



Review

Alkoxyalkylation of Electron-Rich Aromatic Compounds

Péter Simon ¹, Bálint Lőrinczi ¹ and István Szatmári ^{1,2,*}

¹ Institute of Pharmaceutical Chemistry, University of Szeged, Eötvös u. 6, H-6720 Szeged, Hungary; petersimon020@gmail.com (P.S.); lorinczi.balint@szte.hu (B.L.)

² HUN REN SZTE Stereochemistry Research Group, University of Szeged, Eötvös u. 6, H-6720 Szeged, Hungary

* Correspondence: szatmari.istvan@szte.hu

Abstract: Alkoxyalkylation and hydroxyalkylation methods utilizing oxo-compound derivatives such as aldehydes, acetals or acetylenes and various alcohols or water are widely used tools in preparative organic chemistry to synthesize bioactive compounds, biosensors, supramolecular compounds and petrochemicals. The syntheses of such molecules of broad relevance are facilitated by acid, base or heterogenous catalysis. However, degradation of the *N*-analogous Mannich bases are reported to yield alkoxyalkyl derivatives via the *retro*-Mannich reaction. The mutual derivative of all mentioned species are quinone methides, which are reported to form under both alkoxy- and aminoalkylative conditions and via the degradation of the Mannich-products. The aim of this review is to summarize the alkoxyalkylation (most commonly alkoxy-methylation) of electron-rich arenes sorted by the methods of alkoxyalkylation (direct or via *retro*-Mannich reaction) and the substrate arenes, such as phenolic and derived carbocycles, heterocycles and the widely examined indole derivatives.

Keywords: alkoxyalkylation; alkoxy-methylation; hydroxyalkylation; Mannich reaction; *retro*-Mannich reaction; indole; phenol; hydroxyquinoline; quinone methides

1. Introduction

In the field of organic chemistry, C–C coupling reactions are a unique and versatile means of molecular fine-tuning. Coupling a carbon atom bearing active hydrogen with an electron-deficient carbon (e.g., carbonyl) atom has been known to literature. Various methods of synthesizing benzylic-type ethers and alcohols from electron-rich arenes have been introduced using aldehydes as a carbonyl-compound and catalysts such as zeolites, base and (Brønsted or Lewis) acid catalysts or organic amines by the degradation of Mannich bases. These types of products earned significance in pharmaceutical, supramolecular and petrol chemistry, as well as preparative organic chemistry, biosensor chemistry and organic photochemistry.

Regarding alkoxyalkylations, the Mannich or Betti reactions can be regarded as related. The latter reactions can occur via two main mechanisms: one starting with the formation of an iminium ion and its subsequent addition to the electron-rich aromatic ring, the other starting with the formation of a quinone methide and the subsequent *aza*-Michael addition of the amine to the methyldene group [1,2]. Taking the similarities of the hydroxy- or alkoxyalkylation of arenes into consideration, in scientific literature the latter mechanism, starting from quinone methides and the *oxy*-Michael addition of an alcohol, is currently the more frequently proposed mechanism [3,4]. However, considering the fact that alkoxyalkylation is reported as directly using acetals [5–8], the analogous compounds of imines, the hypothesis of their reaction with aromatic rings should not be neglected.

More interestingly, as reported, Mannich bases can undergo deaminative reactions yielding quinone methides [1,6,9–15], from which a broad molecular library can be synthesized of various biological activities. Alkoxyalkyl compounds are also prone to form

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quinone methides under certain conditions [16], thus opening the way towards aminoalkyl derivatives and a possible synthetic circle. (Figure 1)

The aim of this review is to collect and summarize the aforementioned reactions, focusing on the synthesis of alkoxyalkylated derivatives. The literature processed is grouped with regard to the reaction pathways or substrates, such as the direct alkoxyalkylation via inorganic catalysis or through the Mannich and subsequent *retro*-Mannich reactions.

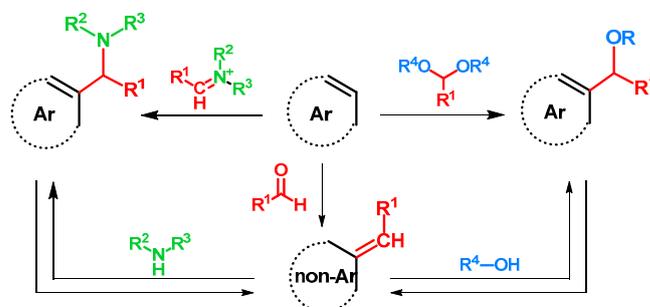
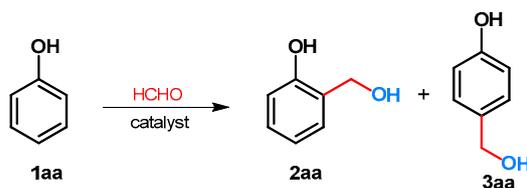


Figure 1. Accepted or experimented reaction pathways of the alkoxyalkylation of electron-rich arenes.

2. Hydroxy- and Alkoxyalkylation of Electron-Rich Arenes: Direct and Catalytic Methods

2.1. Hydroxy- and Alkoxyalkylation of Monocyclic Arenes

The hydroxymethylation of phenol was examined using formaldehyde. Due to the activation of hydroxyl function, two regioisomeric hydroxymethylated products (**2** and **3**) can be formed. Since both of the products are important chemicals in industry [17,18] or are important precursors toward the synthesis of bioactive compounds [19–21], the selectivity of the reaction is critical (Scheme 1). The effect of the divalent metal salts on the regioselectivity was examined by Komiyama and Morozumi [22]. It was found that without catalyst, or by using $MgCl_2$, $CuCl_2$ and $FeCl_2$, the ratio **2aa/3aa** was between 1 and 1.5. By applying divalent zinc salts such as $Zn(H_3CCOO)_2$, $Zn(NO_3)_2$ or $ZnBr_2$, the selectivity could be shifted toward the formation of **2aa**, and the ratio **2aa/3aa** was around 10 [22]. The synthesis of **2aa** was also published by Jeong and Hu [23]. For the synthesis, to provide the selectivity, $Zn(NO_3)_2 \cdot 6H_2O$ was applied, and 2-hydroxymethylphenol (salicyl alcohol: **2aa**) was further transformed to benzofuran derivatives [23].



