Diastereoselective Heck Arylation of Spirolactams: An Approach to Spiroamine-Based Nicotinic Ligands

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This paper is dedicated with respect to Professor Richard Heck, whose work represents a fundamental and lasting contribution to the organic chemistry of palladium.

Abstract: The intermolecular Heck arylations of the cyclopentenyl based spirolactams **6a** and **6c** are stereoselective leading to adducts **7** and **8** derived by face-selective carbopalladation *anti* to the lactam carbonyl.

Key words: Heck reaction, spirocycles, lactams, metathesis, stereoselectivity

Natural product leads, such as epibatidine (**1**)[1] and anatoxin-a (**2**, Figure 1),[2] have attracted interest as leads for selective nicotinic agonists associated with the nicotinic acetylcholine receptor (nAChR).[3]

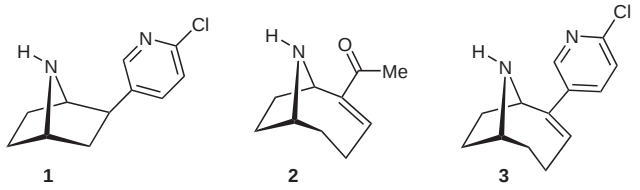

Figure 1

These ligands incorporate key elements associated with contemporary nicotinic pharmacophores,[4] namely a basic amine (protonated at physiological pH) and a π-system incorporating a hydrogen bond acceptor (the pyridyl ring of **1** and the ketone oxygen of **2**). These two pharmacophore elements must be maintained in the appropriate arrangement to interact with the nAChR, and the rigid bicycle associated with **1** and **2** provides the scaffold necessary to achieve optimal orientation. There is an opportunity to explore alternative frameworks to carry these pharmacophore components, and thereby develop new families of nicotinic agonists. We have already generated the first epibatidine–anatoxin-a hybrid, UB-165 (**3**),[5] but there is an on-going need to define a broader and synthetically more accessible range of scaffolds.

In this paper we report initial results aimed at scaffold assemblies based on spirofused bicyclic amines **4** (where m = n = 1, 2; R = Me, H). These were attractive for a number of reasons. Spirocyclic arrangements retain a significant degree of rigidity thereby controlling the location

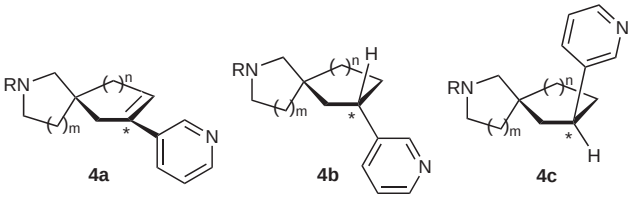

Figure 2

of the basic amine center with respect to the hydrogen bond acceptor. In addition, this spatial relationship can be modulated by varying (i) the ring sizes of the bicyclic core (m vs. n), and (ii) the oxidation level (sp^2 vs. sp^3) and the relative stereochemistry associated with the carbon center carrying the π-moiety (C* in **4a**–**c**, Figure 2). In this way, a greater proportion of receptor space can be probed than is normally the case with synthetically less accessible scaffolds.

This paper deals with our initial approach to this putative class of ligand, with a key feature being use of the Heck arylation reaction[6] as a means of introducing the aryl unit onto the heterocyclic core.

We targeted the *N*-methyl variants (i.e. **4**, R = Me), which offer the possibility of access to the corresponding secondary amines (**4**, R = H) at a later stage. The core spirocyclic scaffolds based on **4** (m = n = 1, 2) were assembled in a straightforward fashion as outlined in Scheme 1.

