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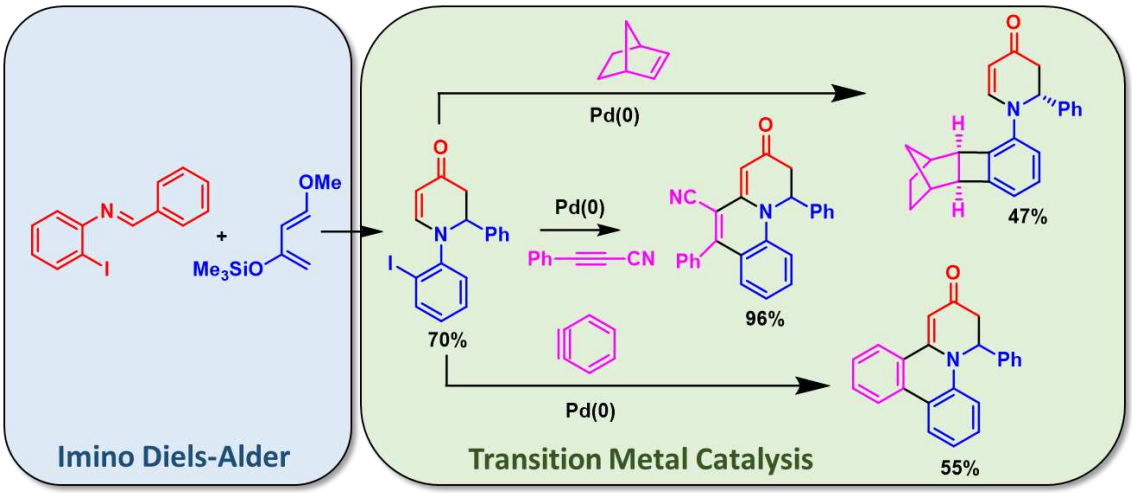
Imino Diels-Alder/Transition Metal Catalyzed Reactions to Synthesise Fused Ring Heterocycles

Connor J. Taylor, Alexander Alter, Christopher M. Pask, Visuvanathar Sridharan*
School of Chemistry, University of Leeds, LS2 9JT, UK.
V.Sridharan@leeds.ac.uk



Abstract:

Imino Diels-Alder reactions were tactically combined with various transition metal catalysed [2+2], [3+2] and [4+2] cycloaddition reactions to form novel syntheses for biologically relevant fused-ring heterocycles with molecular complexity in good yields.

Keywords:

Imino Diels-Alder, catalysis, palladium, cycloaddition, Heck reaction.

1 Introduction

[2,3]-Dihydropyridone and tetrahydroquinoline heterocycles are important structural skeletons as they can provide the structural backbone to many bioactive molecules (Figure 1).[1-4]

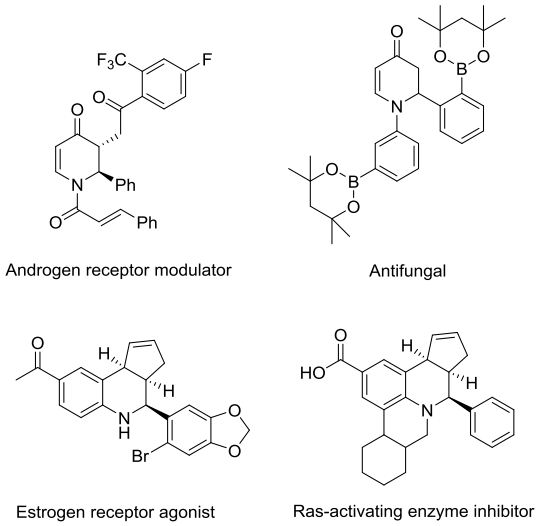
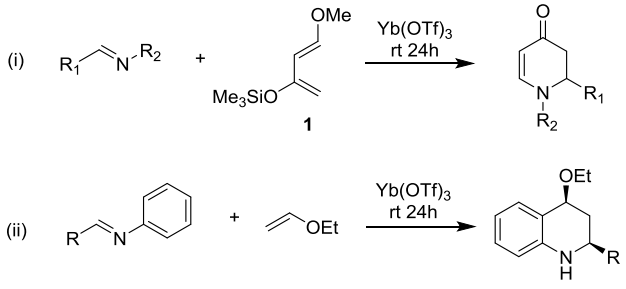


Figure 1: Examples of bioactive molecules featuring an N-heterocycle as a structural skeleton.

There are several methods of constructing these six membered nitrogen-containing heterocycles, although one of the most powerful tools is the imino Diels-Alder reaction. This reaction allows the synthesis of various pyridines and quinolines using dienes and dienophiles, whilst maintaining functionality of attached functional groups. The remaining functionality of the imino Diels-Alder adducts can then be exploited to achieve further structural complexity, and hence have more potential for bioactivity.

These imino Diels-Alder reactions are often catalysed by either Brønsted acids or Lewis acids such as $BF_3{\cdot}OEt_2$ or lanthanide triflates (Scheme 1).[5-7]



Scheme 1: Typical imino Diels-Alder syntheses catalysed by lanthanide triflates.

Tactical pre-selection of starting materials prior to imino Diels-Alder synthesis then results in heterocycles that can be functionalised at specific points within the resulting molecule. The use of transition metal catalysed reactions is then an attractive methodology for this functionalisation. The ability to construct complicated molecules from readily accessible starting materials, whilst using mild conditions is very appealing, especially in the formation of C-C bonds.[8, 9] There are many examples of

using transition metals for different organometallic transformations, with notable examples and reviews reported on palladium,[10-14] rhodium,[15-18] copper[19-21] and many more.[22-24]

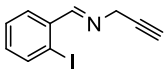
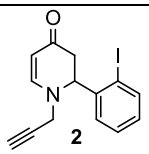
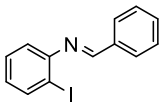
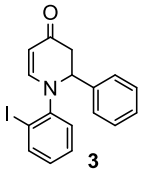
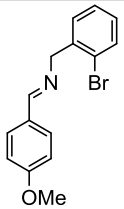
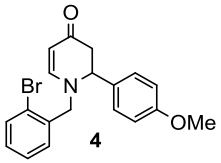
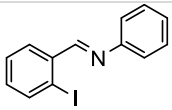
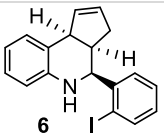
In this article we wish to report tactical combinations of the imino Diels-Alder reaction with transition metal catalysed processes. The examples presented show multiple ways in which further molecular complexity can be attained, by decorating the heterocyclic scaffolds using various transition metal catalysed processes.