Scheme 1. Regioselective catalytic hydroxymethylation of phenol with formaldehyde.

The prepared salicylic alcohol (**2aa**) was reported as a precursor to synthesizing boron-modified phenolic resin composites (BPR) [24,25]. It was proved that BPR has excellent heat resistance, ablative resistance, good mechanical and wear resistance and flame retardancy [25].

The *C-ortho* site-specific monohydroxymethylation of phenol **1aa** was developed by Casiraghi et al. [26]. For the synthesis of salicyl alcohol **2aa**, phenol **1aa** was treated in xylene with an excess of paraformaldehyde in the presence of 1 mol equiv. of dimethoxyethane (DME) as an ether additive (Table 1, entry 1). The synthetic route was then extended for the synthesis of different salicyl alcohols summarized in Table 1. The *ortho*-selective monohydroxymethylation of a series of phenols was described by Wu et al. [27]. The reactions were performed in the presence of $NaBO_2$ at 40 °C. The structures of the

synthesized salicyl alcohols are listed in Table 1. It should be mentioned that by using NaBO₂, the yields were found to be between 80 and 95% (Table 1). Mezzogori et al. reported that the H-mordenite zeolite catalyzed simultaneous synthesis of *o*- (**2ax**), *m*- and *p*-vanillols (Table 1, entry 30) [28].

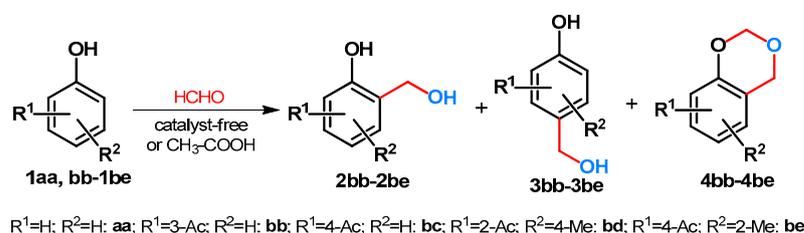
Table 1. *Ortho*-selective hydroxymethylation of substituted phenols using various catalysts.

$$\text{1aa-1ba} + \text{HCHO} \longrightarrow \text{2aa-2ba}$$

Entry	R ¹	R ²	R ³	R ⁴	Product	Conditions	Yield	Reference
1	H	H	H	H	2aa	DME/xylene, 135 °C	66	[26]
2	H	H	H	H	2aa	NaBO ₂ , H ₂ O, 40 °C	93	[27]
3	Me	H	H	H	2ab	DME/xylene, 135 °C	77	[26]
4	Me	H	H	H	2ab	NaBO ₂ , H ₂ O, 40 °C	87	[27]
5	H	H	Me	H	2ac	DME/xylene, 135 °C	92	[26]
6	H	H	Me	H	2ac	NaBO ₂ , H ₂ O, 40 °C	90	[27]
7	H	H	i-Bu	H	2ad	DME/xylene, 135 °C	85	[26]
8	Ph	H	H	H	2ae	DME/xylene, 135 °C	65	[26]
9	cyclohexyl	H	H	H	2af	DME/xylene, 135 °C	85	[26]
10	Me	H	Me	H	2ag	DME/xylene, 135 °C	92	[26]
11	H	Me	Me	H	2ah	DME/xylene, 135 °C	95	[26]
12	<i>t</i> -Bu	H	H	Me	2ai	DME/xylene, 135 °C	95	[26]
13	H	H	Ph	H	2aj	NaBO ₂ , H ₂ O, 40 °C	95	[27]
14	H	H	<i>t</i> -Bu	H	2ak	NaBO ₂ , H ₂ O, 40 °C	86	[27]
15	H	H	Et	H	2al	NaBO ₂ , H ₂ O, 40 °C	89	[27]
16	F	H	H	H	2am	NaBO ₂ , H ₂ O, 40 °C	85	[27]
17	H	H	F	H	2an	NaBO ₂ , H ₂ O, 40 °C	90	[27]
18	F	F	H	H	2ao	NaBO ₂ , H ₂ O, 40 °C	90	[27]
19	F	H	H	F	2ap	NaBO ₂ , H ₂ O, 40 °C	92	[27]
20	H	H	Cl	H	2aq	NaBO ₂ , H ₂ O, 40 °C	80	[27]
21	H	H	Cl	H	2aq	DME/xylene, 135 °C	67	[26]
22	H	Cl	H	H	2ar	NaBO ₂ , H ₂ O, 40 °C	90	[27]
23	H	H	Br	H	2as	DME/xylene, 135 °C	69	[26]
24	H	H	Br	H	2as	NaBO ₂ , H ₂ O, 40 °C	83	[27]
25	H	Br	H	H	2at	NaBO ₂ , H ₂ O, 40 °C	91	[27]
26	H	H	I	H	2au	DME/xylene, 135 °C	70	[26]
27	H	H	OMe	H	2av	DME/xylene, 135 °C	66	[26]
28	H	H	OMe	H	2av	NaBO ₂ , H ₂ O, 40 °C	90	[27]
29	OMe	H	H	H	2aw	NaBO ₂ , H ