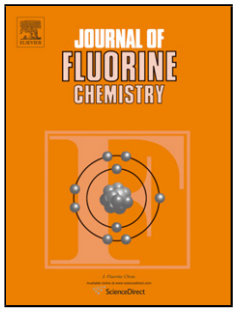


2,2,2-Trifluoroethanol-promoted access to symmetrically 3,3-disubstituted quinoline-2,4-diones

Marcel Manke Selvero, Gabriela N. Ledesma, Ulrich Abram, Ernesto Schulz-Lang, Ademir Farias Morel, Enrique L. Larghi

PII: S0022-1139(20)30071-3

DOI: https://doi.org/10.1016/j.jfluchem.2020.109520

Reference: FLUOR 109520

To appear in: *Journal of Fluorine Chemistry*

Received Date: 11 February 2020

Revised Date: 28 March 2020

Accepted Date: 28 March 2020

Please cite this article as: Selvero MM, Ledesma GN, Abram U, Schulz-Lang E, Morel AF, Larghi EL, 2,2,2-Trifluoroethanol-promoted access to symmetrically 3,3-disubstituted quinoline-2,4-diones, *Journal of Fluorine Chemistry* (2020), doi: https://doi.org/10.1016/j.jfluchem.2020.109520

2,2,2-Trifluoroethanol-promoted access to symmetrically 3,3-disubstituted quinoline-2,4-diones

Marcel Manke Selvero,[1] Gabriela N. Ledesma,[2] Ulrich Abram,[3] Ernesto Schulz-Lang,[1] Ademir Farias Morel,[*,1] and Enrique L. Larghi[*,2]

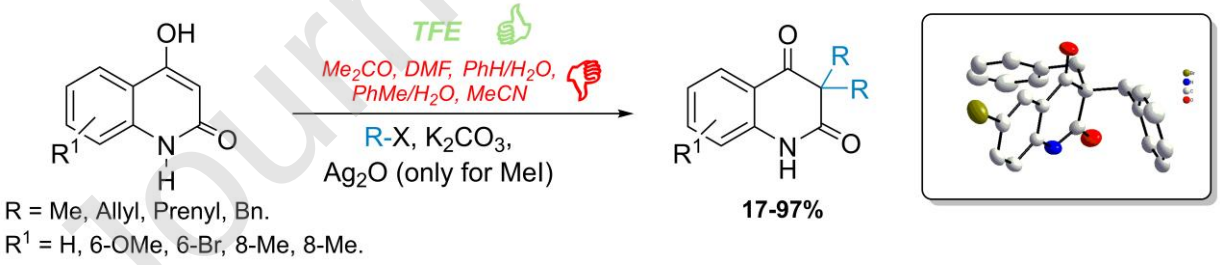
Address: [1]Universidade Federal de Santa Maria, Campus Universitário, Camobi, Santa Maria (RS) Brazil. [2]Instituto de Química Rosario (IQUIR, CONICET-UNR), Suipacha 531, Rosario (SF) Argentina. [3]Institute of Chemistry and Biochemistry, Freie Universität Berlin, Fabeckstrasse 34/36, D-14195 Berlin, Germany.

Email: Ademir F. Morel* - afmorel@base.ufsm.br. Fax: +55-55-3220-8741.

Email: Enrique L. Larghi* - larghi@iquir-conicet.gov.ar. Tel./Fax.: +54-341-437-0477.

* Corresponding authors

Graphical abstract



Highlights

- 2,2,2-trifluoroethanol (TFE) promotes the access to 3,3-dialkylated quinoline-2,4-diones in moderate to high yields in a regioselective fashion.
- Scope and limitations: bromo, methyl and methoxy substituents attached to the 4-hydroxy-2-quinolone core reacted smoothly with benzyl, allyl, and prenyl bromides

under the assistance of K_2CO_3. When using MeI, Ag_2O was added to boost the reaction. Higher alkyl halides were unreactive under these conditions.

Abstract

The unprecedented use of 2,2,2-trifluoroethanol as reaction solvent provided a facile and convenient access to symmetrically 3,3-disubstitued quinoline-2,4-diones in moderate to excellent yields and high regioselectivity, by reaction of 4-hydroxy-2-quinolones with electrophiles like methyl iodide, as well as benzyl and allyl bromides in the presence of K_2CO_3. Silver (I) oxide is required to increase the yield of the methylations.

Keywords: Alkylation; 3,3-disubstituted-quinoline-2,4-diones; fluorinated solvent; heterocycles; 2,2,2-trifluoroethanol.

1. Introduction

Achieving high levels of selectivity in alkylation reactions is a strongly demanding task when dealing with polyphilic nucleophiles. Thus, many efforts have been devoted to find solutions to this intriguing problem [1]. Particularly, heterocyclic systems exhibiting tautomeric equilibria have long been investigated in order to establish regioselective alkylation conditions. In a pioneering work, Kornblum *et al.* [2] studied the course of the alkylation of 2-pyridones (**1**) under different scenarios. They observed that mixtures of *C*, *N* and/or *O*-alkyl derivatives (**4a-c**, Scheme 1) were obtained, depending on the nature of the solvent, the alkylation agent and the leaving group.

Shortly after, Hopkins and Jonak [3] re-examined the alkylation of 2-pyridones, reaching good levels of *N*/*O* selectivity (**4b,c**) and excellent yields. The groups of

Baldwin and Wei [4] employed silver carbonate and methyl iodide in the dialkylation of the parent 4-hydroxy-2-pyridones (**2**), obtaining mixtures of alkylated products mainly composed by **4d,e** (Scheme 1). More recently, the group of Mayr [5] rationalized the ambident reactivity of the heterocyclic pyridone core from the theoretical point of view.

Quite interestingly, however, finding a general solution for the synthetic problem associated to the *C,C*-dialkylation (**4f**, Scheme 1) of the 4-hydroxy-2-quinolones (**3**) achieving high degree of regioselectivity and good yields is a longstanding quest.

Many research groups contributed to solve this stimulating topic. Kappe *et al.* [6] provided a first insight into the *C*,*C*-dialkylation of **3**, obtaining the desired products **4f** by reaction with allyl bromide, BnCl and EtI in H_2O or DMF; however, the yields were variable and strongly dependent on the nature of the base, alkylation agent and solvent. Recently, the group of Buthani [7] described a process which afforded *n*-alkyl, allyl, prenyl and propargyl 3,3-disubstituted-quinoline-2,4-diones (**4f**, Scheme 1) in aqueous medium, in moderate to good yields. According to their findings, formation of the desired products was accompanied by 3-monoalkyl-quinolone derivatives (**4d**, Scheme 1). Interestingly, several of these substances exhibited promising anti-HIV activity.

During our studies on the antimicrobial activity of 3,3-dibenzyl-4-hydroxyquinoline-2-ones [8], we accessed these compunds by reduction of parent derivatives **4f**. In turn, the latter were synthesized following literature methodologies. In our hands, however, the reported procedures gave the expected products **4f** in moderate yields complemented with variable amounts of *N,C,C*-trisalkylated derivatives (**4g**, Scheme 1), which sometime were also troublesome to separate by column chromatography.

A detailed literature survey revealed that most procedures for the alkylation of 4-hydroxy-2-quinolones (**3**) with activated alkylating agents ($C_6H_5CH_2Br$, CH_3I, $CH_2=CHCH_2Br$), provide moderate levels of chemoselectivity, affording mixtures of *O*-, *N*- and *C*-alkylated by-products, depending on the nature of the solvent and base [9]. The concomitant formation of undesired side products reflects the complex nature of this non-trivial synthetic problem. As consequence, when several research groups needed compounds like **4g** into their synthetic work, alternative approaches devoid of the troublesome alkylation scenario were conceived [10,11,12]. These compounds were used as chemical precursors of clinically relevant substances, and as structural parts of specialized catalysts for aldol, Michael and related reactions [13,14].

Therefore, moved by the selectivity limitations of the available alternatives for the 3,3-dialkylation of the heterocyclic core **3**, we decided to develop an alternative method toward quinoline-2,4-dione derivatives (**4f**).

