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PAPER

Synthesis and reactivity of furoquinolines bearing an external methylene-bond: access to reduced and spirocyclic structures†‡

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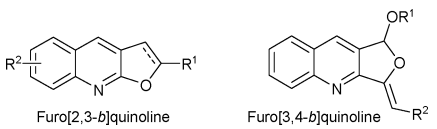
A family of furoquinolines were efficiently obtained through a tandem acetalization/cycloisomerization process catalyzed by (5 mol%) silver imidazolate polymer and triphenylphosphine, and diversity was brought by the use of 7 different alcohol groups. From these furoquinolines, 3 examples of reduced derivatives could be obtained (d.r. up to 94 : 6), 10 different spiroketal derivatives by hetero-Diels–Alder reaction (d.r. up to 20 : 1), 8 hetero-[5,5]-spirocycles by cycloaddition with dibromoformaldoxime (d.r. up to 86 : 14) and finally 6 hetero-[5,6]-spirocycles by [4 + 2] cycloaddition with ethyl 3-bromo-2-(hydroxyimino)propanoate (d.r. up to 90 : 10).

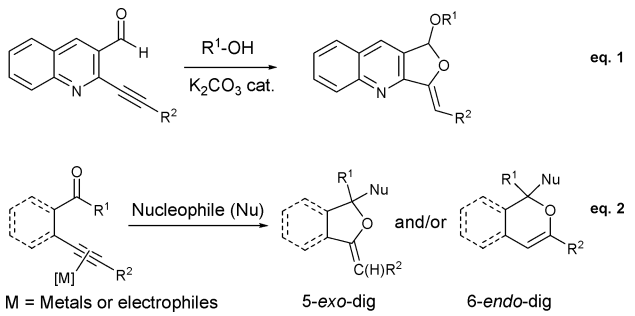
Introduction

Furoquinoline alkaloids are natural products mostly extracted from rutaceous plants (Scheme 1, furo[2,3-*b*]quinoline) and are of interest due to their broad biological properties.[1] Over the last few years we have been involved in the synthesis of isomeric structures, namely furo[3,4-*b*]quinolines (Scheme 1).



Scheme 1 Furo[2,3-*b*]quinoline and furo[3,4-*b*]quinoline cores.

These heterocycles were first obtained using a base-catalyzed tandem acetalization/cycloisomerization reaction from quinoline-carbaldehydes *ortho*-substituted by alkynyl moieties (Scheme 2, eq. 1).[2] Base catalysis had been developed previously on a pyridine scaffold by Ohshiro,[3] and Abbiati[4] reported in parallel to our work an interesting method on indole cores. Extension of these methods has been also published[5] along with thorough mechanistic studies.[6] Due to scope limitation, organometallic conditions were sought after since various electrophilic inorganic and organometallic agents are used by several research groups to activate an alkynyl bond.[7] Initially, theses systems (Scheme 2, eq. 2) were studied by Larock's[8] (I_2, ICl, NBS, PhSeBr, *p*-$NO_2C_6H_4SCl$), Barluenga's[9] (IPy_2BF_4), Asao/Yamamoto's[10] (Pd^{II},[11] Cu^{II} or Cu^{I}, Pd^{II}/Cu^{II}, Au^{I} or Au^{III}) and Mascareñas'[12] (Pd^{II}, W, Pt, Ru) groups.



Scheme 2

Thus, our original contribution[13] has been the use of a range of silver salts were the π-acidic category (AgOTf, $AgPF_6$, $AgSbF_6$, $AgNO_3$) yielded the pyranoquinoline cores through a 6-*endo*-dig cyclization process and the basic category (AgO, Ag_2O, Ag_2CO_3) led to the formation of furoquinolines by a 5-*exo*-dig cyclization process (Scheme 2, eq. 2). This difference of reactivity was rationalized based on different mechanistic pathways.[13] Our implication for studying the regioselectivity of such reactions was crucial since up to that time no general rationale had been established in the literature. Moreover, an interesting nitrogen-effect recently disclosed[14] led us to develop the use of a silver imidazolate polymer, as an easy handling and robust silver catalyst, for the efficient synthesis of a wide range of furoquinoline structures.

In this paper, we wish to expand the scope of the furoquinoline family, and furthermore to study the reactivity of their external methylene unit. Indeed, the reactivity of the enol-ether bond present in the furo[3,4-*b*]quinoline scaffold has not been considered yet for [3 + 2] and [4 + 2] cycloadditions, yielding spirocyclic structures, or for reduction (Scheme 3). Nevertheless, some

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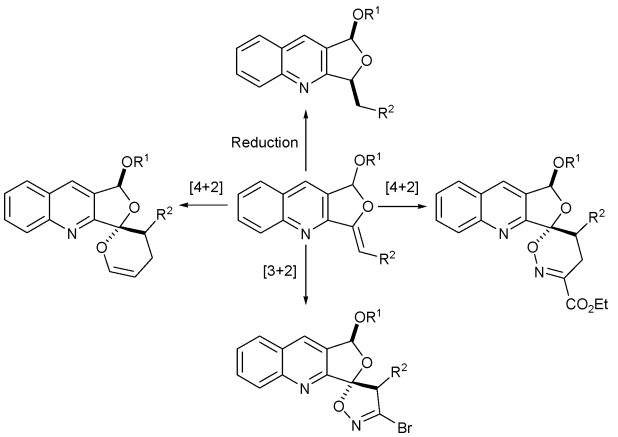
‡ This paper is dedicated to the memory of Pr. François Tillequin



Scheme 3 Target structures.

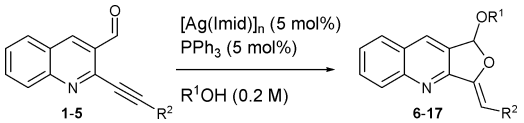
interesting cascade[15] or sequential reactions[16] on *exo*-methylene units have recently been published.

These types of double-bonds have already been widely modified on (tetrahydro)furanes or *exo*-glycal moieties and the resulting spirocycles (spiroketals[17] or hetero-spirocycles[18]) obtained are of interest for their biological relevance and since a number of them can be found in natural products. Therefore, we wish to present our work on the reduction of furoquinolines and also the access to new tetracyclic pharmacophores made of various spirocycles fused on the quinoline nucleus.

Results and discussions

In connection with our ongoing studies on silver/gold-catalyzed cycloisomerization reactions,[7f,13a,19] we have recently disclosed the use of silver imidazolate polymer[14] as a new organometallic catalyst. However only 2-(diethyl)aminoethanol was extensively studied as the nucleophile. Therefore, we wish to begin this report with a nice extension of our methodology using a variety of alcohol groups (R^1OH, see Table 1) at room temperature. Indeed, silver imidazolate and PPh_3 (5 mol% each) added in the appropriate alcohol as the reaction solvent (0.2 M), catalyzed the tandem acetalization/cycloisomerization reaction on quinoline derivatives (bearing at position 2 an akynyl substituent and at position 3 an aldehyde group), leading to furoquinolines bearing an external methylene-bond. The reaction on MOM-substituted alkynyl-quinoline ($R^2 = CH_2OMe$, Table 1) with simple alkyl-OH (MeOH,[14] ^{i}PrOH) is nicely performed with 75% and quantitative isolated yield, respectively (entries 1 and 2). Only the *cis*-products **6** and **7** were obtained (entries 1 and 2, Table 1), resulting from a *trans*-addition onto the alkynyl bond. Then, using functionalized alcohol groups such as an aminoalcohol (entry 3), an unprotected diol (entry 4) or an allyl-alcohol (entry 5) gave furoquinolines **8**, **9** and **10** in good to excellent yields (99%, 63% and 95% respectively). The lower yield observed in the case of the diol (entry 4) can be explained by a difficult purification of **9**, and no traces of dimer were observed. With 1 equivalent of benzylic alcohols (entries 6 and 7, Table 1) the reaction performed in a 1 M solution of dichloroethane yielded products **11** (79%) and **12** (73%). Changing the alkyne substituents R^2 to H, CH_2OTHP, cyclopropyl or Ph (entries 8–12, Table 1), with MeOH or ^{i}PrOH did not have a real impact on the reaction outcome and the synthesis of compounds

Table 1 Furo[3,4-*b*]quinolines synthesis[a]

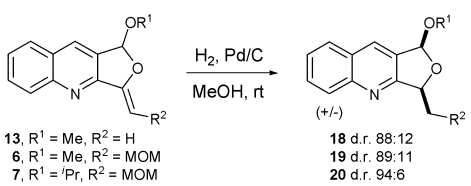


Entry	SM[c]	R^1	R^2	Yield (%)	Product
1	**1**	Me	CH_2OMe	75	**6**
2	**1**	^{i}Pr	CH_2OMe	99	**7**
3	**1**	$CH_2CH_2N(Et)_2$	CH_2OMe	99	**8**
4	**1**	$(CH_2)_2OH$	CH_2OMe	63	**9**
5	**1**	allyl	CH_2OMe	95	**10**
6[b]	**1**	CH_2Ph-*p*-MeO[d]	CH_2OMe	79	**11**
7[b]	**1**	CH_2Ph-*p*-NO_2	CH_2OMe	73	**12**
8	**2**	Me	H	71	**13**
9	**2**	^{i}Pr	H	85	**14**
10	**3**	Me	CH_2OTHP	95	**15**
11	**4**	^{i}Pr		96	**16**
12	**5**	Me	Ph	80	**17**

[a] Reaction conditions: substrate (1 eq), $[Ag(Imid)]_n$ (5 mol%), PPh_3 (5 mol%), alcohol (0.2 M), rt, 2 h. [b] Reaction conditions: substrate (1 eq), $[Ag(Imid)]_n$ (5 mol%), PPh_3 (5 mol%), alcohol (1 eq), $(CH_2Cl)_2$ (0.5 M), rt, 2 h. [c] SM: Starting material. [d] Reaction run at rt, 8 h.

