Short stereoselective synthesis of (+)-monocerin *via* a palladium-catalysed intramolecular alkoxycarbonylation

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A concise stereoselective total synthesis of (+)-monocerin has been accomplished using cross metathesis, tandem dihydroxylation- S_N^2 cyclisation and intramolecular alkoxycarbonylation as key steps. Cross-metathesis of 2-iodo-3,4,5-trimethoxyvinylbenzene and (*R*)-hepten-4-ol, followed by tandem dihydroxylation- S_N^2 cyclisation generated a tri-substituted tetrahydrofuran ring. Finally, the dihydroisocoumarin was obtained by an intramolecular alkoxycarbonylation. In this paper, we have developed an expedient operationally simple Pd(OAc)₂/bathocuproine catalysed alkoxycarbonylation under atmospheric pressure of carbon monoxide. The catalytic system developed here can be useful for the synthesis of various dihydroisocoumarins and phthalides.

Keywords: (+)-monocerin, total synthesis, alkoxycarbonylation, palladium, cross metathesis

Epidemiological, clinical, and experimental evidence suggests that many of the therapeutic agents currently used have their roots in natural products.¹ Dihydroisocoumarins and their derivatives occur widely in nature and serve as key intermediates in the synthesis of biologically active molecules.² As these compounds are known to have a wide range of interesting activities such as antifungal, antiallergenic and antimalarial activities, they are regarded as highly attractive targets in organic chemistry. Monocerin is one such compound that has been isolated as an antifungal, insecticidal, antimalarial and phytotoxic secondary metabolite from several fungal sources including Drechslera monoceras and Fusarium larvarum.³ Structural features such as having 2,3,5-trisubstituted tetrahydrofuran unit with an all cis stereochemistry and its potential for application in pharmaceutical industry, meant that monocerin has attracted the attention of many synthetic chemists. Biosynthetically, monocerin was found to have a heptaketide origin and a recent study demonstrated that cis-fused furanobenzopyranones arose by intramolecular nucleophilic trapping of a quinonemethide intermediate by a pendant alcohol.4

Mori *et al.*⁵ first reported the total synthesis of monocerin, followed by Simpson using a radical benzylic bromination to initiate the formation of *cis*-tetrahydrofuran.⁶ Mallreddy *et al.* reported a total synthesis of monocerin and its analogues from D-glucose by using intramolecular C-glycosidation as a

key step.⁷ Recently, Lee *et al.* used a radical cyclisation of a vinyl ether to construct the *cis*-fused sub-unit of monocerin and achieved its total synthesis.⁸ Fujita *et al.* synthesised monocerin *via* a stereoselective oxylactonisation of *ortho*-alkenylbenzoate with chiral hypervalent iodine.⁹ Through intramolecular trapping of quinonemethide by She *et al.*^{10,11} and copper mediated tandem cyanation-lactonisation by Nookaraju *et al.*¹² we synthesised a monocerin. Herein, we report a short stereoselective total synthesis of monocerin **1** by a palladium catalysed intramolecular carbonylation using carbon monoxide.

Results and discussion

The retrosynthetic analysis of (+)-monocerin has been presented in Scheme 1. We envisioned that the lactone skeleton of the monocerin 1 could be readily obtained from aryl iodide having trisubstituted tetrahydrofuran with hydroxyl group 2 *via* palladium catalysed intramolecular alkoxycarbonylation. The *cis*-fused tetrahydrofuran 2 can be prepared by a tandem dihydroxylation- S_N^2 cyclisation sequence from 3. The requisite allyl alcohol 3 was obtained by cross metathesis of the allyl alcohol 4 and styrene 5 by using Grubbs 2nd generation catalyst.

The synthesis of (+)-monocerin commenced with the preparation of the homoallylic alcohol **4** by asymmetric allylation of the commercially available butyraldehyde **6** with allyltributylstannane **7** using $Ti(OiPr)_4$ as shown in Scheme



Scheme 1 Retrosynthetic analysis of (+)-monocerin.

