FULL PAPER

The Development of a Stereoselective Method for the Synthesis of Tetrasubstituted Derivatives of α,β-Unsaturated Carboxylic Acids

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Dedicated to Prof. Dr. hab. *Janusz Jurczak* on the occasion of his 75th birthday

Alkenes possessing four different carbon-linked substituents are the main structural motif of many biologically active compounds. The derivatives of (2*E*)-3-(3-methoxyphenyl)-2-methylpent-2-enoic acid ((*E*)-**2c**) are suitable precursors for the synthesis of *Tapentadol*, a novel centrally acting analgesic. It was found that the Ni-carbometallation reaction of disubstituted alkyne **8** with CO_2 and an Et_2Zn allows for efficient and practical preparation of (*E*)-**2c** as a single (*E*)-regioisomer in 89% of isolated yield. The influence of the size of the aliphatic substituent of alkyne and the steric hindrance of the organozinc reagent on stereochemical course of the carbometallation reaction was evaluated. Finally, air-stable $Ni(dme)Cl_2$ was proposed as an alternative to widely used $Ni(cod)_2$ catalyst.

Keywords: Tetrasubstituted alkenes, Ni-catalyzed carboxylation, Reductive elimination, Ketone olefination, Carbometallation reaction.

Introduction

The main structural motif of many biologically active ingredients such as *Tamoxifen* [1], *Vioxx* [2], or *Nileprost* [3], is the double-bond bearing four different aryl or alkyl substituents. Moreover, the tetrasubstituted double bond is a common feature of many more complicated compounds possessing other functionalities [4]. Furthermore, tetrasubstituted olefins are often key synthetic intermediates en route to target compounds [5]. Unlike for double-substituted olefins, the stereoselective synthesis of tetrasubstituted alkenes (especially acyclic) still poses a significant synthetic challenge. The effectiveness and stereoselectivity of traditional double-bond formation methods such as *Wittig* or *Horner–Wadsworth–Emmons* reactions are usually unsatisfactory for the preparation of tetrasubstituted olefins [6]. Other synthetic methods are therefore more applicable for the preparation of multisubstituted alkenes. These include the coupling of substituted vinyl halides or *pseudo*-halides with organometallic compounds [7], elimination reaction [8], carbometallation of alkynes [9], and carbonyl olefination [10].

Recently, our research interest has focused on the search for a more effective and practical synthetic route to *Tapentadol* (**1**), a novel centrally acting analgesic (*Scheme 1*) [11].

This analgesic agent exists in four stereoisomeric forms, among which the (*R*,*R*)-enantiomer is approved for clinical use. We envisioned tetrasubstituted derivatives of (2*E*)-3-(3-methoxyphenyl)-2-methylpent-2-enoic acid (**2**) as key precursors for *Tapentadol* preparation. The rare enantioselective hydrogenation of these highly substituted olefins would lead to **1** [12].

Results and Discussion

We tested several recently described approaches to the synthesis of tetrasubstituted α,β-unsaturated carboxylic acid derivatives as possible methods for the preparation of **2a** – **c** [13]. Our first attempt involved the stereoselective synthesis of tetrasubstituted α,β-unsaturated amides **2a** using the *Concéllon et al.* procedure [14]. This method is based on reductive elimination of α,β-epoxyamides or 2-chloro-3-hydroxyamides using SmI_2. In our tests, the original conditions applied to the amide **3a** led mainly to trisubstituted alkene **4**, a product of epoxide eliminative opening (*Scheme 2*). Various conditions were tested (with variations in SmI_2 loading, reaction time, additives) and it was found that the addition of 8 equiv. of HMPA is required to provide the desired product with 55% yield. Unfortunately, no (*E*)/(*Z*) selectivity was observed.

On the other hand, only SmI_2 is needed for the conversion of ester derivative **3b** to olefin **2b** with 60% yield and 2.8:1 (*E*)/(*Z*) selectivity in favor of the required isomer. The assignment of configuration of major (*E*)-**2b** is based on ROESY analysis, (*Fig. 1*), as a result of correlations between *ortho* aromatic H-atoms with H-atoms from Me group. This SmI_2-promoted stereoselective β-elimination methodology can also be used for the

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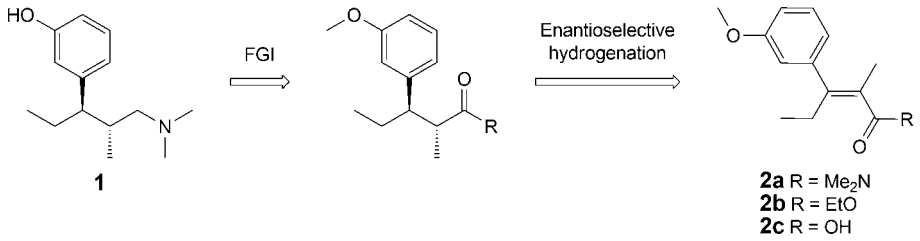
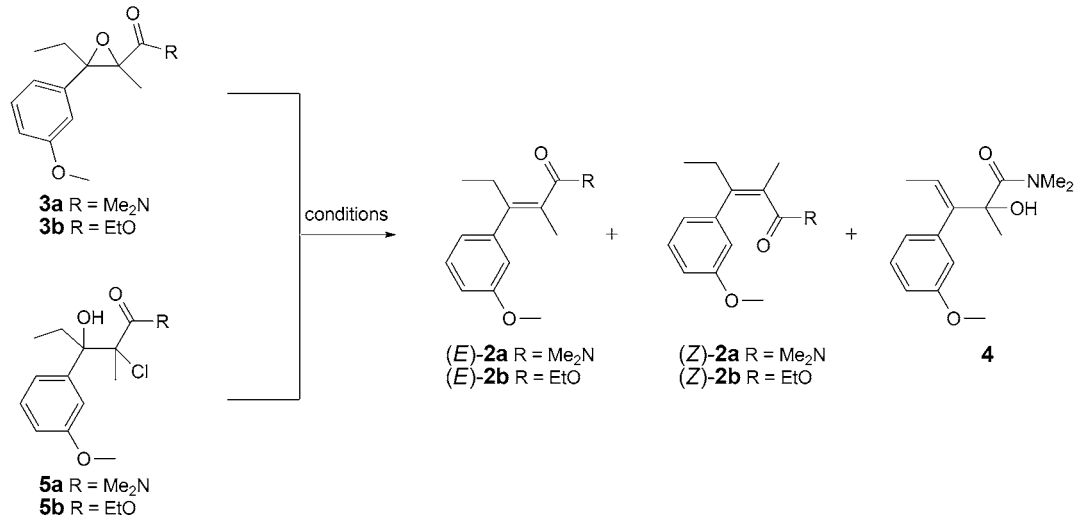
Scheme 1