2. Results and Discussion

Our efforts oriented to *C,C*-dialkylate **5a** commenced by adapting the conditions of Kornblum *et al.* [15] to our synthetic problem. Initially, several solvents and bases were examined, employing BnBr as alkylating agent (Table 1). A model with MeI was also prepared, due to the interesting synthetic and pharmacological applications of the 3,3-dimethyl derivatives [**Error! Bookmark not defined.**c,**Error! Bookmark not defined.**,] [16].

In a biphasic PhH/H_2O medium, using NaOH or K_2CO_3 as bases and different BnBr molar ratios, we were able to cleanly obtain the desired product **6a** in up to 85% yield (entries 1-3). However, repeating the transformation with MeI did not met with the same success. No reaction was observed in the presence of KOH (entry 4), whereas

the use of K_2CO_3 as base afforded a meagre 17% yield of 3,3-dimethylated product **7a** (entry 5).

Unexpectedly, when benzene was replaced with the more convenient toluene, the yield of **6a** dropped to 40%, and the concomitant formation of the tris-benzyl derivative **8** was observed (entry 6) [**Error! Bookmark not defined.**]. Even worse, when MeCN and K_2CO_3 were employed, derivatives **8** and **9** were detected (entries 7 and 8) as the major components of reactions after using BnBr and MeI as electrophiles, respectively [14a].

Further, the methylation in acetone employing K_2CO_3 furnished the desired product **7a** along with polyalkylated derivatives (entry 9), consistent with the observation of Reisch [17]. Other examined solvents (DMF, EtOH, dioxane) mostly afforded complex mixtures or partial reaction, enabling the recovery of the starting quinolone.

After re-examining the conditions of Kornblum and recently rationalized by Adlington [15a,b], we focused our attention on 2,2,2-trifluoroethanol (TFE) as a more suitable reaction medium [18]. This solvent demonstrated to promote the *C*-alkylation of phenols and naphthols, instead of functionalization of the more reactive *O*H group, by blocking the oxygen atom through selective hydrogen bonding [15b]. Moreover, this solvent showed to be particularly useful in promoting otherwise difficult or poorly selective reactions [19].

The unique properties of TFE, including its high ionizing power and relatively non-nucleophilic character (when compared with water and alkanols) facilitate ionic reactions and provide better selectivity for the alkylation with external electrophiles, despite the competing solvolysis of the latter [20].

Therefore, when quinolone **5a** was treated with BnBr in the presence of CF_3CH_2ONa, the desired product **6a** was obtained in 78% yield after 22 h at room temperature (entry 10). Fortunately, replacement of this base with the inexpensive K_2CO_3

consistently provided **6a** in 97% yield, at the expense of the need to stir the mixture at 60 °C during 17 h (entry 11).

Unexpectedly, however, application of the best conditions found for dibenzylation (entry 11) to the *gem*-dimethylation reaction met with failure, and only 17% yield of product **7a** was attained (entry 12). Further, the reaction in the presence of KOH as base had no better fate, giving **7a** in 14% yield (entry 13).

These observations suggested that the reactivity of MeI required an additional fine tuning to more efficiently furnish the expected product. Hence, it was hoped that the addition of silver salts would suffice to enhance the system reactivity [21]. These compounds weaken the C-*Hal* bond during the nucleophilic displacement, and concomitantly form highly insoluble silver halides, which drive the reaction to completion. We have previously used this concept for the preparation of 2,4-dialkoxy quinolines [22]. In addition, despite it has found scattered use in the chemistry of quinolones, this strategy was also employed for the synthesis of sterically hindered heterocycles [23].

Therefore, Ag_2CO_3 was added to the reaction mixture, affording a dissapointing 18% yield of the product (entry 14). Delightfully, when the reaction mixture was supplemented with Ag_2O the 3,3-dimethylquinolone **7a** was obtained in a moderate 52% yield, after stirring the reaction mixture at room temperature during 12 h (entry 15).

With the optimized conditions in hand, the scope and limitations of the procedure were explored. Several 4-hydroxy-2-quinolones (**5a**-**e**) were tested (Table 2), affording benzylated products **6a-e** in good to excellent yields (entries 1-5).

The scope of the optimized methylation conditions was also tested with compounds **5a**-**e**, obtaining products **7a-e** in 17-52% yield (entries 6-10). In addition, we were

glad to observe the formation of products **10a-e** in moderate to good yields (52-62%) when the benzylation protocol was extended to reactions using allyl bromide as alkylating agent (entries 11-15). Further, prenyl bromide reacted smoothly with **5a** to afford the 3,3-diprenyl quinolone **11** in 47% yield (entry 16).

Finally, when the alkylation reaction was tested with the less reactive *n*-propyl iodide, and despite the transformation was performed in the presence of Ag_2O, only 8% yield of the desired product **12** was obtained, accompanied by unreacted starting material (> 80%) [**Error! Bookmark not defined.**a]. Further, alkyl halides with longer carbon chains proved to be essentially unreactive, establishing a limitation to this protocol. The structures of the different heterocyclic products were assessed by NMR and IR spectroscopy. In addition, the solid state structure of the newly synthesized quinolone **6c** was also characterized by single-crystal X-ray diffraction [24], confirming its assignment. Compound **6c** crystallizes in the monoclinic space group *P* $2_1/c$, with four molecules per unit cell (Figure 1) without molecules of solvent.

3. Conclusion

In summary, the unprecedented use of 2,2,2-trifluoroethanol as a unique solvent for the synthesis of 3,3-disubstituted quinoline-2,4-diones by the selective dialkylation of the readily available 4-hydroxy-2-quinolones in the presence of K_2CO_3 as base, was reported. The transformation was optimized for benzylation and methylation reactions, and its scope and limitations were studied.

The procedure selectively gave moderate to excellent yields of the symmetrically *C,C*-dialkylated products, being advantageous because of the use of a more benign solvent, mild reaction conditions and an economically accessible base, as well as the highly stable silver(I) oxide, as promoter for the methylation.

The general applicability of the transformation, which is able to accommodate a variety of substituents and substitution patterns, turns this reaction into a convenient and complementary alternative to other methodologies oriented toward 3,3-disubstituted-quinoline-2,4-diones.

4. Experimental

4.1. General remark

The reactions were performed under dry argon atmosphere, using oven dried glassware. Benzyl bromide, allyl bromide and MeI were distilled prior to use [25]. K_2CO_3 was oven-dried before use. The solvents (TFE, MeCN, Me_2CO and PhH) were of PA grade and were used as received. The 4-hydroxy-2-quinolones were prepared as described by Ferretti *et al.* [8].

The reactions were monitored by TLC (Merck's silica gel 60 GF_{254}) employing mixtures of hexanes/EtOAc for elution. The chromatographic spots were visualized by exposure to UV light (254 and 365 nm) and spraying with ethanolic *p*-anisaldehyde/sulfuric acid reagent, followed by careful heating to improve selectivity. The column chromatographies were executed on silica gel (230-400 mesh), eluting with mixtures of hexanes and EtOAc of increasing polarity.

4.2. Equipment

The melting points (uncorrected) were measured on a Microquímica MQAPF-301 hot-stage microscope and are informed uncorrected. The FT-IR spectra were recorded on Perkin-Elmer 1310 or Bruker IFS-28 spectrophotometers as solid dispersions in KBr compressed disks (solid samples) or as thin films held between NaCl cells (oily samples).

The NMR spectroscopic data were recorded in $CDCl_3$ unless otherwise stated, with a Bruker DPX-200 instrument. Chemical shifts are reported in ppm on the δ scale and the solvent residual signals of $CDCl_3$ (δ = 7.26 and 77.0 ppm for ^1H and ^{13}C NMR, respectively) were used as internal standard. Multiplicities are abbreviated as follows: s = singlet, s_b = broad singlet, d = doublet, dd = doublet of doublets, t = triplet, m = multiplet. Signal assignments were carried out based on ^1H, ^{13}C, DEPT, HSQC, HMBC and COSY spectra. The assigned resonances marked with "*" or "#" are interchangeable. The magnitude of the coupling constant (*J*) values are given in Hertz.

HRMS were obtained with a Bruker MicroTOF-Q II instrument (UMYMFOR, Buenos Aires, Argentina) and a Bruker BioApex spectrometer (FAB technique, at 70 eV) from the Institut of Plant Biochemistry, Halle-Saale, Germany.

The X-ray diffraction data were collected on an automated single crystal CAD4 (Enraf-Nonius, Delft, Netherlands) diffractometer with Mo Kα radiation (FU Berlin, Germany). The structure was solved by direct methods using SHELXS-97 and refined with SHELXL-97 on F^2 using anisotropic temperature parameters for all non-hydrogen atoms [26].Hydrogen atom positions were calculated starting from idealized positions, and the molecular structures were designed with DIAMOND [27]. Table S1 contains crystal data and more details of the data collections and refinements.

4.3. General procedure for the *C,C*-dialkylation of 4-hydroxy-2-quinolones

To the appropriate 4-hydroxy-2-quinolone (1.0 mmol), K_2CO_3 (6.0 mmol) and TFE (8.0 mL) were added. The slurry was magnetically stirred until partial dissolution of the quinolone. After this, the halide (6.0 mmol; 12.0 mmol in case of MeI) was added, the system was capped with a septum and stirred under argon atmosphere at 60 °C until consumption of starting material. For the methylation, Ag_2O (2.0 mmol) was

added before the MeI. The mixture was stirred at room temperature for 12h, protected from light with an aluminum foil. Then, the solvent was recovered by careful distillation at atmospheric pressure, and the resulting solids were suspended in EtOAc (10 mL). The solids were filtered under reduced pressure through a Celite pad and washed with small portions of EtOAc (4 × 2 mL). The combined liquids were concentrated in vacuum and the residue was purified by column chromatography.

4.4. Characterization of the products

(**6a**) [6b]: Colorless solid; mp: 187-188 °C. IR (KBr) v; 3180, 3066, 2937, 1692, 1657, 1605, 1599, 1489, 1391, 1301, 770, 701, 500, 443 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.47 (s_b, 1H, *H*-1), 7.88 (dd, *J* = 7.8, 1.5, 1H, *H*-5), 7.29-6.93 (m, 12H, $C_6H_5CH_2$, *H*-6, 7), 6.55 (d, *J* = 8.0, 1H, *H*-8), 3.51 (d, *J* = 12.8, 2H, $C_6H_5CH_2$), 3.43 (d, *J* = 12.8, 2H, $C_6H_5CH_2$). ^{13}C NMR (50 MHz, $CDCl_3$): δ 197.1 (*C*-4), 173.7 (*C*-2), 140.3 (*C*-5a), 135.8 (*C*-7), 135.6 (2C, *C-ipso,* $C_6H_5CH_2$), 129.8 (4C, *C-ortho*, $C_6H_5CH_2$), 128.0 (4C, *C-meta*, $C_6H_5CH_2$), 126.8 (2C, *C-para*, $C_6H_5CH_2$, *C*-5), 123.1 (*C*-6), 119.5 (*C*-8a), 115.8 (*C*-8), 64.5 (*C*-3), 45.2 (2C, $C_6H_5CH_2$).

(**6b**) [8]: Colorless solid; mp: 180-181 °C. IR (KBr) v; 3180, 3040, 2900, 1680, 1640, 1490, 1410, 1350, 1240, 1170, 1030, 810, 700, 620 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.48 (s_b, 1H, *H*-1), 7.23 (d, *J* = 2.8, 1H, *H*-5), 7.11-6.99 (m, 10H, $C_6H_5CH_2$), 6.87 (dd, *J* = 8.8, 2.8, 1H, *H*-7), 6.51 (d, *J* = 8.8, 1H, *H*-8), 3.75 (OMe-6), 3.53 (d, *J* = 12.8, 2H, $C_6H_5CH_2$), 3.42 (d, *J* = 12.8, 2H, $C_6H_5CH_2$). ^{13}C NMR (50 MHz, $CDCl_3$): δ 197.1 (*C*-4), 173.7 (*C*-2), 155.4 (*C*-6), 135.6 (2C, *C-ipso,* $C_6H_5CH_2$), 134.6 (*C*-5a), 129.8 (4C, *C-ortho*, $C_6H_5CH_2$), 128.0 (4C, *C-meta*, $C_6H_5CH_2$), 126.8 (2C, *C-para*, $C_6H_5CH_2$), 124.5 (*C*-7), 120.3 (*C*-8a), 117.3 (*C*-6), 107.9 (*C*-8), 64.1 (*C*-3), 55.5 (O*Me*-8), 45.2 (2C, $C_6H_5CH_2$).

(**6c**): Yellowish solid; mp: 207-209 °C. IR (KBr) v; 3320, 3040, 2920, 1690, 1650, 1590, 1480, 1350, 1270, 1190, 820, 750, 700 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.11 (s_b, 1H, *H*-1), 7.89 (d, *J* = 2.4, 1H, *H*-5), 7.35 (dd, *J* = 8.6, 2.4, 1H, *H*-7), 7.08-7.01 (m, 10H, $C_6H_5CH_2$), 6.43 (d, *J* = 8.6, 1H, *H*-8), 3.49 (d, *J* = 12.8, 2H, $C_6H_5CH_2$), 3.41 (d, *J* = 12.8, 2H, $C_6H_5CH_2$). ^{13}C NMR (50 MHz, $CDCl_3$): δ 196.1 (*C*-4), 173.7 (*C*-2), 139.1 (*C*-5a) 138.5 (*C*-7), 135.3 (2C, *C-ipso,* $C_6H_5CH_2$), 129.7 (4C, *C-ortho*, $C_6H_5CH_2$), 129.4 (*C*-5), 128.2 (4C, *C-meta*, $C_6H_5CH_2$), 127.0 (2C, *C-para*, $C_6H_5CH_2$), 121.1 (*C*-6*), 117.5 (*C*-8), 115.9 (*C*-8a*), 64.7 (*C*-3), 45.3 (2C, $C_6H_5CH_2$). HRMS (ESI): *m/z* calcd. for $C_{23}H_{19}BrNO_2^+$ $[M+H]^+$: 420.0599; Found: 420.0592. Single crystals suitable for X-ray diffraction were obtained after slow solvent evaporation from an *n*-hexane/EtOAc solution [24].

(**6d**) [8]: Colorless solid; mp. 195-196 °C. IR (KBr) v; 3200, 3060, 2920, 1690, 1650, 1600, 1500, 1380, 1260, 1070, 970, 700 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.86 (s_b, 1H, *H*-1), 7.35 (ddd, *J* = 7.6, 1.8, 0.5, 1H, *H*-5), 7.25-7.01 (m, 10H, $C_6H_5CH_2$), 6.83-6.77 (m, 2H, *H*-6, 7), 3.69 (s, 3H, OMe-8), 3.49 (d, *J* = 12.8, 2H, $C_6H_5CH_2$), 3.42 (d, *J* = 12.8, 2H, $C_6H_5CH_2$). ^{13}C NMR (50 MHz, $CDCl_3$): δ 197.3 (*C*-4), 172.0 (*C*-2), 145.2 (*C*-8), 135.9 (2C, *C-ipso,* $C_6H_5CH_2$), 130.6 (*C*-8a), 129.9 (4C, *C-ortho*, $C_6H_5CH_2$), 128.0 (4C, *C-meta*, $C_6H_5CH_2$), 126.8 (2C, *C-para*, $C_6H_5CH_2$), 122.2 (*C*-6), 120.1 (*C*-8a), 118.0 (*C*-5*), 115.8 (*C*-7*), 64.7 (*C*-3), 60.0 (O*Me*-8), 45.4 (2C, $C_6H_5CH_2$).