2 Results and discussion

Imino Diels-Alder adducts were combined with: (i) rhodium catalysed [2+2+2] cycloaddition reaction[25] or copper catalysed click reaction[26] and (ii) palladium catalysed strained alkene/aryne/alkyne insertion,[27-33] (iii) intramolecular Heck reaction[34] and (iv) palladium catalysed carbonylation[35] reaction to form novel fused-ring heterocycles analogues to the Estrogen receptor agonist shown in Figure 1.

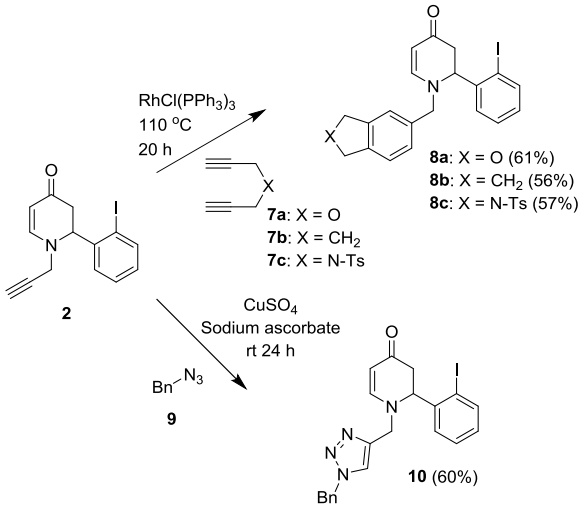
Initially we carried out the reactions of the imino Diels-Alder process to generate several structural skeletons on which to build further molecular complexity (Table 1). The reaction of the dienophile for each entry in Table 1 was conducted on a 1 mmol scale with an excess of diene (1.5 mmol) and $Yb(OTf)_3$ (20 mol %), in toluene (30 mL) at room temperature for 24 h which afforded the imino Diels-Alder products in good yields (Table 1, entries 1-4). The Povarov reaction product was seen exclusively in entry 4.

Table 1. Imino Diels-Alder reactions that were performed.[a]

Entry	Dienophile	Diene	Product[c]	Yield (%)[b]
1		**1**	 **2**	74
2		**1**	 **3**	70
3		**1**	 **4**	49
4		 **5**	 **6**	88

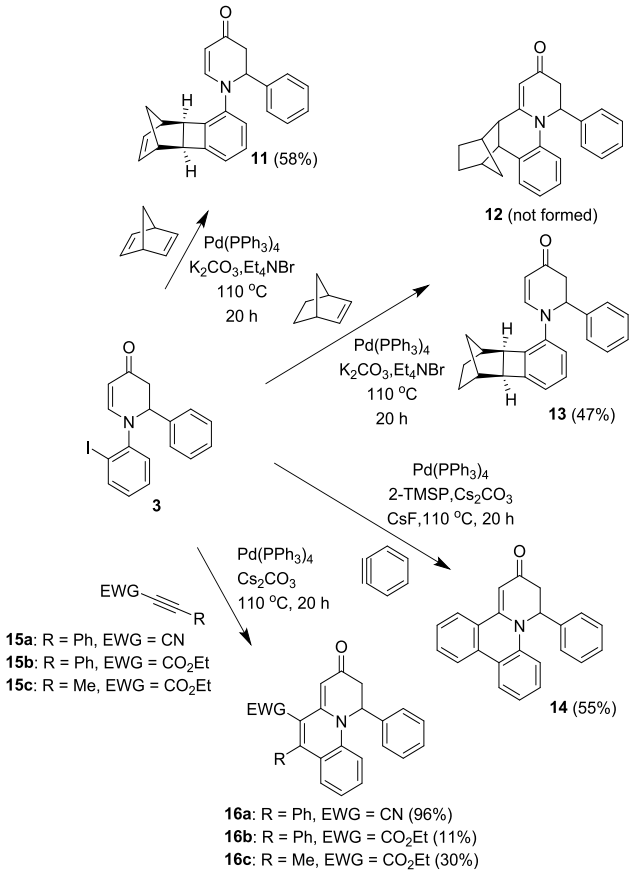
a: Dienophile (1 mmol), diene (1.5 mmol), $Yb(OTf)_3$ (20 mol %), acetonitrile, room temperature, 24 h. b: Isolated yield. c: racemic mixtures generated.

Next, we explored the feasibility of increasing the molecular complexity of the imino Diels-Alder product **2** by taking advantage of the alkyne, by means of the rhodium catalysed [2+2+2] cycloaddition and the copper catalysed click reaction, where both processes achieved products in good yields (Scheme 2). In the case of the rhodium catalysed [2+2+2] reaction, where X = O, CH_2, imino Diels-Alder product **2** (0.1 mmol), dipropargyl ether **7a** or 1,6-heptadiyne **7b** (0.1 mmol) and $RhCl(PPh_3)_3$ (10 mol %) were stirred in toluene at 110 °C for 20 h affording the [2+2+2] cycloaddition products **8a** and **8b** in 56-61% yield. The N-tosyl dipropargylamine **7c** (0.3 mmol), imino Diels-Alder product **2** (0.3 mmol) and $RhCl(PPh_3)_3$ (10 mol %) in toluene at 110 °C for 20 hours afforded the [2+2+2] cycloaddition product **8c** in 57% yield. For the copper catalysed click reaction, imino Diels-Alder product **2** (0.1 mmol), benzyl azide **9** (0.1 mmol), sodium ascorbate (0.1 mmol) and $CuSO_4$ (20 mol %) in $^tBuOH/H_2O$ (1:1, 20 mL) and stirred at room temperature for 24 h afforded the [3+2] cycloaddition product 10 in 60% yield. In both of these transition metal catalysis examples, the 2-iodophenyl group could be further exploited to achieve further molecular complexity with the potential for bioactivity.



Scheme 2: Alkyne functionalisation by using a rhodium catalysed [2+2+2] reaction and a copper catalysed click reaction.