Scheme 2



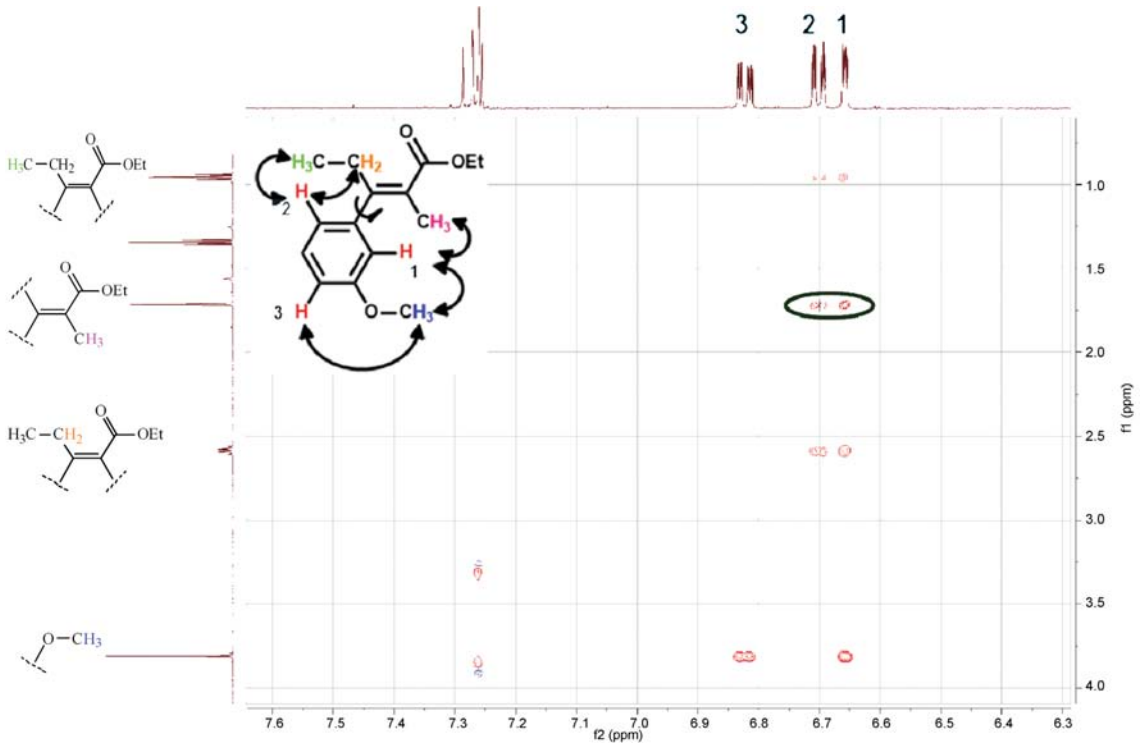
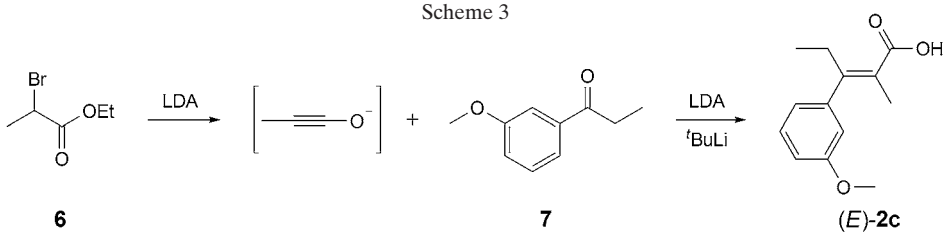


Fig. 1. Configuration assignment of (*E*)-**2b** regioisomer based on analysis of the ROESY spectrum.

Scheme 3



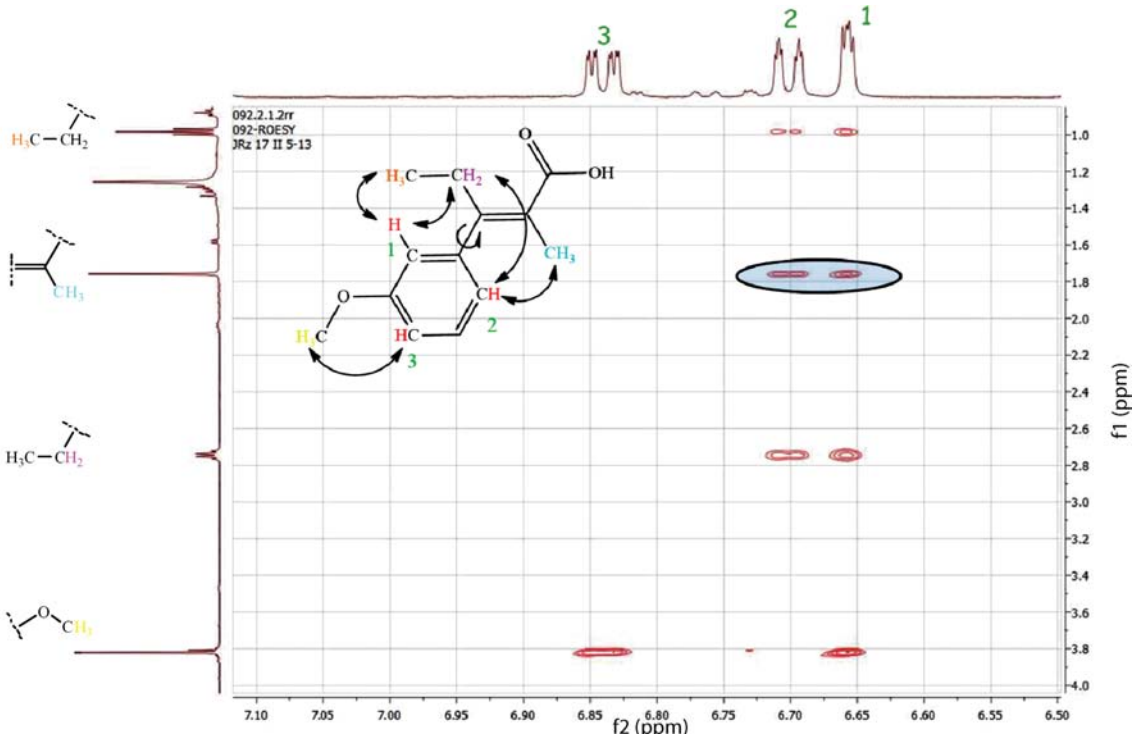
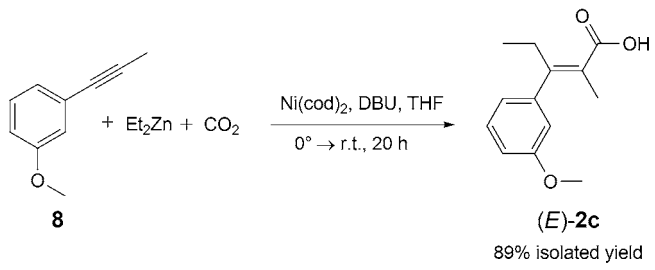


Fig. 2. Configuration assignment of (*E*)-**2c** regioisomer based on analysis of the ROESY spectrum.