13–17 was efficiently achieved in yields ranging from 71 to 96%. With methanol as the nucleophile (entries 8, 10, 12, Table 1) the results were almost the same as for the MOM-substituted alkyne (entry 1, 75%) except for product **15** which was isolated with 95% yield. For isopropanol as the nucleophile (entries 9 and 11, Table 1) a good yield was observed for product **14** (85%), which proves the efficiency of this transformation. Therefore, this reaction is versatile regarding the nature of the R^1 and R^2 groups (Table 1) since the use of functionalized alcohol groups (aminoalcohol, diol, allyl, benzyl) with a variety of alkynyl-quinoline (R^2 = MOM, H, CH_2OTHP, isopropyl or Ph) produce efficiently a family of twelve furoquinolines **6–17**.

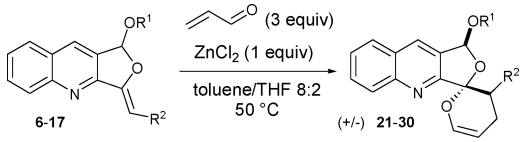
Having in hand these furoquinolines we first focused our attention on the reduction of the external-methylene bond (Scheme 4). The reduction of furoquinoline **13**, under classical conditions (1 atm H_2, Pd/C 5 mol%, 7 h), with no alkynyl substituent (R^2 = H) yielded reduced furoquinoline **18** (73%) with a diastereomeric ratio (d.r.) of 88 : 12. The reduction of the *exo*-methylene group of furoquinoline **6**, bearing a MOM-substituted alkyne, led to furoquinoline **19** (71%) with the same d.r. (89 : 11) in favour of the *syn*-isomer (racemic mixture).



Scheme 4 Reduced furoquinolines **18–20**.

The same ratio was observed using Rh/C, Pt/C or Pd/Al_2O_3 but the starting material was recovered with Ru/C. In order to increase the diastereomeric ratio the reduction was then tested on compound **7** and indeed the presence of the isopropoxy group

Table 2 Hetero-Diels–Alder reaction products[a]



Entry	SM[b]	R^1	R^2	Product	Yield (%)	d.r.[b]
1	**6**	Me	CH_2OMe	**21**	80	20 : 1
2	**7**	^{i}Pr	CH_2OMe	**22**	89	20 : 1
3	**8**	$CH_2CH_2N(Et)_2$	CH_2OMe	—	nr[b]	—
4	**9**	$(CH_2)_2OH$	CH_2OMe	**23**	68	20 : 1
5	**10**	allyl	CH_2OMe	**24**	73	20 : 1
6	**11**	CH_2Ph-*p*-MeO	CH_2OMe	**25**	65	20 : 1
7	**12**	CH_2Ph-*p*-NO_2	CH_2OMe	**26**	74	20 : 1
8	**13**	Me	H	**27**	76	12 : 1
9	**14**	^{i}Pr	H	**28**	81	20 : 1
10	**15**	Me	CH_2OTHP	**29**	86	20 : 1
11	**16**	^{i}Pr		**30**	75	20 : 1
12	**17**	Me	Ph	—	nr[b]	—

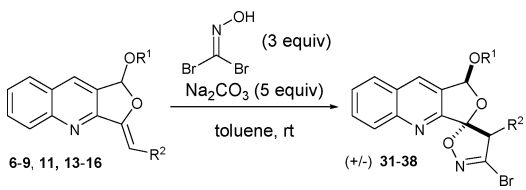
[a] Reaction conditions: substrate (0.2 mmol), $ZnCl_2$ (1 M in Et_2O, 0.2 mmol), acrolein (0.6 mmol), toluene–THF (8 : 2, v/v, 0.2 M), 50 °C, 8 h. [b] SM: Starting material, nr: no reaction, d.r.: diastereomeric ratio.

enhanced the facial selectivity since *syn*-derivative **20** (73%) was produced with a d.r. of 94 : 6. In this manner, the diastereomeric excess was increased from 78 to 88%. Finally, the reduction failed to happen with substrate **5** bearing a phenyl substituent (R^2) and this even under hydrogen pressure (up to 20 bar) where a complex mixture was obtained.

We next turned our attention to cycloaddition reactions. At first, hetero-Diels–Alder reactions with acrolein were performed onto the electron-rich exocyclic-methylene bond of furoquinolines **6–17** by means of $ZnCl_2$ activation (Table 2).[17h,20] Of note, the use of a mixture of solvents toluene–THF (8 : 2, v/v), was found compulsory to obtain a homogeneous reaction mixture (THF solubilising $ZnCl_2$).

Hetero-Diels–Alder products **21–26** (entries 1–2 and 4–7, Table 2) bearing the MOM-substitution were obtained in fair to good yields (65–89%) but with excellent 20 : 1 diastereomeric ratio. Best yields were achieved with the methoxy or isopropoxy R^1 groups giving compounds **21** (80%) and **22** (89%). No reaction from quinoline **8** (entry 3) was seen, probably due to coordination of $ZnCl_2$ by the diethylaminoethyl R^1 group. With the other R^1

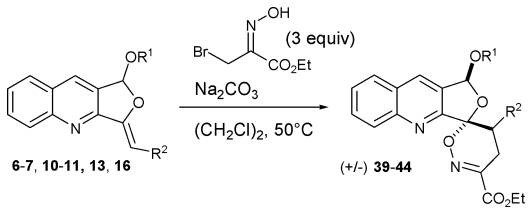
Table 3 Hetero-[5,5]-sprirocyclic products by a [3 + 2] cycloaddition[a]



Entry	SM[b]	R^1	R^2	Product	Yield (%)	d.r.[b]
1	**6**	Me	CH_2OMe	**31**	79	77 : 23
2	**7**	^{i}Pr	CH_2OMe	**32**	96	84 : 16
3	**8**	$CH_2CH_2N(Et)_2$	CH_2OMe	—	—	—
4	**9**	$(CH_2)_2OH$	CH_2OMe	**33**	85	58 : 42
5	**11**	CH_2Ph-*p*-MeO	CH_2OMe	**34**	79	77 : 23
6	**13**	Me	H	**35**	74	77 : 23
7	**14**	^{i}Pr	H	**36**	74	84 : 16
8	**15**	Me	CH_2OTHP	**37**	78	79 : 21
9	**16**	^{i}Pr		**38**	65	86 : 14

[a] Reaction conditions: substrate (0.2 mmol), Br_2C=NOH (0.6 mmol), Na_2CO_3 (1.0 mmol), toluene (0.07 M), rt, 16 h. [b] SM: Starting material, d.r.: diastereomeric ratio.

Table 4 Hetero-[5,6]-sprirocyclic products by a [4 + 2] cycloaddition[a]



Entry	SM[b]	R^1	R^2	Product	Yield (%)	d.r.[b]
1	**6**	Me	CH_2OMe	**39**	83	88 : 12
2	**7**	^{i}Pr	CH_2OMe	**40**	51	88 : 12
3	**10**	allyl	CH_2OMe	**41**	20	86 : 14
4	**11**	CH_2Ph-*p*-MeO	CH_2OMe	**42**	51	90 : 10
5	**13**	Me	H	**43**	59	88 : 12
6	**16**	^{i}Pr		**44**	63	86 : 14

[a] Reaction conditions: substrate (0.2 mmol), ethyl-3-bromo-2-(hydroxyimino)propanoate (0.6 mmol), slow addition, Na_2CO_3 (1.0 mmol), $(CH_2Cl)_2$ (0.07 M), 50 °C, 24 h. [b] SM: Starting material, d.r.: diastereomeric ratio.

groups (ethylalcohol, allyl, benzyls) the acetal-spiroketal quinoline products **23–26** (entries 4–7) were synthesized in 65 to 74% yield. Spiroketal-quinolines **27** and **28** (entries 8–9, Table 2) were formed in respectively 76 and 81% yield. Interestingly, the diastereomeric ratio was only 12 : 1 in the case of the methyl R^1 substituent (**27**, entry 8) whereas it reached a d.r. of 20 : 1 for the isopropyl R^1 group (**28**, entries 9). Also, furoquinoline **15** and **16** (entries 10 and 11) were transformed efficiently to spirocycles **29** (86%) and **30** (75%) with a d.r. of 20 : 1. Noteworthy, as in the case of the reduction reaction (Scheme 4), with a phenyl R^2 group (entry 12, Table 2) no hetero-Diels–Alder product could be formed, probably due to the lack of reactivity of the methylene bond engaged in an extended electronic delocalization.

Furthermore, reaction of furoquinolines **6–9**, **11**, and **13–16** with dibromoformaldoxime, in basic conditions required for the *in situ* formation of bromonitrile oxide,[21] allowed the formation of 8 different hetero-[5,5]-spirocycles by a [3 + 2] room-temperature process (entries 1–9, Table 3).

Compounds **6–7**, **9** and **11** with the MOM-substituent (entries 1–2, 4–5, Table 3) were efficiently converted to the quinoline-fused [5,5]-spirocycles **31–34** bearing as R^1 group a methyl (79%), isopropyl (96%), ethylalcohol (85%) and *p*-methoxybenzyl (79%) with generally good diastereoselectivities ranging from 77 : 23 to 84 : 16. One exception being spirocycle **33**, with the ethylalcohol substituent, that presented almost no facial diastereoselectivity (58 : 42). Then, reaction of furoquinoline **8**, bearing a diethylaminoethyl R^1 group (entry 3, Table 3), led only to degradation or unidentified products, compared to the hetero-Diels–Alder reaction (entry 3, Table 2) where no reaction occurred.

