Organic & Biomolecular Chemistry

Dynamic Article Links

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 7913

www.rsc.org/obc

PAPER

Cu(I)-catalyzed tandem benzyldiazoester coupling with terminal alkyne–allene formation–Michael reaction: Application to the syntheses of oxa and azacycles†

Gullapalli Kumaraswamy,* Neerasa Jayaprakash‡ and Guniganti Balakishan‡

Received 9th July 2011, Accepted 31st August 2011
DOI: 10.1039/c1ob06128c

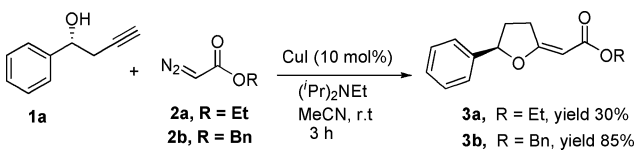
A simple and practical procedure for the synthesis of aza- and oxacycles, which possess an array of stereogenic functionalities, is described. This protocol relies on tandem Cu-catalyzed coupling of suitably functionalized terminal alkyne with diazoester followed by isomerization and subsequent aza or oxa-Michael reaction, thus generating the required scaffold with high diastereoselectivity.

Introduction

Aza- and oxacycles with diverse ring structures possessing pharmacophoric active sites are common structural features of various biologically active natural products.[1] Due to the increasing importance of these compounds, synthetic methods that could provide rapid access to the substituted aza and oxacycles from simple and readily available starting materials are exceedingly desirable. Of the diverse ways to synthesize aza and oxacycles,[2] the most adaptable method is a base initiated oxa- and aza-Michael reaction to electron-deficient alkenes or allenoates.[3] The requisite process in this protocol is the generation of heteroatom tethered electron-deficient allenoates followed by cyclization to give the respective heterocycles. A plethora of synthetic methods has appeared for the generation of electron-deficient allenoates.[4] Recently, Tan and coworkers[5] disclosed an impressive protocol for the synthesis of oxacycles and azacycles from alkynoate by a Brønsted base initiated tandem isomerisation–Michael reaction. The precursor functionalized alkynoates were prepared by a Cu-catalyzed coupling of corresponding terminal alkynes with ethyldiazoacetate in high yield as reported by Suarez and Fu.[6]

Results and discussion

With our continued interest in developing Cu-catalyzed reactions,[7] we envisioned that a one pot tandem process of Cu(I)-catalyzed coupling of diazoesters with terminal alkynes followed by isomerization to allenes and subsequent Michael reaction could provide the required heterocycles in a straightforward approach. With this initiative, we carried out the initial experiment with 3-substituted hydroxy terminal alkyne **1a** and ethyldiazoacetate **2a** in the presence of a catalytic amount of CuI (10 mol%) and Et_3N (20 mol%). After stirring for 24 h at ambient temperature in acetonitrile, the desired product **3a** was isolated with 30% yield along with 6-hydroxyallenoate and unreacted **1a**. The same reaction with one equivalent of Et_3N under otherwise identical conditions increased the product **3a** yield to 75%. After substantial experimentation, benzyldiazoacetate **2b**, and diisopropylethylamine as a base offered a further improvement in terms of yield (**3b**, 85%) and reaction time (3 h) (Scheme 1). Among the solvents tested, only acetonitrile gave a better yield of the desired compound **3b** while other solvents, such as toluene, Et_2O, $ClCH_2CH_2Cl$, DMF and DMSO, either did not initiate the reaction or a multitude of products was observed. A survey of copper salts indicated that CuI and $[Cu(CH_3CN)_4]PF_6$ performed with equal efficiency for this transformation, while CuCl, CuBr and $CuCl_2$ did not initiate the reaction. No trace of the required product **3b** was isolated using DBU, DABCO or inorganic bases such as K_2CO_3, Cs_2CO_3.



Scheme 1 Cu-catalyzed 5-phenyl tetrahydro alkenoate synthesis.

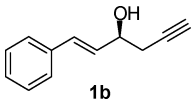
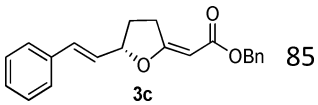
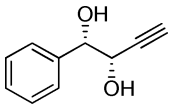
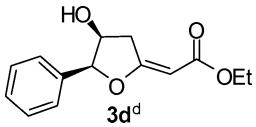
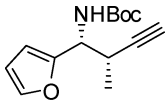
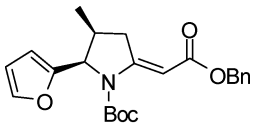
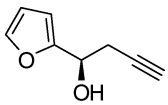
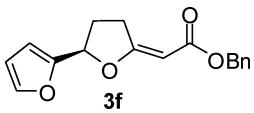
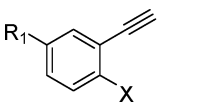
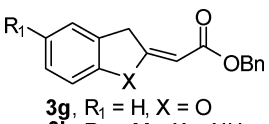
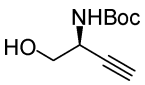
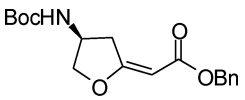
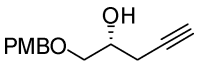
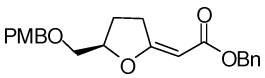
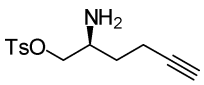
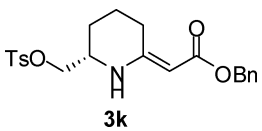
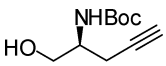
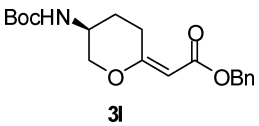
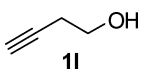
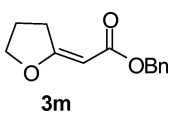
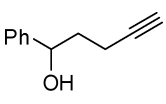
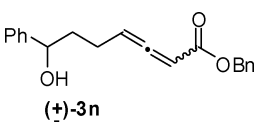
To ensure the generality of this protocol, the scope of the experiment was extended to various terminal alkyne substrates with **2b** under optimized conditions, and the results are summarized in Table 1. Thus, (*S*)-vinylbenzene substituted terminal alkyne (entry 1, Table 1), highly functionalized (*S*,*S*)-1-phenyl-2-hydroxy 3-butyn-1-ol (entry 2, Table 1) and (*R*)-furyl possessing alkyne (entry 4, Table 1) reacted with equal efficiency and the corresponding functionalized tetrahydro-2-ene-benzoates **3c**, **3d**, and **3f** resulted in good yields with complete *E*-selectivity.[5] Similarly, 2-hydroxy phenylacetylene **1f** and 2-hydroxy-5-methyl phenylacetylene **1g** subjected to coupling and cycloisomerization under standard