Scheme 4

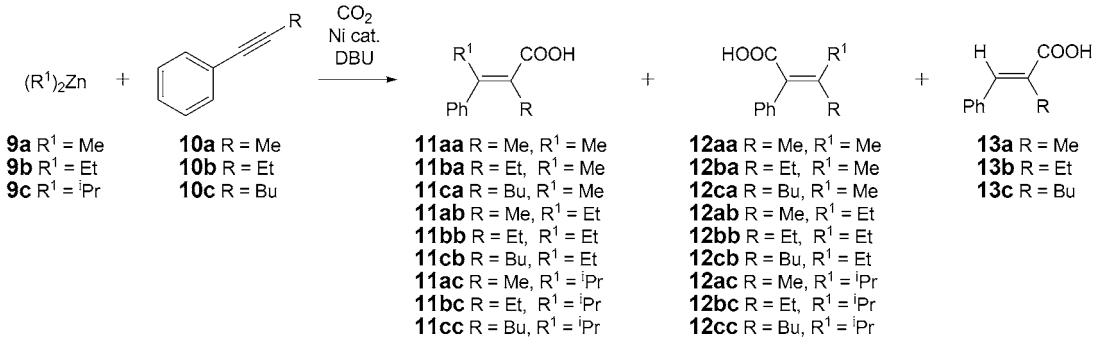


elimination of α,β-halohydrin esters or amides. Interestingly, we observed a large difference between the stereochemical course of the β-elimination of the amide and ester derivatives of α-halohydrins. Specifically, for amide **5a**, SmI_2-promoted elimination gave alkene **2a** with *ca.* 50% yield and near 0.2:1 (*E*)/(*Z*) selectivity in favor of the undesired isomer, whereas using ester **5b** provided product **2b** with 40% yield and near 2.7:1 (*E*)/(*Z*) selectivity.

Since SmI_2 reductive elimination of epoxides as well as halohydrin derivatives proved to give products with moderate yields and stereoselectivities, we shifted our attention to ketone olefination by ynolates described by *Shindo et al.* (*Scheme 3*) [15].

Treatment of ethyl 2-bromopropanoate (**6**) with LDA generates the corresponding ynolate which reacts with ketone **7** [16], leading to acid **2c**. The assignment of configuration of major (*E*)-**2c** product was also based on ROESY analysis (*Fig. 2*) as a result of correlations between *ortho* aromatic H-atoms with H-atoms from the Me group. Unfortunately, the effectiveness of this procedure applied to our substrate was unreliable (the best result obtained being 50% yield and 6.7:1 (*E*)/(*Z*) selectivity). Thus, all the methods described above were found to suffer from low to medium yields and/or low (*E*)/(*Z*) selectivity.

Scheme 5



9a R^1 = Me
9b R^1 = Et
9c R^1 = ^{i}Pr

10a R = Me
10b R = Et
10c R = Bu

11aa R = Me, R^1 = Me
11ba R = Et, R^1 = Me
11ca R = Bu, R^1 = Me
11ab R = Me, R^1 = Et
11bb R = Et, R^1 = Et
11cb R = Bu, R^1 = Et
11ac R = Me, R^1 = ^{i}Pr
11bc R = Et, R^1 = ^{i}Pr
11cc R = Bu, R^1 = ^{i}Pr

12aa R = Me, R^1 = Me
12ba R = Et, R^1 = Me
12ca R = Bu, R^1 = Me
12ab R = Me, R^1 = Et
12bb R = Et, R^1 = Et
12cb R = Bu, R^1 = Et
12ac R = Me, R^1 = ^{i}Pr
12bc R = Et, R^1 = ^{i}Pr
12cc R = Bu, R^1 = ^{i}Pr

13a R = Me
13b R = Et
13c R = Bu

Table 1. Carbometallation reaction of alkynes **10a**, **10b**, and **10c** with various zinc reagents catalyzed by $Ni(cod)_2$

Alkyne	Me_2Zn[a])	Et_2Zn[a])	$^iPr_2Zn$[a])
10a	**10a/11aa/12aa/13a** 41:59:0:0	**10a/11ab/12ab/13a** 15:61:12:12	**10a/11ac/12ac/13a** 10:25:5:60
10b	**10b/11ba/12ba/13b** 20:66:7:7	**10b/11bb/12bb/13b** 17:55:11:17	**10b/11bc/12bc/13b** 40:20:0:40
10c	**10c/11ca/12ca/13c** 38:62:0:0	**10c/11cb/12cb/13c** 21:54:14:10	**10c/11cc/12cc/13c** 34:15:0:51

[a]) 0.4 mmol of alkyne in 0.5 ml of THF, 1.2 mmol of organozinc reagent, 4 mmol DBU, 0.08 mmol $Ni(cod)_2$ in 1 ml of THF, 1 atm CO_2, 0 °C, 20 h. The ratio of products was determined based on 1H-NMR analysis.

Table 2. Carbometallation reaction of alkynes **10a** and **10b** with various zinc reagents catalyzed by $Ni(dme)Cl_2$

Alkyne	Me_2Zn[a])	Et_2Zn[a])
10a	**10a/11aa/12aa/13a** 31:66:0:3	**10a/11ab/12ab/13a** 24:47:13:16
10b	**10b/11ba/12ba/13b** 64:36:0:0	**10b/11bb/12bb/13b** 32:49:5:14

[a]) 0.4 mmol of alkyne in 0.5 ml of THF, 1.2 mmol of organozinc reagent, 4 mmol DBU, 0.08 mmol $Ni(dme)Cl_2$ in 1 ml of THF, 1 atm CO_2, 0 °C, 20 h. The ratio of products was determined based on 1H-NMR analysis.

Continuing our search for a more effective and stereoselective synthetic method for tetrasubstituted derivatives of α,β-unsaturated carboxylic acids, we considered the promising approach to such compounds developed by *Mori et al.* [17]. This method is based on Ni-catalyzed addition of CO_2 and organozinc reagent to disubstituted alkynes. The proposed mechanism of this reaction excludes the formation of unwanted (*Z*) stereoisomer.

However, to synthesize the desired derivatives of pent-2-enoic acid (*E*)-**2c**, alkyne **8** is needed [18]. This type of alkyne had never been applied to Ni-catalyzed carboxylation. The other necessary reagent is Et_2Zn (**9b**). Interestingly, its use was rarely explored in the Ni-mediated carbometallation reaction. For example, the use of Et_2Zn in the preparation of a trisubstitiuted α,β-unsaturated carboxylic acid gave the desired product with only 9% of yield, whereas application of Me_2Zn (**9a**) gave the corresponding product with 81% yield [17].

Therefore, we were pleased to find that treatment of a freshly prepared suspension of $Ni(cod)_2$ (0.8 equiv.), DBU (10 equiv.) in CO_2 atmosphere (1 atm) by alkyne **8** and subsequent Et_2Zn (3 equiv.) addition led to the desired product (*E*)-**2c** with 89% isolated yield (*Scheme 4*).

We found that pure carboxylic acid could be isolated from the reaction mixture without the need to convert it to an ester derivative, as is described in the literature.

More importantly, this can be achieved *via* acid/base extraction, then bulb to bulb distillation without needing chromatographic purification.