Using *N*-methyl pyrrolidinone, stepwise enolate alkylation was carried out to provide the α,α-disubstituted lactams **5a** and **5b**. Ring-closing metathesis (using the Grubbs 2nd generation catalyst in toluene) provided spirocyclic alkenes **6a** and **6b** in 70% and 80% isolated yields, respectively; these reactions were significantly slower and less efficient using the Grubbs 1st generation catalyst. A similar sequence was also applicable to *N*-methyl piperidinone leading to **5c**,**d** and **6c**,**d** in comparable yields.[7,8]

The Heck arylation of **6a**–**d** was examined under a variety of different conditions.[9–11] We observed arylation with the cyclopentene variants **6a** and **6c** (see below), which represent a more reactive and stereochemically less complicated series. However, and despite significant effort, cyclohexenes **6b** and **6d** proved to be much less reactive and with these substrates Heck adducts were produced in

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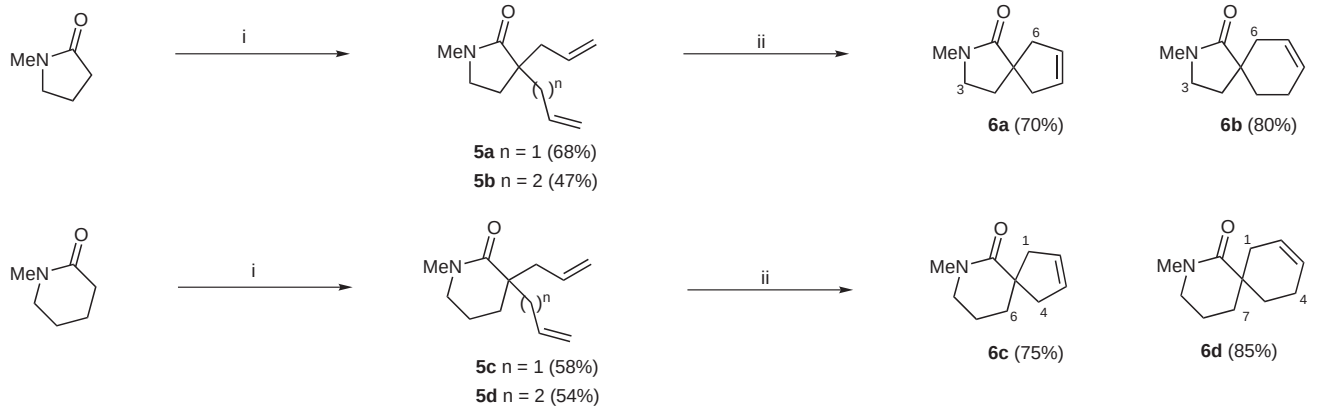


Scheme 1 *Reagents and conditions* (overall yields for the lactam alkylation sequences are shown above): i, **5a** and **5c**: *s*-BuLi, THF, –78 °C, 3-bromoprop-1-ene, –78 °C to r.t., then *s*-BuLi, THF, –78 °C, 3-bromoprop-1-ene, –78 °C to r.t.; i, **5b** and **5d**: *s*-BuLi, THF, –78 °C, 4-bromobut-1-ene, –78 °C to r.t., then *s*-BuLi, THF, –78 °C, 3-bromoprop-1-ene, –78 °C to r.t.; ii, $RuCl_2(=CHPh)(IMes)(PCy_3)$ (1 mol%), PhMe, 70 °C, 1–2 h.

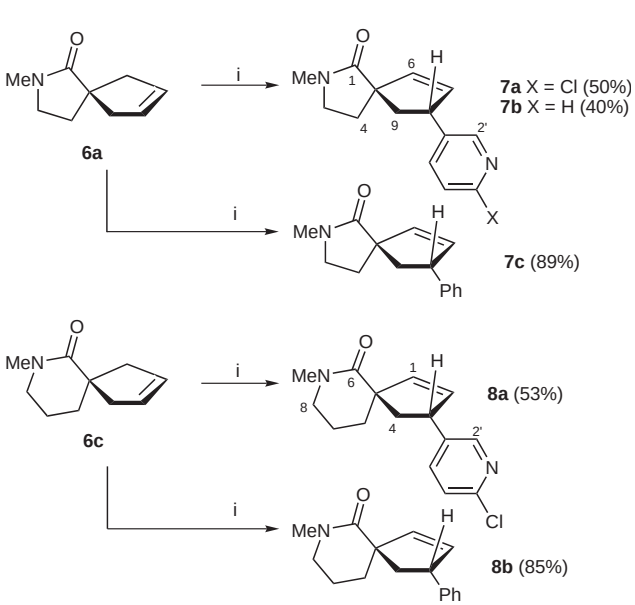
low yields and as inseparable mixtures of regioisomers (see below).