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2. 2-Iodo-3,4,5-trimethoxy-1-vinylbenzene **5** was prepared from 3,4,5-trimethoxybenzaldehyde **8** by iodination using *N*-iodosuccinimide/trifluoro acetic acid followed by a Wittig reaction with methyltriphenylphosphonium bromide (Scheme 3). The coupling of the key intermediates **5** and **6** was achieved by a Grubbs cross-metathesis reaction, which led to **3** in 70% yield. Mesylation of **3** with methanesulfonyl chloride in the presence of diisopropylethylamine, gave **10** in excellent yield. Using the procedure reported by Marshall *et al.*¹⁵ the intermediate **10** was converted to the *cis*-substituted tetrahydrofuran **2** by AD-mix- β with a catalytic amount of potassium osmate (VI) in a tandem asymmetric dihydroxylation and S_N2 cyclisation.

The introduction of a carbonyl group into arenes using carbonylation reactions in the presence of a suitable nucleophile is an interesting method among the array of catalytic conversions of aryl halides performed by palladium complexes.¹⁶ The

advantages of this method include the broad availability of substrates and the high tolerance of palladium catalysts of a variety of functional groups.

With 2 in hand, we next set to investigate different reactions to generate the lactone 11 and envisioned that palladium catalysed intramolecular carbonylation would be a good method. Generally, phosphine ligands are used to complex and activate the palladium species. However, the use of such ligands is undesirable because of their toxicity and air as well as moisture sensitive with conversion to, for example, phosphine oxide species.¹⁷ For these reasons, we examined the use of less expensive nitrogen ligands in place of the phosphines. The reaction conditions were optimised using different catalysts in combination with different solvents and bases. First to test the different ligands, we used palladium acetate as catalyst, potassium carbonate as base and DMF as



Scheme 3 Synthesis of (+)-monocerin.

solvent. Tetramethylguanidine, DABCO and bipyridine did not give any product under these reaction conditions (Table 1, entry 1), whereas, 1,10-phenanthroline gave the product in less yield. However, bathocuproine (BCP) gave the desired product in good yield when compared to other phenanthroline ligands (Table 1, entries 2–5). Following further optimisation by using different bases, we found that Cs₂CO₃ gave the product in good yield when compared to other bases used (Table 1, entries 6-8). Amongst the different solvents that were used DMA was found to be the best solvent for the carbonylation (Table 1, entries 9 and 10). Other palladium catalysts used in this study were ineffective only generating the product in low yield (Table 1, entries 11-13). In summary, 11 was generated in good yield via alkoxycarbonylation using Pd(OAc), as catalyst, Cs₂CO₃ as a base, BCP as a ligand and DMA as a solvent. Finally (+)-monocerin was obtained from 11 by partial demethylation with borontribromide in 55% yield and 20% of the starting material recovered. The characterisation data of (+)-monocerin 1 was consistent with that previously reported.

In conclusion, we have achieved a concise stereoselective total synthesis of (+)-monocerin from commercially available starting materials. The intramolecular alkoxy carbonylation described in this paper can be used for the synthesis of a wide variety of dihydroisocoumarins.

Experimental

All chemicals were purchased from Sigma-Aldrich and S.D. Fine Chemicals Pvt. Ltd. and used as received. ACME silica gel (100–200 mesh) was used for column chromatography and thin-

Table 1 Optimisation of the reaction conditions for the intramolecular alkoxycarbonylation with carbon monoxide $^{\rm a}$