(**6e**): Colorless solid; mp. 215-217 °C. IR (KBr) v; 3230, 2920, 1690, 1650, 1590, 1490, 1380, 700 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.10 (s_b, 1H, *H*-1), 7.67 (d, *J* = 7.5, 1H, *H*-5), 7.13-7.02 (m, 11H, *H*-7, $C_6H_5CH_2$), 6.84 (t, 1H, *J* = 7.6, *H*-6), 3.50 (d, *J* = 12.8, 2H, $C_6H_5CH_2$), 3.41 (d, *J* = 12.8, 2H, $C_6H_5CH_2$), 2.02 (s, 3H, Me-8). ^{13}C NMR

(50 MHz, $CDCl_3$): δ 197.1 (*C*-4), 172.8 (*C*-2), 138.5 (*C*-8), 137.0 (*C*-7), 135.7 (2C, *C-ipso,* $C_6H_5CH_2$), 129.9 (4C, *C-ortho*, $C_6H_5CH_2$), 127.9 (4C, *C-meta*, $C_6H_5CH_2$), 126.9 (2C, *C-para*, $C_6H_5CH_2$), 124.9 (*C*-6), 122.5 (C-5, C-5a), 120.0 (*C*-8a), 64.4 (*C*-3), 45.2 (2C, $C_6H_5CH_2$), 16.2 (*Me*-8). HRMS (FAB) *m/z*: calcd. for $C_{24}H_{22}NO_2^+$ $[M+H]^+$: 356.1645; Found: 356.1654.

(**7a**) [6]: Colorless solid; mp. 163-164 °C. IR (KBr) v; 3190, 3060, 2920, 1690, 1650, 1590, 1430, 1380, 1240, 1180, 980, 830, 750, 660 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 9.32 (s_b, 1H, *H*-1), 7.88 (dd, *J* = 7.8, 1.5, 1H, *H*-5), 7.49 (ddd, *J* = 8.1, 7.4, 1.5, 1H, *H*-7), 7.08 (ddd, *J* = 7.8, 7.4, 1.2, 1H, *H*-6), 6.94 (dd, *J* = 8.1, 1.2, 1H, *H*-8), 1.45 (s, 6H, Me-3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 197.6 (*C*-4), 176.8 (*C*-2), 140.8 (*C*-5a), 135.9 (*C*-7), 127.9 (*C*-5), 123.5 (*C*-6), 118.5 (*C*-8a), 116.3 (*C*-8), 52.7 (*C*-3), 23.5 (2C, *Me*-3).

(**7b**) [10c,d]: Almost colorless solid; mp. 175-176 °C. IR (KBr) v; 3180, 3060, 2960, 1680, 1640, 1590, 1490, 1340, 1220, 1160, 1030, 820, 760, 650 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 9.89 (s_b, 1H, *H*-1), 7.38 (d, *J* = 1.5, 1H, *H*-5), 7.15 (dd, *J* = 7.7, 1.5, 1H, *H*-7), 7.00 (d, *J* = 8.1, 1H, *H*-8), 3.83 (s, 3H, OMe-6), 1.51 (s, 6H, Me-3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 197.8 (*C*-4), 176.3 (*C*-2), 155.8 (C-6), 134.9 (*C*-8a), 124.6 (*C*-7), 118.8 (*C*-4a), 117.7 (*C*-8), 109.0 (C-5), 55.7 (O*Me*-6), 52.4 (*C*-3), 23.6 (2C, *Me*-3). HRMS (FAB) *m/z*: calcd. for $C_{12}H_{14}NO_3^+$ $[M+H]^+$: 220.0974; Found: 220.0974.

(**7c**) [28]: Pale brownish solid, mp. 215-217 °C. IR (KBr) v; 3200, 3060, 2980, 1700, 1660, 1590, 1410, 1320, 1250, 1190, 840, 660 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 9.58 (s_b, 1H, *H*-1), 8.05 (d, *J* = 2.0, 1H, *H*-5), 7.64 (dd, *J* = 8.5, 2.0, 1H, *H*-7), 6.93 (d,

J = 8.5, 1H, *H*-8), 1.51 (s, 6H, Me-3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 196.3 (*C*-4), 176.1 (*C*-2), 139.6 (*C*-5a), 138.5 (*C*-7), 130.6 (*C*-5), 119.9 (*C*-6*), 117.9 (*C*-8*), 116.2 (*C*-8a), 52.9 (*C*-3), 23.4 (2C, *Me*-3).

(**7d**): Colorless solid; mp. 158-159 °C. IR (KBr) v; 3200, 3080, 2940, 1700, 1660, 1590, 1490, 1380, 1330, 1260, 1080, 990, 810, 730 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.03 (s_b, 1H, *H*-1), 7.55-7.52 (m, 1H, *H*-5), 7.08-7.07 (m, 2H, *H*-6, 7), 3.94 (s, 3H, OMe-8), 1.50 (s, 6H, Me-3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 197.7 (*C*-4), 174.3 (*C*-2), 145.8 (*C*-8), 130.9 (*C*-8a), 122.7 (*C*-6), 119.0 (*C*-5), 118.6 (*C*-8a), 115.8 (*C*-7), 56.2 (O*Me*-8), 53.1 (*C*-3), 23.5 (2C, *Me*-3). HRMS (FAB) *m/z*: calcd. for $C_{12}H_{13}NNaO_3^+$ $[M+Na]^+$: 242.0793; Found: 242.0791.

(**7e**): Colorless solid; mp. 150-152 °C. IR (KBr) v; 3200, 3080, 2920, 1680, 1640, 1590, 1450, 1380, 1220, 990, 800, 750, 670 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.33 (s_b, 1H, *H*-1), 7.81 (dd, *J* = 7.7, 1H, *H*-5), 7.40 (dd, *J* = 7.7, 1.5, 1H, *H*-7), 7.06 (t, *J* = 7.7, 1H, *H*-6), 2.36 (s, 3H, Me-8), 1.50 (s, 6H, Me-3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 197.8 (*C*-4), 175.5 (*C*-2), 138.9 (*C*-8), 137.1 (*C*-7), 126.0 (*C*-6*), 123.3 (*C*-5a), 122.9 (*C*-5*), 118.5 (*C*-8a), 52.7 (*C*-3), 23.4 (2C, *Me*-3), 16.7 (*Me*-8). HRMS (FAB) *m/z*: calcd. for $C_{12}H_{14}NO_2^+$ $[M+H]^+$: 204.1019; Found: 204.1019.

(**10a**) [7a]: Colorless solid; mp. 80-82 °C. IR (KBr) v; 3187, 3068, 3000, 2932, 1692, 1661, 1598, 1485, 1380, 1239, 1156, 926, 759, 666, 438 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.99 (s_b, 1H, *H*-1), 7.87 (dd, *J* = 7.9, 1.4, 1H, *H*-5), 7.54 (ddd, *J* = 8.1, 6.9, 1.4, 1H, *H*-7), 7.06 (ddd, *J* = 7.9, 6.9, 1.0, 1H, *H*-6), 6.95 (d, *J* = 8.1, 1H, *H*-8), 5.63-5.43 (m, 2H, CH_2CH=CH_2), 5.02-4.83 (m, 4H, $CH_2CH = CH_2$), 2.80-2.61 (m, 4H, -

C*H*$_2$CH=CH$_2$). ^{13}C NMR (50 MHz, CDCl$_3$): δ 196.8 (*C*-4), 174.8 (*C*-2), 141.2 (*C*-5a), 136.4 (*C*-7), 132.0 (2C, CH$_2$*C*H=CH$_2$), 127.6 (*C*-5), 123.7 (*C*-6), 119.8 (*C*-8a), 119.5 (2C, CH$_2$CH=*C*H$_2$), 116.2 (*C*-8), 61.6 (*C*-3), 42.9 (2C, *C*H$_2$CH=CH$_2$).

(**10b**): Colorless solid; mp. 159-161 °C. IR (KBr) v; 3180, 3050, 2980, 1690, 1650, 1590, 1410, 1350, 1290, 1170, 1030, 910, 840, 700, 650 cm^{-1}. ^{1}H NMR (200 MHz, CDCl$_3$): δ 9.70 (s$_b$, 1H, *H*-1), 7.37 (d, *J* = 2.8, 1H, *H*-5), 7.15 (dd, *J* = 8.8, 2.8, 1H, *H*-7), 6.92 (d, *J* = 8.8, 1H, *H*-8), 5.65-5.51 (m, 2H, CH$_2$C*H*=CH$_2$), 5.07-4.91 (m, 4H, CH$_2$CH=C*H*$_2$), 3.83 (s, 3H, OMe-6), 2.83-2.69 (m, 4H, C*H*$_2$CH=CH$_2$). ^{13}C NMR (50 MHz, CDCl$_3$): δ 196.7 (*C*-4), 173.9 (*C*-2), 155.8 (*C*-6), 135.1 (*C*-5a), 131.8 (2C, CH$_2$*C*H=CH$_2$), 125.0 (*C*-7), 120.1 (*C*-8a), 119.3 (2C, CH$_2$CH=*C*H$_2$), 117.8 (*C*-8), 108.3 (*C*-5), 61.1 (*C*-3), 55.7 (O*Me*-6), 42.8 (2C, *C*H$_2$CH=CH$_2$). HRMS (ESI), *m/z*: calcd. for C$_{16}$H$_{18}$NO$_3^+$ [M+H]$^+$: 272.1281; Found: 272.1293.

