Enediyne-comprising amino aldehydes in the Passerini reaction

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ABSTRACT: Multicomponent reactions represent a highly efficient approach to a broad spectrum of structurally diverse compounds starting from simple and affordable compounds. A focused library of tweezers-like compounds is prepared by employing the multicomponent Passerini reaction comprising enediyne-derived amino aldehydes. The reaction proceeds under mild conditions yielding Passerini products in good to excellent yields. Post-condensation modifications of Passerini products are demonstrated through a simple deprotection/coupling approach comprising amino functionality, furnishing enediyne cores with highly decorated arms.

Introduction

Isolation of biologically active acetylene-containing compounds from natural sources in 1980s boosted the research efforts in different areas of organic chemistry, biochemistry, natural product synthesis, medicinal chemistry, material science, and others. Enediyne anticancer antibiotics isolated from marine and terrestrial plant sources represent a class of antitumor/antimicrobial agents with high cytotoxic activity.[1] The remarkable activity and a striking mode of action made enediyne compounds an attractive target molecules. Motivated by their biological importance, many cyclic and acyclic enediyne derivatives were prepared and their biological activities evaluated.[1-5] Apart from their role in biologically relevant processes, enediynes are versatile building blocks for the construction of complex aromatic systems through thermal or photochemical activation.[6-11] Furthermore, rigid, stable and spatially well-directed enediyne motif can be exploited as an inducer of turn-like conformation. In our previous studies, we showed that enediyne-based small molecule tweezers are efficient Cu(II) atom binders.[12] Comparing stability of studied complexes with those reported for histidine-rich peptide fragments with high affinity for copper(II), revealed that enediyne tweezers effectively mimic properties of copper(II) binding peptides. It is noteworthy that in many proteins, the proline residue is found in the vicinity of Cu(II) binding site, mostly preceding histidine residue. We therefore, concluded that structural rigidity of enediyne tweezers significantly enhances coordination properties of the receptor, thus conforming importance of the turn-like peptide conformation for the copper(II) binding. Furthermore, we demonstrated that amino acid-derived enediyne ligands account for high enantioselectivities observed in a rhodium-catalyzed asymmetric hydrogenation reaction.[13] In both cases, enediyne unit acts as structural element, while function is determined by groups attached at the terminal positions. We are therefore

interested to explore further the potential of enediyne compounds primarily as receptors. In that sense, conjugation of enediynes with peptide-like structures is particularly interesting, since the presence of different functional groups on the periphery of the synthetic receptors, especially chiral ones, is often the key factor for the recognition and/or discrimination of different ligands.[14-18] A nice example is recent study of Delsuc et al. where two peptide segments attached to a rigid template are designed to hybridize with a guest peptide molecule into a collagen-like triple helix.[17] Also, Faggi et al. described a family of pseudopeptidic cage receptors with a remarkable selectivity for N-protected dipeptides with an aromatic amino acid at the C-terminus.[18] Although cyclic and macrocyclic structures hold a prominent position as receptors for chiral molecules[15] and probes for protein-protein interactions,[19] tweezers-like compounds with cavities of flexible size proved to be effective synthetic receptors as well.[14,20] The main advantage of tweezers-like receptors is adaptability of the receptor geometry to the ligand topology. While size and shape of the receptor cavity is influenced by the template, selectivity of the receptor depends on the properties of its arms.

As a part of our ongoing research in enediyne chemistry, we explored methodologies for the easy construction of structurally diverse enediyne cores for the binding of different ligands. Multicomponent reactions (MCRs) offer rapid, efficient and reliable approach to libraries of structurally diverse compounds starting from simple and affordable compounds. Isocyanide-based MCRs, like Passerini and Ugi reaction[21] are exceptionally useful for the assembly of chimeras composed of enediynes and peptide-like structures. Among different approaches, we opted for bifunctional enediyne cores, particularly amino aldehydes **1** and **2** (Figure 1) equipped with two different functional groups that can be used in step-by-step diversification process. Aldehyde group takes part in the first MCR, while amine group is available, (after deprotection)

for the second MRC, or standard peptide coupling reaction. Our main motivation was to build a reliable and robust strategy toward library of receptors for different ligands. In this work, we explored the reactivity of aldehyde group in enediynes **1** and **2** in the Passerini reaction comprising various acids and isocyanides Thus obtained Passerini products can be further functionalized to give tweezers with highly decorated arms available for even further modifications.

