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Deacylative alkylation (DaA) of *N*-methyl-3-acetyl-2-oxindole for the synthesis of symmetrically 3,3-disubstituted 2-oxindoles. An access gate to anticancer agents and natural products.

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ABSTRACT

The synthesis of 3,3-disubstituted *N*-methyloxindoles, starting from 3-acetyl-2-hydroxy-1-methyloxindole employing a sequential one-pot synthesis, is studied. The process involves a first alkylation in the presence of 1 equiv. of both organic halide and Triton B and the second one employs another 1.5 equiv. of each in moderate to high yields. This procedure is compared with the results obtained from the direct dialkylation of *N*-methyloxindole. The metathesis of one of the corresponding diallylated product was also studied obtaining the spiranic oxindole. All these methodologies are directed towards the access to anticancer agents and natural biologically active products.

Key words: deacylation, alkylation, 2-oxindoles, metathesis, anticancer, natural products.

INTRODUCTION

Sophisticated (Zhang et al. 2017, Nadege et al. 2016) or simple (Trost and Zhang 2006) natural compounds incorporating a 3,3-disubstituted 2-oxindole are frequently found (Kaur et al. 2016, Saraswat et al. 2016, Fonseca and Cook 2016, Ziarani et al. 2013). In fact, the generation of this quaternary carbon as a consequence of this 3,3-disubstitution is a key point, based in the Ingold-Thorpe effect, for the construction of very complex natural skeletons or drugs (Cao et al. 2014, Shen et al. 2012, Singh and Desta 2012, Dalpozzo et al. 2012, Zhou et al. 2010, Galliford et al. 2007). For example, 3,3-disubstituted 2-oxindoles are important class of heterocyclic compounds occurring in natural alkaloids such as the alkaloid horsfiline (Trost et al. 2006), esermethole (Trost et al. 2006), acetylcholinesterase inhibitors physostigmine and phenserine (Huang et al. 2004), and muscle relaxant agents flustramides A and B (Trost et al. 2011) (Figure 1). Besides synthetic spiroxindoles, with a rigid heterocyclic ring fused at the 3-position of the oxindole core (Figure 1), become the most effective compounds as inhibitors of the tumor cells proliferation inducing apoptosis

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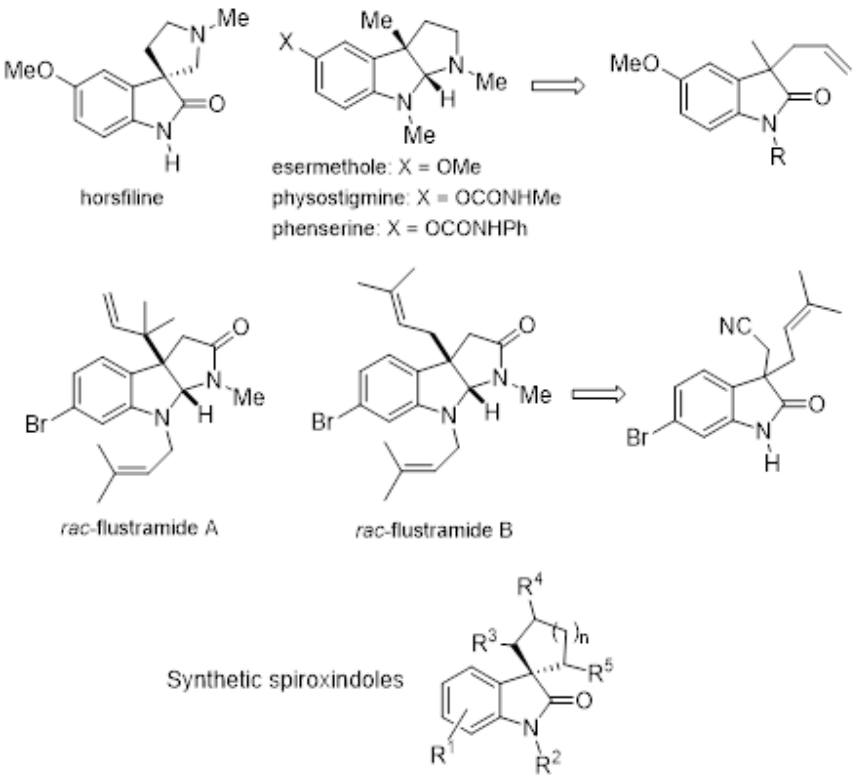


Figure 1 - Natural and synthetic biologically active compounds containing the 2-oxindole unit.

on them without affecting activities of normal cells (Gupta et al. 2017, Dondas et al. 2017, Saraswat et al. 2016, Yu et al. 2015, David et al. 2016).