Compounds **13–14**, without substitution on the external methylene-bond (entries 6–7, Table 3), were similarly transformed into spirocycles **35–36** (74%) but the size of the R^1 group has an impact on the diastereoselectivity since the 77 : 23 ratio with the methyl group (**35**) was increased to a 84 : 16 in the case of the isopropyl group (**36**). Also, playing on the steric hindrance of both R groups was interesting since spirocycle **37** (CH_2OTHP group, entry 8, Table 3) showed a non-significant increase of the d.r. (79 : 21) compared with 77 : 23 d.r. for compound **35** (H group, entry 6, Table 3). In the same manner, comparison of the d.r. of compounds **36** and **38** (84 : 16 *vs.* 86 : 14) demonstrated that the size of the R^2 groups had almost no influence.

Finally, diversity was also made possible with the formation of [5,6]-spirocycles by reacting furoquinolines **6–7**, **10–11**, **13** and **16** (entries 1–6, Table 4) with ethyl 3-bromo-2-(hydroxyimino)propanoate (50 °C in dichloroethane),[22] in basic conditions. Under these conditions whatever the nature of the R groups on the starting material was, good diastereoselectivities were always observed (86 : 14 to 90 : 10). Apart from compound **39** (entry 1, Table 4) which was obtained with a very good 83% yield, the results were not as good for the other derivatives presumably due to formation of regioisomers. Indeed, only 51% yield was attained for spirocycles **40** and **42** (R^1 = ^{i}Pr or *p*-methoxybenzyl, R^2 = MOM, entries 2 and 4, Table 4), 63% for spirocycle **44** bearing the ^{i}Pr (R^1) and cycloPr (R^2) groups (entry 6, Table 4) and 59% for compound **43** (entry 5, Table 4). A deceiving 20% yield was noticed for spirocycle **41**. The reaction was more sluggish than the one developed before (Tables 2–3) and the reagent ethyl-3-bromo-2-(hydroxyimino)propanoate polymerized easily explaining also the lower yields. Therefore, syringe pump slow addition of ethyl-3-bromo-2-(hydroxyimino)propanoate helped for getting the best out of these reactions.

Among these new furo[3,4-*b*]quinolines **6–17** and spirocyclic derivatives **21–44**, some exhibit interesting biological properties that will be reported elsewhere in due time.

Conclusions

In conclusion, we have developed a sequential and efficient transformation of quinoline derivatives to various furoquinolines and spirocyclic structures. Scope and limitations of the *exo*-methylene bond reactivity have been studied widely since 27 new structures were obtained in good to excellent yield and with a good to excellent facial diastereoselectivity. Enantioselectivity

is under study for the tandem acetalization/cycloisomerization reaction, therefore opening the way for the access to enantiopure spirocycles.

Experimental section

General considerations

Dichloromethane was distilled on CaH_2. THF and toluene were distilled on sodium/benzophenone. All other reagents and solvents were used without further purification. ^{1}H NMR (300 MHz) and ^{13}C-{^{1}H} NMR (75 MHz) were recorded on a Bruker ACP-300 spectrometer using the residual peak of chloroform-*d* as internal standard (7.26 ppm for ^{1}H NMR and 77.16 ppm for ^{13}C NMR). Chemical shifts are reported in ppm and coupling constants *J* in Hertz. Flash chromatography was performed using 40–63 μm silica. Analytical TLC's were performed on Merck pre-coated silica 60-F254 plates. IR spectra were recorded on a FTIR spectrometer. Compounds **6**, **7**, **8**, **9**, **11**, **13**, **15** and **17** were already described.[13a]

General procedure for silver catalyzed cyclization (Table 1)

To the appropriate quinoline (1 eq), $[Ag(Im)]_n$ (5 mol%) and PPh_3 (5 mol%) was added the appropriate alcohol (0.2 M). The solution was stirred at rt for 2 h (TLC monitoring) and evaporated under vacuum. The crude mixture was purified by flash chromatography on silica gel using mixtures of pentane and diethyl ether to afford the pure product.

Procedure for silver catalyzed cyclization using *p*-methoxybenzylalcohol and *p*-nitrobenzylalcohol

To the appropriate quinoline (1 eq), $[Ag(Im)]_n$ (5 mol%) and PPh_3 (5 mol%) were added dichloroethane (0.5 M) and the appropriate benzylalcohol (1.0 eq). The solution was stirred at rt for 8 h (TLC monitoring) and evaporated under vacuum. The crude mixture was purified by flash chromatography on silica gel using mixtures of pentane–diethyl ether (gradient 9 : 1 to 7 : 3) to afford the pure product in 79% yield (for *p*-methoxybenzylalcohol, respectively 73% for *p*-nitrobenzylalcohol).

Procedure for reduction by palladium catalyzed hydrogenation

To a solution of the appropriate furoquinoline (1 eq) in degassed (argon bubbling for 5 min) methanol (0.06 M) was added Pd/C (20% in mass). The mixture was stirred under argon bubbling for 5 min and hydrogen was then bubbled for 5 min. The reaction media was then stirred at room temperature for 4 h under 1 atm of hydrogen. The mixture was flushed with argon and dissolved in ethyl acetate. After filtration through a pad of celite, the filtrate was washed with water (×3) and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by preparative TLC or flash chromatography on silica gel using mixtures of cyclohexane and ethyl acetate to afford the pure product.

Procedure for hetero-Diels–Alder reaction with acrolein (Table 2)

In a sealed tube, to a solution of the appropriate furoquinoline (0.2 mmol) in toluene–THF (0.8/0.2 mL) were successively added acrolein (40 μL, 0.6 mmol) and $ZnCl_2$ (1 M in Et_2O, 200 μL, 0.2 mmol). The mixture was then stirred at 50 °C for 8 h, allowed to cool to room temperature and evaporated. The crude product was purified by flash chromatography on silica gel using mixtures of pentane and diethyl ether to afford the pure product.

Procedure for [3 + 2] cycloaddition (Table 3)

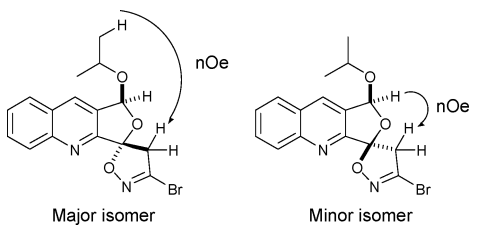
In a sealed tube, to a solution of the appropriate furoquinoline (0.2 mmol) in toluene (0.07 M, 2.9 mL) were successively added sodium carbonate (106.0 mg, 1.0 mmol) and dibromoformaldoxime (121.7 mg, 0.6 mmol). The mixture was then stirred at room temperature for 16 h and water was added. The mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine (5 mL) and dried over $MgSO_4$. The crude product was purified by flash chromatography on silica gel using mixtures of pentane and diethyl ether to afford the pure product.

Procedure for [4 + 2] cycloaddition (Table 4)

To a solution of the appropriate furoquinoline (0.2 mmol) in dichloroethane (0.1 M, 2.0 mL) was added sodium carbonate (106.0 mg, 1.0 mmol). The mixture was heated at 50 °C and a solution of ethyl 3-bromo-2-(hydroxyimino)propanoate (126.2 mg, 0.6 mmol) in dichloroethane (0.75 mL) was then added *via* syringe pump over 24 h. HCl_{aq} 1 M (2.5 mL) was added and the mixture was extracted with dichloromethane (3 × 5 mL). The combined organic layers were washed with brine (5 mL) and dried over $MgSO_4$. The crude product was purified by flash chromatography on silica gel using mixtures of pentane and diethyl ether to afford the pure product.

Assignment of the diastereoisomers by NOESY experiments

NOESY experiments were run on a single product for each family of compounds and assignment was assumed to be correct for the other products. In the [3 + 2] family, a nOe was observed in the major isomer between the methyl groups of the *iso*-propyl moiety and the CH_2 of the newly formed cycle, proving the spatial arrangement of this isomer (scheme below). In addition, a nOe was found in the minor isomer between the proton in α of the *iso*-propyloxy group and the CH_2 of the newly formed cycle.



Compound 10 (Table 1, entry 5)

According to the procedure described above, **10** was isolated in 95% yield (yellow solid). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ (ppm) = 8.20 (s, 1H), 8.13 (d, 1H, J = 8.5 Hz), 7.84 (d, 1H, J = 8.1 Hz), 7.75 (t, 1H, J = 7.1 Hz), 7.54 (t, 1H, J = 7.2 Hz), 6.59 (s, 1H), 6.06–5.95 (m, 1H), 5.95 (t, 1H, J = 7.2 Hz), 5.36 (dd, 1H, J = 1.4, 17.2 Hz), 5.25 (dd, 1H, J = 1.0, 10.4 Hz), 4.42–4.25 (m, 4H), 3.42 (s, 3H). **^{13}C-{^{1}H} NMR** ($CDCl_3$, 75 MHz): δ (ppm) = 153.5, 153.0, 150.0,

133.7, 131.6, 130.7, 129.7, 129.4, 128.6, 127.9, 127.0, 118.2, 103.2, 97.6, 69.2, 66.3, 57.9. **HRMS (ESI$^+$)** m/z calculated for (MH^+): 284.1281. Found: 284.1281. **MS (ESI$^+$)**: 284 (MH^+). **IR (CH_2Cl_2):** ν 2928, 1726, 1627, 1505, 1264 cm^{-1}.