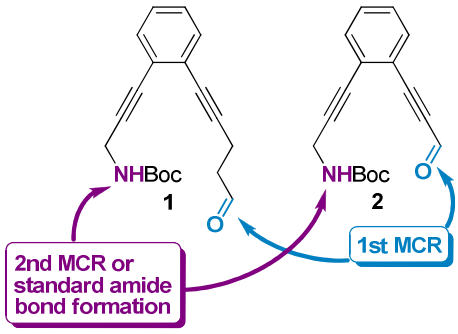
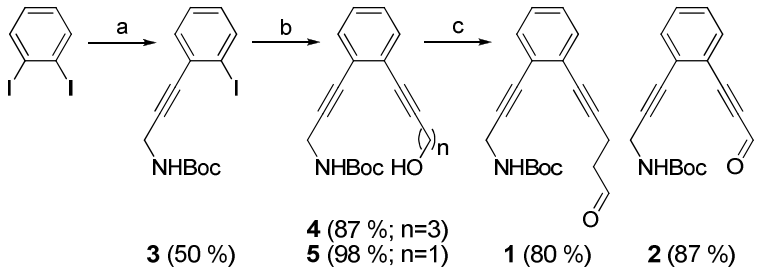


Figure 1. Structures of amino aldehydes **1** and **2**.

Results and Discussion

Boc protected amino aldehydes **1** and **2** were prepared by a straightforward procedure comprising two consecutive Sonogashira couplings[22] followed by an oxidation (Scheme 1). Cross-coupling of Boc-protected propargyl amine with 1,2-diiodobenzene gave Sonogashira product **3** in 50 % yield. Next, coupling of **3** with either pent-4-yn-1-ol or prop-2-yn-1-ol gave amino alcohols **4** and **5** in excellent yields (87 and 98 %, respectively). Finally, oxidation with Dess Martin periodane proceeded smoothly providing enediyne-bridged Boc-protected amino aldehydes **1** (80 % yield) and **2** (87 % yield) (Scheme 1).

Scheme 1. Synthesis of amino aldehydes **1** and **2**



a) *tert*-butyl prop-2-ynylcarbamate, CuI (10 mol %), $Pd(PPh_3)_4$ (3 mol %), in TEA, RT, under Ar, 24 h, 50 % yield; b) pent-4-yn-1-ol or prop-2-yn-1-ol (2 equiv.), CuI (3 mol %), $PdCl_2(PPh_3)_2$ (3 mol %), in TEA, RT, under Ar, 24 , 87 % and 98 % yield, respectively; c) DMP (2 equiv) in DCM, RT, 3 h.

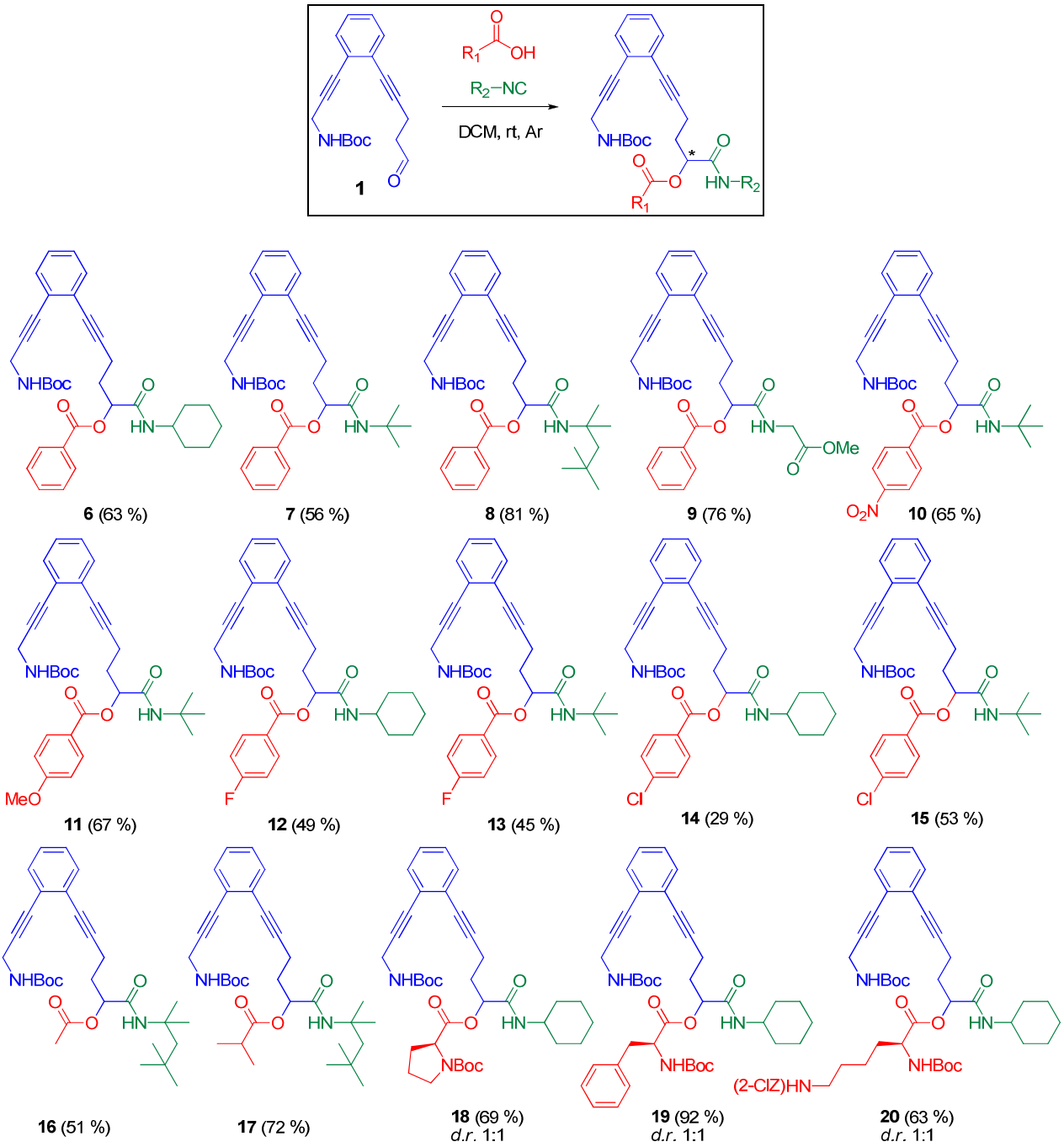
In our initial experiments, Passerini reaction was performed with equimolar amounts of amino aldehyde **1**, benzoic acid and cyclohexyl isocyanide, and after 3 days in different solvents (DCM, ethyl acetate, THF) at room or elevated temperature, still showed presence of starting material. Reactions performed with excess of acid and isocyano components proceeded faster; reaction was completed in 24 h and the Passerini product **6** was obtained in 63 % yield (Chart 1). Therefore, optimized reaction conditions for the Passerini reaction include 3.1 equivalent of acid and isocyanide and reaction were carried out in DCM at room temperature until the consumption of the aldehyde component, typically 24-48h. Three additional isocyanides were used as nucleophiles; with *tert*-butyl isocyanide Passerini product **7** was gained in a 56 % yield, while a highly branched 1,1,3,3-tetramethylbutyl isocyanide gave Passerini products **8** in 81 % yield. Finally, methyl isocyanoacetate was used as a representative of amino acid-derived isocyanides, and the corresponding Passerini product was obtained in a 76 % yield. A robust methodology for the synthesis of libraries should tolerate a broad range of substrates with different electronic and steric features. Therefore, benzoic acids with different electronic properties were tested in the