Further exploration of the feasibility of increasing molecular complexity was carried out using the imino Diels-Alder product **3**, by means of palladium catalysed cycloaddition reaction (Scheme 3). In the case of the strained alkene insertion, **3** (0.1 mmol), norbornadiene (0.2 mmol), $Pd(PPh_3)_4$ (10 mol %), potassium carbonate (0.2 mmol) and tetraethylammonium bromide (0.2 mmol) in toluene (10 mL) at 110 °C for 20 h afforded the formal [2+2] cycloadduct **11** as a single diastereoisomer in 58% yield instead of the formal [4+2] cycloadduct product **12**. The analogous reaction with norbornene gave the formal [2+2] cycloadduct **13** in 47% yield.



Scheme 3: The different palladium catalysed reactions that were explored in this study, including an alkene insertion, a benzyne insertion and an alkyne insertion.

Next we explored further decoration of the imino Diels-Alder adduct using an aryne insertion reaction. Thus, imino Diels-Alder product **3** (0.1 mmol), 2-trimethylsilylphenyl triflate (2-TMSP) (0.15 mmol), $Pd(PPh_3)_4$ (10 mol %), CsF (0.2 mmol) and Cs_2CO_3 (0.2 mmol) in toluene (10 mL) at 110 °C for 24 h afforded the formal [4+2] cycloadduct **14** in 55% yield. Then when varying the R and EWG groups within the alkyne insertion transformation, **3** (0.1 mmol), alkyne **15a** (0.2 mmol), $Pd(PPh_3)_4$ (10 mol %) and Cs_2CO_3 (0.2 mmol) in toluene (10 mL) at 110 °C for 20 h afforded the formal [4+2] cycloadduct **16a** in 96% yield. This cycloaddition adds further complexity to the molecule, where bioactivity has been shown to be present in scaffolds of this kind.[36]

The structure of **13** was confirmed by single crystal X-ray diffraction (Figure 2).[37] These results suggest either the formation of the five membered palladacycle **17** is faster than the formation of the five membered palladacycle **18** and the seven membered palladacycles **19** and **20**, or that the reductive elimination steps from **18-20** are significantly slower than that of palladacycle **17** (Figure 3). Ar-Pd-I insertion into norbornene is likely to be faster than the intramolecular C-H insertion process, favouring the pathway via the palladacycle **17**, which gives the four membered ring as **13**. Formation of the palladacycle **19** may also be slower due to steric factors.

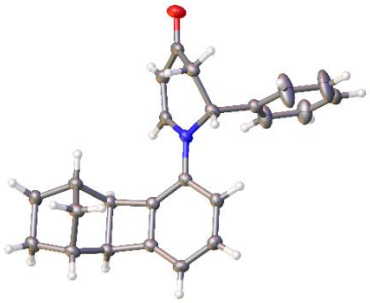


Figure 2. A crystal structure confirming the molecular structure of compound **13**.

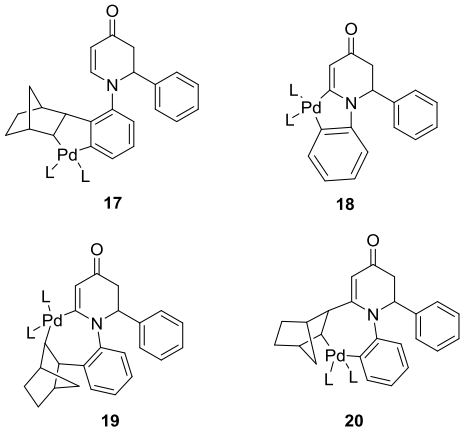
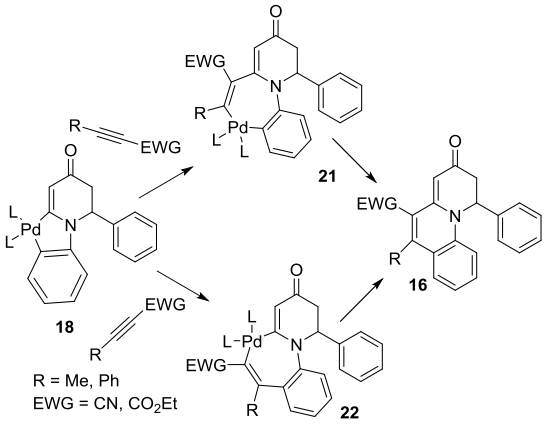


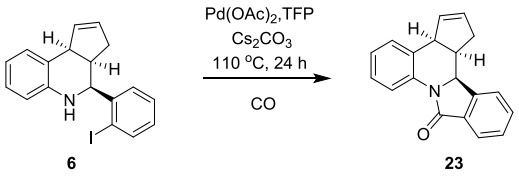
Figure 3. Different potential palladacycles involved in the reaction with norbornene .

Unsymmetrical alkynes can undergo highly regioselective migratory insertion into **18** to give either palladacycle **21** or **22**, resulting in the formation of the single regioisomer **16** shown in Scheme 4.[38, 39] The regiochemistry of **16a,c** was confirmed by NOESY experiment. Use of alkynes **15b,c** in the above reaction resulted in lower yields of the product **16b,c** partly due to the purification of the products from triphenylphosphine oxide via column chromatography. These yields could be increased by using other purification methods such as recrystallization.



Scheme 4: The suggested palladacycles for the studied unsymmetrical alkyne insertions.

We also briefly explored a carbonylation reaction, shown in Scheme 5. The Povarov reaction product **6** (0.1 mmol), $Pd(OAc)_2$ (10 mol %), tri(2-furyl)phosphine (20 mol %) and Cs_2CO_3 (0.2 mmol) in toluene (10 mL) at 110 °C for 24 h with a balloon containing carbon monoxide attached to the condenser afforded **23** in 67% yield.



Scheme 5: The studied palladium catalysed carbonylation reaction.

In summary, we have successfully shown examples of how the imino Diels-Alder reaction can be integrated into tactical syntheses with transition metal catalysis to form highly complex molecules with the potential for bioactivity in good yields. Further exploration into the area could be conducted by the addition of decorated aryls and heteroaryls to imino Diels-Alder adducts to afford more complex heterocycles with bioactivity potential.