Although an unsymmetrical 3,3-substitution is more attractive from the synthetic point of view (Ashimori et al. 1993, Matsuura et al. 1998, Shaughnessy et al. 1998, Kundig et al. 2007, Marsden et al. 2008, Altman et al. 2008, Ruck et al. 2008, Jia and Kundig 2009, Perry and Taylor 2009, Ghosh et al. 2012, Tian et al. 2008, He et al. 2009, Cheng et al. 2009, Weaver et al. 2011, Linton and Kozlowski 2008, Kumar et al. 2017), symmetrically 3,3-disubsitution can be very useful in particular examples. In this sense, there are two main approaches for achieving this last task (compounds **3**); one of them is the cyclization of acylated anilides **1** (Figure 2, eq. a) and, the second (the most frequently used), the direct double alkylation onto **2**, which is currently performed employing alkoxides or stronger bases (Figure 2, eq. b) (Scriven and Ramsden 2015).

In this context, deacylative alkylation (DaA) reaction emerged as an alternative to obtain this type of substitution (Mei et al. 2015, Kumar et al. 2017, Xie et al. 2016). The strategy of this transformation consists in the employment of the acetyl group as protecting, activating and leaving group for the alkylation sequence. It was recently

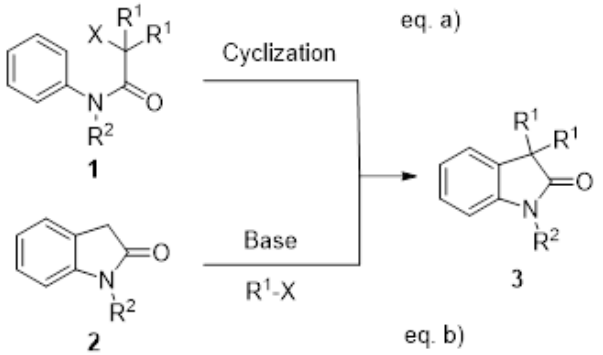


Figure 2 - Approaches to obtain 3,3-disubstituted 2-oxindoles.

demonstrated by our group than the monoalkylation of 3-acetyl-2-oxindoles **4** (Ortega-Martínez et al. 2017) could be performed using alkyl halides and benzyltrimethylammonium hydroxide (Triton B) as base at room temperature in good yields. This methodology was applied to the synthesis of 1,3-dimethyl-2-oxindoles (Ortega-Martínez et al. 2017). Next, a deacylative alkylation (DaA) of the corresponding 3-acetyl-2-oxindole (**5**) with activated alkyl halides took place efficiently using LiOEt (Figure 3). In addition, conjugate addition with electron-deficient alkenes also was produced in the presence of Triton B. In both cases, the corresponding unsymmetrically 3,3-disubstituted 2-oxindoles **6** or **7** were isolated respectively (Figure 3) (Ortega-Martínez et al. 2017).

Continuing with our research looking for applications of this DaA for the synthesis of 3,3-dialkyloxindoles we describe here the synthesis of symmetrical 3,3-disubstituted analogues. We also have compared the results obtained through this DaA methodology *versus* the direct double alkylation of oxindole.

EXPERIMENTAL SECTION

GENERAL

Melting points were determined with a Marienfeld melting-point meter (MPM-H2) apparatus and are uncorrected. For flash chromatography, silica gel 60 (40–60 μm) was employed. The structurally most important peaks of the IR spectra (recorded using a Nicolet Avatar 320 FT-IR Spectrometer and JASCO FT/IR-4100 Fourier Transform Infrared Spectrometer) are listed and wave numbers are given in cm^{-1}. ^{1}H NMR (300, or 400 MHz) and ^{13}C NMR (75 or 101 MHz) spectra were recorded with Bruker AV300 and Bruker AV400, respectively, with $CDCl_3$ as solvent and TMS as internal standard for ^{1}H NMR spectra, and the chloroform signal for ^{13}C NMR spectra; chemical shifts are given in ppm. Low-resolution electron impact (GC-EI) mass spectra were obtained at 70 eV with an Agilent 6890N Network GC system and an Agilent 5973Network Mass Selective Detector. High-resolution mass spectra (GC-EI) were recorded with a QTOF Agilent 7200 instrument for the exact mass and Agilent 7890B for the GC. Analytical TLC was performed using ALUGRAM® Xtra SIL G/UV_{254} silica gel plates, and the spots were detected under UV light (λ=254 nm). The synthesis of *N*-methyl-3-acetyl-2-oxindole was reproduced from the reported procedure (Ortega-Martínez et al. 2017).

