray diffraction analysis to prove their structures definitively.[16]

The molecular structures of trifluoroacetate **3b** and diol **4b** are shown in Figures 2 and 3 as representative examples. Nota-

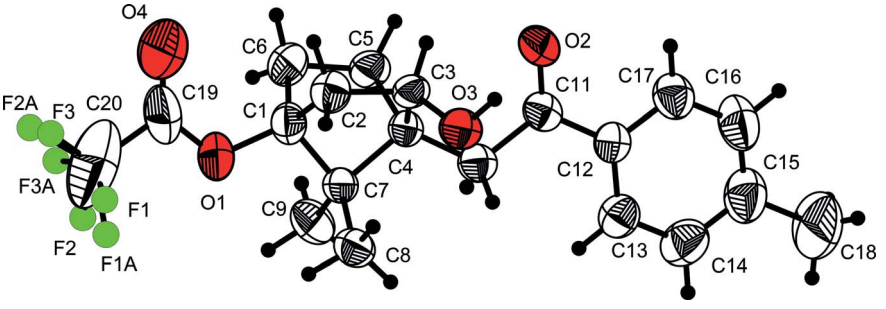


Figure 2. Molecular structure of **3b**.

bly, the spatial arrangement of the benzoyl moiety is different in the structures of these compounds. The torsion angles C4–C10–C11–O2 are equal to 3.67° for **3b** and 75.52° for **4b**. This difference is the result of an O3–H3···O2 intramolecular hydrogen bond in **4b**.

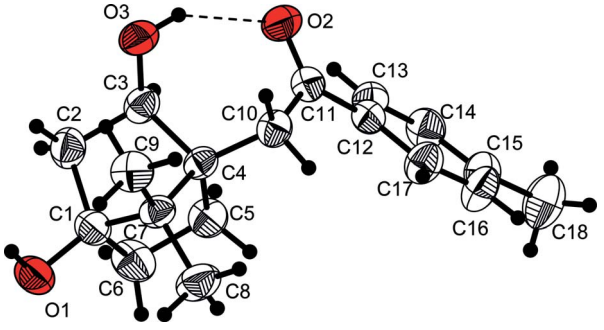


Figure 3. Molecular structure of **4b**.

The obtained structural data allowed a plausible mechanism for the TfOH/TFAA-mediated acylation of camphor with benzoic acids to be assumed (Scheme 3).

At the first stage, *O*-trifluoroacylation of a carbonyl group with acyl trifluoroacetate **I** generated in situ leads to 4-(trifluoroacetoxy)camphene **II** and probably proceeds through successive formation of carbocations **A**, **B**, and **C** as a result of Wagner–Meerwein (W.-M.) and Nametkin rearrangements, with following deprotonation of **C**. Next, benzoylation of the methylene group of **II** with anhydride **I** gives intermediate **D**, which easily undergoes Wagner–Meerwein rearrangement to give cation **E**. Final treatment of the mixture with water yields isobornyl product **3**. The interaction of cations of type **E** with nucleophiles usually affords isobornyl products such as **3** despite the thermodynamic preference for the formation of bornyl derivatives.[13,18] Curiously, in this reaction we observed dual reactivity of anhydride **I** – trifluoroacetylation of the carbonyl group of camphor (hard nucleophilic center) and benzoylation of the double bond of camphene **II** (soft nucleophilic center) – in full compliance with the hard–soft acid–base principle. The formation of the hydroxy (NOT trifluoroacetate or triflate) group at the C3 atom is another peculiarity of the acylation process. This can be explained by hydrolysis of the formed triflic acid esters of alcohols **3** upon treatment of the reaction mixture with water.

Reaction of (+)-(*R*)-**1** with benzoic acid (**2a**) yielded racemic isoborneol *rac*-**3a**. Therefore, trapping of the corresponding carbocation **E** with water follows a racemizing 6,2-hydride shift (Figure 4). This confirmed the ease of racemization of the bornyl cations under the TfOH/TFAA conditions for the acylation of camphor.