(**10c**): Yellowish solid; mp. 140-142 °C. IR (KBr) v; 3180, 3060, 2960, 1690, 1650, 1590, 1410, 1380, 1280, 990, 920, 840, 650 cm^{-1}. ^{1}H NMR (200 MHz, CDCl$_3$): δ 9.75 (s$_b$, 1H, *H*-1), 8.04 (d, *J* = 2.3, 1H, *H*-5), 7.63 (dd, *J* = 8.5, 2.3, 1H, *H*-7), 6.89 (d, *J* = 8.5, 1H, *H*-8), 5.63-5.50 (m, 2H, CH$_2$C*H*=CH$_2$), 5.08-4.93 (m, 4H, CH$_2$CH=C*H*$_2$), 2.83-2.69 (m, 4H, C*H*$_2$CH=CH$_2$). ^{13}C NMR (50 MHz, CDCl$_3$): δ 195.5 (*C*-4), 174.2 (*C*-2), 139.7 (*C*-5a), 138.8 (*C*-7), 131.4 (2C, CH$_2$*C*H=CH$_2$), 129.9 (*C*-5), 120.8 (*C*-6*), 119.7 (2C, CH$_2$CH=*C*H$_2$), 118.1 (*C*-8), 116.4 (*C*-8a*), 61.6 (*C*-3), 42.7 (2C, *C*H$_2$CH=CH$_2$). HRMS (ESI), *m/z*: calcd. for C$_{15}$H$_{15}$BrNO$_2^+$ [M+H]$^+$: 320.0281; Found: 320.0283

(**10d**) [29]: Yellowish solid; mp. 83-85 °C. IR (KBr) v; 3180, 3060, 2940, 1680, 1650, 1590, 1490, 1370, 1270, 920, 730 cm^{-1}. ^{1}H NMR (200 MHz, CDCl$_3$): δ 8.34 (s$_b$, 1H,

H-1), 7.56-7.47 (m, 1H, *H*-5), 7.10-7.01 (m, 2H, *H*-6, 7), 5.66-5.49 (m, 2H, CH_2CH=CH_2), 5.11-4.91 (m, 4H, CH_2CH=CH_2), 3.93 (s, 3H, OMe-8), 2.83-2.65 (m, 4H, -CH_2CH=CH_2). ^{13}C NMR (50 MHz, $CDCl_3$): δ 197.2 (*C*-4), 172.6 (*C*-2), 146.2 (*C*-8), 132.2 (2C, CH_2CH=CH_2), 131.6 (*C*-5a*), 123.1 (*C*-6), 120.2 (*C*-8a*), 119.7 (2C, CH_2CH=CH_2), 118.8 (*C*-5), 116.4 (*C*-7), 62.1 (*C*-3), 56.6 (O*Me*-8), 43.0 (2C, CH_2CH=CH_2).

(**10e**): Almost colorless solid; mp. 75-76 °C. IR (KBr) v; 3240, 3080, 2920, 1690, 1640, 1590, 1470, 1370, 1220, 920, 780, 700 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.98 (s_b, 1H, *H*-1), 7.84-7.79 (m, 1H, *H*-5), 7.42-7.38 (m, 2H, *H*-7), 7.01 (t, 2H, *J* = 7.7, *H*-6), 5.69-5.49 (m, 2H, CH_2CH=CH_2), 5.08-4.90 (m, 4H, CH_2CH=CH_2), 2.82-2.63 (m, 4H, CH_2CH=CH_2), 2.37 (s, 3H, Me-8). ^{13}C NMR (50 MHz, $CDCl_3$): δ 196.7 (*C*-4), 173.5 (*C*-2), 139.2 (*C*-8), 137.4 (*C*-7*), 131.8 (2C, CH_2CH=CH_2), 125.3 (*C*-6*), 123.6 (*C*-5a$^{\#}$), 122.8 (*C*-5*), 119.6 (2C, CH_2CH=CH_2), 119.2 (*C*-8a$^{\#}$), 61.1 (*C*-3), 42.4 (2C, CH_2CH=CH_2), 16.8 (*Me*-3). HRMS (FAB), *m/z*: calcd. for $C_{16}H_{18}NO_2^+$ $[M+H]^+$: 256.1332; Found: 256.1327.

(**11**) [30]: Colorless solid; mp. 103-105 °C (Lit. 126-127 °C). IR (KBr) v; 3200, 3060, 2920, 1690, 1650, 1590, 1440, 1390, 1290, 1160, 840, 750 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.2 (s_b, 1H, *H*-1), 7.82 (dd, *J* = 7.8, 1.4, 1H, *H*-5), 7.44 (m, 1H, *H*-7), 7.03 (m, 1H, *H*-6), 6.95 (d, *J* = 8.0, 1H, *H*-8), 4.87-4.83 (m, 2H, CH_2CH=CMe_2), 1.51 (s, 3H, *Z*-CH_2CH=C*Me*$_2$), 1.43 (s, 3H, *E*-CH_2CH=C*Me*$_2$). ^{13}C NMR (50 MHz, $CDCl_3$): δ 197.7 (*C*-4), 175.5 (*C*-2), 140.8 (*C*-5a), 135.8 (*C*-7*), 135.7 (2C, CH_2CH=CMe_2*), 125.9 (*C*-5), 123.1 (*C*-6), 119.6 (*C*-8a), 117.7 (2C, CH_2CH=CMe_2), 116.2 (*C*-8), 61.9 (*C*-3), 37.4 (2C, CH_2CH=CMe_2), 25.7 (2C, *E*-CH_2CH=C*Me*$_2$), 23.5 (2C, *Z*-CH_2CH=C*Me*$_2$).

(**12**) [7a]: Colorless solid; mp. 101-102 °C. IR (KBr) v; 3200, 2920, 1690, 1650, 1590, 1480, 1380, 750 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.13 (s_b, 1H, *H*-1), 7.95 (dd, *J* = 7.9, 1.6, 1H, *H*-5), 7.54 (ddd, *J* = 8.0, 7.3, 1.6, 1H, *H*-7), 7.08 (dd, *J* = 7.9, 7.3, 1H, *H*-6), 6.94 (d, *J* = 8.0, 1H, *H*-8), 2.03-1.96 (m, 4H, C*H*$_2$CH$_2$Me), 1.26-1.23 (m, 4H, CH$_2$C*H*$_2$Me), 0.83-0.79 (m, 6H, CH$_2$CH$_2$Me). ^{13}C NMR (50 MHz, $CDCl_3$): δ 198.1 (*C*-4), 175.4 (*C*-2), 140.9 (*C*-5a), 135.6 (*C*-7), 127.3 (*C*-5), 123.4 (*C*-6), 119.8 (*C*-8a), 116.1 (*C*-8), 61.9 (*C*-3), 42.0 (2C, *C*H$_2$CH$_2$Me), 18.4 (2C, CH$_2$*C*H$_2$Me), 14.3 (2C, CH$_2$CH$_2$*Me*).

Declaration of Competing Interest

The authors declare no competing financial interest.

Declaration of Competing Interest

No conflict of interest to declare.

Acknowledgments

This work was supported by CNPq (Processo 403471/2013-3), CONICET and MINCyT (PICT 2014-0445). Dr. Ludger A. Wessjohann (Leibniz Institute of Plant Biochemistry, Halle-Saale, Germany) is thanked for several HRMS determinations. Dr. Teodoro S. Kaufman is acknowledged for fruitful discussions and revision of this manuscript.