Compound 12 (Table 1, entry 7)

According to the procedure described above, **12** was isolated in 73% yield (yellow solid). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ (ppm) = 8.24 (s, 1H), 8.22 (d, 2H, J = 8.8 Hz), 8.17 (d, 1H, J = 8.7 Hz), 7.88 (d, 1H, J = 8.1 Hz), 7.80 (dt, 1H, J = 1.4, 7.1, 8.5 Hz), 7.59 (dt, 1H, J = 1.4, 7.0, 8.0 Hz), 7.55 (d, 2H, J = 8.7 Hz), 6.72 (s, 1H), 6.00 (t, 1H, J = 7.3 Hz), 4.91 (AB system, 2H), 4.37–4.23 (m, 2H), 3.41 (s, 3H). **^{13}C-{^{1}H} NMR** ($CDCl_3$, 75 MHz): δ (ppm) = 153.1, 152.6, 150.0, 147.5, 144.8, 131.7, 130.9, 129.6, 128.7, 128.6, 128.0, 127.7, 127.2, 123.6, 103.4, 98.0, 68.4, 66.2, 58.0. **HRMS (ESI$^+$)** m/z calculated for (MH^+): 379.1288. Found: 379.1302. **MS (ESI$^+$):** 379 (MH^+). **IR (CH_2Cl_2):** ν 2928, 2824, 1690, 1626, 1608, 1524, 1348 cm^{-1}.

Compound 14 (Table 1, entry 9)

According to the procedure described above, **14** was isolated in >99% yield (yellow solid). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ (ppm) = 8.06 (d, 1H, J = 8.5 Hz), 8.00 (s, 1H), 7.69 (d, 1H, J = 8.2 Hz), 7.63 (t, 1H, J = 8.4 Hz), 7.41 (t, 1H, J = 7.5 Hz), 6.45 (s, 1H), 5.30 (d, 1H, J = 1.9 Hz), 4.74 (d, 1H, J = 1.9 Hz), 4.13 (sept, 1H, J = 6.2 Hz), 1.28 (d, 3H, J = 6.2 Hz), 1.25 (d, 3H, J = 6.2 Hz). **^{13}C-{^{1}H} NMR** ($CDCl_3$, 75 MHz): δ (ppm) = 157.0, 153.4, 149.7, 131.2, 130.3, 129.9, 129.4, 128.3, 127.7, 126.7, 102.4, 83.6, 71.9, 23.5, 22.3. **HRMS (ESI$^+$)** m/z calculated for (MH^+): 242.1176. Found: 242.1175. **MS (ESI$^+$):** 242 (MH^+). **IR (CH_2Cl_2):** ν 2975, 1784, 1631, 1605, 1506 cm^{-1}

Compound 16 (Table 1, entry 11)

According to the procedure described above, **16** was isolated in 96% yield (yellow solid). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ (ppm) = 8.10 (s, 1H), 8.04 (d, 1H, J = 8.5 Hz), 7.79 (d, 1H, J = 8.1 Hz), 7.68 (t, 1H, J = 8.3 Hz), 7.47 (t, 1H, J = 7.2 Hz), 6.62 (s, 1H), 5.33 (d, 1H, J = 10.1 Hz), 4.23 (sept, 1H, J = 6.2 Hz), 2.00–1.88 (m, 1H), 1.36 (d, 3H, J = 3.0 Hz), 1.34 (d, 3H, J = 3.0 Hz), 0.91 (dd, 2H, J = 2.2, 8.1 Hz), 0.67–0.57 (m, 2H). **^{13}C-{^{1}H} NMR** ($CDCl_3$, 75 MHz): δ (ppm) = 153.9, 150.4, 149.8, 131.3, 130.3, 129.8, 129.2, 128.5, 127.6, 126.3, 107.0, 102.6, 71.9, 23.8, 22.6, 8.7, 7.9, 7.7. **HRMS (ESI$^+$)** m/z calculated for (MH^+): 282.1489. Found: 282.1491. **MS (ESI$^+$):** 282 (MH^+). **IR (CH_2Cl_2):** ν 2977, 2930, 1683, 1627, 1506, 1416, 1373 cm^{-1}.

Compound 18 (Scheme 4)

According to the procedure described above, **18** was obtained as mixture of diastereoisomers 88 : 12 in 73% yield. The major isomer was isolated pure in 46% yield (yellow oil). **^{1}H NMR** ($CDCl_3$, 300 MHz): Major isomer δ (ppm) = 8.13 (s, 1H), 8.11 (d, J = 8.6 Hz, 1H), 7.85 (d, J = 8.1 Hz, 1H), 7.73 (ddd, J = 1.3, 6.9, 8.6 Hz, 1H), 7.53 (ddd, J = 0.9, 6.9, 8.1 Hz, 1H), 6.21 (s, 1H), 5.31 (q, J = 6.7 Hz, 1H), 3.54 (s, 3H), 1.70 (d, J = 6.7 Hz, 3H). Minor isomer δ (ppm) (selected peak) = 6.22 (s, 1H). **^{13}C-{^{1}H} NMR** ($CDCl_3$, 75 MHz): Major isomer δ (ppm) = 164.5, 149.3, 131.4, 130.2, 129.3 (2C), 128.6, 127.5, 126.5, 104.8, 78.9, 54.8, 22.1. **HRMS (ESI$^+$)** m/z calculated for (MH^+): 216.1015. Found: 216.1019. **GC-MS:** m/z $C_{13}H_{13}NO_2$ ($M^{+\bullet}$) 215. **IR (neat):** ν 2976, 2927, 2826, 1632, 1504, 1306 cm^{-1}.

Compound 19 (Scheme 4)

According to the procedure described above, **19** was obtained as mixture of diastereoisomers 89 : 11 in 71% yield. The major isomer was isolated pure in 45% yield (yellow solid). **^{1}H NMR** ($CDCl_3$, 500 MHz): Major isomer δ (ppm) = 8.15 (s, 1H), 8.11 (d, J = 8.7 Hz, 1H), 7.87 (d, J = 7.6 Hz, 1H), 7.74 (ddd, J = 1.6, 7.0, 8.7 Hz, 1H), 7.54 (ddd, J = 1.1, 7.0, 7.6 Hz, 1H), 6.22 (s, 1H), 5.33 (dd, J = 3.7, 9.0 Hz, 1H), 3.77–3.70 (part of AB system, 1H), 3.69–3.67 (part of AB system, 1H), 3.58 (s, 3H), 3.39 (s, 3H), 2.48–2.42 (part of AB system, 1H), 2.12–2.04 (part of AB system, 1H). Minor isomer δ (ppm) (selected peak) = 6.26 (s, 1H). **^{13}C-{^{1}H} NMR** ($CDCl_3$, 125 MHz): Major isomer δ (ppm) = 164.4, 149.4, 131.4, 130.2, 129.4, 129.3, 128.6, 127.5, 126.6, 105.0, 79.8, 69.4, 58.8, 55.3, 36.6. **HRMS (EI)** m/z calculated for ($M^{+\bullet}$): 259.1208. Found: 259.1209. **GC-MS:** m/z $C_{15}H_{17}NO_3$ ($M^{+\bullet}$) 259. **IR (neat):** ν 2956, 2921, 2883, 2829, 1631, 1580, 1504, 1420 cm^{-1}.

Compound 20 (Scheme 4)

According to the procedure described above, **20** was obtained as mixture of diastereoisomers 94 : 6 in 75% yield. The major isomer was isolated pure in 49% yield (yellow solid). **^{1}H NMR** ($CDCl_3$, 300 MHz): Major isomer δ (ppm) = 8.11 (s, 1H), 8.09 (d, J = 8.7 Hz, 1H), 7.85 (dd, J = 1.0, 8.1 Hz, 1H), 7.72 (ddd, J = 1.4, 7.0, 8.7 Hz, 1H), 7.52 (ddd, J = 1.0, 7.0, 8.1 Hz, 1H), 6.37 (s, 1H), 5.29 (dd, J = 3.9, 8.9 Hz, 1H), 4.23 (sept, J = 6.2 Hz, 1H), 3.80–3.68 (part of AB system, 1H), 3.67–3.62 (part of AB system, 1H), 3.38 (s, 3H), 2.49–2.38 (part of AB system, 1H), 2.18–2.06 (part of AB system, 1H). Minor isomer δ (ppm) (selected peak) = 6.40 (s, 1H). **^{13}C-{^{1}H} NMR** ($CDCl_3$, 100 MHz): Major isomer δ (ppm) = 164.7, 149.3, 131.2, 130.2, 130.1, 129.3, 128.6, 127.7, 126.5, 102.7, 79.6, 71.0, 69.4, 58.8, 36.7, 23.9, 22.4. **HRMS (ESI$^+$)** m/z calculated for (MH^+): 288.1591. Found: 288.1594. **GC-MS:** m/z $C_{17}H_{21}NO_3$ ($M^{+\bullet}$) 287. **IR (neat):** ν 2963, 2918, 2868, 2823, 1630, 1504, 1332 cm^{-1}.