SYNTHESIS OF 3,3-DISUBSTITUTED OXINDOLES USING DAA. GENERAL PROCEDURE

To a solution of *N*-methyl-3-acetyl-2-oxindole **4a** (57 mg, 0.3 mmol) and alkyl halide (0.3 mmol) in THF (3 mL) was added benzyltrimethylammonium

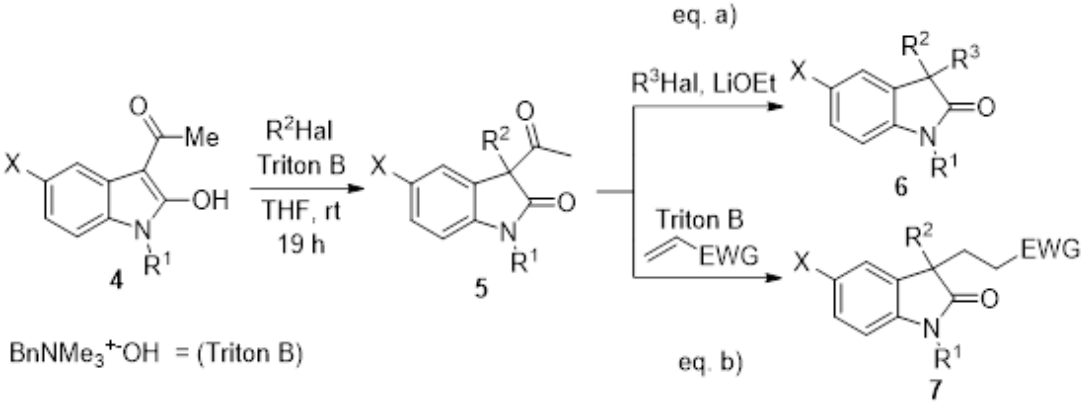


Figure 3 - Synthesis of unsimmetrically 3,3-disubstituted 2-oxindoles by our group.

hydroxide (Triton B) in MeOH (40wt%, 136 µL, 0.3 mmol) dropwise. The reaction was stirred at rt during 4-6 h. The reaction was controlled by gas chromatography until the conversion of **4a** to 3-acetyl-3-alkyl-2-oxindole was ≥90%. Then, alkyl halide (0.45 mmol) and base (0.45 mmol) was added to complete the double alkylation, allowing the reaction to proceed at room temperature overnight. H_2O (10 mL) was added, the mixture was extracted with EtOAc (3 × 10 mL) and the combined organic layers were evaporated and dried over $MgSO_4$. After evaporation of the solvents the residue was purified by flash chromatography (EtOAc/hexane).

*1,3,3-Trimethylindolin-2-one (***3a***)*: colorless oil; R_F 0.3 (hexane/EtOAc 8.5:1.5); IR (neat) ν_{max} 3053, 2970, 2924, 1704, 1613 cm^{-1}; ^1H NMR (300 MHz) δ 7.27 (1H, td, *J* = 7.7, 1.3 Hz, ArH), 7.21 (1H, d, *J* = 7.4 Hz, ArH), 7.07 (1H, td, *J* = 7.5, 0.9 Hz, ArH), 6.85 (1H, d, *J* = 7.8 Hz, ArH), 3.22 (3H, s, NCH_3), 1.37 (6H, s, 2 x CH_3); ^{13}C NMR (101 MHz) δ 181.5 (CO), 142.7 (CH), 135.9 (CH), 127.8 (CH), 122.6 (CH), 122.4 (CH), 108.1 (CH), 44.3 (C), 26.3 (CH_3), 24.5 (2 x CH_3); LRMS (EI) *m/z* 175 (M^+, 66%), 161 (11), 160 (100), 132 (20), 117 (14), 77(6); HRMS (ESI): calcd. for $C_{11}H_{13}NO$ $[M]^+$ 175.0997; found 175.0998.

*3,3-Diethyl-1-methylindolin-2-one (***3b***)*: colorless oil; R_F 0.3 (hexane/EtOAc 9:1); IR (neat) ν 2963, 2924, 2878, 2852, 1706, 1612 cm^{-1}; ^1H NMR (300 MHz) δ 7.31–7.23 (1H, m, ArH), 7.17–7.04 (2H, m, ArH), 6.84 (1H, d, *J* = 7.7 Hz, ArH), 3.22 (3H, s, NCH_3), 2.01–1.68 (4H, m, 2 x CH_2), 0.56 (6H, t, *J* = 7.4 Hz, 2 x CH_3); ^{13}C NMR (101 MHz) δ 180.2 (CO), 144.5 (C), 132.1 (C), 127.7 (CH), 122.8 (CH), 122.5 (CH), 107.8 (CH), 54.5 (C), 30.8 (2 x CH_2), 26.1 (CH_3), 8.8 (2 x CH_3); LRMS (EI) *m/z* 203 (M^+, 72%), 204 (10), 175 (51), 174 (100), 160 (20), 159 (12), 146 (66), 131 (19), 130 (25); HRMS (ESI): calcd. for $C_{13}H_{17}NO$ $[M]^+$ 203.131; found 203.1313.