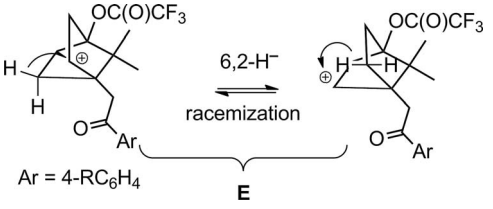
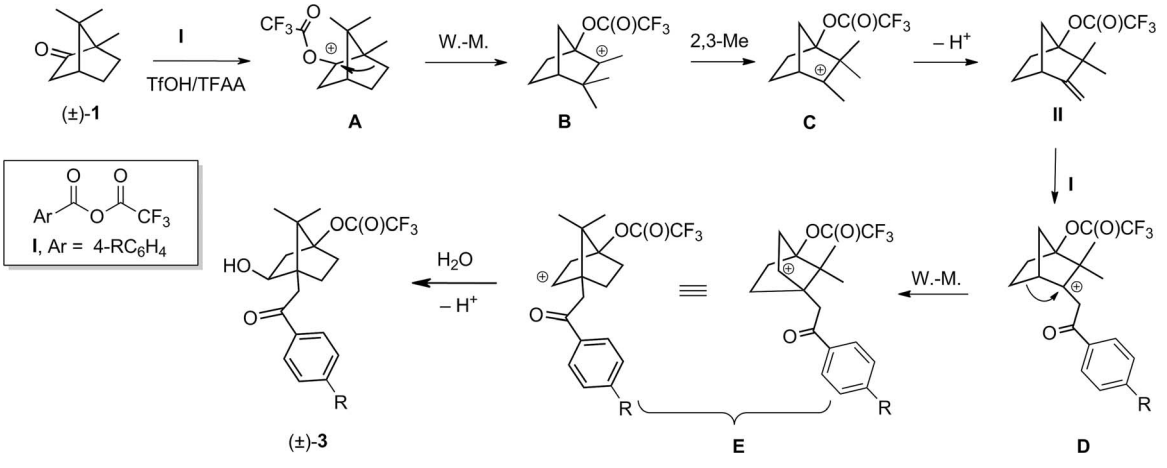


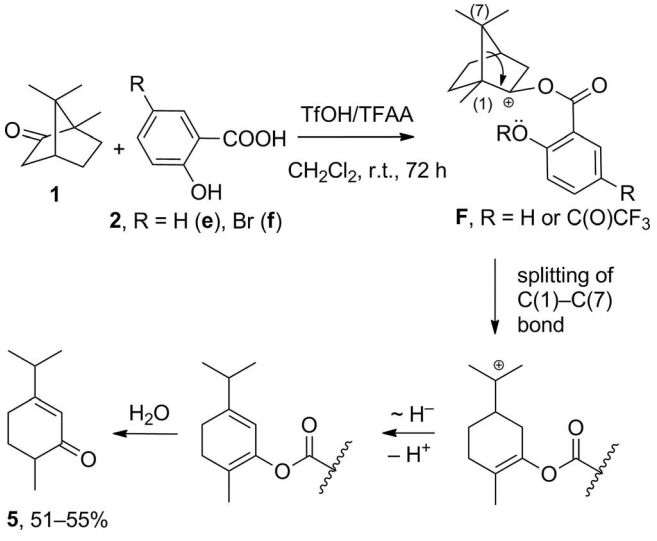
Figure 4. Racemization of precursor carbocations **E**.

The acylation of camphor with benzoic acids **2a**–**d** proved to yield not only trifluoroacylated products **3a**–**d** but also a small amount of carvenone (**5**; 5–8 %), which has a chromatographic mobility similar to that of trifluoroacetates **3**. After removal of the trifluoroacetyl group, **5** could be easily separated from keto diols **4a**–**d**. The analogous course of camphor reactions under acidic conditions is well known.[19,20]

Unexpectedly, carvenone (**5**) became the main reaction product in the reactions of camphor with salicylic acids **2e** and **2f**, and the formation of bicyclic compounds **3** was not observed at all. The yield of **5** was 35–40 % after 48 h and increased to 51–55 % after 72 h for both salicylic acids **2e** and **2f**. It can be assumed that the acylation of camphor with trifluoroacetyl salicylates formed in situ leads to carbocations **F**, which undergo cleavage of the C1–C7 bond with subsequent hydride shift and deprotonation (Scheme 4). Such a transformation may be related to the fact that the *ortho*-OR group in the salicylic fragment of intermediate **F** complicates the Wagner–Meerwein rearrangement and makes cleavage of the C1–C7 bond the preferred process.



Scheme 3. Plausible mechanism for the formation of isoborneols **3a**–**d** in the acylation of camphor (**1**) with benzoic acids **2a**–**d**.



Scheme 4. TFAA/TfOH-mediated isomerization of camphor by salicylic acids.