With **6a** and **6c** use of the Larock-modified Jeffery conditions provided the best yields (Scheme 2).[10a,b] Use of 5-iodo-2-chloropyridine [cf UB-165 (**3**)] gave the Heck adducts **7a**[12] and **8a**[12] in 50% and 53% yield, respectively. Heck arylations were also carried using 3-bromopyridine to give **7b** (40%), and **7c** (89%) and **8b** (85%) were obtained using iodobenzene.

While we anticipated (based on mechanistic grounds) that **6a** and **6c** would lead to formation of the deconjugated adduct (compare e.g. **7a** with **9** below) we were surprised that in all cases studied the Heck adducts **7a–c** and **8a** and **8b** were isolated as single diastereoisomers. No evidence for the formation of the other diastereomer was seen. The structure of **7a** was established initially by NOE studies, aided by the rigidity of the spiro framework, and this assignment was then confirmed by X-ray crystallography (Figure 3).

The stereochemical assignment of Heck adducts **7b** and **7c** and **8a** and **8b** was also based on NOE studies and by comparison with the spectroscopic data from **7a**.

In both spirolactams **6a** and **6c**, the amide carbonyl appears to exert a significant influence on the diastereofacial selectivity of the Heck arylations step, and carbopalladation step occurred exclusively on the face of the alkene moiety opposite to the carbonyl unit of the adjacent lactam ring. No direct precedent exists for the process outlined in Scheme 2. Intramolecular Heck reactions taking place in close proximity to carbonyl functions (esters and amides) have been reported,[13] but the outcomes associated with these reactions are generally determined by other factors. Recently, Ung and Pyne[14] and co-workers have described the intermolecular Heck arylation of cyclopentenyl-based amino acid derivatives. These reactions also display a high degree of facial selectivity, but in these cases this was attributed to precomplexation of a Cbz-protected amino function to Pd(II) in order to direct the carbopalladation step to take place from one face.

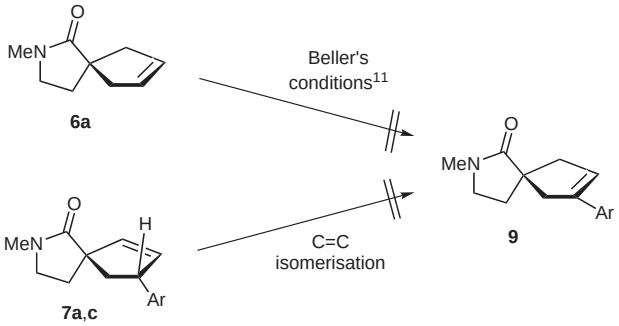


Scheme 2 *Reagents and conditions:* $Pd(OAc)_2$, NaOAc, *n*-$Bu_4NCl{\cdot}H_2O$, ArI or ArBr (see text), DMF, 50 °C, 24 h.

Figure 3 X-ray crystal structure of Heck adduct **7a**

Such an 'internal delivery' option to control delivery of the aryl moiety is not available with spirocycles **6a** and **6c**. However, the extent to which the outcomes reported in Scheme 2 are driven by electronic vs. steric interactions during the carbopalladation reaction is not yet clear. Further work to elucidate those factors that control this process and determine the diastereoselectivity associated with Heck reactions leading to adducts **7** and **8** is underway.