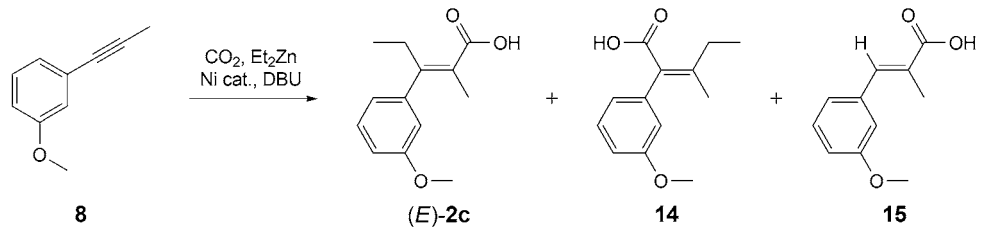
We evaluated the effect of catalyst loading on reaction efficiency. While 0.1 equiv. of $Ni(cod)_2$ was employed, only 40% of product was isolated. The crude reaction mixture also contains a large amount of unreacted alkyne **8** and *ca.* 10% of trisubstituted acid of type **13**. Increasing the catalyst loading to 0.4 equiv. gave 69% yield.

To explore the scope of the carbometallation of alkynes of type **10**, various commercially available alkynes and organozinc reagents were examined (*Scheme 5*). Many trends can be seen from the data collected in *Table 1*.

In a first rough estimate, the size of the alkyne linear aliphatic substituent appears to exert little influence on the conversion. In contrast, the steric hindrance of the organozinc reagent has a major effect on the product distribution. However, while Me_2Zn (**9a**) and Et_2Zn (**9b**) gave similar yields of major product **11**,[1]) the use of $^iPr_2Zn$ (**9c**) dramatically lowered the reaction effectiveness (15 – 25% yield). In Me_2Zn (**9a**), a large amount of unreacted substrate was present without formation of side products, whereas for Et_2Zn, a higher conversion of the substrate was present in favor of the unwanted

[1]) For **11aa** and **11ac** see [19a][19b]; for **11ba**, see [19c]; for **11ca**, see [19d]; for **11ab**, see [19e]; for **11bb**, see [19f]; for **11cb**, see [19g].

Scheme 6



regioisomer **12**[2]) and trisubstituted alkene **13** [21]. These results highlighted the differences between reactivity of Me_2Zn and Et_2Zn. Due to the significant steric hindrance of $^iPr_2Zn$, the Ni-promoted catalyzed carboxylation reaction led mainly to alkene **13**, a product of only CO_2 addition without subsequent organozinc transmetallation.

Although $Ni(cod)_2$ is an efficient catalyst for carbometallation reaction, it is very air and water sensitive and its application requires the use of a glovebox. Therefore, air-stable catalyst would greatly simplify the synthetic procedure. Toward this end, we tested application of other Ni^{II} complexes (0.2 equiv.) in reaction of alkyne **8** with Et_2Zn, in the presence of 3 equiv. of DBU under an atmosphere of CO_2 (*Scheme 6*).

Simple $NiCl_2$ is almost inactive under those conditions (8% of product (*E*)-**2c**) and 87% of unreacted alkyne **8** was recovered. However, commercially available nickel (II) acetylacetonate ($Ni(acac)_2$) gave 45% of desired product (*E*)-**2c** along with 12% of regioisomer **14** and 7% of **15** [22]. Next, we turned our attention toward Ni(dme)Cl_2, a complex readily prepared in a single step from $NiCl_2$ and 1,2-dimethoxyethane [23]. This complex is air stable and can be stored in a desiccator without decomposition. Application of this catalyst (0.2 mol.-equiv.) led to alkene (*E*)-**2c** in 61% yield. To evaluate the effectiveness of Ni(dme)Cl_2 in broader scope of substrates, the reaction of Me_2Zn and Et_2Zn reagents with alkynes **10a** and **10b** were examined (*Table 2*, *Scheme 5*).

The comparison of *Tables 1, 2* revealed similar product distribution. However, the yield of major products **11** is slightly lower for the Ni(dme)Cl_2 complex as compared to $Ni(cod)_2$, with one noticeable example for the preparation of **11ba** (36% conversion).

Conclusions

In summary, we tested several methods suitable for the synthesis of tetrasubstituted alkenes. Reductive elimination of amide or ester derivatives of α,β-epoxycarboxylic acid or 2-chloro-3-hydroxy carboxylic acids using SmI_2, as well as ketone olefination by ynolates proved to be ineffective methods in terms of yield and selectivity. In contrast, the application of Ni-catalyzed carboxylation of double-substituted alkynes provided derivatives of (2*E*)-3-(3-methoxyphenyl)-2-methylpent-2-enoic acid (**2**) with high yields. This method circumvents the problem of unwanted (*Z*)-isomer formation. From a practical point of view, we found that acid/base extraction, followed by bulb-to-bulb distillation is suitable for isolation and purification of acid (*E*)-**2c**. We have shown that the aliphatic unbranched substituents in the tested alkynes have a modest influence on yield. However, the steric bulkiness of substituents in organozinc reagent has a major effect on conversion and product distribution. Finally, we showed that, an air stable Ni(dme)Cl_2 complex could be used as catalyst for carbometallation reaction with only slight loss of efficiency for the desired target (*E*)-**2c**.

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Experimental Part

General

All commercially available compounds were purchased and used as received. THF, toluene, CH_2Cl_2, and Et_2O were purchased from *Sigma–Aldrich* and used as received. Thin-layer chromatography was performed using *Merck* TLC SiO_2 *60 F_{254}* aluminum sheets. Flash chromatography separations were performed on *Merck* SiO_2 *60M* (230 – 400 mesh). ^{1}H- (300 or 200 MHz) and ^{13}C-NMR (75 or 50 MHz) spectra were recorded with a *Bruker AVANCE* spectrometer (300 MHz) or *Varian UNITYplus* (200 MHz). The NMR analyses were performed in $CDCl_3$ at 298 K. H-atom chemical shifts are reported relative to residual solvent peak of $CDCl_3$ at $\delta = 7.26$. C-atom chemical shifts are reported relative to $CDCl_3$ at $\delta = 77.0$. High-resolution mass spectra (HR-MS) were measured with a *Quattro LC Micromass* unit using ESI technique.

Typical Procedure for Reductive Elimination of α,β-Epoxy-2-chloro-3-hydroxy-amides or Esters. A soln. of SmI_2 (0.1M in THF, 7.57 ml, 0.757 mmol) was slowly added to a soln. of either **3a**, or **3b**, or **5a**, or **5b**

[2]) For **12aa**, see [20a][20b][20c]; for **12ba**, see [20d][20e]; for **12ab** and **12bb**, see [20f].