Compound 21 (Table 2, entry 1)

According to the procedure described above, **21** was isolated in 80% yield as a single isomer (white solid). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ (ppm) = 8.24 (d, 1H, J = 8.5 Hz), 8.20 (s, 1H), 7.88 (d, 1H, J = 8.1 Hz), 7.76 (t, 1H, J = 7.6 Hz), 7.58 (t, 1H, J = 7.4 Hz), 6.43 (d, 1H, J = 7.9 Hz), 6.39 (s, 1H), 5.05 (t, 1H, J = 5.1 Hz), 3.66 (s, 3H), 3.24–3.00 (m, 3H), 3.00 (s, 3H), 2.43–2.34 (m, 1H), 2.22–2.12 (m, 1H). **^{13}C-{^{1}H} NMR** ($CDCl_3$, 75 MHz): δ (ppm) = 159.7, 149.9, 141.4, 131.9, 130.4, 130.1, 129.5, 128.5, 128.3, 127.3, 105.9, 104.5, 101.4, 73.2, 58.4, 56.3, 37.8, 20.9. **HRMS (ESI$^+$)** m/z calculated for (MH^+): 314.1387. Found: 314.1383. **MS (ESI$^+$):** 314 (MH^+). **IR (CH_2Cl_2):** ν 2929, 1658, 1630, 1505, 1447, 1397 cm^{-1}.

Compound 22 (Table 2, entry 2)

According to the procedure described above, **22** was isolated in 89% yield as a single isomer (white solid). **^{1}H NMR** ($CDCl_3$,

300 MHz): δ (ppm) = 8.23 (d, 1H, J = 8.4 Hz), 8.17 (s, 1H), 7.88 (d, 1H, J = 8.1 Hz), 7.75 (ddd, 1H, J = 1.3, 6.9, 8.4 Hz), 7.57 (ddd, 1H, J = 1.0, 6.9, 8.0 Hz), 6.58 (s, 1H), 6.43 (dd, 1H, J = 1.4, 6.2 Hz), 5.04 (dt, 1H, J = 1.9, 5.9 Hz), 4.26 (sept, 1H, J = 6.2 Hz), 3.28–3.22 (m, 1H), 3.17–3.12 (m, 1H), 3.04–2.96 (m, 1H), 3.03 (s, 3H), 2.43–2.34 (m, 1H), 2.21–2.10 (m, 1H), 1.35 (d, 6H, J = 6.2 Hz). **^{13}C-{^{1}H} NMR** ($CDCl_3$, 75 MHz): δ (ppm) = 159.7, 149.9, 141.5, 131.7, 130.2, 130.1, 128.5, 128.3, 127.1, 105.8, 102.5, 101.3, 73.3, 72.2, 58.5, 38.0, 24.0, 22.5, 21.0. **HRMS (ESI$^+$)** m/z calculated for (MH^+): 342.1700. Found: 342.1697. **MS (ESI$^+$):** 342 (MH^+). **IR (CH_2Cl_2):** ν 2977, 2927, 1658, 1631, 1506, 1401, 1383 cm^{-1}.

Compound 23 (Table 2, entry 4)

According to the procedure described above, **23** was isolated in 68% yield as a single isomer (white solid). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ (ppm) = 8.24 (s, 1H), 8.23 (d, 1H, J = 8.8 Hz), 7.89 (d, 1H, J = 8.3 Hz), 7.77 (ddd, 1H, J = 1.3, 6.9, 8.4 Hz), 7.59 (ddd, 1H, J = 1.1, 7.0, 8.0 Hz), 6.52 (s, 1H), 6.43–6.39 (m, 1H), 5.04 (dt, 1H, J = 2.1, 5.9 Hz), 4.10–3.94 (m, 2H), 3.85 (t, 2H, J = 4.3 Hz), 3.21–3.19 (m, 2H), 3.09–2.98 (m, 1H), 3.02 (s, 3H), 2.40–2.30 (m, 1H), 2.26–2.15 (m, 1H). **^{13}C-{^{1}H} NMR** ($CDCl_3$, 75 MHz): δ (ppm) = 159.5, 149.9, 141.3, 132.1, 130.5, 130.1, 129.3, 128.6, 128.3, 127.4, 106.0, 104.3, 101.5, 73.0, 72.0, 62.3, 58.6, 37.8, 20.8. **HRMS (ESI$^+$)** m/z calculated for (MH^+): 344.1492. Found: 344.1500. **MS (ESI$^+$):** 344 (MH^+). **IR (CH_2Cl_2):** ν 2928, 2882, 1658, 1631, 1506, 1397 cm^{-1}.

Compound 24 (Table 2, entry 5)

According to the procedure described above, **24** was isolated in 73% yield as a single isomer (white solid). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ (ppm) = 8.25 (d, 1H, J = 8.8 Hz), 8.22 (s, 1H), 7.89 (d, 1H, J = 8.3 Hz), 7.76 (ddd, 1H, J = 1.5, 6.9, 8.4 Hz), 7.59 (ddd, 1H, J = 1.1, 7.0, 8.1 Hz), 6.53 (s, 1H), 6.43 (ddd, 1H, J = 1.2, 1.3, 6.2 Hz), 6.10–5.97 (m, 1H), 5.39 (dq, 1H, J = 1.6, 17.2 Hz), 5.26 (dq, 1H, J = 1.2, 10.4 Hz), 5.05 (dt, 1H, J = 1.9, 5.9 Hz), 4.53–4.29 (AB system, 2H), 3.26–3.20 (m, 1H), 3.16–3.11 (m, 1H), 3.07–2.97 (m, 1H), 3.01 (s, 3H), 2.44–2.34 (m, 1H), 2.23–2.11 (m, 1H). **^{13}C-{^{1}H} NMR** ($CDCl_3$, 75 MHz): δ (ppm) = 159.8, 150.0, 141.4, 134.1, 131.9, 130.4, 130.1, 129.6, 128.5, 128.3, 127.2, 117.8, 106.0, 103.0, 101.4, 73.3, 69.8, 58.5, 38.0, 20.9. **HRMS (ESI$^+$)** m/z calculated for (MH^+): 340.1543. Found: 340.1551. **MS (ESI$^+$):** 340 (MH^+). **IR (CH_2Cl_2):** ν 2926, 2893, 1658, 1631, 1506, 1399 cm^{-1}.

Compound 25 (Table 2, entry 6)

According to the procedure described above, **25** was isolated in 65% yield as a single isomer (colorless oil that crystallized on standing). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ (ppm) = 8.24 (d, 1H, J = 8.5 Hz), 8.18 (s, 1H), 7.87 (d, 1H, J = 8.0 Hz), 7.76 (t, 1H, J = 8.1 Hz), 7.58 (t, 1H, J = 7.5 Hz), 7.38 (d, 2H, J = 8.5 Hz), 6.92 (d, 2H, J = 8.5 Hz), 6.59 (s, 1H), 6.46 (dd, 1H, J = 1.2, 6.0 Hz), 5.05 (dt, 1H, J = 1.6, 5.8 Hz), 4.88 (AB system, 2H), 3.81 (s, 3H), 3.26–3.00 (m, 3H), 3.00 (s, 3H), 2.47–2.37 (m, 1H), 2.25–2.15 (m, 1H). **^{13}C-{^{1}H} NMR** ($CDCl_3$, 75 MHz): δ (ppm) = 159.6, 149.9, 141.4, 132.0, 131.9, 130.4, 130.0, 129.9, 129.6, 129.5, 128.5, 128.2, 127.2, 114.0, 106.0, 102.7, 101.4, 73.2, 70.7, 58.5, 55.4, 37.9, 20.9. **HRMS (ESI$^+$)** m/z calculated for (MH^+): 420.1805. Found: 420.1817. **MS (ESI$^+$):** 420 (MH^+). **IR (CH_2Cl_2):** ν 2926, 1658, 1631, 1607, 1505, 1392 cm^{-1}.

Compound 26 (Table 2, entry 7)

According to the procedure described above, **26** was isolated in 74% yield as a single isomer (colorless oil that crystallized on standing). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ (ppm) = 8.27–8.22 (m, 4 Hz), 7.92 (dd, 1H, J = 0.7, 7.4 Hz), 7.80 (ddd, 1H, J = 1.5, 7.0, 8.4 Hz), 7.65–7.58 (m, 3H), 6.63 (s, 1H), 6.44 (dd, 1H, J = 1.4, 6.2 Hz), 5.07 (dt, 1H, J = 2.0, 6.0 Hz), 5.04 (AB system, 2H), 3.21–3.02 (m, 3H), 2.98 (s, 3H), 2.43–2.33 (part of AB system, 1H), 2.19–2.08 (part of AB system, 1H). **^{13}C-{^{1}H} NMR** ($CDCl_3$, 75 MHz): δ (ppm) = 159.5, 150.0, 147.6, 145.0, 141.4, 132.0, 130.7, 130.1, 129.0, 128.6, 128.4, 128.1, 127.5, 123.9, 106.3, 103.3, 101.4, 73.2, 69.4, 58.5, 37.7, 20.9. **HRMS (ESI$^+$)** m/z calculated for (MH^+): 435.1551. Found: 435.1543. **MS (ESI$^+$):** 435 (MH^+). **IR (CH_2Cl_2):** ν 3057, 2926, 1658, 1631, 1607, 1524, 1348 cm^{-1}.