*3,3-Dibenzyl-1-methylindolin-2-one (***3c***)*: (Shi et al. 2014)

*1-Methyl-3,3-bis(2-methylbenzyl)indolin-2-one (***3d***)*: pale yellow solid; mp 102-104 °C (hexane/EtOAc) ; R_F 0.3 (hexane/EtOAc 9:1); IR (neat) ν 3058, 2963, 2923, 2857, 1709, 1611 cm^{-1}; ^1H NMR (400 MHz) δ 7.11 (1H, td, *J* = 7.6, 1.5 Hz, ArH), 7.02–6.94 (4H, m, ArH), 6.92-6.80 (6H, m, ArH), 6.51 (1H, d, *J* = 7.8 Hz, ArH), 3.31 (4H, s, 2 x CH_2), 2.93 (3H, s, NCH_3), 2.11 (6H, s, 2 x CH_3); ^{13}C NMR (101 MHz) δ 179.5 (CO), 143.8 (C), 137.19(C), 134.9 (C), 130.4 (C), 130.3 (2 x CH), 130.1 (2 x CH), 128.0 (CH), 126.6 (2 x CH), 125.2 (2 x CH), 124.8 (CH), 121.6 (CH), 107.7 (CH), 55.2 (2 x C), 39.2 (2 x CH_2), 26.0 (CH_3), 20.3 (2 x CH_3); LRMS (EI) *m/z* 355 (M^+, 55%), 356 (15), 251 (22), 250 (100), 222 (44), 207 (14), 159 (17), 105 (47); HRMS (ESI): calcd. for $C_{25}H_{25}NO$ $[M]^+$ 355.1936; found 355.1943.

*1'-Methyl-1,3-dihydrospiro[indene-2,3'-indolin]-2'-one (***3e***)*: (Frost et al. 2015)

*3,3-Diallyl-1-methylindolin-2-one (***3f***)*: (Ortega-Martínez et al. 2017)

*3,3-Dicinnamyl-1-methylindolin-2-one (***3g***)*: yellow oil; R_F 0.3 (hexane/EtOAc 9:1); IR (neat) ν 3053, 3024, 2926, 1701, 1614 cm^{-1}; ^1H NMR (400 MHz) δ 7.32–7.12 (12H, m, ArH), 7.08 (1H, t, *J* = 7.0 Hz, ArH), 6.78 (1H, d, *J* = 7.7 Hz, ArH), 6.36 (2H, d, *J* = 15.8 Hz, 2 x CH), 5.86 (2H, dt, *J* = 15.5, 7.5 Hz, 2 x CH), 3.13 (1H, s, NCH_3), 2.75 (4H, d, *J* = 7.4 Hz, 2 x CH_2); ^{13}C NMR (101 MHz) δ 179.0 (CO), 143.8 (C), 137.4 (2 x C), 133.9 (2 x CH), 131.4 (C), 128.5 (4 x CH), 128.1 (CH), 127.3 (2 x CH), 126.3 (4 x CH), 124.1 (2 x CH), 123.6 (CH), 122.5 (CH), 108.1 (CH), 53.4 (C), 40.4 (2 x CH_2), 26.3 (CH_3); LRMS (EI) *m/z* 379 (M^+, 32%) 380 (12), 288 (12), 281 (17), 262 (43), 261 (14), 234 (11), 208 (11), 207 (54), 147 (45), 146 (23), 118 (23), 117 (100), 116 (10), 115 (34), 91 (14); HRMS (ESI): calcd. for $C_{27}H_{25}NO$ $[M]^+$ 379.1936; found 379.1939.

*3,3-Bis((E)-3,7-dimethylocta-2,6-dien-1-yl)-1-methylindolin-2-one (***3h***)*: yellow oil; R_F 0.2 (hexane/EtOAc 9.5:0.5); IR (neat) ν 2965, 2921,