(0.189 mmol, 1 equiv.) in THF (2 ml) under Ar. The mixture was then stirred at 20 °C for 30 min – 1.5 h (depending on the substrate used). Then, the mixture was quenched with 0.1M aq. HCl (9.5 ml) followed by addition of AcOEt (10 ml) and finally addition of sat. aq. soln. of potassium sodium tartrate and $NaHCO_3$ (10 ml, 1:1 mixture). The resulting mixture was extracted with AcOEt (2 × 20 ml). The combined org. layers were dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (SiO_2, hexane/AcOEt 10:1) to afford compound (*E*)-**2a** or (*E*)-**2b** as colorless viscous oil.

(2*E*)-3-(3-Methoxyphenyl)-*N*,*N*,2-trimethylpent-2-enamide ((*E*)-**2a**). Obtained in 3% yield according to the general above procedure. ^{1}H-NMR: 0.86 (*t*, *J* = 7.5, 3 H); 1.70 (*s*, 3 H); 2.29 (*q*, *J* = 7.5, 2 H); 3.05 (*d*, *J* = 12, 6 H); 3.80 (*s*, 3 H); 6.68 – 6.72 (*m*, 2 H); 6.75 – 6.82 (*m*, 1 H); 7.23 – 7.27 (*m*, 1 H). ^{13}C-NMR: 12.4 (*q*); 16.9 (*q*); 28.5 (*t*); 34.1 (*q*); 37.6 (*q*); 55.2 (*q*); 112.1 (*d*); 114.2 (*d*); 120.9 (*d*); 127.8 (*s*); 129.2 (*d*); 139.8 (*s*); 141.4 (*s*); 159.4 (*s*); 172.9 (*s*). HR-ESI-MS: 270.1470 ([*M* + Na]$^+$, $C_{15}H_{21}NNaO_2^+$; calc. 270.1461).

(2*Z*)-3-(3-Methoxyphenyl)-*N*,*N*,2-trimethylpent-2-enamide ((*Z*)-**2a**). Obtained in 45% yield according to the general above procedure. ^{1}H-NMR: 0.93 (*t*, *J* = 7.5, 3 H); 2.01 (*s*, 3 H); 2.40 (br. *s*, 1 H); 2.55 (br. *s*, 1 H); 2.60 (*s*, 3 H); 2.63 (*s*, 3 H); 3.79 (*s*. 3 H); 6.73 – 6.81 (*m*, 3 H); 7.20 (*ddd*, *J* = 8.1, 7.3, 0.8, 1 H). ^{13}C-NMR: 12.4 (*q*); 16.1 (*q*); 26.1 (*t*); 34.1 (*q*); 37.7 (*q*); 55.2 (*q*); 112.9 (*d*); 113.2 (*d*); 120.2 (*d*); 127.3 (*s*); 128.8 (*d*); 140.5 (*s*); 142.5 (*s*); 159.1 (*s*); 173.6 (*s*). HR-ESI-MS: 270.1470 ([*M* + Na]$^+$, $C_{15}H_{21}NNaO_2^+$; calc. 270.1461).

Ethyl (2*E*)-3-(3-Methoxyphenyl)-2-methylpent-2-enoate ((*E*)-**2b**). Obtained in 25% yield according to the general above procedure. ^{1}H-NMR: 0.98 (*t*, *J* = 7.5, 3 H); 1.36 (*t*, *J* = 7.2, 3 H); 1.74 (*s*, 3 H); 2.59 – 2.64 (*m*, 2 H); 3.83 (*s*, 3 H); 4.28 (*q*, *J* = 7.2, 2 H); 6.66 – 6.72 (*m*, 2 H); 6.80 – 6.83 (*m*, 1 H); 7.24 – 7.28 (*m*, 1 H). ^{13}C-NMR: 12.8 (*q*); 14.3 (*q*); 17.4 (*q*); 29.4 (*t*); 55.2 (*q*); 60.4 (*t*); 112.3 (*d*); 113.6 (*d*); 120.3 (*d*); 124.9 (*s*); 129.3 (*d*); 143.1 (*s*); 150.3 (*s*); 159.7 (*s*); 170.0 (*s*). HR-ESI-MS: 271.1310 ([*M* + Na]$^+$, $C_{15}H_{20}NaO_3^+$; calc. 271.1310).

Ethyl (2*Z*)-3-(3-Methoxyphenyl)-2-methylpent-2-enoate ((*Z*)-**2b**). Obtained in 11% yield according to the general above procedure. ^{1}H-NMR: 0.86 (*t*, *J* = 7.2, 3 H); 0.96 (*t*, *J* = 7.5, 3 H); 2.05 (*s*, 3 H); 2.48 (*q*, *J* = 7.2, 2 H); 3.81 (*s*, 3 H); 3.86 (*q*, *J* = 7.2, 2 H); 6.70 – 6.72 (*m*, 2 H); 6.78 – 6.81 (*m*, 1 H); 7.22 – 7.25 (*m*, 1 H). ^{13}C-NMR: 11.9 (*q*); 13.5 (*q*); 15.6 (*q*); 28.0 (*t*); 55.2 (*q*); 60.1 (*t*); 111.8 (*d*); 113.0 (*d*); 120.1 (*d*); 125.7 (*s*); 128.9 (*d*); 144.2 (*s*); 148.3 (*s*); 159.2 (*s*); 170.8 (*s*). HR-ESI-MS: 271.1302 ([*M* + Na]$^+$, $C_{15}H_{20}NaO_3^+$; calc. 271.1310).

Synthesis of (*E*)-**2c** *via Ketone Olefination by Ynolates.* A soln. of ethyl 2-bromopropanoate (**6**; 164 mg, 1 mmol) in THF (2 ml) was added dropwise to a soln. of lithium diisopropylamide (1M in THF/hexane, 1.05 ml, 1.05 mmol) at −78 °C. After 20 min, a ^{t}BuLi soln. (1.7M in pentane, 1.88 ml, 3.2 mmol) was added dropwise. The mixture was stirred at −78 °C for 90 min, after which it was allowed to warm to 0 °C. After 30 min, the mixture was allowed to warm to r.t. and a soln. of 1-(3-methoxyphenyl)propan-1-one (181 mg, 1 mmol) in THF (2 ml) was added dropwise. The mixture was stirred overnight under Ar. Then, sat. aq. NH_4Cl was added (5 ml), and the mixture was acidified with 10% HCl soln. (5 ml) and was extracted with CH_2Cl_2 (2 × 20 ml). The org. phase was then extracted with 5% NaOH soln. (2 × 30 ml). The alkaline aq. phase was then acidified with HCl and the product was extracted with CH_2Cl_2 (2 × 50 ml). The org. phase was washed with brine, dried ($MgSO_4$) and concentrated. The residue was then purified by column chromatography (SiO_2, CH_2Cl_2) to give (*E*)-**2c** as yellow oil (103 mg, 47%). ^{1}H-NMR: 0.89 (*t*, *J* = 7.5, 3 H); 1.68 (*s*, 3 H); 2.67 (*q*, *J* = 7.5, 2 H); 3.75 (*s*, 3 H); 6.58 – 6.64 (*m*, 2 H); 6.75 – 6.78 (*m*, 1 H); 7.28 – 7.33 (*m*, 1 H). ^{13}C-NMR: 12.8 (*q*); 17.5 (*q*); 29.7 (*t*); 55.2 (*q*); 112.4 (*d*); 113.3 (*d*); 120.0 (*d*); 123.3 (*s*); 129.4 (*d*); 143.4 (*s*); 155.2 (*s*); 159.5 (*s*); 175.0 (*s*). LR-ESI-MS: 219.08 ([*M* − H]$^-$).