3 Materials and methods

3.1 General Experimental Information

Unless otherwise stated all chemicals were obtained commercially with no additional purification. Chromatography columns were prepared using Geduran Silicagel 60 (40 - 63 µm) silica powder. Nuclear magnetic resonance spectra were recorded using 500 MHz (^{1}H) and 125 MHz (^{13}C) upon a Bruker Avance 500 spectrometer in each case. Unless otherwise stated all NMR were obtained in deuterated chloroform at room temperature (25 °C). NMR chemical shifts are reported in parts per million (ppm) (δ) compared against tetramethylsilane as an internal reference unless otherwise stated. Abbreviations used: Ar = aromatic, d = doublet, dd = double doublet, dt = double triplet, m = multiplet, q = quartet, s = singlet, t = triplet. Accurate molar masses were obtained using a maXis impact spectrometer employing ESI (electrospray ionisation) 46 technique in positive ion polarity mode. Infra-red spectra were obtained using a FT-IR ATR Bruker Alpha spectrometer. Melting points are uncorrected.

3.2.1 General Procedure 1 for imino Diels-Alder synthesis

An imine (1 mmol), Danishefsky's diene (1.5 mmol) and $YbOTf_3$ (0.2 mmol, 20 mol %) were then added to toluene (30 mL) and stirred (r.t. 24 h). The reaction was monitored by LC-MS and TLC. The crude mixture was evaporated and dissolved in dichloromethane (5 mL) and purified using column chromatography monitored by TLC.

3.2.2 rac-(S)-2-(2-iodophenyl)-1-(prop-2-ynyl)-2,3-dihydropyridin-4(1H)-one (2)

Prepared using general procedure **1** on a 1 mmol scale using the imine *N*-[(2-iodophenyl)methylene]-2-propyn-1-amine. The crude mixture was then purified using column chromatography, eluting ethyl acetate:hexane/60:40 v/v to give the isolated product as a yellow amorphous solid with a yield of 250 mg, 74% (m.p. 109 °C). δH ppm (500 MHz $CDCl_3$); 7.88 (d, 1H, J 8.0 Hz, N-CH=C), 7.42 (d, 1H, J 7.3 Hz, ArH), 7.38 (t, 1H, J 7.3 Hz, ArH), 7.28 (d, 1H, J 7.8 Hz, ArH), 7.03 (t, 1H, J 7.8 Hz, ArH), 5.20 (d, 1H, J 8.0 Hz, =CH-CO), 5.06 (dd, 1H, J 10.5/6,6 Hz, N-CH), 3.82 (dd, 1H, J 17.6/2.5 Hz, N-CH*H*), 3.73 (dd, 1H, J 17.6/2.1 Hz, N-C*H*H), 2.84 (dd, 1H, J 16.5/6.4 Hz, CH*H*), 2.62 (dd, 1H, J 16.5/10.5 Hz, C*H*H), 2.42 (t, 1H, J 2.0 Hz, C≡CH); δC ppm (125 MHz, $CDCl_3$); 190.4, 153.7, 140.6, 140.1, 130.1, 129.0, 127.3, 101.8, 98.4, 75.1, 65.3, 60.4, 42.6; H.R.M.S [ES+] found MH+ 337.923 $C_{14}H_{13}INO$ requires 337.9220 ; υ_{MAX}/cm^{-1}; 3210, 2113, 1622, 1571.

3.2.3 rac-(S)-1-(2-iodophenyl)-2-phenyl-2,3-dihydropyridin-4(1H)-one (3)

Prepared using general procedure **1** on a 1 mmol scale using the imine 2-iodo-*N*-(phenylmethylene)-benzenamine. The crude mixture was then purified using column chromatography, eluting ethyl acetate:hexane/80:20 v/v to give the isolated product as an orange

amorphous solid with a yield of 262 mg, 70% (m.p. 112 °C). δH ppm (500 MHz $CDCl_3$); 7.86 (d, 1H, J 8.3 Hz, N-CH=C), 7.27 (m, 6H, ArH), 7.24 (d, 1H, J 7.1 Hz, ArH), 7.16 (t, 1H, J 7.6 Hz, ArH), 7.10 (d, 1H, J 7.8 Hz, ArH), 5.29 (d, 1H, J 8.3 Hz, =CH-CO), 5.13 (t, 1H, J 7.6 Hz, CH-N), 3.10 (brs, 1H, CH*H*), 3.00 (brs, 1H, C*H*H); δC ppm (125 MHz, $CDCl_3$); 191.1, 152.9, 146.4, 140.3, 138.4, 129.1, 128.7, 128.3, 127.6, 100.9, 97.8, 63.9, 41.7; H.R.M.S [ES+] found MH+ 376.0189 $C_{17}H_{15}INO$ requires 376.01928; υ_{MAX}/cm^{-1}; 3053, 1623, 1560.

3.2.4 rac-(2S)-1-[(2-bromophenyl)methyl]-2-(4-methoxyphenyl)-1,2,3,4-tetrahydropyridin-4-one (4)

Prepared using general procedure **1** on a 1 mmol scale using 2-bromo-*N*-methoxybenzylidene aniline as the imine. The crude mixture was then purified using column chromatography, eluting ethyl acetate:hexane/80:20 v/v to give the isolated product as a colourless oil with a yield of 180 mg, 49%. δH ppm (500MHz $CDCl_3$); 7.54 (dd, 1H, J 7.9Hz, 1.02Hz, C=CH-N), 7.35 (td, 1H, J 7.4Hz, 1.0Hz, ArH) 7.27 (m, 1H, ArH), 7.23 (m, 1H, ArH), 7.17 (m, 2H, ArH), 6.87 (m, 1H, ArH), 6.80 (d, 2H, J 7.5Hz, ArH), 5.08 (d, 1H, J 7.7Hz, C=CH-CO), 4.53 (t, 1H, J 7.0Hz, N-CH), 4.34 (s, 2H, N-CH_2), 3.89 (s, 3H, Ar-O-CH_3), 2.92 (dd, 1H, J 16.4Hz, 7.2Hz, NC-CH*H*), 2.67 (dd, 1H, J 16.4Hz, 6.9Hz, NC-C*H*H); δC ppm (125MHz, $CDCl_3$); 190.4, 159.6, 153.9, 135.3, 133.5, 130.4, 129.7, 129.5, 128.3, 127.8, 123.9, 114.5, 98.6, 67.1, 60.5, 57.0, 55.4, 43.6, 29.7; H.R.M.S [ES+] found MH+ 372.0597 $C_{19}H_{19}BrNO_2$ requires 372.0593; υ_{MAX}/cm^{-1}; 3057, 2957, 2835, 1733, 1636, 1577.