2855, 1717, 1612 cm^{-1}; ^1H NMR (300 MHz) δ 7.26–7.18 (2H, m, ArH), 7.01 (1H, td, *J* = 7.5, 0.9 Hz, ArH), 6.77 (1H, d, *J* = 7.7 Hz, ArH), 4.99–4.88 (2H, m, 2 x CH), 4.80 (2H, t, *J* = 7.0 Hz, 2 x CH), 3.16 (3H, s, NCH_3), 2.53 (4H, d, *J* = 7.5 Hz, 2 x CH_2), 1.90-1.65 (8H, m, 4 x CH_2), 1.63 (6H, s, 2 x CH_3), 1.53 (6H, s, 2 x CH_3), 1.51 (6H, s, 2 x CH_3); ^{13}C NMR (75 MHz) δ 180.0 (CO), 144.0 (C), 138.6 (2 x C), 132.3 (C), 131.4 (2 x C), 127.6 (CH), 124.3 (2 x CH), 123.5 (CH), 122.0 (CH), 118.3 (2 x CH), 107.5 (CH), 53.4 (C), 39.9 (2 x CH_2), 35.3 (2 x CH_2), 26.8 (2 x CH_2), 26.1 (CH_3), 25.8 (2 x CH_3), 17.7 (2 x CH_3), 16.5 (2 x CH_3); LRMS (EI) *m/z* 419 (M^+, 3%), 283 (35), 214 (10), 198 (18), 161 (11), 160 (91), 159 (100), 147 (24), 146 (14), 81 (12), 69 (39); HRMS (ESI): calcd. for $C_{29}H_{41}NO$ $[M]^+$ 419.3188; found 419.3191.

*Dimethyl 4,4'-(1-methyl-2-oxoindoline-3,3-diyl)bis(but-2-enoate) (***3i***)*: pale oil; R_F 0.25 (hexane/EtOAc 7:3); IR (neat) ν 2950, 1707, 1611 cm^{-1}; ^1H NMR (300 MHz) δ 7.30 (1H, td, *J* = 7.7, 1.3 Hz, ArH), 7.21–7.17 (1H, m, ArH), 7.09 (1H, td, *J* = 7.5, 0.9 Hz, ArH), 6.85 (1H, d, *J* = 7.8 Hz, ArH), 6.54 (2H, dt, *J* = 15.4, 7.6 Hz, 2 x CH), 5.79 (2H, d, *J* = 15.6 Hz, 2 x CH), 3.65 (6H, s, 2 x OCH_3), 3.19 (3H, s, NCH_3), 2.70 (4H, dd, *J* = 7.7, 1.3 Hz, 2 x CH_2); ^{13}C NMR (75 MHz) δ 177.55 (CO), 166.3 (2 x CO), 143.4 (C), 142.1 (2 x CH), 129.6 (C), 128.9 (CH), 124.9 (2 x CH), 123.3 (CH), 123.0 (CH), 108.7 (CH), 51.7 (C), 51.6 (2 x CH_3), 39.5 (2 x CH_2), 26.4 (CH_3); LRMS (EI) *m/z* 343 (M^+, 30%) 312 (14), 245 (14), 244 (88), 212 (46), 185 (23), 184 (100); HRMS (ESI): calcd. for $C_{19}H_{21}NO_5$ $[M]^+$ 343.142; found 343.1424.

*Diethyl 4,4'-(1-methyl-2-oxoindoline-3,3-diyl) (2E,2'E)-bis(but-2-enoate) (***3j***)*: brown oil; R_F 0.3 (hexane/EtOAc); IR (neat) ν 2981, 2937, 1716, 1655 cm^{-1}; ^1H NMR (300 MHz) δ 7.30 (1H, t, *J* = 7.7 Hz, ArH), 7.16–7.07 (2H, m, ArH), 6.84 (1H, d, *J* = 7.8 Hz, ArH), 6.53 (2H, dt, *J* = 15.4, 7.6 Hz, 2 x CH), 5.78 (2H, d, *J* = 15.5 Hz, 2 x CH), 4.34–3.95 (4H, m, 2 x CH_2), 3.19 (3H, s, NCH_3), 2.70 (4H, dd, *J* = 7.7, 1.3 Hz, 2 x CH_2), 1.26 (6H, dt, *J* = 22.4, 7.1 Hz, 2 x CH_3); ^{13}C NMR (101 MHz) δ 177.6 (CO), 165.9 (2 x CO), 143.4 (C), 141.7 (2 x CH), 129.6 (CH), 128.8 (C), 125.3 (2 x CH), 123.3 (CH), 123.0 (CH), 108.6 (CH), 60.4 (2 x CH_2), 51.7 (C), 39.4 (2 x CH_2), 26.3 (CH_3), 14.2 (2 x CH_3); LRMS (EI) *m/z* 371 (M^+, 13%), 258 (54), 230 (10), 212 (24), 186 (14), 185 (27), 184 (100), 158 (11), 156 (14), 147 (11), 144 (12), 130 (10), 128 (13), 77 (13); HRMS (ESI): calcd. for $C_{21}H_{25}NO_5$ $[M]^+$ 371.1733; found 371.1728.

*1-Methyl-3,3-di(prop-2-yn-1-yl)indolin-2-one (***3k***)*: (Zhou et al. 2013).