References

[1] (a) F. Zaragoza Dörwald, Side Reactions in Organic Synthesis: A Guide to Successful Synthesis Design. Wiley, Chichester, UK, 2006. (b) H. Mayr, M. Breugst, A. R. Ofial, Farewell to the HSAB Treatment of Ambident Reactivity, Angew. Chem. Int. Ed. 50 (2011) 6470-6505. (c) J. Hartung, R. Kneuer, M. Schwarz, I. Svoboda, H. Fuess, On the Selective O-Alkylation of Ambident Nucleophiles – The Synthesis of Thiohydroxamic Acid O-Esters by Phase-Transfer Reactions, Eur. J. Org. Chem. (1999) 97–106.

[2] (a) N. Kornblum, G.P. Coffey, The Reaction of Triethyloxonium Fluoroborate with the Sodium Salt of α-Pyridone, J. Org. Chem. 31 (1966) 3449–3451. (b) N. Kornblum, R.A. Smiley, R.K. Blackwood, D.C. Iffland, The Mechanism of the Reaction of Silver Nitrite with Alkyl Halides. The Contrasting Reactions of Silver and Alkali Metal Salts with Alkyl Halides. The Alkylation of Ambident Anions, J. Am. Chem. Soc. 77 (1955) 6269–6280 and references cited therein.

[3] (a) G.C. Hopkins, J.P. Jonak, H.J. Minnemeyer, H. Tieckelmann, Alkylations of Heterocyclic Ambident Anions. I. 2-Hydroxypyrimidines, J. Org. Chem. 31 (1966) 3969–3973. (b) Ibid., Alkylations of heterocyclic ambident anions II. Alkylation of 2-pyridone salts, J. Org. Chem. 32 (1967) 4040–4044. (c) M.C. Chung, H. Tieckelmann, Alkylations of heterocyclic ambident anions. IV. Alkylation of 5-carbethoxy-and 5-nitro-2-pyridone salts, J. Org. Chem. 35 (1970) 2517–2520.

[4] (a) Z.L. Wei, P.A. Petukhov, Y. Xiao, W. Tuckmantel, C. George, K.J. Kellar, A.P. Kozikowski, Synthesis, nicotinic acetylcholine receptor binding affinities, and molecular modeling of constrained epibatidine analogues, J. Med. Chem. 46 (2003) 921–924. (b) J.E. Baldwin, R.M. Adlington, A. Conte, N.R. Irlapati, R. Marquez, G.J.

Pritchard, Total synthesis of pyridovericin: Studies toward the biomimetic synthesis of pyridomacrolidin, Org. Lett. 4 (2002) 2125–2127.

[5] M. Breugst, H. Mayr, Ambident reactivities of pyridone anions, J. Am. Chem. Soc. 132 (2010) 15380–15389.

[6] (a) T. Kappe, P.F. Fritz, E. Ziegler, Alkylierung ambidenter Heterocyclen-Anionen, V. Umlagerung von Heterocyclen, III. Zur Allylierung des 4-Hydroxy-2-chinolons, Chem. Ber. 106 (1973) 1927–1942. (b) T. Kappe, E. Ziegler, Alkylierung ambidenter Heterocyclen-Anionen, 1. Mitt.: Über die Benzylierung des 4-Hydroxy-carbostyrils, Monatsch. Chem. 99 (1968) 1943–1949. (c) T. Kappe, H. Sterk, E. Ziegler, Alkylierung ambidenter Heterocyclen-Anionen, 2. Mitt.: Zur Alkylierung von 4-Hydroxy-carbostyrilen, Monatsch. Chem. 99 (1968) 1950–1957.

[7] (a) N. Ahmed, K.G. Brahmbhatt, I.P. Singh, K.K. Bhutani, Efficient chemoselective alkylation of quinoline 2,4-diol derivatives in water, J. Heterocyclic Chem. 48 (2010) 237–240. (b) N. Ahmed, K.G. Brahmbhatt, S. Sabde, D. Mitra, I.P. Singh, K.K. Bhutani, Synthesis and anti-HIV activity of alkylated quinoline 2,4-diols, Bioorg. Med. Chem. 18 (2010) 2872–2879.

[8] M.D. Ferretti, A.T. Neto, A.F. Morel, T.S. Kaufman, E.L. Larghi, Synthesis of symmetrically substituted 3,3-dibenzyl-4-hydroxy-3,4-dihydro-1H-quinolin-2-ones, as novel quinoline derivatives with antibacterial activity, Eur. J. Med. Chem. 81 (2014) 253–266.

[9] (a) S.K. Chattopadhyay, R. Dey, S. Biswas, Regioselective synthesis of oxepin- and oxocin-annulated 2-quinolones, Synthesis (2005) 403–406. (b) M.F. Grundon, V.N. Ramachandran, A reversible Claisen rearrangement of 3-(3,3-dimethylallyl)-4-(3,3-dimethylallyloxy)quinolin-2-one; synthesis of buchapsine and loss of its 1, 1-dimethylallyl group, Tetrahedron Lett. 26 (1985) 4253–4256. (c) M.F. Grundon, V.N. Ramachandran, M.E. Donnelly, Quinoline alkaloids. Part 22. Synthesis of the

monoterpenoid quinoline alkaloid, bucharaine, J. Chem. Soc. Perkin Trans. 1 (1981) 633–635. (d) J. Reisch, A. Bathe, Acetylenchemie, 5. Mitt. PTC-Umsetzung von 4-Hydroxychinolin-2-on und Indolin-2-on mit 3-Bromprop-1-in, Arch. Pharm. 320 (1987) 737–742.

[10] (a) C. Zikou, O. Igglessi-Markopoulou, Modified Mukaiyama reaction for the synthesis of quinoline alkaloid analogues: total synthesis of 3,3-diisopentenyl-N-methylquinoline-2,4-dione, Synthesis (2008) 1861–1866. (b) A.L. Zografos, C.A. Mitsos, O. Igglessi-Markopoulou, One-step synthesis for the preparation of quinoline alkaloid analogues, Org. Lett. 1 (1999) 1953–1955. (c) U.-M. Billhardt-Troughton, M. Roesner, R. Bender, C. Meichsner, 4-iminoquinolines, processes for their preparation, and their use. Patent U.S. 5,602,146, Feb. 11, 1997. (d) R. Kirsch, J.-P. Kleim, G. Riess, M. Roesner, I. Winkler, Substituted quinoline derivatives, a process for their preparation, and their use. Patent US 5,798,365, Aug. 25, 1998.

[11] T. Sheradsky, N. Itzhak, Reaction of carbanions with N-tosyloxyphthalimide. Formation of 3,3-disubstituted quinoline-2,4-diones, J. Chem. Soc. Perkin Trans. 1 (1986) 13–16.

[12] (a) F. Burg, M. Gicquel, S. Breitenlechner, A. Pöthig, T. Bach, Site- and Enantioselective C−H Oxygenation Catalyzed by a Chiral Manganese Porphyrin Complex with a Remote Binding Site, Angew. Chem. Int. Ed. 57 (2018) 2953–2957. (b) Q.-Y. Hu, G.M. Ksander, 4-imidazolyl-1,2,3,4-tetrahydroquinoline derivatives and their use as aldosterone/11-beta-hydroxylase inhibitors. Patent WO 076860, Jun. 26, 2008.

[13] D. Brundish, A. Bull, V. Donovan, J.D Fullerton, S.M. Garman, J.F. Hayler, D. Janus, P.D. Kane, M. McDonnell, G.P. Smith, R. Wakeford, C.V. Walker, G. Howarth, W. Hoyle, M.C. Allen, J Ambler, K. Butler, M.D. Talbot, Design and synthesis of

thrombin inhibitors: analogues of MD-805 with reduced stereogenicity and improved potency, J. Med. Chem. 42 (1999) 458–477.