Compound 27 (Table 2, entry 8)

According to the procedure described above, **27** was isolated in 76% yield (white solid). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ (ppm) = 8.24 (d, 1H, J = 9.6 Hz), 8.23 (s, 1H), 7.92 (d, 1H, J = 8.2 Hz), 7.78 (ddd, 1H, J = 1.2, 7.0, 9.6 Hz), 7.63 (dd, 1H, J = 1.2, 7.0, 8.2 Hz), 6.49 (d, 1H, J = 8.5 Hz), 6.47 (s, 1H), 5.05 (dd, 1H, J = 4.7, 6.2 Hz), 3.59 (s, 3H), 2.60–2.54 (m, 2H), 2.10 (m, 1H), 2.05 (m, 1H). **^{13}C-{^{1}H} NMR** ($CDCl_3$, 75 MHz): δ (ppm) = 160.9, 150.5, 142.2, 132.9, 132.4, 130.8, 130.2, 129.1, 127.7, 105.0, 104.3, 102.2, 55.7, 30.5, 17.0. **HRMS (ESI$^+$)** m/z calculated for (MH^+): 270.1125. Found: 270.1128. **MS (ESI$^+$):** 270 (MH^+). **IR (CH_2Cl_2):** ν 2933, 2852, 1654, 1631, 1506, 1399, 1297 cm^{-1}.

Compound 28 (Table 2, entry 9)

According to the procedure described above, **28** was isolated in 81% yield (white solid). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ (ppm) = 8.21 (d, 1H, J = 9.0 Hz), 8.19 (s, 1H), 7.88 (d, 1H, J = 8.1 Hz), 7.77 (t, 1H, J = 7.5 Hz), 7.57 (t, 1H, J = 7.5 Hz), 6.58 (s, 1H), 6.47 (d, 1H, J = 5.9 Hz), 5.02 (t, 1H, J = 5.6 Hz), 4.23 (sept, 1H, J = 6.1 Hz), 2.63–2.46 (m, 2H), 2.32–2.06 (m, 2H). **^{13}C-{^{1}H} NMR** ($CDCl_3$, 75 MHz): δ (ppm) = 160.8, 149.7, 142.0, 131.8, 130.3, 130.2, 130.0, 128.5, 128.4, 127.2, 104.7, 102.1, 101.8, 71.7, 30.5, 23.9, 22.6, 16.8. **HRMS (ESI$^+$)** m/z calculated for (MNa^+): 320.1257. Found: 320.1261. **MS (ESI$^+$):** 320 (MNa^+). **IR (CH_2Cl_2):** ν 2975, 2931, 2851, 1654, 1632, 1506, 1400, 1384, 1332, 1294 cm^{-1}.

Compound 29 (Table 2, entry 10)

According to the procedure described above, **29** was isolated in 86% yield (white solid). Presence of 2 diastereoisomers (50 : 50) due to the presence of a THP group. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ (ppm) = 8.24–8.17 (m, 2H), 7.86 (d, 1H, J = 8.1 Hz), 7.74 (ddd, 1H, J = 1.3, 7.1, 8.2 Hz), 7.56 (ddd, 1H, J = 1.1, 7.0, 8.0 Hz), 6.45–6.38 (m, 2H), 5.04 (dt, 1H, J = 1.9, 5.9 Hz), 4.41 (t, 1H, J = 3.2 Hz, 50%), 4.13 (t, 1H, J = 3.2 Hz, 50%), 3.64 (s, 3H), 3.61–3.15 (m, 4H), 3.03 (sept, 1H, J = 6.1 Hz), 2.42–2.10 (m, 2H), 1.38–0.55 (m, 6H). **^{13}C-{^{1}H} NMR** ($CDCl_3$, 75 MHz): δ (ppm) = 160.1, 159.8, 149.9,

141.4, 131.7, 131.6, 130.2, 130.0, 129.6, 129.5, 128.4, 128.4, 128.3, 128.2, 127.2, 127.1, 106.3, 106.1, 104.6, 104.5, 101.4, 101.2, 98.5, 98.1, 67.8, 67.7, 61.6, 61.5, 56.3, 56.2, 38.4, 38.3, 30.4, 30.2, 30.0, 29.8, 25.4, 25.3, 21.0, 20.8, 18.6. **HRMS (ESI$^+$)** *m/z* calculated for (MH^+): 384.1805. Found: 384.1798. **MS (ESI$^+$):** 384 (MH^+). **IR (CH_2Cl_2):** ν 2941, 2878, 2852, 1658, 1631, 1506, 1398, 1355, 1299 cm^{-1}.

Compound 30 (Table 2, entry 11)

According to the procedure described above, **30** was isolated in 75% yield as a single isomer (white solid). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ (ppm) = 8.21 (d, 1H, J = 8.8 Hz), 8.20 (s, 1H), 7.90 (d, 1H, J = 8.1 Hz), 7.75 (ddd, 1H, J = 1.1, 6.9, 8.1 Hz), 7.59 (ddd, 1H, J = 1.0, 7.0, 8.0 Hz), 6.63 (s, 1H), 6.43–6.40 (m, 1H), 5.00 (dt, 1H, J = 2.0, 5.9 Hz), 4.29 (sept, 1H, J = 6.1 Hz), 2.42–2.20 (m, 2H), 1.89–1.79 (m, 1H), 1.84 (ddd, 1H, J = 6.0, 6.0, 9.8 Hz), 1.35 (d, 3H, J = 5.2 Hz), 1.34 (d, 3H, J = 5.2 Hz), 0.79–0.67 (m, 1H), 0.35–0.26 (m, 1H), 0.10–0.02 (m, 1H), (–)0.24– (–)0.35 (m, 2H). **^{13}C-{^{1}H} NMR** ($CDCl_3$, 75 MHz): δ (ppm) = 160.2, 149.6, 141.4, 131.6, 130.6, 130.2, 129.9, 128.5, 128.3, 127.1, 108.1, 102.6, 101.9, 72.1, 43.5, 24.0, 23.6, 22.5, 11.7, 5.2, 2.5. **HRMS (ESI$^+$)** *m/z* calculated for (MH^+): 338.1751. Found: 338.1754. **MS (ESI$^+$):** 338 (MH^+). **IR (CH_2Cl_2):** ν 2976, 2928, 1656, 1632, 1506, 1384, 1294 cm^{-1}.

Compound 31 (Table 3, entry 1)

According to the procedure described above, **31** was isolated in 79% yield (white solid). Mixture of diastereoisomers 77 : 23. **^{1}H NMR** ($CDCl_3$, 300 MHz): Major isomer δ (ppm) = 8.23 (s, 1H), 8.18 (d, 1H, J = 8.5 Hz), 7.90 (d, 1H, J = 8.1 Hz), 7.78 (t, 1H, J = 8.4 Hz), 7.61 (t, 1H, J = 8.0 Hz), 6.50 (s, 1H), 4.38 (t, 1H, J = 6.2 Hz), 3.83–3.71 (m, 2H), 3.64 (s, 3H), 3.22 (s, 3H). Minor isomer (selected signals) δ (ppm) = 6.28 (s, 1H), 3.50 (s, 3H), 3.14 (s, 3H). **^{13}C-{^{1}H} NMR** ($CDCl_3$, 75 MHz): Major isomer δ (ppm) = 156.5, 150.0, 140.8, 132.1, 130.9, 130.0, 129.3, 128.6, 128.5, 127.8, 114.4, 105.3, 66.9, 59.0, 56.6, 56.4. Minor isomer (selected signals) δ (ppm) = 157.0, 150.0, 139.7, 113.1, 104.0, 67.3, 59.0, 56.0, 54.3. **HRMS (ESI$^+$)** *m/z* calculated for (MH^+): 379.0288. Found: 379.0286. **MS (ESI$^+$):** 379 (MH^+). **IR (CH_2Cl_2):** ν 2932, 2838, 1723, 1628, 1584, 1506, 1448, 1397, 1299 cm^{-1}.

Compound 32 (Table 3, entry 2)

According to the procedure described above, **32** was isolated in 96% yield (white solid). Mixture of diastereoisomers 84 : 16. **^{1}H NMR** ($CDCl_3$, 300 MHz): Major isomer δ (ppm) = 8.21–8.17 (m, 2H), 7.90 (d, 1H, J = 8.1 Hz), 7.77 (t, 1H, J = 7.5 Hz), 7.60 (t, 1H, J = 7.4 Hz), 6.65 (s, 1H), 4.37 (t, 1H, J = 6.0 Hz), 4.24 (sept, 1H, J = 6.1 Hz), 3.77 (d, 2H, J = 6.1 Hz), 3.24 (s, 3H), 1.36 (t, 6H, J = 5.7 Hz). Minor isomer (selected signals) δ (ppm) = 6.34 (s, 1H), 3.14 (s, 3H). **^{13}C-{^{1}H} NMR** ($CDCl_3$, 75 MHz): Major isomer δ (ppm) = 156.5, 150.0, 141.0, 132.0, 130.7, 130.1, 129.9, 128.6, 128.5, 127.7, 114.4, 103.4, 72.9, 67.1, 59.0, 56.6, 23.8, 22.5. **HRMS (ESI$^+$)** *m/z* calculated for (MH^+): 407.0601. Found: 407.0599. **MS (ESI$^+$):** 407 (MH^+). **IR (CH_2Cl_2):** ν 2977, 2929, 1724, 1628, 1583, 1506, 1467, 1385, 1337, 1295 cm^{-1}.