3.2.5 rac-(3aR,4S,9bS)-4-(2-iodophenyl)-3a,4,5,9b-tetrahydro-3H-cyclopenta[c]quinolone (6)

Prepared using general procedure **1** on a 1 mmol scale using the imine 2-iodo-*N*-(phenylmethylene)-benzenamine and using cyclopentadiene in replacement of Danishefsky's diene. The crude mixture then was purified using column chromatography, eluting ethyl acetate:hexane/80:20 v/v to give the isolated product as an orange-brown amorphous solid with a yield of 328 mg, 88% (m.p. 139 °C). δH ppm (500 MHz $CDCl_3$); 7.87 (d, 1H, J 7.6 Hz, ArH), 7.58 (d, 1H, J 7.6 Hz, ArH), 7.39 (t, 1H, J 7.6 Hz, ArH), 7.08 (d, 1H, J 7.6 Hz, ArH), 7.00 (t, 2H, J 7.6 Hz, ArH), 6.77 (t, 1H, J 7.6 Hz, ArH), 6.64 (d, 1H, J 7.6 Hz, ArH), 5.87 (brs, 1H, =CH), 5.65 (brs, 1H, =CH), 4.81 (d, 1H, J 3.0 Hz, N-CH), 4.16 (d, 1H, J 9.2 Hz, =C-CH), 3.64 (brs, 1H, NH), 3.26 (m, 1H, CH*H*), 2.62 (m, 1H, CH), 1.72 (m, 1H, C*H*H); H.R.M.S [ES+] found MH+ 374.0405 $C_{18}H_{17}IN$ requires 374.040; υ_{MAX}/cm^{-1}; 3337, 2919, 1494.

3.2.6 rac-(S)-1-((1,3-dihydroisobenzofuran-5-yl)methyl)-2-(2-iodophenyl)-2,3-dihydropyridin- 4(1H)-one (8a)

2 (0.1 mmol), propargyl ether (0.1 mmol) and Wilkinson's catalyst (0.01 mmol, 10 mol %) were added to toluene (20 mL) and stirred under reflux (110 °C, 20 h). The reaction was monitored by LC-MS and TLC. The crude mixture was concentrated and dissolved in dichloromethane (5 mL) and purified using column chromatography, eluting ethyl acetate:hexane/80:20 v/v to give the isolated product as a pale brown oil with a yield of 26 mg, 61%. δH ppm (500 MHz $CDCl_3$); 7.84 (d, 1H, J 8.7 Hz, N-CH=C), 7.55 (t, 1H, J 7.6 Hz, ArH), 7.38 (d, 1H, J 7.3 Hz, ArH), 7.35 (d, 1H, J 7.8 Hz, ArH), 7.22 (d, 1H, J 7.8 Hz, ArH), 7.02 (m, 2H, ArH), 6.94 (s, 1H, ArH), 5.10 (s, 4H, O-(CH2)2), 5.09 (d, 1H, J 8.7 Hz, =CH-CO), 4.78 (t, 1H, J 7.6 Hz, N-CH), 4.33 (d, 1H, J 14.9 Hz, N-CH*H*), 4.11 (d, 1H, 14.9 Hz, N-C*H*H), 2.82 (dd, 1H, J 16.7/7.6 Hz, CH*H*-CO), 2.57 (dd, 1H, J 16.7/7.6 Hz, C*H*H-CO); δC ppm (125 MHz, $CDCl_3$); 154.2, 140.4, 140.2, 139.6, 134.5, 132.2, 131.9, 130.0, 129.0, 128.6, 128.4, 127.6, 127.4, 121.6, 121.0, 99.1, 73.3, 64.1, 57.5, 41.9; H.R.M.S [ES+] found MNa+ 454.0272. $C_{20}H_{18}INO_2Na$ requires 454.0274; υ_{MAX}/cm^{-1}; 2849, 1634, 1578.

3.2.7 rac-(S)-1-((2,3-dihydro-1H-inden-5-yl)methyl)-2-(2-iodophenyl)-2,3-dihydropyridin-4(1H)-one (8b)

2 (0.1 mmol), 1-6-heptadiyne (0.1 mmol) and Wilkinson's catalyst (0.01 mmol, 10 mol %) were added to toluene (20 mL) and stirred under reflux (110 °C, 20 h). The reaction was monitored by LC-MS and TLC. The crude mixture was concentrated and dissolved in dichloromethane (5 mL) and

purified using column chromatography, eluting 100% ethyl acetate to give the isolated product as a pale brown oil with a yield of 24 mg, 56%. δH ppm (500 MHz $CDCl_3$); 7.87 (d, 1H, J 8.0 Hz, N-CH=C), 7.51 (d, 1H, J 7.8 Hz, ArH), 7.39 (d, 1H, J 7.6 Hz, ArH), 7.37 (d, 1H, J 7.6 Hz, ArH), 7.23 (d, 1H, J 7.6 Hz, ArH), 7.04 (t, 1H, J 7.6 Hz, ArH), 6.98 (s, 1H, ArH), 6.91 (d, 1H, J 7.6 Hz, ArH), 5.10 (d, 1H, J 8.0 Hz, =CH-CO), 4.85 (t, 1H, J 7.6 Hz, N-CH), 4.32 (d, 1H, J 14.4 Hz, N-CH*H*), 4.08 (d, 1H, J 14.4 Hz, N-C*H*H), 2.93 (t, 4H, J 7.0 Hz, C-(CH2)2), 2.87 (dd, 1H, J 16.7/7.8 Hz, CH*H*-CO), 2.58 (dd, 1H, J 16.7/7.1 Hz, C*H*H-CO), 2.12 (t, 2H, J 7.0 Hz, C-CH2-C); δC ppm (125 MHz, $CDCl_3$); 189.7, 154.1, 145.3, 144.7, 140.4, 132.9, 129.8, 128.9, 127.5, 126.2, 124.9, 124.4, 98.6, 64.1, 58.0, 41.8, 32.8, 32.6, 25.5; H.R.M.S [ES+] found MNa+ 452.0487.069 $C_{21}H_{20}INONa$ requires 452.0481; υ_{MAX}/cm^{-1}; 2847, 1630, 1576.