	•-<	Pd(OAc)2/ ligand	I		o-<
H ₃ CO		CO (baloon)	→ ^H	^{3CO}	\swarrow
H.CO	И рн	Base, Solvent, 130	°C		<u>`</u> {
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Entry	Catalyst	Ligand	Base	Solvent	Yield (%)
1	Pd(OAc) ₂	L1 or L2 or L3	K ₂ CO ₃	DMF	0
2	Pd(OAc) ₂	L4	K ₂ CO ₃	DMF	26
3	Pd(OAc) ₂	L5	K ₂ CO ₃	DMF	40
4	Pd(OAc) ₂	L6	K ₂ CO ₃	DMF	42
5	Pd(OAc) ₂	L7	K,CO3	DMF	55
6	Pd(OAc) ₂	L7	K ₃ PO ₄	DMF	20
7	Pd(OAc) ₂	L7	NEt ₃	DMF	0
8	Pd(OAc) ₂	L7	Cs ₂ CO ₃	DMF	65
9	Pd(OAc) ₂	L7	Cs ₂ CO ₃	DMS0	25
10	Pd(OAc) ₂	L7	Cs ₂ CO ₃	DMA	72
11	PdCl ₂	L7	Cs ₂ CO ₃	DMA	10
12	Pd(CH ₃ CN) ₂	L7	Cs ₂ CO ₃	DMA	34
13	Pd(acac)2	L7	Cs ₂ CO ₃	DMA	20
NH	4				
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L1	L2	1	L3		L4
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^aReaction conditions: **2** (0.1 mmol), Pd catalyst (3 mol%), ligand (6 mol%), C0 (1 Atm), base (1.2 equiv.), 24 h.

L7

L6

L5

layer chromatography was performed on Merck-precoated silica gel 60- F_{254} plates. All other chemicals and solvents were obtained from commercial sources and purified using standard methods. The IR spectra of all compounds were recorded on a Perkin-Elmer Spectrum GX FTIR spectrometer. The IR values are reported in reciprocal centimetres (cm⁻¹). The ¹H NMR and ¹³C NMR spectra were recorded on a Bruker-Avance 300 MHz spectrometer. Chemical shifts (δ) are reported in ppm, using TMS ($\delta = 0$) as an internal standard in CDCl₃. ESI mass spectra was recorded on AB sciex QTRAP 5500 mass spectrometer.

(R)-Hept-1-en-4-ol (4): To (S,S)-BINOL (0.85 g, 3.1 mmol) in CH₂Cl₂ (8.0 mL) was added Ti(OiPr)₄ (0.67 mL, 2.1 mmol) in the presence of molecular sieves (2.5 g) and stirred at reflux temperature. After 1 h, the reaction mixture was cooled to room temperature and butyaldehyde 6 (1.5 g, 21 mmol) in CH₂Cl₂ was added and stirred for 10 min. After 10 min the reaction mixture was cooled to -78 °C and allyltri-n-butyltin 7 (7 mL, 21 mmol) was added and the reaction was continued for 24 h at -20 °C. After completion of the reaction, saturated aqueous solution of sodium bicarbonate was added to quench the reaction mixture, and then extracted with dichloromethane (3×50) mL). The organic phase was washed with water and dried over Na₂SO₄, and the crude product was purified by column chromatography using hexane and ethyl acetate. Colourless liquid: yield 75%; $[\alpha]_{D}^{25}$ -18.2 (c 1.0, CHCl₃) [lit.¹³[α]²⁵_D -22.5 (c 0.65, CHCl₃)]. IR (neat) max 3250, 2895, 1644, 1501, 1199, 746 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz): δ 0.96 (t, 3H, J = 7.2 Hz), 1.28–1.49 (m, 4H), 2.1–2.29 (m, 2H), 3.56–3.69 (m, 1H), 5.01-5.12 (m, 2H), 5.65-5.75 (m, 1H). ¹³C NMR (CDCl₂, 75 MHz): δ 14.3, 18.6, 40.2, 42.6, 70.9, 115.6, 134.9. ESI MS (m/z): 115 (M + H). Anal. calcd for C₇H₁₄O: C 73.34, H 12.36; found: C 73.15, H 12.52%.