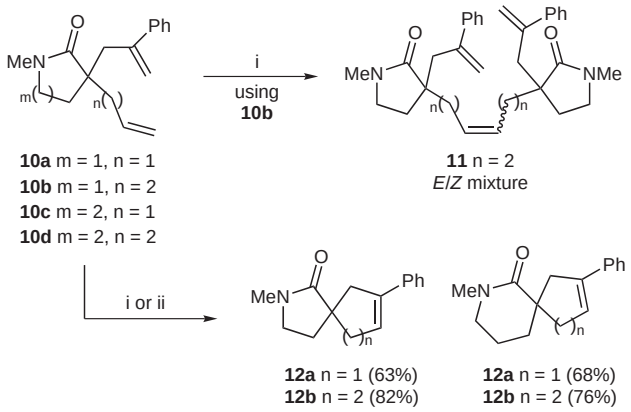
The formation of the deconjugated adducts **7** and **8** is a consequence of the stereospecificity of the PdH elimination step associated with Heck arylation. In order to provide an entry to conjugated isomers **9** (i.e. precursors to **4a**), we explored the applicability of Beller's conditions[11] who has reported the direct formation of conjugated arylated cyclopentenes using $Pd_2(dba)_3$·dba/PCy_3/Na_2CO_3/DMA. Attempts to apply these modifications to spirolactam **6a** did not, however, provide the desired conjugated adducts **9** [Ar = 3-(6-chloropyridyl) or Ph]. Furthermore efforts to isomerize adducts **7a**,**c** under a variety of both metal- and base-mediated conditions were unsatisfactory (Scheme 3).[15]



Scheme 3

An alternative approach to adducts **9**, which also overcomes the issues associated with arylation of cyclohexenes **6b** and **6d**, based on ring-closing metathesis is available, and is exemplified in Scheme 4 for the phenyl-substituted series. Assembly of the requisite precursors **10a**–**d** was achieved by use of the same lactam alkylation strategy as used in Scheme 1. While ring closure to generate the substituted five-membered ring (from **10a**,**c**) proceeded smoothly in PhMe, application of the same process to the cyclohexenyl precursor **10b** led only to formation of cross metathesis dimer **11**. This was solved by a change of solvent (PhMe to CH_2Cl_2), which cleanly gave in all cases the desired conjugated spirolactams **12a**–**d** in good yields.

In conclusion, the Heck reaction of spirolactams **6a** and **6c** leads to the formation of the expected deconjugated Heck adducts **7** and **8** in a highly diastereoselective fashion. Introduction of an aryl substitutent can also be achieved directly via ring-closing metathesis (leading to **12a**–**d**),[16] which complements the Heck arylation sequence. The further application of the methodologies described here to the synthesis of a range of spiroamines and their evaluation as nicotinic agonists will be reported in due course.



Scheme 4 *Reagents and conditions*: i, $RuCl_2$(=CHPh)(IMes)(PCy_3) (1 mol%), PhMe, 70 °C, 1 h (applicable to **10a** and **10c**); ii, $RuCl_2$(=CHPh)(IMes)(PCy_3) (1 mol%), CH_2Cl_2, 40 °C, 4 h (applicable to **10a**–**d**).

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(8) All compounds reported in this paper are racemic. Nicotinic activity may only be associated with one enantiomeric series as is the case with anatoxin-a (**2**) and UB-165 (**3**). This is not the case with epibatidine (**1**) where both enantiomers are equipotent. As predicting the biologically active enantiomer is difficult and subject to pitfalls, our initial targets were racemates. All novel compounds were characterized by ^{1}H NMR and ^{13}C NMR, IR, MS, and HRMS or elemental analysis. The numbering systems used for NMR assignments are indicated on the relevant structures.
^{1}H NMR and ^{13}C NMR data in $CDCl_3$ for spirolactams **6a**–**d**:
Compound **6a**: ^{1}H NMR (300 MHz): δ = 2.00 (2 H, t, *J* = 6.5 Hz, 2 × H-4), 2.26 (2 H, d, *J* = 14.5 Hz, H-6, H-9), 2.82 (2 H, d, *J* = 14.5 Hz, H-6, H-9), 2.88 (3 H, s, CH_3), 3.30 (2 H, t, *J* = 6.5 Hz, 2 × H-3), 5.65 (2 H, br s, H-7, H-8). ^{13}C NMR (75.5 MHz): δ = 30.0 (CH_3), 35.7 (C-4), 43.6 (C-6, C-9), 49.7 (C-5), 46.5 (C-3), 128.4 (C7, C-8), 179.1 (CO).
Compound **6b**: ^{1}H NMR (400 MHz): δ = 1.42–1.51 (1 H, m, H-10), 1.76–1.91 (4 H, m, 2 × H-9, 2 × H-4), 2.06–2.16 (2 H, m, H-6, H-10), 2.32–2.42 (1 H, m, H-6), 2.86 (3 H, s, CH_3), 3.30 (2 H, td, *J* = 7.5, 2.0 Hz, 2 × H-3), 5.61–5.71 (2 H, m). ^{13}C NMR (100 MHz): δ = 21.9 (C-10), 28.4 (C-4), 29.2 (C-9), 29.7 (CH_3), 32.3 (C-6), 42.8 (C-5), 46.2 (C-3), 126.3 and 124.6 (C-7, C-8), 179.0 (C-1).
Compound **6c**: (300 MHz): δ = 1.75–1.89 (4 H, m, 2 × H-9, 2 × H-10), 2.23 (2 H, d, *J* = 14.5, H-1, H-4), 2.95 (3 H, s, CH_3), 2.99 (2 H, d, *J* = 14.5, H-1, H-4), 3.31 (2 H, t, *J* = 6, 2 × H-8), 5.61 (2 H, br s, H-2, H-3). ^{13}C NMR (75.5 MHz): δ = 20.0 (C-9), 35.4 (C-10), 35.3 (CH_3), 46.2 (C-1, C-4), 47.8 (C-5), 50.4 (C-8), 128.1 (C-2, C-3), 176.0 (CO).
Compound **6d**: ^{1}H NMR (300 MHz): δ = 1.55 (1 H, ddt, *J* = 12.5, 4.5, 2.0 Hz, H-11), 1.67 (1 H, dd, *J* = 9.0, 3.5 Hz, H-5), 1.76–1.85 (4 H, m, 2 × H-10, 1 × H-5, 1 × H-11), 1.89–1.93 (1 H, m, H-7), 2.00–2.07 (1 H, m, H-4), 2.09–2.12 (1 H, m, H-4), 2.64 (1 H, dd, *J* = 17.0, 13.0 Hz, H-7), 2.93 (3 H, s, CH_3), 3.24–3.32 (2 H, m, 2 × H-3), 5.60–5.66 (2 H, m, CH=CH). ^{13}C NMR (100 MHz): δ = 19.1 (C-10), 21.6 (C-4), 29.1 (C-5), 30.5 (C-11), 33.6 (C-7), 35.4 (CH_3), 39.9 (C-6), 50.3 (C-3), 125.3 and 125.0 (C-8, C-9), 175.0 (C-1).

(9) Three sets of Heck conditions were used: a) $Pd(OAc)_2$, NaOAc, *n*-Bu_4NCl, H_2O, PhI, DMF, 50 °C, 24 h;[10] b) Herrmann palladacycle catalyst (10 mol%), NaOAc, PhI, DMA, 100 °C, 24 h;[11] c) $Pd_2(dba)_3$ (0.1 mol%), 4 PCy_3, Na_2CO_3, PhI, DMA, 140 °C, 24 h[11] (Heck arylation of **6a** and **6c** was not observed under these latter conditions). A number of other conditions, including use of Ag(I) as an activator, were also evaluated.