Organic Division III, Indian Institute of Chemical Technology, Hyderabad, 500 607, India. E-mail: gkswamy_iict@yahoo.co.in; Fax: + 91-40-27193275; Tel: + 91-40-27193154

† Electronic supplementary information (ESI) available: Copies of ^1H and ^{13}C NMR spectra. See DOI: 10.1039/c1ob06128c

‡ N.J. and G.B. made equal contributions to this work

Table 1 Reaction of various substituted aromatic, heteroaromatic and aliphatic terminal alkynes with benzyldiazoacetate **2b** under standard conditions[a]

Entry	Substrate	Product[c,e]	% Yield[b]
1	 **1b**	 **3c**	85
2	 **1c**	 **3d**[d]	89
3	 **1d**	 **3e**	81
4	 **1e**	 **3f**	80
5	 **1f**, R_1 = H, X = OH **1g**, R_1 = Me, X = NH_2	 **3g**, R_1 = H, X = O **3h**, R_1 = Me, X = NH	82 84
6	 **1h**	 **3i**	86
7	 **1i**	 **3j**	88
8	 **1j**	 **3k**	85
9	 **1k**	 **3l**	82
10	 **1l**	 **3m**	73
11	 **(±)-1m**	 **(±)-3n**	75

[a] All reactions were carried out with 1 mmol of substrate, 1.2 mmol of benzyldiazoacetate, 1 mmol of diisopropylethylamine and 0.1 mmol of CuI in MeCN (5 mL) at rt. [b] Yields were isolated but not optimized. [c] All products are fully characterized. [d] Ethyldiazoacetate was employed in place of benzyldiazoacetate. [e] In all cases, only the *E* diastereomer was observed.

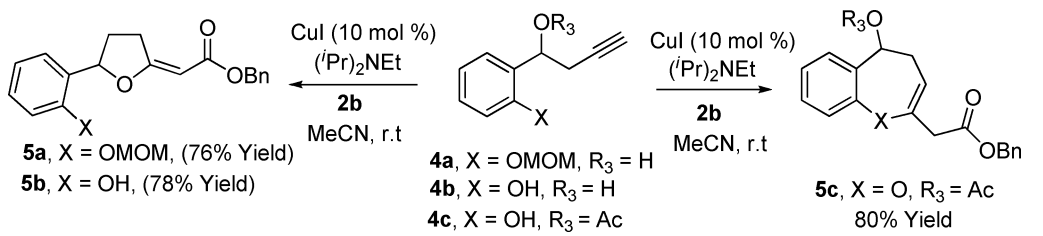
methodology led to **3g** and **3h** in high yield (entry 5, Table 1). 1-(*R*)-Furyl-2-(*S*)-methyl-*N*-Boc-protected homopropargylamine **1d** underwent tandem coupling–isomerization–aza-Michael reaction furnishing the aza-heterocycle **3e** in 81% yield. Significantly, aliphatic terminal alkynes possessing various stereogenic groups were also subjected to the above protocol and the respective expected products were isolated in good to high yield (Table 1).

Primary alcohol tethered alkynes **1h, 1k** and **1l** underwent tandem coupling–isomerization–aza-Michael reaction and provided the five and six membered oxacycles **3i, 3l**, and **3m** respectively. The secondary alcohol tethered alkyne **1i** furnished five membered functionalized tetrahydro-2-ene-benzoate **3j**, whereas, 1-phenyl-4-pentyn-1-ol **1m**, which has a secondary alcohol did not cyclize under the present protocol, instead it isomerized to the corresponding allenoate **3n**. The probable reason for this transformation could be the formation of a 6-membered transition state leading to oxy-Michael addition destabilized by phenyl substitution. (*S*)-2-Aminohex-5-ynyl 4-methylbenzenesulfonate **1j** was successfully coupled with **2b** and isomerization followed by aza-Michael addition provided the required aza-heterocyclic compound **3k** in 85% isolated yield, while Boc-protected (*S*)-2-(Boc-amino)hex-5-ynyl 4-methylbenzenesulfonate led to the corresponding benzylallenoate as the sole product (entry 9, Table 1).

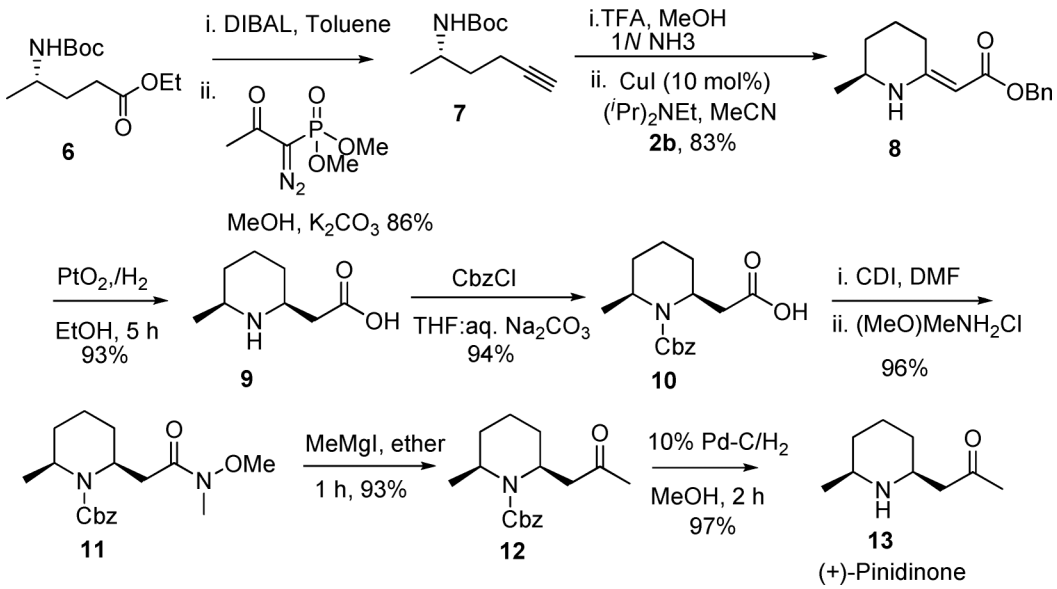
Further, we prepared the substrates **4a–c** and subjected them to the same protocol. In the case of **4a**, the expected product **5a** was isolated in 76% yield. Next, benzylic as well as phenolic hydroxyl containing substrate **4b** was underwent a tandem reaction. Only 5-(2-hydroxyphenyl) substituted 5-membered oxacycle **5b** was obtained, whereas using benzylic hydroxy protected acetate **4c** as a substrate under otherwise identical conditions resulted in the 7-membered oxacycle **5c** in 80% yield (Scheme 2).