2-Iodo-3,4,5-trimethoxybenzaldehyde (9): Commercially available 3,4,5-trimethoxybenzaldehyde (0.93 g, 5 mmol) and TFA (0.5 mL) was dissolved in acetonitrile (5 mL) and N-iodosuccinimide (1.35 g, 6 mmol) was added in portions over 1 h at 0 °C. The reaction was then continued at room temperature until the completion of reaction was indicated by TLC. It was quenched by the addition of saturated sodium bicarbonate and extracted with ethyl acetate $(3 \times 20 \text{ mL})$. The organic phase was washed with sodium thiosulfate solution, concentrated and the crude product was purified by silica gel column chromatography using hexane/ethyl acetate as an eluent. Half-white solid (1.45 g, 90.6%); m.p.: 65-68 °C [lit.14 67-68 °C]. IR (KBr): 2989, 1685, 1564, 1481, 1380, 1281, 1045, 945 cm $^{-1}.$ $^1\rm H$ NMR (300 MHz, CDCl_3): δ 3.91 (s, 3 H), 3.92 (s, 3 H), 3.98 (s, 3 H), 7.32 (s, 1H), 10.15 (s, 1H). ¹³C NMR (75 MHz, CDCl₂): 56.2, 61.1, 61.2, 91.5, 107.4, 128.8, 148.7, 150.6, 152.9, 190.9. ESI MS (m/z): 323 (M + H). Anal. calcd for C₁₀H₁₁IO₄: C 37.29, H 3.44; found: C 37.35, H 3.61%.

2-Iodo-3,4,5-trimethoxy-1-vinylbenzene (5): Methyltriphenylphosphonium bromide (1.78 g, 5 mmol) and potassium tert-butoxide (1.1 g, 10 mmol) were placed in a round-bottomed flask and dry THF was added under a nitrogen atmosphere. When the reaction turned a deep yellow colour, 2-iodo-3,4,5-trimethoxybenzaldehyde (1.28 g, 4 mmol) was added in THF and the reaction was stirred for 3 h at room temperature. After completion of the reaction, the reaction mixture was filtered and the filtrate was evaporated. The crude product was purified by column chromatography using hexane and ethyl acetate. White solid (0.87 g, 68%); m.p.: 61-63 °C. IR (KBr): 3512, 2918, 1566, 1415, 1375, 1159 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 3.83 (s, 3H), 3.90 (s, 3H), 3.95 (s, 3H), 5.26 (dd, J = 1.2, 11.2 Hz), 5.51 (d, 1H, J = 18.1 Hz), 6.86 (s, 1H), 6.93 (dd, J = 11.2, 18.1 Hz). ¹³C NMR (75 MHz, CDCl₂): 56.3, 60.9, 61.1, 89.2, 106.3, 116.2, 136.1, 141.2, 141.9, 154.1, 154.6. ESI MS (m/z): 321 (M + H). Anal. calcd for C₁₁H₁₃IO₃: C 41.27, H 4.09; found: C 41.29, H 4.11%.

(R,E)-1-(2-Iodo-3,4,5-trimethoxyphenyl)hept-1-en-4-ol (3): To a solution of 2-iodo-3,4,5-trimethoxy-1-vinylbenzene (0.8 g, 2.5 mmol) and (*R*)-hept-1-en-4-ol (0.34 g, 3 mmol) in anhydrous dichloromethane (10 mL) was added Grubbs-II catalyst (250 mg, 6 mol%) and stirred at reflux for 6 h. It was then stirred for an additional 1 h at room temperature in the open air to deactivate the catalyst. The reaction

mixture was filtered through Celite, concentrated, and the residue was purified by column chromatography on silica gel using hexane and ethylacetate as an eluent. Pale yellow solid (0.56 g, 70%); $[\alpha]^{25}_{D} -11.2$ (c 1.2, CHCl₃). M.p.: 58–59 °C. IR (KBr): 3371, 2929, 1718, 1599, 1258, 1021 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 0.96 (t, 3H, *J* = 7.2 Hz), 1.38–1.59 (m, 4H), 1.65–1.67 (m, 1H), 2.19–2.40 (m, 2H), 3.81 (s, 3H), 3.83 (s, 3H), 3.84 (s, 3H), 5.82–5.92 (m, 1H), 6.47 (d, 1H, *J* = 15.6 Hz), 6.69 (s, 1H). ¹³C NMR (75 MHz, CDCl₃): 14.1, 18.9, 26.6, 39.1, 40.8, 56.3, 60.7, 71.2, 106.2, 127.6, 128.9, 129.6, 134.9, 136.9, 152.3, 153.8. ESI MS (*m/z*): 307 (M + H). Anal. calcd for C₁₆H₂₃IO₄: C 47.30, H 5.71; found: C 47.33, H 5.79%.