*Dimethyl 2,2'-(1-methyl-2-oxoindoline-3,3-diyl)diacetate (***3l***)*: yellow wax; R_F 0.3 (hexane/EtOAc 6.5:3.5); IR (neat) ν 2997, 2950, 1711, 1612 cm^{-1}; ^1H NMR (300 MHz) δ 7.30 (2H, t, *J* = 7.0 Hz, ArH), 7.03 (1H, t, *J* = 7.6 Hz, ArH), 6.87 (1H, d, *J* = 8.0 Hz, ArH), 3.50 (6H, s, 2 x OCH_3), 3.28 (3H, s, NCH_3), 3.06 (2H, d, *J* = 16.2 Hz, 2 x C*H*H), 2.87 (2H, d, *J* = 16.2 Hz, 2 x CH*H*); ^{13}C NMR (75 MHz) δ 178.3 (CO), 170.0 (2 x CO), 144.4 (C), 130.0 (C), 128.8 (CH), 123.4 (CH), 122.5 (CH), 108.3 (CH), 51.8 (2 x CH_3), 46.9 (C), 40.5 (2 x CH_2), 26.6 (CH_3); LRMS (EI) *m/z* 291 (M^+, 100%), 292 (17), 232 (29), 218 (13), 200 (13), 186 (21), 176 (51), 174 (21), 159 (43), 144 (16), 130 (25); HRMS (ESI): calcd. for $C_{15}H_{17}NO_5$ $[M]^+$ 291.1107; found 291.1103.

*2,2'-(1-Methyl-2-oxoindoline-3,3-diyl) diacetonitrile (***3m***)*: orange solid; mp 104-106 °C; R_F 0.3 (hexane/EtOAc 6.5:3.5); IR (neat) ν 2964, 2932, 1705, 1615 cm^{-1}; ^1H NMR (400 MHz) δ 7.58 (1H, d, *J* = 8.0 Hz, ArH), 7.46 (1H, td, *J* = 7.8, 1.2 Hz, ArH), 7.22 (1H, td, *J* = 7.7, 0.9 Hz, ArH), 6.98 (1H, d, *J* = 7.9 Hz, ArH), 3.29 (3H, s, NCH_3), 3.02 (2H, d, *J* = 16.7 Hz, 2 x C*H*H), 2.82 (2H, d, *J* = 16.7 Hz, 2 x CH*H*); ^{13}C NMR (101 MHz) δ 173.9 (CO), 143.2 (C), 130.8 (CH), 124.0 (CH), 126.4 (C), 123.6 (CH), 115.1 (2 x CN), 109.5 (CH), 45.8 (C), 26.9 (CH_3), 24.8 (2 x CH_2); LRMS (EI) *m/z* 225 (M^+, 33%), 186 (13), 185 (100), 155 (5), 142

(6), 128 (7); HRMS (ESI): calcd. for $C_{13}H_{11}N_3O$ $[M]^+$ 225.0902; found 225.0907

SYNTHESIS OF SPIROOXINDOLE **9** THROUGH A RUTHENIUM CATALYZED METATHESIS REACTION

To a solution of 2nd generation Grubbs catalyst (0.002 mmol, 1.7 mg) in dry dichloromethane (20 mL) compound **3f** (0.2 mmol, 45 mg) was added. The mixture was stirred during 1.5 h at 42°C under Ar atmosphere. The solution was filtered off through a short plug of celite. Finally, the solution was concentrated (15 Torr) and the residue was purified by column chromatography (hexane/EtOAc) obtaining *1'-Methylspiro[cyclopentane-1,3'-indolin]-3-en-2'-one (***9***)* (Kattela et al. 2017).

RESULTS AND DISCUSSION

The reaction was initially optimized using different bases (Ortega-Martínez et al. 2017) concluding that the most appropriate base was benzyltrimethylammonium hydroxide (Triton B) in THF as solvent at room temperature. The direct transformation employing 2.5 equiv. of both organic halide and base was not useful due to the formation of monoalkylated deacylated 2-oxindoles. For this reason, the double alkylation was performed in a one pot sequential process. On it, the first step consisted in the addition of the electrophile and the base (1 equiv. each reagent) in this order. After 4 h another addition of the same electrophile and base (1.5 equiv. each reagent) took place in order to complete the double alkylation mediated by the deacylative process, allowing the reaction to proceed at room temperature overnight. Compounds **3** were finally purified and isolated after column chromatography (flash silica gel) in very good to moderate yields (Figure 4, and Table I). When alkyl iodides were employed the chemical yields of products **3a** and **3b** were 51 and 33%, respectively (Table I, entries 1 and 2). This low conversion was caused by the relative low reactivity towards these alkyl

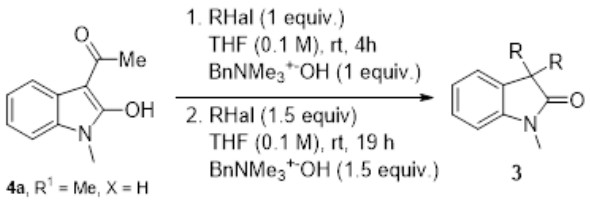


Figure 4 - DaA in the generation of 3,3-disubstituted oxindole **3**.