[14] (a) N. Kise, K. Sasaki, T. Sakurai, Reductive coupling of isatins with ketones and aldehydes by low-valent titanium, Tetrahedron 70 (2014) 9668–9675. (b) A.R. Evans, R. Martin, G.A. Taylor, C.H.M. Yap, Ketene. Part 26. The reactions of 3,4-dihydroisoquinoline N-oxide with ketenes, and an attempted synthesis of 3,4-dihydro-3,3-dimethylquinoline N-oxide, J. Chem. Soc. Perkin Trans. 1 (1987) 1635–1640. (c) J. Bergman, A. Brynolf, E. Vuorinen, A new synthesis of 4-amino-2-quinolinones, Tetrahedron 42 (1986) 3689–3696. (d) A.B. Daruwala, J.E. Gearien, W.J. Dunn III, P.S. Benoit, L. Bauer, beta.-Amino ketones. Synthesis and some biological activities in mice of 3,3-dialkyl-1,2,3,4-tetrahydro-4-quinolinones and related Mannich bases, J. Med. Chem. 17 (1974) 819–824.

[15] (a) L.J. Diorazio, D.R.J. Hose, N.K. Adlington, Toward a more holistic framework for solvent selection, Org. Proc. Res. Dev. 20 (2016) 760–773. (b) N. Kornblum, R. Seltzer, P. Haberfiel, Solvation as a factor in the alkylation of ambident anions: The importance of the dielectric factor, J. Am. Chem. Soc. 85 (1963) 1148–1154.

[16] S. Samajdar, C. Abbineni, S. Sasmal, S. Hosahalli, Bicyclic heterocyclic derivatives as bromodomain inhibitors. Patent WO 104653, Jul. 16, 2015.

[17] (a) J. Reisch, I. Mester, Über die Methylierung von 4-Hydroxy-2-chinolon, Arch. Pharm. 313 (1980) 751–755. (b) K. Jones, X. Roset, S. Rossiter, P. Whitfield, Demethylation of 2, 4-dimethoxyquinolines: the synthesis of atanine, Org. Biomol. Chem. 1 (2003) 4380–4383.

[18] (a) J. Wencel-Delord, F. Colobert, A remarkable solvent effect of fluorinated alcohols on transition metal catalysed C–H functionalizations, Org. Chem. Front. 3 (2016) 394–400. (b) C. Venkateswarlu, P.V. Balaji, K. De, B. Crousse, B. Figadère, J. Legros, Straightforward synthesis of 2-propylquinolines under multicomponent

conditions in fluorinated alcohols, J. Fluorine Chem. 152 (2013) 94–98. (c) S. Khaksar, M. Yaghoobi, A concise and versatile synthesis of 2-amino-3-cyanopyridine derivatives in 2,2,2-trifluoroethanol, J. Fluorine Chem. 142 (2012) 41–44. (d) J.-P. Bégué, D. Bonnet-Delpon, B. Crousse, Fluorinated alcohols: A new medium for selective and clean reaction, Synlett (2004) 18–29.

[19] (a) D. Gimenez, A. Dose, N.L. Robson, G. Sandford, C. Cobb, C.R. Coxon, 2, 2, 2-Trifluoroethanol as a solvent to control nucleophilic peptide arylation, Org. Biomol. Chem. 15 (2017) 4081–4085. (b) B. Carbain, C.R. Coxon, H. Lebraud, K.J. Elliott, C.J. Matheson, E. Meschini, A.R. Roberts, D.M. Turner, C. Wong, C. Cano, R.J. Griffin, I.R. Hardcastle, B.T. Golding, Trifluoroacetic Acid in 2,2,2-Trifluoroethanol Facilitates SNAr Reactions of Heterocycles with Arylamines, Chem. Eur. J. 20 (2014) 2311–2317. (c) H. Lebraud, C. Cano, B. Carbain, I.R. Hardcastle, R.W. Harrington, R.J. Griffin, B.T. Golding, Trifluoroethanol solvent facilitates selective N-7 methylation of purines, Org. Biomol. Chem. 11 (2013) 1874–1878.

[20] (a) B. Denegri, A.R. Ofial, S. Jurić, A. Streiter, O. Kronja, H. Mayr, How Fast Do R–X Bonds Ionize? A Semiquantitative Approach, Chem. Eur. J. 12 (2006) 1657–1666 and references therein cited. (b) K.-T. Liu, Y.-F. Duann, S.-J. Hou, Nucleophilic solvent participation in the solvolysis of 4-methoxybenzyl bromide and chloride, J. Chem. Soc. Perkin Trans. 2 (1998) 2181–2186. (c) D.J. Raber, M.D. Dukes, J. Gregory, Hexaflouroisopropanol - a solvent of high ionizing power and low nucleophilicity, Tetrahedron Lett. 15 (1974) 667–670. (d) D.A. da Roza, L.J. Andrews, R.M. Keefer, Solvent system ethanol-2,2,2-trifluoroethanol as a medium for solvolytic displacement, J. Am. Chem. Soc. 95 (1973) 7003–7009.

[21] R. Scheffold, E. Bertele, H. Gschwend, W. Häusermann, P. Wehrli, W. Huber, A. Eschenmoser, Corrin Syntheses. Part II: Synthesis of Corrin Complexes via A→B Ring Closure. Preparation of Hemicorrinoid B/C-Components, and Model Studies on

Enamides and Imido Ester C,C Condensations, Helv. Chim. Acta 98 (2015) 1601–1682.

[22] A.F. Morel, E.L. Larghi, M.M. Selvero, Mild, efficient and selective silver carbonate mediated O-alkylation of 4-hydroxy-2-quinolones: Synthesis of 2,4-dialkoxyquinolines, Synlett (2005) 2755–2758.

[23] R. Šarac-Arneri, M. Mintas, N. Pustet, A. Mannschreck, Syntheses, separation of enantiomers and barriers to racemization of some sterically hindered N-aryl-1,2,3,4-tetrahydro-3,3-dimethyl-2,4-quinolinediones and their thio analogues, Monatsh. Chem. 125 (1994) 457–468.

[24] The Cambridge Crystallographic Data Centre (CCDC) contains supplementary crystallographic data for compound **6c** (CCDC 1876517). These data can be obtained free of charge via www.ccdc.cam.uk/data_request/cif.

[25] W.L.F. Armarego, C.L.L. Chai, Purification of Laboratory Chemicals, 5th Ed. Butterworth-Heinemann, Oxford, UK, 2003.

[26] G.M. Sheldrick, A short history of SHELX, Acta Cryst. A64 (2008) 112–122.

[27] K. Brandenburg, DIAMOND. Crystal Impact GbR, Bonn, Germany, 2006.

[28] J. Chao, I.J. Enyedy, K. Guertin, R.H. Hutchings, J.H. Jones, N. Powell, K.D. Vanvloten, Biaryl-containing compounds as inverse agonists of ror-gamma receptors. Patent WO 008214, Jan. 9, 2014.

[29] N. Shobana, P. Shanmugam, Partial Deallylation of 3,3-Diallyl-1,2,3,4-tetrahydroquinolin-2,4-diones by Sodium Hydrogen Telluride, Ind. J. Chem. 25B (1986) 1264–1265.

[30] F. O'Donnell, T.J.P. Smyth, V.N. Ramachandran, W.F. Smyth, A study of the antimicrobial activity of selected synthetic and naturally occurring quinolines, Int. J. Antimicrob. Ag. 35 (2010) 30–38.