Passerini reaction. As seen in Chart 1, benzoic acid with strong electron-withdrawing group at the *para*-position gave product **10** in the same yield (65 %) as benzoic acid with strong electron-donating group at the same position (product **11**, 67 %). Therefore, electronic properties of the acid component do not affect its reactivity in the Passerini reaction. When halogen atoms were introduced at the *para* position of the benzoic acid aromatic ring, isolated yields were slightly lower (29-53 % for products**12**-**15**), regardless of isocyanide used (Chart 1). Next, aliphatic carboxylic acids were investigated. Acetic and isobutyric acid reacted with 1,1,3,3-tetramethylbutyl isocyanide and gave rise to Passerini products **16** and **17** in 51 % and 72 % yield, respectively. Amino acids are preferable building blocks in multicomponent reactions, since they provide possibility for multiple post-condensation modifications, mainly through deprotection/cyclization protocols. Moreover, as discussed previously, amino acids and peptides are often key elements important for recognition of different ligands. Three Boc-protected amino acids were used as acid components: cyclic amino acid proline, aromatic phenylalanine and aliphatic lysine. Cyclohexyl isocyanide was used in all three reactions and Passerini products **18**-**20** were isolated in 63-92 % yield as a 1:1 mixture of two diastereoisomers. It is known that stereoselectivity of the Passerini reaction performed with chiral components is mainly influenced by the aldehyde component, while contribution of acid and isocyanide is generally negligible.[21] Therefore, the absence of stereoselectivity in the reaction performed with achiral amino aldehyde **1** is expected.

Next, we examined the reactivity of amino aldehyde **2** in the Passerini reaction with selected carboxylic acid and isocyanides. All reactions proceeded smoothly and Passerini products were isolated in 54-91 % yield (Chart 2). The influence of scale-up on the efficiency of the presented

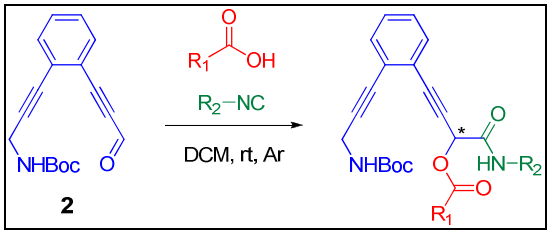
methodology was also examined. Reaction performed with 1 mmol of aldehyde **2**, 3.1 mmol of Boc-protected phenylalanine and cyclohexyl isocyanide gave Passerini product **25** in 87 % yield. An interesting feature of Passerini products **21**-**26** is presence of triple bond attached to the sp^3 carbon atom. Recently, synthesis of structurally analogous propargylic alcohol derivatives by a copper-catalyzed oxy-alkynylation of diazo compounds with hypervalent iodine reagents was reported.[23] Here, presented Passerini reaction comprising easy accessible aldehyde **2** offers an alternative, metal-free approach to sp-sp^3 carbon bonds in very good yields and under mild reaction conditions.

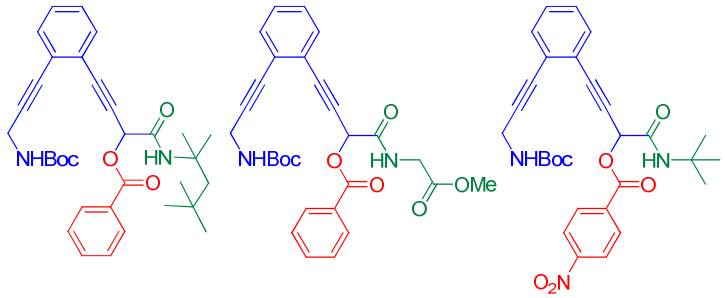
Chart 1. Passerini reactions performed with aldehyde **1**[a]