We next turned our attention to the application of this approach for the synthesis of piperidine alkaloid (+)-pinidinone, **13**. The 2,6-disubstituted piperidine ring motif is a common structural moiety in a number of biologically active alkaloids.[8] Thus, considerable synthetic efforts have been made to produce the piperidine alkaloid **13**.[9] Our approach starts from a known synthetic precursor **6**[10] which was reduced using DIBAL, followed by exposure to the Ohira–Bestmann reagent under basic conditions in MeOH to give the *N*-Boc-protected amino terminal alkyne **7** in 86% yield. Deprotection of Boc under acidic conditions was followed by evaporation and the resulting residue was subjected to tandem coupling–isomerization–aza-Michael reaction to give **8** as the pure (*E*)-diastereomer in 83% yield. Reduction of the double bond over PtO_2 under hydrogen balloon pressure led to the protected 2,6-disubstituted piperidine carboxylic acid **9** as a single diastereomer[11] and subsequent protection with Cbz-Cl under basic conditions resulted in **10** in 94% yield. Treatment of **10** with Weinreb's reagent followed by methyl magnesium iodide and removal of Cbz group over 10% Pd–C under hydrogen led to the final compound **13** which was identical by all spectral comparisons with that reported in the literature[9] (Scheme 3).

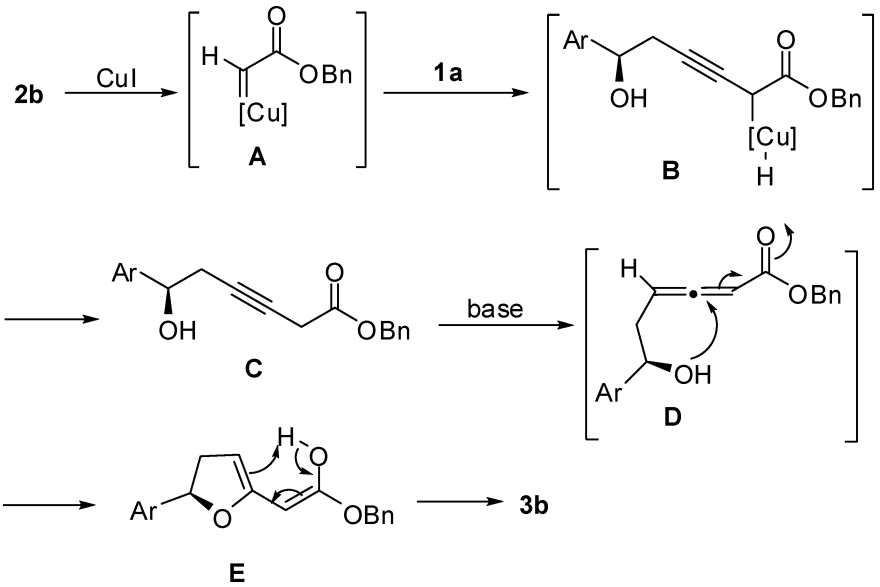
Although the exact mechanistic aspect of this transformation at this juncture has not been rigorously established, the following



Scheme 2 Synthesis of 5- and 7-membered oxacycles.



Scheme 3 Synthesis of (+)-pinidinone.



Scheme 4 Plausible reaction pathway.

pathway could be conceived based on product formation as well as earlier reports.[4a,12] The reaction of **2b** in the presence of CuI leads to the copper-carbene species **A**, which in turn reacts with the terminal alkyne **1a** resulting in **C** through an intermediate **B**. Base mediated rearrangement of internal acetylene to allene **D** and subsequent intramolecular oxy-Michael addition provides the cyclized product **E**, which upon isomerization[5] leads to the more stable (*E*)-2-alkylidenetetrahydrofuranoate **3b** (Scheme 4).

Conclusions

In conclusion, we have developed a method that provides easy access to the syntheses of corresponding functionalized oxa- and aza-heterocycles by a Cu(I)-catalyzed tandem coupling of benzyldiazoester by a terminal alkyne–isomerization–Michael reaction under mild conditions in good to high yield. Additionally, a highly diastereoselective synthesis of the 2,6-disubstituted piperidine alkaloid (+)-pinidinone was accomplished employing the above protocol coupled with diastereoselective hydrogenation as strategic steps. Further work is in progress using this protocol for the synthesis of biologically active oxa- and aza-heterocycles.

Experimental section

General information

All reactions were conducted under an inert atmosphere, if argon is mentioned. The apparatus used for reactions were perfectly oven dried. CH_3CN was distilled from CaH_2. Ether was distilled from sodium benzophenone ketyl. ^1H NMR spectra were recorded at 300, 400 and 500 MHz and ^{13}C NMR at 75 and 125 MHz in $CDCl_3$. *J* values were recorded in hertz and abbreviations used are s–singlet, d–doublet, m–multiplet, br–broad. Chemical shifts (δ) are reported relative to TMS ($\delta = 0.0$) as an internal standard. IR (FT-IR) spectra were measured as KBr pellets or as film. Mass spectral data were compiled using MS (ESI), HRMS mass spectrometers. Optical rotations were recorded on a highly sensitive polarimeter with a 10 mm cell.

Typical procedure for the synthesis of alkene-substituted derivatives of furan, pyran, pyrrolidine and piperidines

Diisopropylethyl amine (1 mmol) was added to a stirred solution of CuI (0.1 mmol), acetylene (1 mmol) and benzyldiazoacetate (1.2 mmol) in acetonitrile (5 mL). The resulting reaction mixture was stirred at ambient temperature for 3 h. The reaction mixture was passed through a Celite pad and washed with EtOAc (2 × 3 mL). The combined filtrate solutions were concentrated under reduced pressure. The crude residue was subjected to silica gel column chromatography (100–200 mesh) using hexane–ethyl acetate as eluent to afford the corresponding aza or oxacycle product.

(*R*,*E*)-Benzyl 2-(5-phenyldihydrofuran-2(3*H*)-ylidene) acetate (3b)

Yield (250 mg, 85%); Pale yellow solid; m.p. 80–82 °C; HPLC analysis on a Daicel chiralpak OD-H column: 95 : 5 hexane–*i*-PrOH, flow rate 0.5 mL min^{-1}, λ = 254 nm: t_{minor} = 27.89 min, t_{major} = 29.21 min; $[\alpha]_D^{24}$ −17.1 (*c* 0.6, $CHCl_3$); IR (KBr): 3388, 3033, 2941, 1700, 1640, 1123, 736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26–7.37 (m, 10H), 5.44 (s, 1H), 5.37 (t, *J* = 6.9 Hz, 1H), 5.11 (s, 2H), 3.33–3.44 (m, 1H), 3.02–3.14 (m, 1H), 2.47–2.57 (m, 1H), 1.99–2.10 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 168.3, 139.7, 128.6, 128.2, 127.9, 125.5, 89.6, 84.7, 67.1, 65.2, 60.7, 32.4, 30.7; MS (ESI) *m*/*z*: 295 (M + H)$^+$. HRMS: calcd for $C_{19}H_{19}O_3$ 295.1334; found 295.1330.