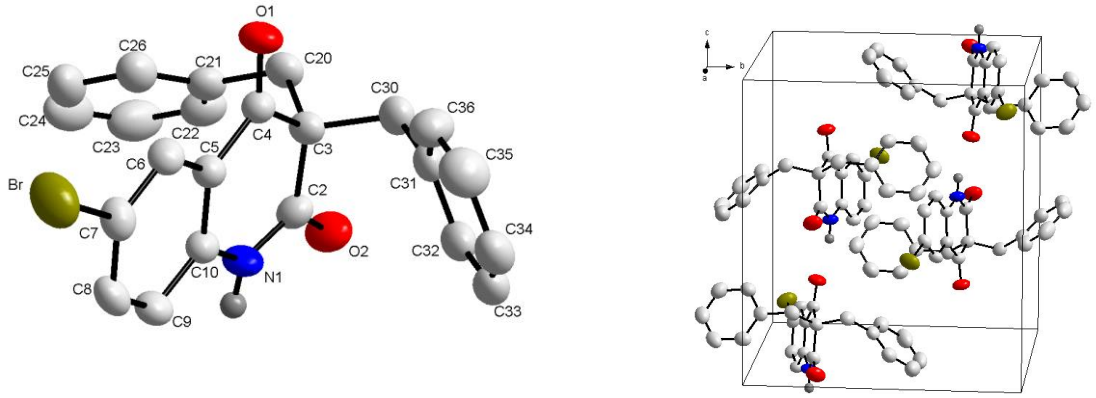
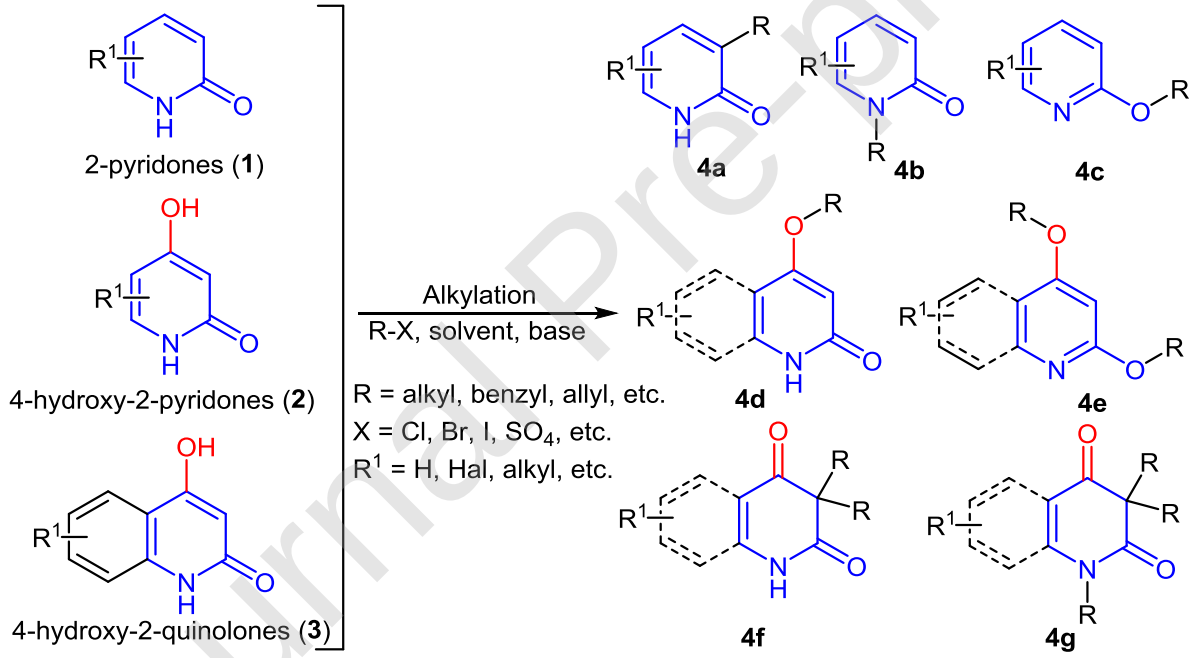
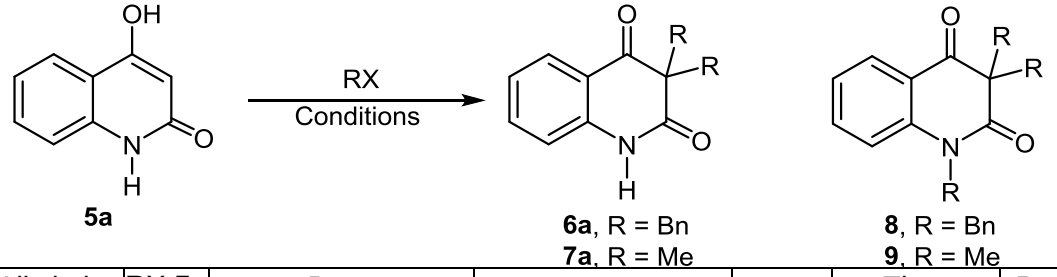


Figure 1. a) Molecular structure of **6c**. The displacement ellipsoids were drawn at the 50% probability level and the hydrogen atoms were omitted for the sake of clarity; b) unit cell of **6c**.



Scheme 1. Alkylation of heterocyclic scaffolds **1-3** and products formation **4a-g**.

Table 1. Optimization of the *C,C*-dialkylation of **5a** to afford **6a** and **7a**.



5a

6a, R = Bn
7a, R = Me

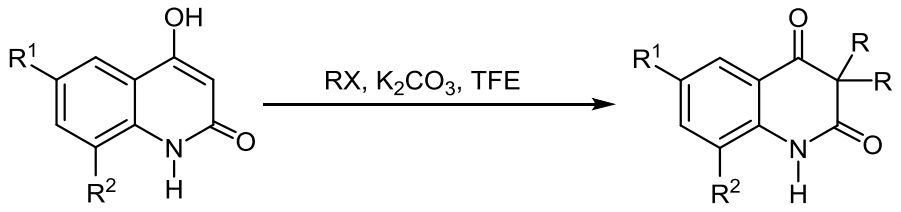
8, R = Bn
9, R = Me

Entry N°	Alkylating agent	RX:**5a** ratio	Base (equiv.)	Solvent	Temp.	Time (h)	Product (Yield, %)
1	BnBr	2:1	NaOH (2.0)	PhH/H_2O (1:1)	reflux	24	**6a** (43)
2	BnBr	4:1	NaOH (4.0)	PhH/H_2O (1:1)	reflux	24	**6a** (68)
3	BnBr	6:1	K_2CO_3 (6.0)	PhH/H_2O (1:1)	reflux	12	**6a** (85)
4	MeI	12:1	KOH (6.0)	PhH/H_2O	reflux	12	-
5	MeI	12:1	K_2CO_3 (6.0)	PhH/H_2O	reflux	12	**7a** (17)
6	BnBr	6:1	K_2CO_3 (6.0)	PhMe/H_2O (1:1)	reflux	48	**6a** (40)
7	BnBr	6:1	K_2CO_3 (6.0)	MeCN	reflux	24	-[a]
8	MeI	12:1	K_2CO_3 (6.0)	MeCN	reflux	12	**7a** (34)[b]
9	MeI	12:1	K_2CO_3 (6.0)	Acetone	reflux	12	**7a** (11)
10	BnBr	6:1	CF_3CH_2ONa (6.0)	TFE	rt	22	**6a** (78)
11	BnBr	6:1	K_2CO_3 (6.0)	TFE	60 °C	17	**6a** (97)
12	MeI	12:1	K_2CO_3 (6.0)	TFE	reflux	12	**7a** (17)
13	MeI	12:1	KOH (6.0)	TFE	reflux	12	**7a** (14)
14	MeI	12:1	Ag_2CO_3 (6.0)	TFE	reflux	12	**7a** (18)
15	MeI	12:1	K_2CO_3 (Ag_2O)	TFE	rt	12	**7a** (52)

[a] 1,3,3-*tris*-benzylated quinolone (**8**) was mainly recovered.

[b] Compound **9** was the main product of this reaction.

Table 2. Scope of the *C,C*-dialkylation affording the 3,3-disubstituted quinoline-2,4-diones.



5a-e **6a-e**, **7a-e, 10a-e, 11, 12**

Entry N°	RX	R^1	R^2	Product N°	Yield (%)
1	BnBr	H	H	**6a**	97
2	BnBr	OMe	H	**6b**	94
3	BnBr	Br	H	**6c**	81
4	BnBr	H	OMe	**6d**	92
5	BnBr	H	Me	**6e**	97
6	MeI	H	H	**7a**	52[a]
7	MeI	OMe	H	**7b**	31[a]
8	MeI	Br	H	**7c**	17[a]
9	MeI	H	OMe	**7d**	40[a]
10	MeI	H	Me	**7e**	37[a]
11	AllylBr	H	H	**10a**	61
12	AllylBr	OMe	H	**10b**	60
13	AllylBr	Br	H	**10c**	54
14	AllylBr	H	OMe	**10d**	56
15	AllylBr	H	Me	**10e**	62
16	PrenylBr	H	H	**11**	47
17	*n*-PrI	H	H	**12**	8[a]

[a]The reaction was performed in the presence of Ag_2O.