Compound 33 (Table 3, entry 4)

According to the procedure described above, **33** was isolated in 85% yield (white solid). Mixture of diastereoisomers 58 : 42. **^{1}H NMR** ($CDCl_3$, 300 MHz): mixture of isomers δ (ppm) = 8.27–8.26 (m, 2H), 8.18 (d, 1H, J = 8.4 Hz), 7.80–7.75 (m, 1H), 7.60 (t, 1H, J = 7.6 Hz), 6.62 (s, 1H, major isomer), 6.34 (s, 1H, minor isomer), 4.47–4.41 (m, 1H), 4.00–3.69 (m, 6H), 3.20 (s, 3H, major isomer), 3.14 (s, 3H, minor isomer), 2.72 (br s, 1H). **^{13}C-{^{1}H} NMR** ($CDCl_3$, 75 MHz): Major isomer δ (ppm) = 156.3, 149.9, 140.5, 132.4, 131.0, 129.8, 129.2, 128.7, 128.5, 127.9, 114.3, 104.8, 71.6, 66.8, 61.9, 58.9, 56.1. Minor isomer δ (ppm) = 156.7, 149.8, 140.0, 132.3, 130.9, 129.8, 128.8, 128.7, 128.4, 127.9, 113.2, 103.7, 70.0, 67.1, 62.0, 58.9, 56.0. **HRMS (ESI$^+$)** *m/z* calculated for (MH^+): 409.0394. Found: 409.0388. **MS (ESI$^+$):** 409 (MH^+). **IR (CH_2Cl_2):** ν 2930, 1725, 1628, 1584, 1507, 1459, 1396, 1298 cm^{-1}.

Compound 34 (Table 3, entry 5)

According to the procedure described above, **34** was isolated in 79% yield (white solid). Mixture of diastereoisomers 77 : 23. **^{1}H NMR** ($CDCl_3$, 300 MHz): Major isomer δ (ppm) = 8.20–8.17 (m, 2H), 7.89 (d, 1H, J = 8.1 Hz), 7.78 (dt, 1H, J = 1.0, 7.2, 8.2 Hz), 7.60 (t, 1H, J = 7.1 Hz), 7.36 (d, 2H, J = 8.7 Hz), 6.92 (d, 2H, J = 8.6 Hz), 6.66 (s, 1H, major isomer), 6.38 (s, 1H, minor isomer), 4.84 (AB system, 2H), 4.40 (dd, 1H, J = 5.5, 6.6 Hz), 3.81 (s, 3H), 3.80–3.77 (m, 2H), 3.19 (s, 3H). **^{13}C-{^{1}H} NMR** ($CDCl_3$, 75 MHz): Major isomer δ (ppm) = 159.6, 156.4, 149.9, 141.0, 132.2, 130.8, 129.9, 129.5, 129.1, 129.0, 128.6, 128.4, 127.8, 114.5, 114.1, 103.3, 70.6, 66.9, 59.1, 56.7, 55.4. **HRMS (ESI$^+$)** *m/z* calculated for (MH^+): 485.0707. Found: 485.0694. **MS (ESI$^+$):** 485 (MH^+). **IR (CH_2Cl_2):** ν 2930, 1613, 1585, 1514, 1464, 1392, 1342, 1300 cm^{-1}.

Compound 35 (Table 3, entry 6)

According to the procedure described above, **35** was isolated in 74% yield (white solid). Mixture of diastereoisomers 77 : 23. **^{1}H NMR** ($CDCl_3$, 300 MHz): Major isomer δ (ppm) = 8.25 (s, 1H), 8.20 (d, 1H, J = 8.5 Hz), 7.93 (d, 1H, J = 8.1 Hz), 7.81 (ddd, 1H, J = 1.4, 6.9, 8.4 Hz), 7.64 (ddd, 1H, J = 1.1, 6.9, 8.1 Hz), 6.48 (s, 1H), 4.16 (part of AB system, 1H, J = 18.2 Hz), 3.59 (s, 3H), 3.51 (part of AB system, 1H, J = 18.2 Hz). Minor isomer (selected signals) δ (ppm) = 6.25 (s, 1H), 4.17 (part of AB system, 1H, J = 18.2 Hz), 3.57 (s, 3H), 3.42 (part of AB system, 1H, J = 18.2 Hz). **^{13}C-{^{1}H} NMR** ($CDCl_3$, 75 MHz): Major isomer δ (ppm) = 156.2, 150.1, 137.7, 132.1, 131.0, 129.9, 129.4, 128.7, 128.4, 128.0, 114.3, 104.9, 56.2, 50.2. **HRMS (ESI$^+$)** *m/z* calculated for (MH^+): 335.0026. Found: 335.0028. **MS (ESI$^+$):** 335 (MH^+). **IR (CH_2Cl_2):** ν 2931, 2854, 1724, 1628, 1582, 1507, 1399, 1336, 1313 cm^{-1}.

Compound 36 (Table 3, entry 7)

According to the procedure described above, **36** was isolated in 74% yield (white solid). Mixture of diastereoisomers 85 : 15. **^{1}H NMR** ($CDCl_3$, 300 MHz): Major isomer δ (ppm) = 8.20 (s, 1H), 8.18 (d, 1H, J = 8.5 Hz), 7.91 (d, 1H, J = 8.1 Hz), 7.79 (t, 1H, J = 7.1 Hz), 7.62 (t, 1H, J = 7.5 Hz), 6.61 (s, 1H), 4.24 (sept, 1H, J = 6.2 Hz), 4.16 (part of AB system, 1H, J = 18.2 Hz), 3.48 (part

of AB system, 1H, J = 18.2 Hz), 1.36 (d, 3H, J = 6.1 Hz), 1.33 (d, 3H, J = 6.1 Hz). Minor isomer (selected signals) δ (ppm) = 6.33 (s, 1H), 3.37 (part of AB system, 1H, J = 18.2 Hz). **^{13}C-{^{1}H} NMR** ($CDCl_3$, 75 MHz): Major isomer δ (ppm) = 156.3, 150.0, 137.6, 132.0, 131.8, 130.8, 130.3, 129.8, 128.6, 128.5, 127.8, 114.2, 102.9, 72.9, 50.1, 23.7, 22.4. **HRMS (ESI$^+$)** m/z calculated for (MNa^+): 385.0158. Found: 385.0148. **MS (ESI$^+$):** 385 (MNa^+). **IR (CH_2Cl_2):** ν 2977, 2929, 1725, 1630, 1582, 1507, 1405, 1385 cm^{-1}.

Compound 37 (Table 3, entry 8)

According to the procedure described above, **37** was isolated in 78% yield (white solid). Mixture of diastereoisomers 40 : 40 : 10 : 10. **^{1}H NMR** ($CDCl_3$, 300 MHz): Major isomers δ (ppm) = 8.25–8.17 (m, 2H), 7.91 (d, 1H, J = 8.1 Hz), 7.81–7.76 (m, 1H), 7.64–7.59 (m, 1H), 6.48 & 6.46 (s, 1H), 4.63 (br s, 1H, 50%), 4.49 (br s, 1H, 50%), 4.48–4.41 (m, 1H), 4.18–4.07 (m, 1H), 3.81–3.71 (m, 2H), 3.65 & 3.63 (s, 3H), 3.53–3.39 (m, 1H), 1.50–1.06 (m, 6H). Minor isomers (selected signals) δ (ppm) = 6.32 & 6.23 (s, 1H), 3.50 & 3.49 (s, 3H). **^{13}C-{^{1}H} NMR** ($CDCl_3$, 75 MHz): Major isomers δ (ppm) = 156.5, 156.4, 149.9, 141.3, 140.8, 132.0, 131.9, 130.9, 129.9, 129.5, 128.6, 128.4, 127.8, 127.7, 114.6, 114.4, 105.5, 105.3, 99.3, 98.8, 62.5, 61.9, 61.6, 56.9, 56.8, 56.7, 56.3, 30.1, 29.8, 25.3, 18.7, 18.6. **HRMS (ESI$^+$)** m/z calculated for (MH^+): 449.0707. Found: 449.0699. **MS (ESI$^+$):** 449 (MH^+). **IR (CH_2Cl_2):** ν 2944, 2854, 1724, 1628, 1584, 1507, 1446, 1398, 1356, 1298 cm^{-1}.

Compound 38 (Table 3, entry 9)

According to the procedure described above, **38** was isolated in 65% yield (white solid). Mixture of diastereoisomers 86 : 14. **^{1}H NMR** ($CDCl_3$, 300 MHz): Major isomer δ (ppm) = 8.25–8.22 (m, 1H), 8.15 (d, 1H, J = 8.5 Hz), 7.92 (d, 1H, J = 8.2 Hz), 7.78 (t, 1H, J = 8.3 Hz), 7.64–7.59 (m, 1H), 6.69 (s, 1H, major isomer), 6.40 (s, 1H, minor isomer), 4.24 (sept, 1H, J = 6.2 Hz), 3.35 (d, 1H, J = 10.8 Hz), 1.35 (d, 3H, J = 6.1 Hz), 1.29 (d, 3H, J = 6.2 Hz), 1.18–1.06 (m, 1H), 0.87–0.70 (m, 1H), 0.51–0.23 (m, 2H). **^{13}C-{^{1}H} NMR** ($CDCl_3$, 75 MHz): Major isomer δ (ppm) = 156.8, 149.9, 144.8, 132.1, 130.8, 130.7, 129.8, 128.7, 128.6, 127.8, 114.6, 103.2, 72.5, 62.4, 23.7, 22.4, 7.0, 4.7, 2.4. **HRMS (ESI$^+$)** m/z calculated for (MH^+): 403.0652. Found: 403.0647. **MS (ESI$^+$):** 403 (MH^+). **IR (CH_2Cl_2):** ν 2977, 2928, 1724, 1628, 1582, 1506, 1403, 1384 cm^{-1}.