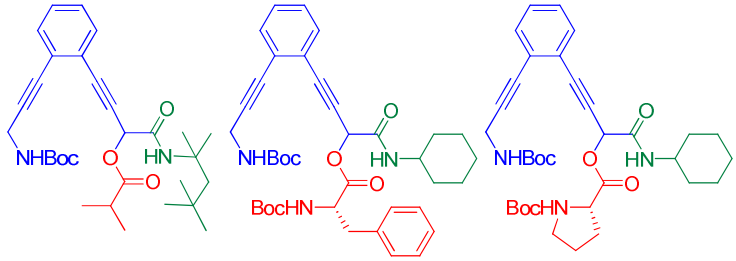
[a]Reactions were performed with ~ 0.05 mmol of **1**, 3.1 equiv. of acid and 3.1 equiv. of isocyanide component. Isolated yields are given in parentheses.

Chart 2. Passerini reactions performed with aldehyde **2**[a]





21 (54 %) **22** (54 %) **23** (76 %)



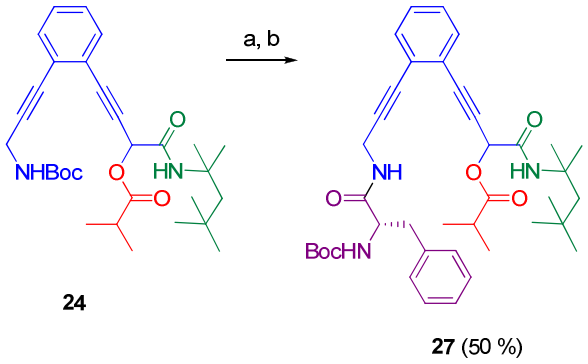
24 (82 %) **25** (91%) *d.r.* 1:1 **26** (55 %) *d.r.* 1:1

[a] Reactions were performed with ~ 0.05 mmol of **2**, 3.1 equiv. of acid and 3.1 equiv. of isocyanide component. Isolated yields are given in parentheses.

Increasing the structural complexity of receptor is often needed to increase the binding selectivity, especially in competitive solvents, and can be achieved by adding new "arm" through a straightforward approach.[18] Multicomponent approach coupled with post-condensation modification(s) provides efficient strategy for the synthesis of structurally and functionally different receptors, where binding site can be crafted by careful selection of starting compounds.

Thus, multiple-arm receptors carrying hydrophobic or hydrophilic peripheral structures can be designed to probe binding of different ligands. To demonstrate the susceptibility of prepared Passerini products toward further modifications, we subjected compound **24** to Boc deprotection under acid conditions followed by coupling with *N*-terminally protected phenylalanine, and compound **27** was obtained in 50 % yield over two steps. Thus, presented Passerini reaction/post-Passerini coupling of enediyne-related amino aldehydes can be used as synthetic tool to produce tweezers-like molecules with tailored binding site. Synthesis of multiple-arm derivatives through here presented strategy, as well as a thorough complexation study of prepared Passerini compounds with a range of metal ions is currently underway, and will be published in due course.

Scheme 2. Post-Passerini modification



a) TFA/H_2O (9/1) RT, 30 min; b) Boc-Phe-OH (1.2 equiv), BOP (1.5 equiv.), HOBt (1.5 equiv.), NMM (2 equiv.), in DMF, RT, overnight

Conclusions

In summary, we successfully introduced Boc-protected enediyne-related amino aldehydes as carbonyl components in the Passerini reaction. Reactions were performed under mild reaction

conditions affording Passerini products in good to excellent yields. The reaction was tolerant of aromatic and aliphatic carboxylic acids, including amino acids, as well as of various isocyanides. Furthermore, we demonstrated that Passerini products can be additionally modified by a deprotection/coupling approach through their amino functionality.