3.2.8 rac-(S)-2-(2-iodophenyl)-1-((2-tosylisoindolin-5-yl)methyl)-2,3-dihydropyridin-4(1H)-one (8c)

Dipropargylamine (2 mmol), *p*-toluenesulfonyl chloride (2 mmol) and trimethylamine (2 mmol) were added to toluene (40 mL) and stirred (0 °C, 24 h). The resulting protected dipropargylamine (0.3 mmol), **2** (0.3 mmol) and Wilkinson's catalyst (0.03 mmol, 10 mol %) were added to toluene (30 mL) and stirred under reflux (110 °C, 20 h). The reaction was monitored by LC-MS and TLC. The crude mixture was concentrated and dissolved in dichloromethane (5 mL) and purified using column chromatography, eluting 100% ethyl acetate to give the isolated product as a brown amorphous solid with a yield of 33 mg, 57% (m.p. 95 °C). δH ppm (500 MHz $CDCl_3$); 7.71 (d, 2H, J 8.0 Hz, ArH), 7.38 (d, 1H, J 7.9 Hz, N-CH=C), 7.31-7.21 (m, 5H, ArH), 7.07 (d, 1H, J 7.8 Hz, ArH), 6.92 (t, 1H, J 8.9 Hz, ArH), 6.90 (d, 1H, J 8.3 Hz, ArH), 6.76 (s, 1H, ArH), 5.00 (d, 1H, J 7.9 Hz, =CH-CO), 4.59 (t, 1H, J 7.8 Hz, N-CH), 4.54 (m, 4H, N-(CH2)2), 4.20 (d, 1H, J 14.9 Hz, N-CH*H*), 3.97 (d, 1H, J 14.9 Hz, N-C*H*H), 2.67 (dd, 1H, J 16.7/7.6 Hz, CH*H*-CO), 2.46 (dd, 1H, J 16.7/8.5 Hz, C*H*H-CO), 2.34 (s, 3H, Ph-Me); δC ppm (125 MHz, $CDCl_3$); 189.8, 154.1, 143.8, 140.3, 140.1, 137.2, 136.6, 135.0, 133.7, 130.0, 129.0, 127.8, 127.7, 127.6, 123.3, 122.6, 99.3, 98.7, 77.2, 64.2, 57.4, 53.6, 53.5, 42.0; H.R.M.S [ES+] found MNa+ 607.0522 $C_{27}H_{25}IN_2O_3SNa$ requires 607.0522; υ_{MAX}/cm^{-1}; 2921, 1731, 1635, 1578.

3.2.9 rac-(S)-1-((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-2-(2-iodophenyl)-2,3-dihydropyridin-4(1H)-one (10)

2 (0.1 mmol), benzyl azide (0.1 mmol), sodium ascorbate (0.1 mmol) and CuSO4 (0.02 mmol, 20 mol %) were added to $^tBuOH/H_2O$ (1:1, 20 mL) and stirred (r.t. 24 h). The reaction was monitored by LC-MS and TLC. The crude mixture was concentrated and dissolved in dichloromethane (5 mL) and purified using column chromatography, eluting ethyl acetate:hexane/1:1 v/v to give the isolated product as an orange-brown amorphous solid with a yield of 28 mg, 60% (m.p. 77 °C). δH ppm (500 MHz $CDCl_3$); 7.82 (d, 1H, J 7.8 Hz, N-CH=C), 7.50-7.28 (m, 7H, ArH), 7.22 (s, 1H, N-C=CH-N), 7.00 (t, 1H, J 7.3 Hz, ArH), 5.55 (d, 1H, J 14.9 Hz, N-CH*H*), 5.50 (d, 1H, J 14.9 Hz, N-C*H*H), 5.13 (d, 1H, J 7.8 Hz, =CH-CO), 4.78 (t, 1H, J 7.8 Hz, N-CH), 4.38 (d, 1H, J 15.4 Hz, N-CH*H*-Ph), 4.22 (d, 1H, J 15.4 Hz, N-C*H*H-Ph), 2.77 (dd, 1H, J 16.7/6.9 Hz, CH*H*-CO), 2.56 (dd, 1H, J 16.7/9.3 Hz, C*H*H-CO); δC ppm (125 MHz, $CDCl_3$); 190.0, 154.5, 142.2, 140.4, 140.3, 134.2, 130.0, 129.2, 129.1, 129.0, 128.4, 127.8, 122.6, 100.2, 98.3, 64.8, 54.3, 48.1, 42.3, 29.7; H.R.M.S [ES+] found MNa+ 493.0496 $C_{21}H_{19}IN_4ONa$ requires 493.0495; υ_{MAX}/cm^{-1}; 2922, 1633, 1577.

3.2.10 (2R)-2-phenyl-1-[(2R,9S)-tetracyclo[8.2.1.02,9.03,8]trideca-3(8),4,6,11-tetraen-4-yl]-1,2,3,4-tetrahydropyridin-4-one (11)

3 (0.1mmol, 38mg), norbornadiene (0.2 mmol), $Pd(PPh_3)_4$ (0.01 mmol, 10% mol), potassium carbonate (0.2mmol) and tetraethylammonium bromide (0.2mmol) were added together in toluene (5mL) and stirred (100 °C, 20 hrs). The reaction was monitored by LC-MS and TLC. The crude mixture was concentrated and dissolved in the minimum amount of DCM, and purified using column chromatography, eluting ethyl acetate:hexane/90:10 v/v to give the product as a yellow amorphous solid with a yield of 20mg, 58 % (m.p. 163°C). δH ppm (500 MHz CDCl3); 7.90 (d, 1H, J 7.9Hz, C=H-N), 7.29 (m, 4H, ArH), 7.14 (m, 1H ArH), 6.80 (d, 1H, ArH), 6.65 (d, 1H, J 8.4 Hz, ArH), 6.24 (m, C-CH=C), 6.18 (m, C-C=CH), 5.36 (d, 1H, 7.6Hz, C=CH-CO), 5.32 (dd, 1H, J 7.9Hz, 1.1Hz, N-CH), 3.33 (m, 2H, CH),

3.20 (brs, 1H, CH), 2.80 (m, 2H, CH), 2.50 (*brs*, 1H,CH), 1.30 (d, 1H,CH), 0.9 (d, J 9.5 Hz, 1H, CH); δC ppm (125 MHz, CDCl3); 190.1, 148.5, 147.1, 137.7, 136.8, 136.3, 129.3, 129.0, 129.0, 127.9, 126.1, 126.0, 117.4, 114.9, 102.9, 60.1, 48.3, 47.4, 43.3, 41.5, 41., 41.0; H.R.M.S. [ES+] found MH+ 340.1700 $C_{24}H_{22}NO$ requires 340.1695; υ_{MAX}/cm^{-1}; 3061, 2965, 1646, 1571.