The proposed mechanism is speculative and requires proof. Interestingly, 4-hydroxybenzoic acid was polymerized under the same conditions as a result of self-acylation, and camphor was returned from the reaction without change.

Conclusions

In this study we found that the trifluoromethanesulfonic acid/trifluoroacetic anhydride mediated acylation of camphor with benzoic acids radically depends on the nature of the acid used. In whole, the reaction is accompanied by regioselective Wagner–Meerwein and Nametkin rearrangements and provides access to previously unknown polyfunctional isoborneols. However, the presence of an *ortho*-hydroxy group in the benzoic acid changes the course of the reaction: the interaction of camphor with the salicylic acids proceeds through cleavage of the bicycloheptane skeleton and leads to carvenone. These results once again show the unique chemical properties of camphor in its transformations in electrophilic reactions and the wide possibilities of its modification.

Experimental Section

General Procedure for the TfOH/TFAA-Mediated Acylation of Camphor: A solution of camphor (1 mmol), carboxylic acid (1.5–2 mmol), and TFAA (1.07 mL, 8 mmol) in dichloromethane (3 mL) was stirred at room temp. for 15 min. Triflic acid (132 μL, 1.5 mmol) was then added, and the resulting solution was kept under the conditions indicated in Scheme 2 (TLC monitoring). Volatile components of the mixture were evaporated under reduced pressure, and after quenching with water, the residue was redissolved in CH_2Cl_2 (20 mL), washed with 5 % $NaHCO_3$ (2 × 5 mL) and water (2 × 5 mL), and dried with $MgSO_4$. The solvent was removed in vacuo, and the crude mixture was purified by silica gel chromatography (column 20 × 1.5 cm, *n*-hexane/CH_2Cl_2).

***exo*-3-Hydroxy-7,7-dimethyl-4-(2-oxo-2-phenylethyl)-1-(trifluoroacetoxy)bicyclo[2.2.1]heptane (3a):** Obtained from camphor (**1**; 152 mg, 1 mmol), benzoic acid (**2a**; 244 mg, 2 mmol), TFAA (1.07 mL, 8 mmol), and TfOH (132 μL, 1.5 mmol). Yield: 62 % (230 mg), white solid, m.p. 122–124 °C, R_f = 0.27 (CH_2Cl_2). ^{1}H NMR (600 MHz, $CDCl_3$, 303 K): δ = 7.98 (m, 2 H, ArH_o), 7.61 (m, 1 H, ArH_p), 7.50 (m, 2 H, ArH_m), 4.08 (dd, $^3J_{H2n-H3n}$ = 8.6 Hz, $^3J_{H2x-H3n}$ = 4.0 Hz, H_{3n}), 3.30 (br. s, OH), 3.22 (d, ^2J = –14.3 Hz, 1 H, CH_2CO), 2.95 (d, ^2J = –14.3 Hz, 1 H, CH_2CO), 2.77 (dd, $^2J_{H2n-H2x}$ = –12.7 Hz, $^3J_{H2n-H3n}$ = 8.6 Hz, H_{2n}), 2.15 (ddd, $^3J_{H5n-H6n}$ = 9.8 Hz, $^3J_{H5x-H6n}$ = 4.1 Hz, $^2J_{H6n-H6x}$ = –12.3 Hz, H_{6n}), 1.94 (dt, $^2J_{H2n-H2x}$ = –12.7 Hz, $^3J_{H2x-H3n}$ = 4.0 Hz, $^4J_{H2x-H6x}$ = 4.1 Hz, H_{2x}), 1.73 (tt, $^4J_{H2x-H6x}$ = 4.1 Hz, $^3J_{H5n-H6x}$ = 4.1 Hz, $^3J_{H5x-H6x}$ = 12.5 Hz, $^2J_{H6n-H6x}$ = –12.3 Hz, H_{6x}), 1.65 (ddd, $^2J_{H5n-H5x}$ = –12.6 Hz, $^3J_{H5x-H6n}$ = 4.1 Hz, $^3J_{H5x-H6x}$ = 12.5 Hz, H_{5x}), 1.30 (ddd, $^2J_{H5n-H5x}$ = –12.6 Hz, $^3J_{H5n-H6n}$ = 9.8 Hz, $^3J_{H5n-H6x}$ = 4.1 Hz, H_{5n}), 1.21 (s, 3 H, Me_s), 0.99 (s, 3 H, Me_a) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, 303 K): δ = 201.9 (CO), 156.8 (q, $^2J_{CF}$ = 41.6 Hz, OCO), 137.5 ($C^{Ar}{}_i$), 133.7 ($CH^{Ar}{}_p$), 128.8 (2 $CH^{Ar}{}_m$), 128.4 (2 $CH^{Ar}{}_o$), 114.4 (q, $^1J_{CF}$ = –286.4 Hz, CF_3), 90.5 (C1), 74.7 (C3), 48.6 (C7), 48.4 (C4), 40.0 (C2), 34.5 (C10), 29.5 (C6), 29.1 (C5), 17.9 (C9, Me_a), 17.2 (C8, Me_s) ppm. $C_{19}H_{21}F_3O_4$ (370.37): calcd. C 61.62, H 5.72; found C 61.30, H 5.42.