(*E*)-Benzyl 2-((*S*)-5-styryldihydrofuran-2(3*H*)-ylidene)acetate (3c)

Yield (272 mg, 85%); White solid; m.p. 78–80 °C; $[\alpha]_D^{24}$ = +10.0 (*c* = 0.04, $CHCl_3$); IR (KBr): 3382, 3088, 2941, 2811, 1756, 1640, 1456, 1233, 736, 636 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23–7.37 (m, 10H), 6.60 (d, *J* = 15.8 Hz, 1H), 6.12 (dd, *J* = 6.9, 15.8 Hz, 1H), 5.36 (s, 1H), 5.09 (s, 2H), 4.95 (q, *J* = 6.9 Hz, 1H), 3.29–3.40 (m, 1H), 2.97–3.09 (m, 1H), 2.26–2.37 (m, 1H), 1.86–1.98 (m, 1H); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 176.4, 168.3, 136.8, 135.8, 133.0, 128.6, 126.6, 126.4, 89.5, 84.1, 65.1, 30.5, 30.2; MS (ESI) *m/z*: 321 (M + H)$^+$. HRMS: calcd for $C_{21}H_{21}O_3$ 321.1491; found 321.1497.

(*E*)-Ethyl 2-((4*S*,5*S*)-4-hydroxy-5-phenyldihydrofuran-2(3*H*)-ylidene)acetate (3d)

Yield (220 mg, 89%); White solid; m.p. 78–81 °C; $[\alpha]_D^{24}$ = +7.5 (*c* = 0.04, $CHCl_3$); IR (KBr): 3364, 2092, 1685, 1521, 1163, 750, 632 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.42 (m, 5H), 5.46 (s, 1H), 5.31 (m, 1H), 4.51 (s, 1H), 4.12 (q, *J* = 6.9 Hz, 2H), 3.61 (d, *J* = 18.6 Hz, 1H), 3.12 (dd, *J* = 1.2, 18.6 Hz, 1H), 1.28 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 129.0, 126.0, 91.7, 87.8, 71.3, 59.5, 39.8, 29.6, 25.5, 14.4; MS (ESI) *m/z*: 271 (M + Na)$^+$. HRMS: calcd for $C_{14}H_{16}O_4Na$ 271.0946; found 271.0953.

(2*R*,3*S*,*E*)-*tert*-Butyl 5-(2-(benzyloxy)-2-oxoethylidene)-2-(furan-2-yl)-3-methylpyrrolidine-1-carboxylate (3e)

Yield (321 mg, 81%); Pale yellow solid; m.p. 88–90 °C; $[\alpha]_D^{24}$ −19.8 (*c* 0.9, $CHCl_3$); IR (KBr): 3356, 2978, 2934, 1736, 1684, 1514, 1450, 1280, 1045, 908, 615 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.36 (m, 6H), 6.53 (d, *J* = 5.3 Hz, 1H), 6.36 (d, *J* = 5.7 Hz, 1H), 5.4 (s, 1H), 5.3 (d, *J* = 3.0 Hz, 1H), 5.04 (q, *J* = 12.3 Hz, 2H), 3.95–4.0 (m, 1H), 3.77–3.88 (m, 1H), 3.03–3.10 (m, 1H), 1.43 (s, 9H), 1.27 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 140.3, 135.9, 132.9, 128.5, 128.1, 124.4, 82.6, 66.6, 59.9, 51.6, 47.9, 28.2, 18.7; MS (ESI) *m/z*: 420 (M + Na)$^+$. HRMS: calcd for $C_{23}H_{27}NO_5Na$ 420.1786; found 420.1766.

(*R*,*E*)-Benzyl 2-(5-(furan-2-yl)dihydrofuran-2(3*H*)-ylidene)acetate (3f)

Yield (227 mg, 80%); colorless oil; HPLC analysis on a Daicel chiralpak OD-H column: 95 : 5 hexane–*i*-PrOH, flow rate 0.5 mL min^{-1}, λ = 254 nm: t_{major} = 29.99 min, t_{minor} = 33.63 min; $[\alpha]_D^{24}$ −70.8 (*c* 0.9, $CHCl_3$); IR (KBr): 3064, 3033, 2953, 2362, 2334, 1730, 1703, 1641, 1499, 1352, 1208, 1107, 1029, 878, 823, 743, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (t, *J* = 1.5 Hz, 1H), 7.23–7.34 (m, 5H), 6.32 (d, *J* = 1.5 Hz, 2H), 5.33–5.38 (m, 2H), 5.10 (s, 2H), 3.35–3.47 (m, 1H), 3.07–3.20 (m, 1H), 2.31–2.39 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9, 168.2, 164.8, 151.5, 143.2, 136.7, 135.1, 129.7, 128.4, 127.8, 110.3, 108.8, 89.7, 77.6, 66.9, 65.1, 30.6, 29.6, 27.9; MS (ESI) *m/z*: 307 (M + Na)$^+$. HRMS: calcd for $C_{17}H_{16}O_4Na$ 307.0946; found 307.0957.

(*E*)-Benzyl 2-(benzofuran-2(3*H*)-ylidene)acetate (3g)

Yield (218 mg, 82%); Colorless oil; IR (KBr): 3447, 3058, 1735, 1612, 1191, 955, 741, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.10–7.24 (m, 7H), 6.59 (s, 1H), 5.17 (s, 2H), 3.83 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 128.5, 128.2, 123.9, 122.7, 120.7, 110.0, 105.2, 67.0, 34.6; MS (ESI) *m/z*: 289 (M + Na)$^+$. HRMS: calcd for $C_{17}H_{14}O_3Na$ 289.0840; found 289.0853.

(*E*)-Benzyl 2-(5-methylindolin-2-ylidene)acetate (3h)

Yield (234 mg, 84%); Yellow solid; m.p. 84–87 °C; IR (KBr): 3369, 2887, 1730, 1584, 1431, 1209, 792, 725, 644 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (bs, 1H), 7.30–7.33 (m, 6H), 7.15 (d, *J* = 8.3 Hz, 1H), 6.91 (dd, *J* = 1.5, 8.3 Hz, 1H), 6.19 (s, 1H), 5.16 (s, 2H), 3.84 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4, 135.3, 134.6, 130.3, 128.7, 123.7, 120.2, 110.4, 101.5, 67.1, 33.9, 21.4; MS (ESI) *m/z*: 280 (M + H)$^+$. HRMS: calcd for $C_{18}H_{18}NO_2$ 280.1334; found 280.1330.