Compound 39 (Table 4, entry 1)

According to the procedure described above, **39** was isolated in 83% yield. Mixture of diastereoisomers 88 : 12. **^{1}H NMR** ($CDCl_3$, 300 MHz): Major isomer δ (ppm) = 8.23–8.18 (m, 2H), 7.89 (d, 1H, J = 7.8 Hz), 7.77 (t, 1H, J = 7.3 Hz), 7.59 (t, 1H, J = 7.6 Hz), 6.39 (s, 1H), 4.36 (q, 2H, J = 7.1 Hz), 3.60 (s, 3H), 3.23–3.04 (m, 4H), 3.07 (s, 3H), 2.51–2.39 (m, 1H), 1.37 (t, 3H, J = 7.1 Hz). **^{13}C-{^{1}H} NMR** ($CDCl_3$, 75 MHz): Major isomer δ (ppm) = 163.1, 157.3, 150.7, 149.8, 132.0, 130.6, 130.0, 129.8, 128.6, 128.3, 127.6, 105.1, 104.9, 72.4, 62.2, 58.7, 56.4, 33.5, 21.9, 14.3. **HRMS(ESI$^+$)** m/z calculated for (MNa^+): 409.1370. Found: 409.1370. **MS (ESI$^+$):** 409 (MNa^+). **IR (CH_2Cl_2):** ν 2985, 2932, 1721, 1628, 1506, 1447, 1398 cm^{-1}.

Compound 40 (Table 4, entry 2)

According to the procedure described above, **40** was isolated in 51% yield (white solid). Mixture of diastereoisomers 88 : 12. **^{1}H NMR** ($CDCl_3$, 300 MHz): Major isomer δ (ppm) = 8.23–8.19 (m, 2H), 7.91 (dd, 1H, J = 1.0, 8.2 Hz), 7.78 (ddd, 1H, J = 1.4, 7.0, 8.4 Hz), 7.61 (ddd, 1H, J = 1.0, 7.0, 8.0 Hz), 6.58 (s, 1H), 4.38 (q, 2H, J = 7.1 Hz), 4.19 (sept, 1H, J = 6.2 Hz), 3.26–3.05 (m, 4H), 3.11 (s, 3H), 2.43 (AB system, 1H), 1.39 (t, 3H, J = 7.1 Hz), 1.35 (d, 3H, J = 6.1 Hz), 1.33 (d, 3H, J = 6.1 Hz). **^{13}C-{^{1}H} NMR** ($CDCl_3$, 75 MHz): Major isomer δ (ppm) = 163.3, 157.3, 150.7, 149.9, 131.9, 130.7, 130.6, 130.1, 128.6, 128.5, 127.6, 105.1, 103.1, 72.8, 72.6, 62.3, 58.8, 33.6, 23.9, 22.5, 22.0, 14.3. **HRMS (ESI$^+$)** m/z calculated for (MH^+): 415.1864. Found: 415.1865. **MS (ESI$^+$):** 415 (MH^+). **IR (CH_2Cl_2):** ν 2979, 2929, 1721, 1629, 1506, 1378 cm^{-1}.

Compound 41 (Table 4, entry 3)

According to the procedure described above, **41** was isolated in 20% yield (white solid). Mixture of diastereoisomers 86 : 14. **^{1}H NMR** ($CDCl_3$, 300 MHz): Major isomer δ (ppm) = 8.24–8.21 (m, 2H), 7.92 (dd, 1H, J = 1.0, 8.3 Hz), 7.79 (ddd, 1H, J = 1.4, 6.9, 8.3 Hz), 7.62 (ddd, 1H, J = 1.0, 7.0, 8.0 Hz), 6.54 (s, 1H), 6.01 (ddt, 1H, J = 6.0, 10.5, 16.5 Hz), 5.38 (dd, 1H, J = 1.5, 17.2 Hz), 5.27 (dd, 1H, J = 1.3, 10.4 Hz), 4.45–4.26 (m, 4H), 3.26–3.04 (m, 4H), 3.09 (s, 3H), 2.51–2.39 (m, 1H), 1.39 (t, 3H, J = 7.1 Hz). **^{13}C-{^{1}H} NMR** ($CDCl_3$, 75 MHz): Major isomer δ (ppm) = 163.2, 157.4, 150.7, 149.9, 133.7, 132.1, 130.7, 130.1, 128.6, 128.4, 127.7, 118.3, 105.2, 103.5, 72.5, 70.1, 62.3, 58.8, 33.6, 21.9, 14.3. **HRMS (ESI$^+$)** m/z calculated for (MH^+): 413.1707. Found: 413.1704. **MS (ESI$^+$):** 413 (MH^+). **IR (CH_2Cl_2):** ν 2985, 2929, 1721, 1628, 1582, 1506, 1399, 1377 cm^{-1}.

Compound 42 (Table 4, entry 4)

According to the procedure described above, **42** was isolated in 51% yield (white solid). Mixture of diastereoisomers 90 : 10. **^{1}H NMR** ($CDCl_3$, 300 MHz): Major isomer δ (ppm) = 8.23–8.19 (m, 2H), 7.89 (dd, 1H, J = 1.0, 8.2 Hz), 7.78 (ddd, 1H, J = 1.4, 7.3, 8.4 Hz), 7.60 (ddd, 1H, J = 1.0, 7.0, 8.0 Hz), 7.35 (d, 2H, J = 8.6 Hz), 6.9 (d, 2H, J = 8.6 Hz), 6.58 (s, 1H), 4.81 (AB system, 2H), 4.39 (q, 2H, J = 7.1 Hz), 3.81 (s, 3H), 3.23–3.04 (m, 4H), 3.07 (s, 3H), 2.50–2.38 (m, 1H), 1.40 (t, 3H, J = 7.1 Hz). **^{13}C-{^{1}H} NMR** ($CDCl_3$, 75 MHz): Major isomer δ (ppm) = 163.2, 159.7, 157.3, 150.7, 149.8, 132.1, 130.6, 130.1, 129.2, 128.6, 128.4, 127.6, 114.1, 105.2, 103.2, 72.5, 71.0, 62.3, 58.8, 55.4, 33.7, 22.0, 14.3. **HRMS (ESI$^+$)** m/z calculated for (MH^+): 493.1969. Found: 493.1970. **MS (ESI$^+$):** 493 (MH^+). **IR (CH_2Cl_2):** ν 2983, 2931, 2840, 1721, 1613, 1514, 1299 cm^{-1}.

Compound 43 (Table 4, entry 5)

According to the procedure described above, **43** was isolated in 59% yield (white solid). Mixture of diastereoisomers 88 : 12. **^{1}H NMR** ($CDCl_3$, 300 MHz): Major isomer δ (ppm) = 8.25 (s, 1H), 8.19 (d, 1H, J = 8.5 Hz), 7.92 (d, 1H, J = 8.2 Hz), 7.79 (ddd, 1H, J = 1.4, 7.1, 8.4 Hz), 7.63 (ddd, 1H, J = 1.0, 7.1, 8.1 Hz), 6.48 (s, 1H), 4.38 (q, 2H, J = 7.1 Hz), 3.56 (s, 3H), 3.04–2.96 (part of AB system, 1H), 2.87–2.64 (part of AB system, 2H), 2.32–2.26 (part of

AB system, 1H), 1.39 (t, 3H, J = 7.1 Hz). **^{13}C-{^{1}H} NMR** ($CDCl_3$, 75 MHz): Major isomer δ (ppm) = 163.4, 158.5, 150.6, 149.8, 132.2, 130.7, 130.0, 129.8, 128.7, 128.5, 127.7, 104.7, 103.9, 62.3, 55.8, 24.9, 17.9, 14.3. **HRMS (ESI$^+$)** m/z calculated for (MH^+): 343.1288. Found: 343.1288. **MS (ESI$^+$):** 343 (MH^+). **IR (CH_2Cl_2):** ν 2983, 2938, 1720, 1628, 1506, 1398, 1378, 1296 cm^{-1}.

Compound 44 (Table 4, entry 6)

According to the procedure described above, **44** was isolated in 63% yield (white solid). Mixture of diastereoisomers 86 : 14. **^{1}H NMR** ($CDCl_3$, 300 MHz): Major isomer δ (ppm) = 8.25–8.17 (m, 2H), 7.93 (d, 1H, J = 8.2 Hz), 7.79 (t, 1H, J = 7.1 Hz), 7.62 (t, 1H, J = 7.1 Hz), 6.63 (s, 1H), 4.37 (q, 2H, J = 7.1 Hz), 4.21 (sept, 1H, J = 6.2 Hz), 3.00–2.89 (part of AB system, 1H), 2.63–2.52 (part of AB system, 1H), 2.01–1.92 (m, 1H), 1.39 (t, 3H, J = 7.1 Hz), 1.35 (d, 3H, J = 6.2 Hz), 1.31 (d, 3H, J = 6.2 Hz), 0.77–0.65 (m, 1H), 0.43–0.34 (m, 1H), 0.18–0.07 (m, 1H), –0.04–(–)0.18 (m, 2H). Minor isomer δ (ppm) (selected peak) = 6.45 (s, 1H). **^{13}C-{^{1}H} NMR** ($CDCl_3$, 75 MHz): Major isomer δ (ppm) = 163.5, 157.9, 150.8, 149.6, 131.8, 131.1, 130.5, 129.9, 128.6, 128.5, 127.5, 107.4, 103.3, 72.7, 62.2, 38.6, 24.2, 23.9, 22.6, 14.3, 11.4, 5.0, 2.3. **HRMS (ESI$^+$)** m/z calculated for (MH^+): 411.1914. Found: 411.1914. **MS (ESI$^+$):** 411 (MH^+). **IR (CH_2Cl_2):** ν 2979, 2928, 1720, 1629, 1608, 1506, 1376, 1299 cm^{-1}.

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