(R,E)-1-(2-iodo-3,4,5-trimethoxyphenyl)hept-1-en-4-yl *methanesulfonate* (10): To the dichloromethane solution of (R, E)-1-(2-iodo-3,4,5-trimethoxyphenyl)hept-1-en-4-ol (0.5 g, 1.2 mmol), diisopropylethylamine (0.1 mL, 1.5 mmol) was added and stirred for 30 min at room temperature. Methanesulfonyl chloride (0.1 mL 1.5 mmol) was added slowly at 0 °C and the reaction was monitored by TLC. After completion of the reaction, it was diluted with dichloromethane and washed with water, and concentrated. The crude product was purified by column chromatography using hexane and ethyl acetate as eluents. White solid (0.52 g, 95%); $[\alpha]^{25}$ –12.2 (c 1.0, CHCl₃). M.p.: 64-66 °C. IR: 2926, 2855, 1469, 1337, 1168, 1102, 908 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 0.98 (t, 3H, J = 7.2 Hz), 1.39–1.57 (m, 2H), 1.62-1.83 (m, 2H), 2.54-2.65 (m, 2H), 2.94 (s, 3H), 3.82 (s, 3H), 3.83 (s, 3H), 3.86 (s, 3H), 4.77-4.83 (m, 1H), 5.84-5.91 (m, 1H), 6.62 (d, 1H, J = 15.4 Hz), 6.84 (s, 1H). ¹³C NMR (75 MHz, CDCl₂): 13.7, 18.6, 37.0, 38.4, 38.7, 55.7, 60.4, 81.9, 95.9, 105.5, 125.9, 127.1, 136.1, 137.4, 144.1, 151.6, 152.3. ESI MS (m/z): 485 (M + H). Anal. calcd for $C_{17}H_{25}IO_6S$: C 42.16, H 5.20, S 6.62; found: C 42.21, H 5.16, S 6.64%.

(2S, 3aR, 9bR)-6, 7, 8-trimethoxy-2-propyl-2, 3, 3a, 9b-tetrahydro-5H-furo[3,2-c]isochromen-5-one (2): Methane sulfonamide (0.2 g, 2 mmol) and $K_2OsO_2(OH)_4$ (5 mg) were added to AD-mix β (1.4 g) in t-butanol/water (1:1) (9 mL). The solution was stirred thoroughly for 30 min until one phase was present. The reaction mixture was cooled to 0 °C and a solution of (R, E)-1-(2-iodo-3,4,5-trimethoxyphenyl) hept-1-en-4-yl methanesulfonate (0.48 g, 1 mmol) in 1 mL of t-butanol/water (1:1) was added. The reaction mixture was warmed to room temperature over 2 h and stirred overnight. The mixture was quenched with a saturated solution of Na2SO3 and stirred for 1 h. The aqueous layer was extracted with dichloromethane (3 \times 20 mL) and the combined organic extracts were dried over Na₂SO₄, and concentrated under reduced pressure. The product was purified by column chromatography using hexane and ethyl acetate as an eluent. Viscous oil (0.52 g, 95%); $[\alpha]^{25}_{D}$ -32.8 (c 1.0, CHCl₃). M.p.: 64–66 °C. IR: 3451, 2926, 2855, 1469, 1337, 1168, 1102, 908 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 0.98 (t, 3H, J = 7.2 Hz), 1.35–1.61 (m, 4H), 1.65–1.70 (m, 1H), 1.81-1.91 (m, 1H), 2.15-2.28 (m, 1H), 3.81 (s, 3H), 3.83 (s, 3H), 3.84 (s, 3H), 4.41-4.51 (m, 1H), 4.71-4.81 (m, 1H), 5.01-5.12 (m, 1H), 6.98 (s, 1H). ¹³C NMR (75 MHz, CDCl₂): 14.1, 19.2, 37.6, 41.0, 56.3, 60.4, 71.7, 75.4, 84.3, 92.8, 106.8, 132.8, 140.5, 151.6, 152.3. ESI MS (m/z): 423 (M + H). Anal. calcd for C₁₆H₂₅IO₅: C 45.51, H 5.49; found: C 45.49, H 5.56%.