3.2.11 (2R)-2-phenyl-1-[(2R,9S)-tetracyclo[8.2.1.02,9.03,8]trideca-3(8),4,6-trien-4-yl]-1,2,3,4 tetrahydropyridin-4-one (13)

3 (0.1 mmol), norbornene (0.2 mmol), $Pd(PPh_3)_4$ (0.01 mmol, 10 mol %), potassium carbonate (0.2mmol) and tetraethylammonium bromide (0.2 mmol) were added together in toluene (5 mL) and stirred (110 °C, 20 h). The reaction was monitored by LC-MS and TLC. The crude mixture was concentrated and dissolved in the minimum amount of DCM, and purified using column chromatography, eluting ethyl acetate:hexane/40:60 v/v to give the product as a yellow amorphous solid with a yield of 32 mg, 47 % (m.p. 164 °C). δH ppm (500 MHz $CDCl_3$); 7.89 (dd, 1H, J 7.9Hz, 1.2Hz, C=CH-N), 7.30 (m, 4H, ArH), 7.10 (t, 1H, J 8.1Hz, ArH), 6.72 (d, 1H, J 7.2Hz, ArH), 6.62 (d, 1H, J 8.4Hz, ArH), 5.32 (m, 2H, C=CH-CO and N-CH), 5.29 (m,1H, N-CH),3.30 (m, 2H, CH), 2.80 (d, 1H, CH),2.30 (brs , 1H, CH), 2.14 (brs, 1H, CH), 1.59 (m, 2H, CH), 1.27 (m, 1H, CH), 0.96 (d, 1H, J 10.4Hz,CH), 0.83 (d, 1H, J 9Hz,); δC ppm (125 MHz, $CDCl_3$); 147.2, 129.3, 129.0, 127.8, 126.0, 117.4, 114.7, 102.7, 60.0, 51.3, 50.3, 43.2, 36.6, 35.9, 31.9, 27.7, 27.6; H.R.M.S. [ES+] found MH+ 342.1850 $C_{24}H_{24}NO$ requires 342.1852; υ_{MAX}/cm^{-1}; 2940, 2106, 1649, 1574.

3.2.12 rac-(S)-6-phenyl-6H-pyrido[1,2-f]phenanthridin-8(7H)-one (14)

3 (0.1 mmol), 2-trimethylsilylphenyl triflate (0.15 mmol), $Pd(PPh_3)_4$ (0.01 mmol, 10 mol %), CsF (0.2 mmol), Cs_2CO_3 (0.02 mmol) were added to toluene and stirred (110 °C, 24 h). The reaction was monitored by LC-MS and TLC. The crude mixture was concentrated and dissolved in dichloromethane (5 mL) and purified using column chromatography, eluting ethyl acetate:hexane/80:20 v/v to give the isolated product as an orange amorphous solid with a yield of 17 mg, 55% (m.p. 159 °C). δH ppm (500 MHz $CDCl_3$); 8.19 (d, 1H, J 8.3 Hz, ArH), 8.14 (d, 1H, J 8.0 Hz, ArH), 8.00 (d, 1H, J 8.3 Hz, ArH), 7.60 (m, 3H, ArH), 7.47 (t, 1H, J 8.0 Hz, ArH), 7.38 (dd, 1H, J 8.0/2.8 Hz, ArH), 7.27 (t, 1H, J 8.3 Hz, ArH), 7.21-7.07 (m, 4H, ArH), 6.10 (s, 1H, C=CH), 6.00 (d, 1H, J 7.3 Hz, N-CH), 3.30 (dd, 1H, J 16.3/7.6 Hz, CH*H*), 2.86 (d, 1H, J 16.3 Hz, C*H*H); δC ppm (150 MHz, $CDCl_3$); 188.4, 132.2, 132.1, 131.9, 131.9, 131.1, 130.1, 129.1, 128.7, 128.6, 128.5, 127.9, 126.3, 126.2, 123.4, 122.7, 122.3, 114.5, 96.1, 58.1, 41.1, 29.7; H.R.M.S [ES+] found MH+ 324.1378 $C_{23}H_{18}NO$ requires 324.1382; υ_{MAX}/cm^{-1}; 2918, 1615, 1529.

3.2.13 rac-(1S)-3-oxo-1,6-diphenyl-1H,2H,3H-pyrido[1,2-a]quinoline-5-carbonitrile (16a)

3 (0.1 mmol), 3-phenylprop-2-ynenitrile (0.2 mmol), $Pd(PPh_3)_4$ (0.01mmol, 10 mol %) and caesium carbonate (0.2 mmol) were added together in toluene (5 mL) and stirred (110 °C, 20 h). The reaction was monitored by LC-MS and TLC. The crude mixture was concentrated and dissolved in the minimum amount of DCM, and purified using column chromatography, eluting ethyl acetate:methanol /99:1 v/v to give the product as a red amorphous solid with a yield of 36 mg, 96% (m.p. 187 °C). δH ppm (500 MHz $CDCl_3$); 7.53 (m, 3H, ArH), 7.37 (m, 3H, ArH), 7.19 (m, 7H, ArH), 6.94 (m, 1H, ArH), 5.87 (d, 1H, J 9.0Hz), N-CH), 5.76 (s, 1H, C=CH-CO), 3.28 (dd, 1H, J 7.6Hz, 16.5Hz, NC-CH*H*), 2.81 (d, 1H, J 16.5Hz, NC-C*H*H); δC ppm (125 MHz, $CDCl_3$); 187.4, 155.7, 148.7, 140.3, 136.2, 134.3, 134.3, 133.9, 130.2, 130.0, 129.4, 129.1, 129.0, 128.8, 128.8, 128.4, 125.9, 122.9, 121.8, 114.4, 113.8, 106.7, 98.4, 58.5, 41.1, 30.3, 29.7; H.R.M.S. [ES+] found MH+ 375.149 $C_{25}H_{18}N_2O$ requires 375.149; υ_{MAX}/cm^{-1}; 2920, 2850, 1634, 1588.