halides, and with the competition with the easy oxidation at the benzylic position. Thus, a 88:12 mixture of **3a**:3-hydroxy-1,3-dimethyloxindole and a 61:39 mixture of **3b**:3-hydroxy-3-ethyl-1-methyloxindole was observed by ^{1}H NMR (crude product). More activated halides such as benzylic bromides appearing in the three next entries of Table I furnished higher chemical yields in a range of 69-85%. Bisbenzylic unit was efficiently introduced providing spiranic oxindole derivative **3e**, whose skeleton is present in antitumor agents (Yang et al. 2016) and aldose reductase inhibitors (Howard et al. 1992). Allylic bromides such as allyl bromide and cinnamyl bromide also gave good conversions and yields 65 and 84%, respectively and no other byproduct was identified by ^{1}H NMR of the crude product (Table I, entries 6 and 7). The employment of geranyl bromide furnished a complex reaction mixture, which, after flash chromatography, allowed to isolate an inseparable 65:35 mixture of **3h** together with its corresponding deacylated 3-monoalkylated compound (Table I, entry 8). Technical methyl bromocrotonate and ethyl *E*-bromocrotonate gave similar results of **3i** and **3j** after this transformation, the crude compound **3i** being much more complex due to the presence of *Z*- and *E*-steroisomers (Table I, entries 9 and 10). Another three halides with π-extended conjugation were tested. Propargyl bromide gave a 58% yield of the disubstituted product **3k** (Table I, entry 11), methyl bromoacetate afforded a similar 61% yield (Table I, entry 12) and finally, bromoacetonitrile furnished the best chemical 82% yield of this

TABLE I
Synthesis of 3,3-disubstituted-2-oxindoles 3 using a DaA of 4a.

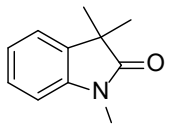
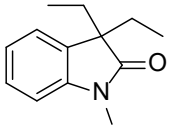
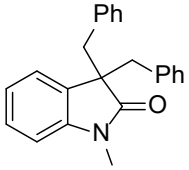
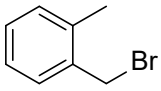
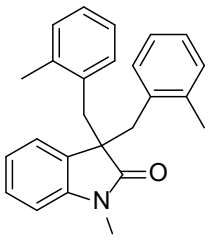
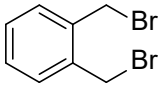
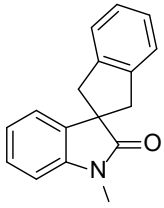
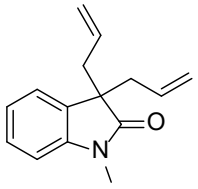
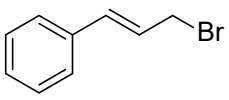
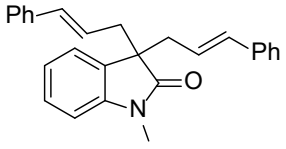
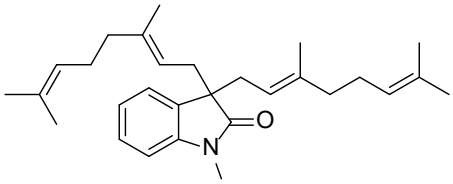
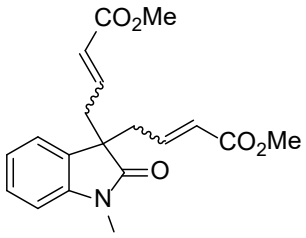
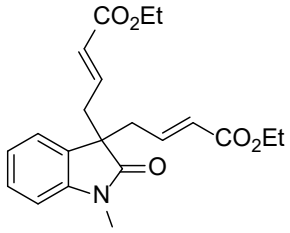
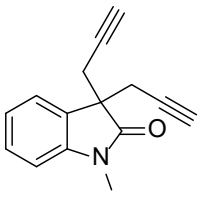
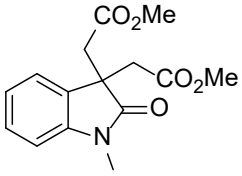
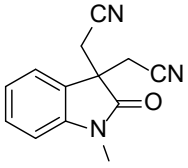
Entry	R-Hal	Compound	No.	Yield (%)[a,b]
1	MeI[c]		**3a**	51 (65)
2	EtI[d]		**3b**	33
3	$PhCH_2Br$		**3c**	83
4			**3d**	85 (58)
5			**3e**	69 (65)
6	$H_2C{=}CHCH_2Br$		**3f**	65 (59)
7			**3g**	84
8	Geranyl bromide[e]		**3h**	48

TABLE I (continuation)

Entry	R-Hal	Compound	No.	Yield (%)[a,b]
9	MeO_2C Br [f,g]		**3i**	58
10	EtO_2C Br [h]		**3j**	62
11	$HC\equiv CCH_2Br$		**3k**	58
12	$BrCH_2CO_2Me$[g]		**3l**	61
13	$BrCH_2CN$		**3m**	82

[a] Isolated yield after column chromatography (flash silica).