3-Ethyl-3-(3-methoxyphenyl)-*N*,*N*,2-trimethyloxirane-2-carboxamide (**3a**). A soln. of LDA (1M in THF, 1.1 ml, 2.2 mmol) was slowly added to a soln. of 2-chloro-*N*,*N*-dimethylpropanamide (0.13 ml, 1 mmol) in THF (1 ml) at −78 °C under Ar. After 10 min, a soln. of ketone **7** (144 mg, 0.875 mmol) in THF (1 ml) was slowly added. The mixture was then stirred for 1 h at −78 °C. Then, the mixture was warmed, and the reaction was quenched with a sat. aq. soln. of NH_4Cl_{aq} (5 ml). The mixture was extracted with CH_2Cl_2 (2 × 10 ml). The combined org. layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, hexane/AcOEt 95:5) to afford compound **3a** (colorless viscous oil, 144 mg, 63%). ^{1}H-NMR: 0.77 (*t*, *J* = 7.2, 3 H); 1.11 (*s*, 3 H); 1.27 – 1.31 (*m*, 1 H); 2.08 – 2.12 (*m*, 1 H); 2.91 (*s*, 3 H); 3.12 (br. *s*, 3 H); 3.74 (*s*, 3 H); 6.81 (*m*, 3 H); 7.18 – 7.22 (*m*, 1 H). ^{13}C-NMR: 9.0 (*q*); 17.5 (*q*); 29.2 (*t*); 35.2 (*q*); 36.8 (*q*); 55.3 (*q*); 67.2 (*s*); 70.5 (*s*); 112.4 (*d*); 113.1 (*d*); 119.4 (*d*); 129.2 (*d*); 138.9 (*s*); 159.5 (*s*); 170.1 (*s*). HR-ESI-MS: 286.1418 ([*M* + Na]$^+$, $C_{15}H_{21}NNaO_3^+$; calc. 286.1419).

Ethyl 3-Ethyl-3-(3-methoxyphenyl)-2-methyloxirane-2-carboxylate (**3b**). A soln. of potassium bis(trimethylsilyl) amide (HMDSK; 0.38 g, 1.91 mmol) in toluene (4 ml) was slowly added to a soln. of ethyl 2-chloropropanoate (0.2 g, 1.47 mmol) in THF (2.5 ml) at −78 °C under Ar. After 10 min, a soln. of ketone **7** (0.24 g, 1.47 mmol) in THF (2.5 ml) was slowly added. Then, the mixture was warmed, and the reaction was quenched with a sat. aq. soln. of NH_4Cl (12 ml). The mixture was extracted with CH_2Cl_2 (2 × 20 ml). The combined org. layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, hexane/AcOEt 14:1) to afford compound **3b** (colorless viscous oil, 250 mg, 65%). ^{1}H-NMR: 0.88 (*t*, *J* = 7.5, 3 H); 1.21 (*s*, 3 H); 1.35 (*t*, *J* = 7.2, 3 H); 1.60 – 1.64 (*m*, 1 H); 2.05 – 2.09 (*m*, 1 H); 3.82 (*s*, 3 H); 4.30 (*q*, *J* = 7.2, 2 H); 6.85 – 6.89

(*m*, 3 H); 7.23 – 7.27 (*m*, 1 H). ^{13}C-NMR: 9.2 (*q*); 14.3 (*q*); 16.8 (*q*); 26.9 (*t*); 55.2 (*q*); 61.4 (*t*); 65.6 (*s*); 70.3 (*s*); 112.7 (*d*); 113.0 (*d*); 119.3 (*d*); 129.3 (*d*); 138.5 (*s*); 159.5 (*s*); 170.7 (*s*). HR-ESI-MS: 287.1260 ([*M* + Na]$^+$, $C_{15}H_{20}NaO_4^+$; calc. 287.1259).

(3*E*)-2-Hydroxy-3-(3-methoxyphenyl)-*N*,*N*,2-trimethylpent-3-enamide ((***E***)-**4**). Isolated in 85% yield during the CC/SiO_2 purification of (*E*)-**2a** (hexane/AcOEt 6:4) ^{1}H-NMR: 1.59 (*d*, *J* = 6.6, 3 H); 1.60 (*s*, 3 H); 2.92 (br. *s*, 3 H); 3.15 (br. *s*, 3 H); 3.81 (*s*, 3 H); 5.97 (*q*, *J* = 6.6, 1 H); 6.78 – 6.82 (*m*, 3 H); 7.21 (*ddd*, *J* = 8.2, 7.5, 0.6, 1 H). ^{13}C-NMR: 14.9 (*q*); 23.9 (*q*); 37.4 (*q*); 38.5 (*q*); 55.2 (*q*); 75.8 (*s*); 112.5 (*d*); 115.0 (*d*); 121.6 (*d*); 123.8 (*d*); 128.8 (*d*); 138.8 (*s*); 142.8 (*s*); 159.1 (*s*); 174.6 (*s*). LR-ESI-MS. 286.1 ([*M* + Na]$^+$, 549.5 ([2*M* + Na]$^+$).

2-Chloro-3-hydroxy-3-(3-methoxyphenyl)-*N*,*N*,2-trimethylpentanamide (**5a**). A soln. of LDA (1M in THF, 1.1 ml, 2.2 mmol) was slowly added to a soln. of 2-chloro-*N*,*N*-dimethylpropanamide (0.13 ml, 1 mmol) in THF (0.5 ml) at −85 °C under Ar. After 10 min, a soln. of ketone **7** (82 mg, 0.5 mmol) in THF (0.5 ml) was slowly added. The mixture was then stirred for 1 h at −78 °C. Then, the reaction was quenched with a sat. aq. soln. of NH_4Cl (0.54 ml), and the mixture was warmed and extracted with CH_2Cl_2 (2 × 5 ml). The combined org. layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, hexane/AcOEt 10:0.5) to afford compound **5a** (colorless viscous oil, 30 mg, 20%) as a mixture of two diastereoisomers A and B (relative configuration was not determined). Diastereoisomer A: ^{1}H-NMR: 0.75 (*t*, *J* = 7.2, 3 H); 1.65 (*s*, 3 H); 2.26 – 2.30 (*m*, 1 H); 2.54 – 2.58 (*m*, 1 H); 3.09 (br. *s*, 3 H); 3.27 (br. *s*, 3 H); 3.85 (*s*, 3 H); 5.97 (*s*, 1 H); 6.84 – 6.88 (*m*, 1 H); 7.27 – 7.31 (*m*, 3 H). ^{13}C-NMR: 8.2 (*q*); 23.9 (*q*); 28.2 (*t*); 39.6 (*q*); 40.2 (*q*); 55.2 (*q*); 72.4 (*s*); 82.9 (*s*); 112.1 (*d*); 115.5 (*d*); 121.5 (*d*); 127.9 (*d*); 141.2 (*s*); 158.8 (*s*); 173.0 (*s*). Diastereoisomer B: ^{1}H-NMR: 0.78 (*t*, *J* = 7.2, 3 H); 1.98 (*s*, 3 H); 2.04 – 2.08 (*m*, 1 H); 2.35 – 2.39 (*m*, 1 H); 2.82 (*s*, 6 H); 3.83 (*s*, 3 H); 5.38 (*s*, 1 H); 6.78 – 6.83 (*m*, 1 H); 7.11 – 7.14 (*m*, 2 H); 7.21 – 7.27 (*m*, 1 H). ^{13}C-NMR: 7.9 (*q*); 27.2 (*q*); 27.3 (*t*); 39.6 (*q*); 55.2 (*q*); 75.4 (*s*); 81.3 (*s*); 112.4 (*d*); 114.6 (*d*); 120.9 (*d*); 128.1 (*d*); 142.8 (*s*); 158.9 (*s*); 172.1 (*s*). HR-ESI-MS: 322.1172 ([*M* + Na]$^+$, $C_{15}H_{22}ClNNaO_3^+$; calc. 322.1186).