3.2.14 rac-ethyl (1S)-3-oxo-1,6-diphenyl-1H,2H,3H-pyrido[1,2-a]quinoline-5-carboxylate (16b)

3 (0.1 mmol), ethyl 3-phenylprop-2-ynoate (0.2 mmol), $Pd(PPh_3)_4$ (0.01 mmol, 10 mol %) and caesium carbonate (0.2 mmol) were added together in toluene (3 mL) and stirred (110 °C, 20 h). The reaction was monitored by LC-MS and TLC. The crude mixture was concentrated and dissolved in the

minimum amount of DCM, and purified using column chromatography, eluting ethyl acetate:hexane/80:20 v/v. The product was found to be contaminated with triphenyl phosphine oxide and further purified via HPLC to give the pure product as a yellow amorphous solid with a yield of 4.5 mg, 11% (m.p. 195 °C).For the case of this compound, the ^{13}C NMR was measured using a 600 MHz (JEOL) machine. δH ppm (600 MHz $CDCl_3$); 7.50 (m, 1H, ArH), 7.48 (m, 1H, ArH), 7.39-7.34 (m, 4H, ArH), 7.29-7.26 (m, 5H, ArH), 7.21 (d, 1H, J 8.7Hz, ArH), 7.17 (dd, 1H, J 8.0Hz, 1.42Hz, ArH), 7.00 (t, 1H, J 7.2Hz, ArH), 5.97 (d, 1H, J 7.6Hz, N-CH), 5.26 (s, 1H, C=CH-CO), 4.01 (q, 2H, J 7.2Hz, C(O)O-CH_2), 3.40 (dd, 1H, J 16.5Hz, 7.8Hz, NC-CH*H*), 2.85 (d, 1H, NC-C*H*H, J 16.3Hz), 1.54 (t, 3H, J 7.2Hz, CO_2C-CH_3); δC ppm (150)MHz, $CDCl_3$); 187.3, 165.8, 148.8, 144.0, 139.2, 136.8, 134.7, 132.0, 129.3, 129.2, 129.2, 129.0, 128.8, 128.5, 128.5, 128.1, 127.6, 127.2, 126.2, 122.9, 122.6, 113.5, 97.2, 97.1, 61.8, 58.6, 41.2, 13.6; H.R.M.S. [ES+] found MNa+ 444.1581 $C_{28}H_{23}NO_3Na$ requires 444.1570; υ_{MAX}/cm^{-1}; 2921, 2851, 1721, 1593.

3.2.15 rac-methyl(1S)-5-methyl-3-oxo-1-phenyl-1H,2H,3H-pyrido[1,2-a]quinoline-6-carboxylate (16c)

3 (0.1 mmol), ethyl but-2-ynoate (0.2 mmol) $Pd(Ph_3)_4$ (0.01 mmol, 10 mol %) and caesium carbonate (0.2 mmol) were added together in toluene (3 mL) and stirred (110 °C, 20 h). The reaction was monitored by LC-MS and TLC. The crude mixture was concentrated and dissolved in the minimum amount of DCM, and purified using column chromatography, eluting ethyl acetate:hexane/80:20 v/v to give the product as a yellow amorphous solid with a yield of 10 mg, 30% (m.p. 191 °C). δH ppm (500 MHz $CDCl_3$); 7.62 (d, 1H, J 9.0Hz, ArH), 7.60 (d, 1H, J 8.9Hz, ArH), 7.48 (m, 1H, ArH), 7.40 (m, 1H, ArH), 7.31 (m, 1H, ArH), 7.23-7.03 (m, 4H, ArH), 5.85 (d, 1H, J 9.3Hz, N-CH), 5.04 (s, 1H, C=CH-CO), 4.36 (q, 2H, J 8.9Hz, C(O)O-CH_2), 3.24 (dd, 1H, J 12.0Hz, 4.0Hz, NC-CH*H*), 2.74 (d, 1H, J 12.9Hz, NC-C*H*H), 2.33 (s, 3H, Me), 1.44 (t, 3H, J 7.7Hz, CO_2CH_2-C*H*$_3$); δC ppm (125 MHz, $CDCl_3$); 187.0, 166.8, 148.8, 138.9, 136.7, 132.1, 131.8, 129.1, 128.5, 127.2, 126.0, 125.7, 122.7, 113.7, 96.5, 62.2, 58.2, 41.0, 31.4, 30.2, 29.7, 16.5, 14.1; H.R.M.S. [ES+] found MH+ 360.1594 requires $C_{23}H_{22}NO_3$ requires 360.1594; υ_{MAX}/cm^{-1}; 2922, 2852, 1723, 1596, 1524.

3.2.16 rac-(3aS,13bS,13cR)-13b,13c-dihydro-1H-cyclopenta[c]isoindolo[2,1-a]quinolin-9(3aH)- one (23)

6 (0.1 mmol), $Pd(OAc)_2$ (0.01 mmol, 10 mol %), TFP (0.02 mmol, 20 mol %), Cs_2CO_3 (0.2 mmol) were added to toluene and stirred (110 °C, 24 h) with a balloon containing carbon monoxide attached to the condenser. The reaction was monitored by LC-MS and TLC. The crude mixture was concentrated and dissolved in dichloromethane (5 mL) and purified using column chromatography, eluting ethyl acetate:hexane/1:1 v/v to give the isolated product as a dark brown amorphous solid with a yield of 18 mg, 67% (m.p. 135 °C). δH ppm (500 MHz $CDCl_3$); 8.40 (d, 1H, J 8.3 Hz, ArH), 7.96 (d, 1H, J 7.6 Hz, ArH), 7.63 (t, 1H, J 7.6 Hz, ArH), 7.53 (m, 2H, ArH), 7.27 (m, 2H, ArH), 7.14 (t, 1H, J 7.6 Hz, ArH), 5.86 (m, 1H, C=CH), 5.57 (m, 1H, CH=C), 5.10 (d, 1H, J 4.1 Hz, N-CH), 4.42 (d, 1H, J 8.7 Hz, Ar-CH-C=C), 3.53 (m, 1H, CH), 1.95 (dd, 1H, J 16.5/8.9 Hz,CH), 1.72 (m, 1H,CH); δC ppm (125 MHz, $CDCl_3$); 166.3, 143.2, 141.7, 140.3, 140.3, 135.4, 132.2, 132.1, 129.6, 129.6, 128.8, 128.5, 128.1, 127.3, 124.7, 114.5, 99.6, 88.0, 29.7; H.R.M.S [ES+] found MH+ 274.123 $C_{19}H_{16}NO$ requires 274.122; υ_{MAX}/cm^{-1}; 2914, 1644, 1601.

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