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(12) Characterization data for Heck adducts **7a** and **8a**.
Compound **7a**: colorless solid; mp 88 °C (EtOAc–cyclohexane). IR (neat): 3060, 3019, 2930, 2870, 1950, 1740, 1660, 1600, 1490, 1654 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.59 (1 H, dd, *J* = 13.0, 6.5 Hz, H-9), 1.97 (1 H, ddd, *J* = 13.0, 8.0, 6.0 Hz, H-4), 2.23 (1 H, ddd, *J* = 13.0, 8.0, 5.0 Hz, H-4), 2.88 (1 H, dd, *J* = 13.0, 8.5 Hz, H-9), 2.89 (3 H, s, CH_3), 3.31 (1 H, ddd, *J* = 10.0, 8.0, 5.0, H-3), 3.39 (1 H, ddd, *J* = 10.0, 8.0, 6.0 Hz, H-3), 4.27 (1 H, ddt, *J* = 8.5, 6.5, 2.0 Hz, H-8), 5.82 (1 H, dd, *J* = 5.5, 2.0 Hz, CH=CH), 5.94 (1 H, dd, *J* = 5.5, 2.0 Hz, CH=CH), 7.26 (1 H, d, *J* = 8.0 Hz, H-5′), 7.46 (1 H, dd, *J* = 8.0, 2.5 Hz, H-4′), 8.23 (1 H, d, *J* = 2.5 Hz, H-2′). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 30.3 (CH_3), 32.9 (C-4), 44.9 (C-9), 46.7 (C-3), 47.7 (C-8), 57.8 (C-5), 124.1 (C-5′), 135.2 (C-6, C-7), 137.7 (C-4′), 139.7 (C-3′), 148.8 (C-2′), 149.5 (C-6′), 176.9 (CO). MS (EI$^+$): *m/z* (%) = 264, 262 (100) [M$^+$]. HRMS (EI$^+$): *m/z* calcd for $C_{14}H_{15}{}^{35}ClN_2O$: 262.0873; found: 262.0864. Anal. Calcd for $C_{14}H_{15}ClN_2O$: C, 64.10; H, 5.77; N, 10.68. Found: C, 64.15; H, 5.80; N, 10.60.
Compound **8a**: mp 89 °C (EtOAc–cyclohexane). IR (neat): 3046, 2970, 2904, 1660, 1580, 1560, 1452, 1273, 1109, 808 cm^{-1}. ^{1}H NMR: (400 MHz, $CDCl_3$): δ = 1.44 (1 H, dd, *J* = 13.0, 7.5 Hz, H-4), 1.80–1.89 (2 H, m, H-9, H-10), 1.91–1.99 (2 H, m, H-9, H-10), 2.96 (1 H, dd, *J* = 13.0, 8.0 Hz, H-4), 2.97 (3 H, s, -CH_3), 3.34 (2 H, t, *J* = 6.0 Hz, 2 × H-8), 4.35 (1 H, ddt, *J* = 8.0, 7., 2.0 Hz, H-3), 5.91 (1 H, dd, *J* = 5.5, 1.5 Hz, -CH=CH-), 5.93 (1 H, dd, *J* = 5.5, 2.5 Hz, -CH=CH-), 7.26 (1 H, d, *J* = 8.0 Hz, H-5′), 7.46 (1 H, dd, *J* = 8.0, 2.5 Hz, H-4′), 8.23 (1 H, d, *J* = 2.5 Hz, H-2′). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.7 (C-9), 35.5 (-CH_3), 35.6 (C-10), 47.3 (C-4), 48.4 (C-3), 50.4 (C-8), 56.9 (C-5), 124.1 (C-5′), 136.9 and 134.8 (C-1, C-2), 137.7 (C-4′), 140.1 (C-6′), 148.9 (C-2′), 149.4 (C-3′), 174.0 (CO). MS (EI$^+$): *m/z* (%) = 278, 276 (100) [M$^+$]. HRMS (EI$^+$): *m/z* calcd for $C_{15}H_{17}{}^{35}ClN_2O$: 276.1029; found: 276.1022. Anal. Calcd for $C_{15}H_{17}ClN_2O$: C, 65.19; H, 6.20; N, 10.14. Found: C, 65.25; H, 6.11; N, 10.24.