(2S,3aR,9bR)-6,7,8-Trimethoxy-2-propyl-2,3,3a,9b-tetrahydro-5H-furo[3,2-c]isochromen-5-one (11): Compound 2 (0.4 g, 1 mmol), Cs₂CO₃ (0.41 g, 1.2 mmol), Pd (OAc)₂ (3 mol%), bathocuproine (6 mol%) and DMA (3 mL) were placed in an oven-dried flask. The reaction mixture was purged with carbon monoxide and connected with a carbon monoxide balloon through an adaptor. The reaction mixture was heated at 130 °C with vigorous stirring until 2 had been completely consumed as monitored by TLC. The reaction mixture was then allowed to cool to room temperature, diluted with ethyl acetate, filtered through a plug of Celite (eluting with ethyl acetate), and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using hexane/ethyl acetate as an eluent to afford the pure product. Clear oil (231 mg, 72%); $[\alpha]_{D}^{25}$ +13.1 (c 1.0, CHCl₃) [lit¹² $[\alpha]_{D}^{25}$ +23.2 (c 0.56, CHCl₃)]. IR: 3451, 2926, 2855, 1469, 1337, 1168, 1102, 908 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 0.97 (t, 3H, J = 7.2 Hz), 1.36–1.57 (m, 4H), 1.81–1.91 (m, 1H), 2.52–2.60 (m, 1H), 3.85 (s, 6H), 3.95 (s, 3H), 4.35–4.41 (m, 1H), 4.68 (d, 1H, J = 2.4 Hz), 4.92–5.01 (m, 1H), 6.71 (s, 1H). ¹³C NMR (75 MHz, CDCl₃): 14.0, 19.1, 37.5, 38.2, 56.3, 60.8, 61.1, 74.3, 79.2, 90.8, 106.5, 132.4, 141.2, 152.3, 157.4, 169.2. ESI MS (m/z): 323 (M + H). Anal. calcd for C₁₇H₂₂O₆: C 63.34, H 6.88; found: C 63.31, H 6.74%.

(+)-Monocerin (1): To the compound 11 (0.1 g, 0.3 mmol) in dichloromethane, boron tribromide (1.0 M in hexanes, 0.1 mL, 1 mmol) was added at -25 °C. The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction was quenched by the addition of saturated aqueous NaHCO₂ solution and the product was extracted with dichloromethane (3 \times 20 mL). The combined organic phases were washed with water, and dried over Na₂SO₄. The crude product was purified by column chromatography using hexane and ethyl acetate as an eluent. Colourless oil (0.058 g) 55%; $[\alpha]_{D}^{25}$ +54.1 (c 1.0, CHCl₃) [lit.¹² $[\alpha]^{26}_{D}$ +53 (c 1.0, CHCl₃)]. IR: 2973, 2836, 1703, 1633, 1278, 1122, 989 cm⁻¹. ¹H NMR (300 MHz, CDCl₂): δ 0.95 (t, 3H, J = 7.3 Hz), 1.34–1.48 (m, 2H), 1.59–1.66 (m, 1H), 1.69–1.81 (m, 1H), 2.13-2.21 (m, 1H), 2.45-2.62 (m, 1H), 3.83 (s, 3H), 3.95 (s, 3H), 4.12-4.25 (m, 1H), 4.56 (d, J = 3.2 Hz), 5.03-5.12 (m, 1H), 6.61 (s, 1H), 11.25 (s, 1H). ¹³C NMR (75 MHz, CDCl₃): 14.1, 19.1, 37.5, 38.2, 56.1, 60.8, 74.3, 79.2, 81.8, 102.3, 105.0, 132.1, 137.5, 156.2, 157.4, 168.2. ESI MS (m/z): 309 (M + H). Anal. calcd for C₁₆H₂₀O₆: C 62.33, H 6.54; found: C 62.28, H 6.61%.

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