[b] In brackets, yields obtained from a direct dialkylation of *N*-methyloxindole.

[c] A 88:12 mixture of **3a**:3-hydroxy-1,3-dimethyloxindole was observed by NMR (crude product).

[d] A 61:39 mixture of **3b**:3-hydroxy-3-ethyl-1-methyloxindole was observed by NMR (crude product).

[e] This compound was obtained as an inseparable 65:35 mixture of **3h** and its corresponding deacylated 3-monoalkylated compound.

[f] This compound was obtained as 81:19 mixture of **3i** and its corresponding deacylated 3-monoalkylated compound, but **3i** could be finally separated.

[g] In this example, the sequential process was performed using: 1. RHal (1 equiv.) and Triton B (1 equiv.) at rt for 4 h; 2. RHal (1 equiv.) and Triton B (1 equiv.) at rt for 19 h; 3. RHal (0.5 equiv.) and Triton B (0.5 equiv.) at rt for 19 h.

[h] This compound was obtained as an inseparable 65:35 mixture of **3j** and its corresponding deacylated 3-monoalkylated compound.

series (Table I, entry 13). In entries 9 and 12 of the Table I a different protocol was employed in order to achieve higher yields. Thus, the addition of the total amount of reagents was performed adding RHal (1 equiv.) and Triton B (1 equiv.) at rt for 4 h, followed by de addition of RHal (1 equiv.) and Triton B (1 equiv.) at rt for 19 h and, finally RHal (0.5 equiv.) and Triton B (0.5 equiv.) at rt for 19 h completed the sequence.

In some examples depicted in Table I, a comparison of this deacylative route with the direct dialkylation of oxindole **8** with excess of both Triton B and the corresponding halide (Figure 5) was made. The direct alkylation was much more efficient when methyl iodide was tested (65% *versus* 51%, see Table I, entry 1). However, the yield of compound **3d**, using the DaA route, increased manifold (85% *versus* 58%, Table I, entry 4). 2-(Bromomethyl)benzyl bromide and allyl bromide gave very similar results using both reaction sequences such as it was depicted in Table I (entries 5 and 6) but the crude of the DaA mediated reactions were cleaner than the corresponding ones for the direct dialkylation way.

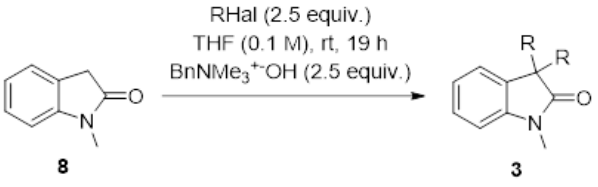


Figure 5 - Synthesis of 3,3-disubstituted oxindole **3** from *N*-methyloxindole (**8**).

The application of **3f** for the synthesis of other structurally complex containing this oxindole unit was envisaged. The metathesis reaction employing the 2nd generation Grubbs' catalyst produced spirocompound **9** in quantitative yield after 1.5 h under refluxing dichloromethane (Figure 6). The presence of the residual carbon-carbon double bond would allow the access to core framework of natural compounds citrinadins A and B (Bian et al. 2014) as well as the preparation of families of mentioned antitumor spiroxindole derivatives (see above).

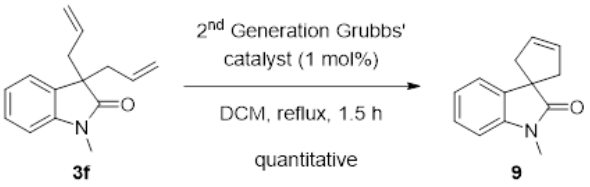


Figure 6 - Synthesis of spirooxindole **9** through a ruthenium-catalyzed metathesis reaction.

CONCLUSIONS

The sequential one-pot monoalkylation of 3-acetyl-1-methyl-2-oxindole, followed by a DaA-second alkylation is an alternative way to obtain symmetrical 3,3-disubstituted oxindole derivatives. The process competes with the direct dialkylation of *N*-methyloxindole because, in many cases, yields are higher and the crude materials cleaner, which are two very strong points in favor of this strategy. Some compounds obtained in this work (specifically **3e** and **9**) were suitable candidates to access interesting antitumor agents and natural compounds.

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