Ethyl 2-Chloro-3-hydroxy-3-(3-methoxyphenyl)-2-methylpentanoate (**5b**). A soln. of potassium bis(trimethylsilyl) amide (HMDSK; 0.22 g, 1.1 mmol) in toluene (0.5 ml) was slowly added to a soln. of ethyl 2-chloropropanoate (0.14 g, 1.1 mmol) in THF (0.5 ml) at −85 °C under Ar. After 10 min, a soln. of ketone **7** (82 mg, 0.5 mmol) in THF (0.5 ml) was slowly added. The mixture was stirred for 1 h at −78 °C. Then, the reaction was quenched with a sat. aq. soln. of NH_4Cl (0.54 ml), and the mixture was warmed and extracted with CH_2Cl_2 (2 × 5 ml). The combined org. layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, hexane/AcOEt 10:0.5) to afford compound **5b** (colorless viscous oil, 37 mg, 25%). ^{1}H-NMR: 0.79 (*td*, *J* = 7.3, 0.8, 3 H); 0.91 – 0.96 (*m*, 1 H); 1.20 – 1.24 (*m*, 3 H); 1.60 – 1.64 (*m*, 1 H); 3.83 (*s*, 3 H); 4.16 – 4.20 (*m*, 2 H); 6.89 – 6.93 (*m*, 2 H); 7.25 – 7.29 (*m*, 2 H). ^{13}C-NMR: 7.8 (*q*); 13.8 (*q*); 24.8 (*q*); 28.9 (*t*); 55.3 (*q*); 62.6 (*t*); 80.4 (*s*); 87.1 (*s*); 112.4 (*d*); 112.6 (*d*); 120.1 (*d*); 128.3 (*d*); 140.6 (*s*); 159.6 (*s*); 170.7 (*s*). LR-ESI-MS 323.1 ([*M* + Na]$^+$).

1-Methoxy-3-(prop-1-yn-1-yl)benzene (**8**). To a suspension of CuI (360 mg, 1.88 mmol) and $(Ph_3P)_4Pd$ (360 mg, 0.31 mmol) in dry toluene (10 ml) was added 1-iodo-3-methoxybenzene (0.76 ml, 6.3 mmol), trimethyl(prop-1-ynyl)silane (0.94 ml, 6.3 mmol), Et_3N (3 ml, 21 mmol), and Bu_4NF (1M in THF, 6.3 ml, 6.3 mmol). The mixture was stirred under Ar overnight at 20 °C. Then, H_2O was added (5 ml), and the resulting mixture was extracted with Et_2O (2 × 10 ml). The org. phase was dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography (SiO_2, hexane/AcOEt 10:1) to give **8** (717 mg, 78%). ^{1}H-NMR: 7.17 – 7.19 (*m*, 1 H); 6.94 – 6.98 (*m*, 2 H); 6.81 – 6.85 (*m*, 1 H); 3.77 (*s*, 3 H); 2.04 (*s*, 3 H). ^{13}C-NMR: 4.5 (*q*); 55.4 (*q*); 79.9 (*s*); 85.9 (*s*); 114.3 (*d*); 116.6 (*d*); 124.2 (*d*); 125.2 (*s*); 129.5 (*d*); 159.5 (*s*). During the LR-ESI-MS analysis, **8** was not ionizable.

Typical Procedure for Nickel-Catalyzed Carboxylation of **8**. DBU (0.51 ml, 3.4 mmol) was added to a stirred suspension of $Ni(cod)_2$ (19 mg, 0.07 mmol) in dry, degassed THF (2 ml) under Ar at 0 °C. A balloon filled with CO_2 was connected to the reaction vessel. After 15 min, a soln. of 1-methoxy-3-(prop-1-ynyl)benzene **8** (50 mg, 0.34 mmol) in dry, degassed THF (2 ml) was added dropwise to the resulting pale green mixture. After that, a soln. of Et_2Zn (1M in hexane, 1.02 ml, 1.02 mmol) was added dropwise. The mixture was allowed to warm to r.t. and stirred overnight, after which it was acidified at 0 °C with 10% HCl. The mixture was then extracted with AcOEt (2 × 10 ml), washed with brine (10 ml), dried (Na_2SO_4) and concentrated. The residue was further purified by distillation giving (*E*)-**2c** (89% isolated yield) or **11aa** – **11cc**.

(2*E*)-2-Methyl-3-phenylbut-2-enoic Acid (**11aa**). Obtained in 54% yield (38 mg). ^{1}H-NMR: 1.83 (*d*, *J* = 1.5, 3 H); 2.13 (*d*, *J* = 1.8, 3 H); 2.05 (*s*, 3 H); 7.16 – 7.21 (*m*, 2 H); 7.29 – 7.31 (*m*, 1 H); 7.38 – 7.41 (*m*, 2 H); 11.8 (br. *s*, 1 H). ^{13}C-NMR: 17.4 (*q*); 23.7 (*q*); 123.8 (*s*); 126.9 (*d*); 127.2 (*d*); 128.4 (*d*); 143.8 (*s*); 150.3 (*s*); 175.3 (*s*). LR-ESI-MS: 175.2 ([*M* − H]$^-$).

(2*E*)-2-Ethyl-3-phenylbut-2-enoic Acid (**11ba**). Obtained in 59% yield (45 mg). ^{1}H-NMR: 1.00 (*t*, *J* = 7.5, 3 H); 2.22 (*q*, *J* = 7.5, 2 H); 2.35 (*s*, 3 H); 7.16 – 7.19 (*m*, 2 H); 7.29 – 7.33 (*m*, 1 H); 7.37 – 7.41 (*m*, 2 H); 11.7 (br. *s*, 1 H). ^{13}C-NMR: 13.9 (*q*); 23.9 (*q*); 24.3 (*t*); 126.9 (*d*); 127.1 (*d*); 128.4 (*d*); 130.6 (*s*); 143.5 (*s*); 148.4 (*s*); 175.1 (*s*). LR-ESI-MS: 189.3 ([*M* − H]$^-$).