***exo*-1,3-Dihydroxy-7,7-dimethyl-4-(2-oxo-2-phenylethyl)bicyclo[2.2.1]heptane (4a):** A mixture of **3a** (200 mg, 0.54 mmol), NaOH (50 mg, 1.3 mmol), ethanol (9 mL), and water (1 mL) was kept at room temperature for ca. 15 min. Upon completion of the reaction (TLC control), the solvent was evaporated, and the residue was acidified with 1 N HCl (pH ≈ 5) and extracted with CH_2Cl_2. The organic phase was washed with H_2O, dried ($MgSO_4$), and concentrated under vacuum. Purification of the product was performed by column chromatography (silica gel; CH_2Cl_2/MeOH, 98:2). Yield: 91 % (135 mg), white solid, m.p. 80–82 °C, R_f = 0.17 (CH_2Cl_2/MeOH, 98:2). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 7.98 (m, 2 H, H^{Ar}), 7.59 (m, 1 H, H^{Ar}), 7.48 (m, 2 H, H^{Ar}), 3.93 (dd, *J* = 8.4, 3.9 Hz,1 H, H_3), 3.24 (d, *J* = 13.8 Hz, 1 H, CH_2CO), 2.87 (d, *J* = 13.8 Hz, 1 H, CH_2CO), 2.59 (br. s, 2OH), 2.05 (dd, *J* = 8.4, 12.6 Hz, 1 H of CH_2), 1.86 (m, 1 H of CH_2), 1.64 (m, 1 H of CH_2), 1.53 (m, 1 H of CH_2), 1.43 (m, 1 H of CH_2), 1.11 (s, 3 H, CH_3), 1.09 (m, 1 H of CH_2), 0.91 (s, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): δ = 202.3 (CO), 137.2 (C^{Ar}), 133.2 (CH^{Ar}), 128.3 (CH^{Ar}), 128.1 (CH^{Ar}), 81.0 (C1), 73.9 (C3), 50.7 (C), 47.0 (C), 43.6 (CH_2), 34.9 (CH_2), 32.5 (CH_2), 28.5 (CH_2), 17.4 (Me), 16.8 (Me) ppm. $C_{17}H_{22}O_3$ (274.36): calcd. C 74.42, H 8.08; found C 74.31, H8.21.

Carvenone (5): Obtained from camphor (**1**; 1 mmol), salicylic acid (**2e**; 207 mg, 1.5 mmol), TFAA (1.07 mL, 8 mmol), and TfOH (132 μL, 1.5 mmol), 72 h. Yield: 51 % (78 mg), oil, R_f = 0.28 (CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 5.83 (s, 1 H, CH=C), 2.38–2.25 (m, 4 H), 2.04 (m, 1 H), 1.68 (m, 1 H), 1.10 (d, *J* = 6.8 Hz, CH_3), 1.07 (d, *J* = 6.8 Hz, CH_3), 1.05 (d, *J* = 6.8 Hz, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.2 (CO), 170.3 (*C*=CH), 122.6 (C=*CH*), 40.6 (CH), 35.1 (CH), 30.6 (CH_2), 26.8 (CH_2), 20.4 (CH_3), 20.1 (CH_3), 14.7 (CH_3) ppm. Data for **5** from ref.[21]: ^{13}C NMR (20 MHz, $CDCl_3$, room temp.): δ = 201.9, 170.5, 123.0, 41.1, 35.5, 31.3, 27.3, 20.9, 20.5, 15.1 ppm.

Acknowledgments

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Keywords: Acylation · Isoborneols · Natural products · Rearrangement · Regioselectivity

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