(*S*,*E*)-Benzyl 2-(4-(*tert*-butoxycarbonylamino)dihydrofuran-2(3*H*)-ylidene)acetate (3i)

Yield (286 mg, 86%); White solid; m.p. 76–78 °C; $[\alpha]_D^{24}$ = +10.65 (*c* = 0.84, $CHCl_3$); IR (KBr): 3230, 2910, 1688, 1611, 1555, 1148, 1033, 925, 866, 788, 664 cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29–7.34 (m, 5H), 5.4 (s, 1H), 5.1 (s, 2H), 4.66–4.70 (m, 1H), 4.3–4.41 (bs, 1H), 4.17–4.29 (m, 2H), 3.11–3.27 (m, 2H), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 168.0, 128.4, 127.9, 91.1, 65.3, 49.4, 37.0, 29.6, 28.2; MS (ESI) *m/z*: 356 (M + Na)$^+$. HRMS: calcd for $C_{18}H_{23}NO_5Na$ 356.1473; found 356.1459.

(*R*,*E*)-Benzyl 2-(5-((4-methoxybenzyloxy)methyl)dihydrofuran-2(3*H*)-ylidene)acetate (3j)

Yield (323 mg, 88%). Colorless oil; $[\alpha]_D^{24}$ −14.7 (*c* 0.09, $CHCl_3$); IR (KBr): 2930, 1698, 1634, 1511, 1244, 1097, 1025, 816, 738, 694 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17–7.33 (m, 8H), 6.79–6.84 (m, 2H), 5.32 (s, 1H), 5.08 (s, 1H), 4.50–4.57 (m, 1H), 4.46 (s, 2H), 3.78 (s, 3H), 3.44–3.54 (m, 2H), 3.18–3.29 (m, 1H), 2.94–3.06 (m, 1H), 2.07–2.27 (m, 1H), 1.85–1.97 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9, 168.3, 159.2, 136.8, 129.3, 128.4, 113.8, 89.3, 82.7, 73.1, 70.9, 65.1, 55.2, 30.4, 25.7; MS (ESI) *m/z*: 391 (M + Na)$^+$. HRMS: calcd for $C_{22}H_{24}O_5Na$ 391.1521; found 391.1528.

(*S*,*E*)-Benzyl 2-(6-(tosyloxymethyl)piperidin-2-ylidene)acetate (3k)

Yield (352 mg, 85%); colorless oil; $[\alpha]_D^{24}$ −40.0 (*c* 0.06, $CHCl_3$); IR (KBr): 2921, 2853, 1740, 1648, 1599, 1453, 1360, 1233, 1165, 959, 818, 779, 747, 694, 667 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (bs, 1H), 7.80 (d, *J* = 7.9 Hz, 2H), 7.20–7.31 (m, 7H), 5.06 (q, *J* = 12.8 Hz, 2H), 4.42 (s, 1H), 3.99–4.02 (m, 1H), 3.82–3.86 (m, 1H), 3.58–3.63 (m, 1H), 2.43 (s, 3H), 2.26–2.32 (m, 2H), 1.90–1.95 (m, 1H), 1.74–1.79 (m, 1H), 1.25–1.63 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 161.6, 144.9, 129.9, 128.4, 128.0, 127.3, 82.1, 72.0, 64.2, 50.0, 43.4, 29.1, 25.0, 21.7, 18.4; MS (ESI) *m/z*: 416 (M + H)$^+$. HRMS: calcd for $C_{22}H_{26}NO_5S$ 416.1531; found 416.1520.

(*S*,*E*)-Benzyl 2-(5-(*tert*-butoxycarbonylamino)tetrahydro-2*H*-pyran-2-ylidene)acetate (3l)

Yield (284 mg, 82%); colorless oil; $[\alpha]_D^{24}$ = +1.6 (*c* = 0.04, $CHCl_3$); IR (KBr): 3440, 3365, 2937, 1694, 1613, 1528, 1380, 1247, 1172, 1086, 1015, 948, 630 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.35 (m, 5H), 6.38 (s, 1H), 5.05–5.15 (m, 2H), 4.24–4.31 (m, 1H), 3.67 (d, *J* = 5.1 Hz, 2H), 3.37–3.46 (m,1H), 2.94–3.07 (m, 1H), 2.27–2.38 (m, 1H), 1.88–2.06 (m, 1H), 1.53(s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 158.2, 151.9, 128.4, 127.6, 96.1, 82.6, 66.6, 64.9, 63.7, 62.3, 44.1, 30.6, 28.0, 23.6; MS (ESI) *m/z*: 348 (M + H)$^+$. HRMS: calcd for $C_{19}H_{26}NO_5$ 348.1844; found 348.1850.

(*E*)-Benzyl 2-(dihydrofuran-2(3*H*)-ylidene)acetate (3m)

Yield (159 mg, 73%); colorless oil; IR (KBr): 2933, 1612, 1627, 1511, 1233, 987, 811, 748, 612 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25–7.34 (m, 5H), 5.31 (s, 1H), 5.08 (s, 2H), 4.20 (t, J = 6.98 Hz, 3H), 3.10 (dt, J = 1.7, 7.9 Hz, 2H), 2.03–2.14 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 168.1, 128.4, 128.0, 89.5, 71.7, 65.0, 30.3, 23.9; MS (ESI) m/z: 241 $(M + Na)^+$ HRMS: calcd for $C_{13}H_{14}O_3Na$ 241.0840; found 241.0852.

Benzyl 7-hydroxy-7-phenylhepta-2,3-dienoate (3n)

Yield (180 mg, 75%); colorless oil; IR (KBr): 3360, 3065, 3020, 2981, 2890, 1961, 1745, 1718, 1448, 1259, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20–7.35 (m, 10H), 5.59–5.72 (m, 2H), 5.12–5.17 (m, 2H), 4.78–4.84 (m, 1H), 4.68–4.75 (m, 1H), 3.25–3.28 (m, 1H), 2.18–2.32 (m, 2H), 1.73–1.97 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.6, 212.5, 168.5, 166.0, 165.9, 144.4, 144.1, 135.7, 135.2, 128.3, 128.2, 127.9, 127.2, 125.6, 95.2, 94.9, 88.3, 88.1, 72.8, 72.6, 73.0, 66.9, 66.4, 37.4, 23.6; MS (ESI) m/z: 331 $(M + Na)^+$ HRMS: calcd for $C_{20}H_{20}O_3Na$ 331.1860; found 331.1872.