(2*E*)-2-(1-Phenylethylidene)hexanoic Acid (**11ca**). Obtained in 59% yield (52 mg). ^{1}H-NMR: 0.80 (*t*, *J* = 7.2, 3 H); 1.19 – 1.22 (*m*, 2 H); 1.37 – 1.40 (*m*, 2 H); 2.19 (*t*, *J* = 7.5,

2 H); 2.35 (*s*, 3 H); 7.15 – 7.17 (*m*, 2 H); 7.27 – 7.30 (*m*, 1 H); 7.36 – 7.40 (*m*, 2 H); 11.7 (br. *s*, 1 H). ^{13}C-NMR: 13.8 (*q*); 22.5 (*t*); 23.9 (*q*); 30.7 (*t*); 31.5 (*t*); 126.8 (*d*); 127.1 (*d*); 128.4 (*d*); 129.6 (*s*); 143.5 (*s*); 148.2 (*s*); 175.6 (*s*). LR-ESI-MS: 217.3 ([*M* − H]$^-$).

(2*E*)-2-Methyl-3-phenylpent-2-enoic Acid (11ab). Obtained in 57% yield (44 mg). ^{1}H-NMR: 1.01 (*t*, *J* = 7.5, 3 H); 1.78 (*s*, 3 H); 2.80 (*q*, *J* = 7.5, 2 H); 7.28 – 7.32 (*m*, 2 H); 7.36 – 7.41 (*m*, 3 H); 11.7 (br. *s*, 1 H). ^{13}C-NMR: 12.8 (*q*); 17.5 (*q*); 29.7 (*t*); 123.4 (*s*); 127.2 (*d*); 127.6 (*d*); 128.3 (*d*); 141.9 (*s*); 155.5 (*s*); 175.6 (*s*). LR-ESI-MS: 189.2 ([*M* − H]$^-$).

(2*E*)-2-Ethyl-3-phenylpent-2-enoic Acid (11bb). Obtained in 51% yield (41 mg). ^{1}H-NMR: 1.01 (*t*, *J* = 7.5, 3 H); 1.02 (*t*, *J* = 7.5, 3 H); 2.16 (*q*, *J* = 7.5, 2 H); 2.71 (*q*, *J* = 7.5, 2 H); 7.13 – 7.17 (*m*, 2 H); 7.28 – 7.40 (*m*, 3 H); 11.6 (br. *s*, 1 H). ^{13}C-NMR: 12.7 (*q*); 13.9 (*q*); 24.5 (*t*); 29.9 (*t*); 127.4 (*d*); 128.2 (*d*); 130.3 (*d*); 133.9 (*s*); 141.6 (*s*); 153.3 (*s*); 175.6 (*s*). LR-ESI-MS: 203.2 ([*M* − H]$^-$).

(2*E*)-2-(1-Phenylpropylidene)hexanoic Acid (11cb). Obtained in 50% yield (46 mg). ^{1}H-NMR: 0.80 (*t*, *J* = 7.3, 3 H); 1.01 (*t*, *J* = 7.2, 3 H); 1.20 (*q*, *J* = 7.2, 2 H); 1.34 – 1.44 (*m*, 2 H); 2.14 (*t*, *J* = 7.8, 2 H); 2.71 (*q*, *J* = 7.5, 2 H); 7.11 – 7.15 (*m*, 2 H); 7.28 – 7.44 (*m*, 3 H); 11.7 (br. *s*, 1 H). ^{13}C-NMR: 12.8 (*q*); 13.8 (*q*); 22.5 (*t*); 29.9 (*t*); 30.8 (*t*); 31.4 (*t*); 127.6 (*d*); 128.2 (*d*); 129.3 (*d*); 132.9 (*s*); 141.6 (*s*); 153.1 (*s*); 175.8 (*s*). LR-ESI-MS: 231.3 ([*M* − H]$^-$).

(2*E*)-2,4-Dimethyl-3-phenylpent-2-enoic Acid (11ac). Obtained in 19% yield (16 mg). ^{1}H-NMR: 0.98 (*d*, *J* = 6.9, 6 H); 1.63 (*s*, 3 H); 3.64 – 3.66 (*m*, 1 H); 7.01 – 7.04 (*m*, 2 H); 7.33 – 7.42 (*m*, 3 H); 12.0 (br. *s*, 1 H). ^{13}C-NMR: 13.7 (*q*); 17.5 (*q*); 21.4 (*q*); 31.6 (*d*); 126.8 (*s*); 127.9 (*d*); 128.5 (*d*); 129.8 (*d*); 135.6 (*s*); 141.2 (*d*); 156.6 (*s*); 174.4 (*s*). LR-ESI-MS: 203.2 ([*M* − H]$^-$).

(2*E*)-2-Ethyl-4-methyl-3-phenylpent-2-enoic Acid (11bc). Obtained in 15% yield (13 mg). ^{1}H-NMR: 0.93 (*t*, *J* = 7.4, 3 H); 0.98 (*d*, *J* = 6.9, 6 H); 2.01 (*q*, *J* = 7.5, 2 H); 3.46 – 3.49 (*m*, 1 H); 7.04 – 7.07 (*m*, 2 H); 7.32 – 7.39 (*m*, 3 H); 11.5 (br. *s*, 1 H). ^{13}C-NMR: 13.6 (*q*); 13.8 (*q*); 20.6 (*t*); 21.4 (*q*); 32.0 (*d*); 128.6 (*d*); 130.6 (*d*); 133.9 (*s*); 135.5 (*s*); 140.9 (*d*); 153.9 (*s*); 174.2 (*s*). LR-ESI-MS: 217.3 ([*M* − H]$^-$).

(2*E*)-2-(2-Methyl-1-phenylpropylidene)hexanoic Acid (11cc). Obtained in 12% yield (12 mg). ^{1}H-NMR: 0.73 (*t*, *J* = 7.2, 3 H); 0.97 (*d*, *J* = 9, 6 H); 1.22 – 1.25 (*m*, 2 H); 1.31 – 1.34 (*m*, 2 H); 1.96 – 199 (*m*, 2 H); 3.42 – 3.46 (*m*, 1 H); 7.03 – 7.05 (*m*, 2 H); 7.35 – 7.44 (*m*, 3 H); 12.1 (br. *s*, 1 H). ^{13}C-NMR: 13.8 (*q*); 13.9 (*q*); 21.4 (*q*); 22.8 (*t*); 27.1 (*t*); 31.0 (*t*); 31.4 (*d*); 128.5 (*d*); 129.4 (*d*); 132.8 (*s*); 135.6 (*s*); 140.9 (*d*); 154.5 (*s*); 174.2 (*s*). LR-ESI-MS: 245.3 ([*M* − H]$^-$).

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