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(15) Alkene isomerisation under basic conditions (*t*-BuOK, DME, 60 °C) was observed but this could not be controlled and an inseparable 1:1 mixture of regioisomers was obtained.

(16) ^{1}H NMR and ^{13}C NMR data for spirolactams **12a**–**d** (all compounds were characterized by IR, microanalysis and/or HRMS).
Compound **12a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.05 (2 H, m), 2.39 (1 H, ddd, *J* = 17.0, 2.5, 2.5 Hz), 2.60 (1 H, d, *J* = 16.0 Hz), 3.00 (1 H, dddd, *J* = 17.0, 2.5, 2.5, 2.5 Hz), 3.25 (1 H, dddd, *J* = 16.0, 2.5, 2.5, 2.5 Hz), 3.32 (2 H, t, *J* = 6.5 Hz), 6.03–6.06 (1 H, m), 7.20–7.41 (5 H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.0, 35.8, 43.8, 43.9, 46.4, 50.1, 123.1, 125.4, 127.0, 128.2, 135.9, 140.1, 178.5.
Compound **12b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.54 (1 H, ddt, *J* = 13.0, 6.5, 2.5 Hz), 1.88–1.98 (3 H, m), 2.18 (1 H, dt, *J* = 17.0, 2.5 Hz), 2.24–2.31 (1 H, m), 2.36–2.45 (1 H, m), 2.82 (1 H, dd, *J* = 17.0, 2.5 Hz), 2.90 (3 H, s), 3.32–3.34 (2 H, m), 3.34 (1 H, dd, *J* = 8.0, 2.0 Hz), 6.12 (1 H, dt, *J* = 5.0, 2.0 Hz), 7.20–7.37 (5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.5, 27.9, 29.3, 29.7, 34.4, 43.2, 45.9, 122.9, 125.3, 126.6, 128.0, 134.2, 141.8, 178.5
Compound **12c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.78–1.92 (4 H, m), 2.42 (1 H, ddd, *J* = 17.0, 2.5, 2.5 Hz), 2.58 (1 H, d, *J* = 15.5 Hz), 3.18 (1 H, dddd, *J* = 17.0, 2.5, 2.5, 2.5 Hz), 3.35 (2 H, t, *J* = 6.5 Hz), 3.42 (1 H, dddd, *J* = 15.5, 2.5, 2.5, 2.5 Hz), 6.02–6.06 (1 H, m), 7.20–7.40 (5 H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.9, 35.5, 35.8, 46.3, 48.1, 50.2, 122.5, 125.5, 126.7, 128.2, 136.2, 139.6, 175.7.
Compound **12d**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.63 (1 H, dddd, *J* = 9.0, 4.5, 2.0, 2.0 Hz), 1.67–1.74 (1 H, m), 1.76–1.85 (3 H, m), 2.15–2.20 (3 H, m), 2.28 (1 H, dt, *J* = 16.0, 2.0 Hz), 2.97 (3 H, s), 3.08 (1 H, dt, *J* = 16.0, 2.0 Hz), 3.27–3.32 (2 H, m), 6.07 (1 H, dt, *J* = 5.0, 2.0 Hz), 7.21–7.38 (5 H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2, 22.3, 29.0, 30.1, 35.4, 35.9, 40.5, 50.3, 122.5, 125.0, 126.7, 128.2, 134.7, 142.4, 175.8.