(*E*)-Benzyl 2-(5-(2-(methoxymethoxy)phenyl)dihydrofuran-2(3*H*)-ylidene)acetate (5a)

Yield (269 mg, 76%); Slight yellow oil; IR (KBr): 2950, 2900, 2828, 2362, 1702, 1640, 1154, 1036, 993, 752, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.18–7.35 (m, 7H), 7.06 (d, J = 8.4 Hz, 1H), 6.96 (t, J = 7.5 Hz, 1H), 5.65–5.68 (m, 1H), 5.45 (s, 1H), 5.18 (s, 2H), 5.11 (s, 2H), 3.45 (s, 3H), 3.25–3.31 (m, 1H), 3.09–3.16 (m, 1H), 2.51–2.58 (m, 1H), 1.94–2.01 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 168.4, 153.6, 136.8, 129.0, 128.4, 127.9, 125.6, 121.7, 113.7, 94.2, 89.4, 80.6, 65.2, 56.1, 31.0, 30.4; MS (ESI) m/z: 377 $(M + Na)^+$. HRMS: calcd for $C_{21}H_{22}O_5Na$ 377.1364; found 377.1356.

(*E*)-Benzyl 2-(5-(2-hydroxyphenyl)dihydrofuran-2(3*H*)-ylidene)-acetate (5b)

Yield (241 mg, 78%); colorless oil; IR (KBr): 3566, 3067, 2966, 2362, 1741, 1694, 1530, 1392, 1229, 752 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23–7.37 (m, 5H), 7.07–7.15 (m, 2H), 6.72–6.86 (m, 2H), 5.63 (t, J = 6.8 Hz, 1H), 5.48 (s, 1H), 5.12 (s, 2H), 3.26–3.37 (m, 1H), 3.02–3.13 (m, 1H), 2.46–2.57 (m, 1H), 1.99–2.11 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 150.6, 135.7, 128.5, 128.1, 126.3, 124.2, 120.1, 115.9, 106.2, 78.1, 66.5, 42.2, 36.2; MS (ESI) m/z: 333 $(M + Na)^+$. HRMS: calcd for $C_{19}H_{18}O_4Na$ 333.1102; found 333.1099.

Benzyl 2-(5-acetoxy-4,5-dihydrobenzo[*b*]oxepin-2-yl)acetate (5c)

Yield (281 mg, 80%); colorless oil; IR (film): 3453, 3034, 1738, 1692, 1235, 1147, 1036, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20–7.30 (m, 5H), 7.01–7.15 (m, 3H), 6.80 (d, J = 7.9 Hz, 1H), 6.16 (dd, J = 3.4, 8.5 Hz, 1H), 5.15 (s, 2H), 4.77 (t, J = 4.5 Hz, 1H), 3.17–3.30 (m, 2H), 2.46–2.66 (m, 2H), 2.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 155.3, 148.1, 135.6, 131.3, 128.7, 126.1, 124.0, 120.9, 104.0, 71.0, 66.6, 42.2, 32.6, 21.1; MS (ESI) m/z: 375 $(M + Na)^+$. HRMS: calcd for $C_{21}H_{20}O_5Na$ 375.1208; found 375.1190.

(*S*)-*tert*-Butyl hex-5-yn-2-ylcarbamate (7)

To a stirred solution of **6** (2.0 g, 8.2 mmol) in 20 mL of toluene was added 9 mL of DIBAL-H (1.5 M in toluene), dropwise at −78 °C. The reaction mixture was kept at −78 °C for 45 min, and then quenched with 1 mL of methanol. The reaction mixture was diluted with 25 mL of 1 N HCl at 0 °C, and then stirred for 15 min. The resulting solution was extracted with (2 × 30 mL) of EtOAc. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The crude aldehyde was then immediately subjected to the next step.

A methanol (20 mL) solution of aldehyde and the Ohira–Bestmann reagent (1.9 g, 9.9 mmol) was cooled to 0 °C. To this, potassium carbonate (2.27 g, 16.0 mmol) was added. The reaction mixture was warmed to room temperature and stirred for 6 h. Then, methanol was removed under vacuum and saturated aqueous ammonium chloride (30 mL) was added and the aqueous solution extracted with EtOAc (2 × 30 mL). The organic layer was separated, dried over Na_2SO_4, and the solvent evaporated under reduced pressure. After purification by column chromatography (eluent hexane–ethyl acetate 90 : 10), alkyne **7** (1.3 g, 86%) was isolated as a colourless liquid, $[\alpha]_D^{24}$ = +12.5 (c = 0.9, $CHCl_3$); IR (KBr): 3364, 2092, 1685, 1521, 1163, 750, 632 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.36 (bs, 1H), 3.70–3.78 (m, 1H), 2.24 (td, J = 1.9, 6.9 Hz, 2H), 1.95 (t, J = 1.9 Hz, 1H), 1.59–1.68 (m, 2H), 1.44 (s, 9H), 1.14 (d, J = 5.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 83.7, 78.9, 68.5, 45.9, 35.8, 28.3, 20.8, 15.3; MS (ESI) m/z: 220 $(M + Na)^+$. HRMS: calcd for $C_{11}H_{19}NO_2Na$ 220.1313; found 220.1320.

A solution of (*S*)-*tert*-butyl hex-5-yn-2-ylcarbamate **7** (1.0 g, 5.1 mmol) in MeOH was cooled in an ice water bath and trifluoroacetic acid (1.17 mL, 15.2 mmol) added. The combined contents were stirred for 4 h at 0 °C. The reaction mixture was evaporated *in vacuo* to remove the solvent and excess TFA. To the residue, water was added, and the mixture was basified with 1 N NH_3 aq (pH 9–10) and extracted with EtOAc. The combined extracts were dried over Na_2SO_4, followed by solvent evaporation resulting in a crude residue. This crude residue was used for the next step without further characterization.

(*S*, *E*)-Benzyl 2-(6-methylpiperidin-2-ylidene)acetate (8)

Diisopropyl amine (1.0 mL, 6.19 mmol), acetylene (600 mg, 6.19 mmol), benzyldiazoacetate (1.1 g, 6.19 mmol) and catalyst CuI (117 mg, 10 mol%) were subjected to the typical procedure described above. The crude residue was subjected to column chromatography eluting with hexane–EtOAc (80 : 20) which furnished **8** as a colorless liquid (1.2 g, 83%). $[\alpha]_D^{24}$ = +22.0 (c = 0.9, $CHCl_3$); IR (KBr): 2921, 2853, 1740, 1648, 1599, 1453, 1360, 1233, 1165, 959, 818, 779, 747, 694, 667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.65 (bs, 1H), 7.22–7.34 (m, 5H), 5.00–5.09 (m, 2H), 4.36 (s, 1H), 3.35–3.46 (m, 1H), 2.28–2.36 (m, 2H), 1.73–1.94 (m, 2H), 1.53–1.68 (m, 1H), 1.29–1.43 (m, 1H), 1.24 (d, J = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 163.0, 137.6, 128.4, 79.6, 64.1, 47.6, 31.1, 29.0, 23.0, 19.5; MS (ESI) m/z: 246 $(M + H)^+$. HRMS: calcd for $C_{15}H_{20}NO_2$ 246.1494; found 246.1488.