Experimental procedures

General procedure for the Passerini reaction (Charts 1 and 2) Compound **1** or **2** (~ 0.05 mmol) were dissolved in dichloromethane under argon. Carboxylic acid (3.1 equiv.) and isocyanide (3.1 equiv.) were added and the reaction mixture was stirred at room temperature until the consumption of the aldehyde component, typically 24-48h. The reaction was quenched with saturated $NaHCO_3$ and the product was extracted with dichloromethane. Organic layer was washed with brine and water, dried over Na_2SO_4 and concentrated under reduced pressure. The product was obtained by flash column chromatography (petrol/ethyl acetate (v/v = 2/1)) to afford corresponding products **6** – **26.**

Representative example of the Passerini product (Chart 1)

6-(2-(3-(*tert*-butoxycarbonylamino)prop-1-ynyl)phenyl)-1-(cyclohexylamino)-1-oxohex-5-yn-2-yl benzoate (6) Compound **6** was obtained from *tert*-butyl 3-(2-(5-hydroxypent-1-ynyl)phenyl)prop-2-ynylcarbamate (**1**) (23 mg), benzoic acid (28 mg) and cyclohexyl isocyanide (28 μL) according to the general procedure in 63% yield (25 mg, 0.046 mmol) as a yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.08 (d, J = 7.6 Hz, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.7 Hz, 2H), 7.38 (s, 1H), 7.32 – 7.30 (m, 1H), 7.20 – 7.18 (m, 2H), 6.12 (s, 1H), 5.57 (d, J = 30.9 Hz, 2H), 4.21 (s, 2H), 3.84 – 3.79 (m, 1H), 2.66 (t, J = 6.8 Hz, 2H), 2.41 – 2.28 (m, 2H), 1.90 (t, J = 11.5 Hz, 2H), 1.68 – 1.65 (m, 3H), 1.45 (s, 9H), 1.35 – 1.33 (m, 2H), 1.16 – 1.10 ppm

(m, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 167.9, 165.1, 133.1, 131.7, 131.3, 129.4, 128.6, 128.1, 127.4, 126.9, 125.4, 124.7, 91.6, 89.1, 81.0, 80.0, 79.1, 73.1, 59.9, 47.7, 32.4, 32.3, 30.3, 27.9, 24.9, 24.2, 24.1, 15.3 ppm; HRMS (M + Na^+) calculated 565.2678, found 565.2660; IR: $\tilde{\upsilon}_{max}$ = 3307, 2930, 1714, 1407, 1249, 814, 710 cm^{-1}.

Representative example of the Passerini product (Chart 2)

4-(2-(3-(*tert*-butoxycarbonylamino)prop-1-ynyl)phenyl)-1-oxo-1-(2,4,4-trimethylpentan-2-ylamino)but-3-yn-2-yl benzoate (21) Compound **21** was obtained from *tert*-butyl 3-(2-(3-oxoprop-1-ynyl)phenyl)prop-2-ynylcarbamate (**2**) (32 mg), benzoic acid (30 mg) and 1,1,3,3-tetramethylbutyl isocyanide (42 μL) according to the general procedure in 54 % yield (33 mg, 0.061 mmol) as a yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.15 – 8.12 (m, 2H), 7.65 – 7.60 (m, 1H), 7.51 – 7.40 (m, 4H), 7.32 – 7.22 (m, 2H), 6.36 (s, 1H), 6.15 (s, 1H), 5.78 (s, 1H), 4.20 (s, 2H), 1.77 (d, J = 4.9 Hz, 2H), 1.49 – 1.47 (m, 15H), 1.01 ppm (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 164.3, 162.8, 133.3, 131.2, 129.5, 128.5, 128.3, 128.1, 127.4, 125.8, 123.8, 90.0, 85.6, 85.4, 80.6, 65.0, 55.4, 51.6, 30.9, 30.8, 28.5, 28.3, 27.9 ppm; HRMS (M + Na^+) calculated 567.2835, found 567.2831; IR: $\tilde{\upsilon}_{max}$ = 3324, 3127, 2953, 1681, 1409, 1366, 1246, 1303, 1026, 898, 710 cm^{-1}.

ASSOCIATED CONTENT

Supporting Information. General methods, synthetic procedures, characterization data and copies of ^{1}H, ^{13}C and HRMS spectra are included in the SI file (PDF).

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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