2-((2*S*, 6*S*)-6-Methylpiperidin-2-yl)acetic acid (9)

Compound **8** (900 mg, 3.68 mmol) was hydrogenated over platinum oxide (30 mg) in ethanol (25 mL) for 5 h at room temperature under H_2 atmosphere (1 atm). The catalyst was filtered off through a short pad of Celite. The filtrate was concentrated *in vacuo* to give a white solid **9**, Yield: 537 mg (93%); m.p. 90–92 °C; $[\alpha]_D^{24}$ = +35.0 (*c* = 0.04, MeOH); IR (KBr): 3235, 2928, 1732, 1647, 1602, 1498, 1381, 1271, 1147, 1020, 781, 696 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 3.33–3.41 (m, 1H), 3.15–3.25 (m, 1H), 2.52 (dd, *J* = 2.3, 6.0 Hz, 2H), 1.85–1.99 (m, 3H), 1.38–1.67 (m, 4H), 1.34 (d, *J* = 6.0 Hz, 3H);^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 56.5, 54.4, 40.6, 31.7, 29.3, 23.5, 19.9; MS (ESI) *m*/*z*: 180 (M + Na)$^+$. HRMS: calcd for $C_8H_{15}NO_2Na$ 180.1000; found 180.0994.

2-((2*S*,6*S*)-1-(Benzyloxycarbonyl)-6-methylpiperidin-2-yl)acetic acid (10)

Compound **9** (400 mg, 2.54 mmol) was taken up in THF (5 mL) and then Na_2CO_3 10% water solution (3 mL) and benzyl chloroformate (0.725 mL, 5.09 mmol) were consecutively added. The solution was stirred for 3 h at room temperature and concentrated under vacuum. The mixture was poured into a separating funnel over water (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (1 × 5 mL), dried over anhydrous Na_2SO_4, concentrated under vacuum, and purified by means of flash chromatography on silica gel using hexane–EtOAc as the eluent, producing **10** (Yield: 694 mg, 94%). $[\alpha]_D^{24}$ = +25.2 (*c* = 0.6, $CHCl_3$); IR (KBr): 2932, 1728, 1693, 1450, 1412, 1340, 1271, 1082, 736, 694 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30–7.41 (m, 5H), 5.11–5.18 (m, 2H), 4.59–4.69 (m, 1H), 4.31–4.44 (m, 1H), 2.47–2.76 (m, 2H), 1.42–1.76 (m, 6H), 1.17 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 155.7, 136.7, 128.5, 127.5, 126.9, 67.1, 65.2, 47.2, 46.2, 39.1, 29.7, 27.8, 20.4, 13.6; MS (ESI) *m*/*z*: 314 (M + Na)$^+$. HRMS: calcd for $C_{16}H_{21}NO_4Na$ 314.1368; found 314.1359.

(2*S*,6*S*)-Benzyl 2-(2-(methoxy(methyl)amino)-2-oxoethyl)-6-methylpiperidine-1-carboxylate (11)

A solution of compound **10** (384 mg, 1.32 mmol) in DMF (5 mL) was cooled to 0 °C in an ice bath, to which was added *N*,*N*′-carbonyldiimidazole (235 mg, 1.45 mmol) in a single portion. After stirring for 30 min at 0 °C, (MeO)MeNH$_2$Cl (153 mg, 1.58 mmol) was added. The mixture was stirred for 2 h at room temperature. Then 6 mL of water was added, followed by 8 mL of EtOAc. The resulting biphasic solution was separated. The aqueous phase was extracted with EtOAc (2 × 5 mL), and the combined organic phases were washed with H_2O (2 × 5 mL). The organic phase was dried over Na_2SO_4, filtered and then concentrated. Purification by silica gel chromatography (10% EtOAc–hexanes) afforded a colorless oil **11** (423 mg, 96%). $[\alpha]_D^{24}$ = +12.1 (*c* = 0.3, $CHCl_3$); IR (KBr): 3398, 2934, 1741, 1689, 1624, 1464, 1413, 1265, 1074 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31–7.46 (m, 5H), 5.11–5.17 (m, 2H), 4.67–4.75 (m, 1H), 4.35–4.45 (m, 1H), 3.61 (s, 3H), 3.14 (s, 3H), 2.76–2.88 (m, 1H), 2.50–2.59 (m, 1H), 1.48–1.82 (m, 6H), 1.22 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.5, 137.0, 135.0, 129.2, 128.5, 128.7, 117.1, 96.0, 69.8, 66.8, 61.1, 47.1, 45.9, 29.8, 27.8, 20.5, 13.7; MS (ESI) *m*/*z*: 357 (M + Na)$^+$. HRMS: calcd for $C_{18}H_{26}N_2O_4Na$ 357.1790; found 357.1791.

***N*-Benzyloxycarbonyl-2*S*-(2-oxopropyl)-6*S*-methyl-piperidine (12)**

Weinreb amide **11** (400 mg, 1.20 mmol) was dissolved in ether (5 mL) and cooled to −10 °C. A freshly prepared solution of methyl magnesium iodide (3.5 mL, 1 M in ether, 3.6 mmol) was added at such a rate that the internal temperature did not rise above −10 °C. After one hour, it was quenched cautiously by the addition of a saturated aq. NH_4Cl solution (5 mL), then poured into H_2O (5 mL) and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic extract was washed with brine (5 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography of the resulting residue (hexane–EtOAc 8 : 2) yielded **12** (322 mg, 93%) as a colorless oil. $[\alpha]_D^{24}$ = +8.2 (*c* = 0.4, $CHCl_3$); {lit.[13] $[\alpha]^{25}{}_D$ = −7.1 (*c* = 1.0, $CHCl_3$)}; IR (KBr): 3352, 3022, 2974, 2872, 1775, 1630, 1502, 1232, 1039, 997, 879, 719, 518 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26–7.37 (m, 5H), 5.04–5.15 (m, 2H), 4.62–4.68 (m, 1H), 4.31–4.42 (m, 1H), 2.75 (dd, *J* = 15.6, 10.5 Hz, 1H), 2.56 (dd, *J* = 15.9, 8.4 Hz, 1H), 2.08 (s, 3H), 1.48–1.71 (m, 6H), 1.16 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.8, 155.4, 136.8, 128.4, 127.8, 66.9, 48.4, 46.2, 45.9, 29.9, 27.6, 20.1, 13.4; MS (ESI) *m*/*z*: 312 (M + Na)$^+$. HRMS: calcd for $C_{17}H_{23}NO_3Na$ 312.1575; found 312.1562.

(+)-Pinidinone (13)

10% Pd/C (10 mg) was added to a solution of the *N*-Cbz-protected piperidine **12** (100 mg, 0.347 mmol) in MeOH (5 mL) and the suspension was stirred under H_2 (1 atm) for 2 h. The reaction mixture was then filtered through a short pad of Celite and washed with diethyl ether to afford **13** (52 mg, 97%) as a colorless oil. $[\alpha]_D^{24}$ = +25.6 (*c* = 0.03, MeOH); {lit.[9a] $[\alpha]_{D=}$ +25.3 (*c* = 0.4, MeOH)}; IR (KBr): 3396, 3442, 2924, 2854, 1705, 1637, 1378, 1360, 1158, 563 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.35 (bs, 1H), 3.03–3.08 (m, 1H), 2.71–2.78 (m, 1H), 2.60 (d, *J* = 6.3 Hz, 2H), 2.10 (s, 3H), 1.18–1.80 (m, 6H), 1.10 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.3, 52.7, 52.4, 48.6, 32.4, 30.2, 29.6, 23.8, 21.6; MS (ESI) *m*/*z*: 156 (M + H)$^+$. HRMS: calcd for $C_9H_{18}NO$ 156.1388; found 156.1393.

Acknowledgements

We are grateful to Dr J. S. Yadav, Director, IICT, for his constant encouragement. Financial support was provided by the DST, New Delhi, India (Grant No: SR/SI/OC-12/2007). CSIR (New Delhi) is gratefully acknowledged for awarding the fellowship to N. J. and G. B. K. Thanks is also due to Dr G. V. M. Sharma, Head, organic III division, for his support.

Notes and references

1 (*a*) T. Yasumoto and M. Murata, *Chem. Rev.*, 1993, **93**, 1897; (*b*) D. L. Boger, C. W. Boyce, R. M. Garbaccio and J. A. Goldberg, *Chem. Rev.*, 1997, **97**, 787; (*c*) S. E. Denmark, C. S. Regens and T. J. Kobayashi, *J. Am. Chem. Soc.*, 2007, **129**, 2774; (*d*) K. C. Niclaou, K. P. Cole, M. O. Frederick, R. J. Aversa and R. M. Deton, *Angew. Chem., Int. Ed.*, 2007, **46**, 8875; (*e*) E. Keinan and S. C. Sinha, *Pure Appl. Chem.*, 2002, **74**, 93; (*f*) S. C. Sinha and E. Keinan, *J. Am. Chem. Soc.*, 1993, **115**, 4891.
2 (*a*) S. V. Pansare and V. A. Adsool, *Org. Lett.*, 2006, **8**, 5897; (*b*) G. Kumaraswamy, K. Sadaiah, D. S. Ramakrishna, P. Naresh, B. Sridhar and B. Jagadeesh, *Chem. Commun.*, 2008, 5324; (*c*) H. K. Lee, J. Kim and C. S. Pak, *Tetrahedron Lett.*, 1999, **40**, 6267; (*d*) K. Kato, A.

Nishimura, Y. Yamamoto and H. Akita, *Tetrahedron Lett.*, 2001, **42**, 4203; (*e*) M. R. Detty, *J. Org. Chem.*, 1979, **44**, 2073; (*f*) E. Bellur and P. Langer, *J. Org. Chem.*, 2005, **70**, 10013; (*g*) E. Bellur, H. Gorls and P. Langer, *Eur. J. Org. Chem.*, 2005, 2074; (*h*) Y-W. Sun, X-Y. Guan and M. Shi, *Org. Lett.*, 2010, **12**, 5664.

3 (*a*) S. Kitagaki, T. Kawamura, D. Shibata and C. Mukai, *Tetrahedron Lett.*, 2008, **64**, 11086; (*b*) R. D. Little and M. R. Masjedizadeh, *Org. React.*, 1995, **47**, 315.

4 (*a*) M. Hassink, X. Liu and J. M. Fox, *Org. Lett.*, 2011, **13**, 2388; (*b*) H. Liu, D. Leow, K-W. Huang and C-H. Tan, *J. Am. Chem. Soc.*, 2009, **131**, 7212; (*c*) Y. Matsumoto, M. Naito, Y. Uozumi and T. Hayashi, *J. Chem. Soc., Chem. Commun.*, 1993, 1468; (*d*) A. Hoffmann-Roder and N. Krause, *Angew. Chem., Int. Ed.*, 2002, **41**, 2933.

5 H. Liu, W. Feng, C. W. Kee, D. Leow, W-T. Loh and C-H. Tan, *Adv. Synth. Catal.*, 2010, **352**, 3373.

6 A. Suarez and G. C. Fu, *Angew. Chem., Int. Ed.*, 2004, **43**, 3580.

7 (*a*) G. Kumaraswamy, D. Rambabu, N. Jayaprakash, G. Venkata Rao and B. Sridhar, *Eur. J. Org. Chem.*, 2009, 4158; (*b*) G. Kumaraswamy, G. Venkata Rao and G. Ramakrishna, *Synlett*, 2006, 1122; (*c*) G. Kumaraswamy, G. Venkata Rao, A. Narayana Murthy and B. Sridhar, *Synlett*, 2009, 1180; (*d*) G. Kumaraswamy, A. Ankamma and A. Pitchaiah, *J. Org. Chem.*, 2007, **72**, 9822.

8 (*a*) J. W. Daly, H. M. Garraffo and T. F. Spande, in *Alkaloids: Chemical and Biological Perspectives*, S. W. Ed., Pergamon Press, New York, 1999, Vol. **13**, pp 1-161; (*b*) X. Pu and D. Ma, *J. Org. Chem.*, 2003, **68**, 4400.

9 (*a*) M. J. Munchhof and A. I. Meyers, *J. Am. Chem. Soc.*, 1995, **117**, 5399; (*b*) J. N. Tawara, A. Blokhin, T. A. Foderaro and F. R. Stermitz, *J. Org. Chem.*, 1993, **58**, 4813.

10 Compound **8** was prepared starting from L-(+) alanine in 3 steps, *i.e.* esterification followed by reduction, 2-carbon Wittig reaction and hydrogenation. Q. Meng and M. Hesse, *Tetrahedron*, 1991, **47**, 6251.

11 The enantioselectivity and relative stereochemistry of the hydrogenated product **9** was determined in comparison with the sign and magnitude of the specific rotation of the piperidine alkaloid **13**.

12 Q. Xiao, Y. Xia, H. Li, Y. Zhang and J. Wang, *Angew. Chem., Int. Ed.*, 2011, **50**, 1114.

13 S. Fustero, S. Monteagudo, M. Sánchez-Roselló, S. Flores, P. Barrio and C. del Pozo, *Chem.–Eur. J.*, 2010, **16**, 9835.

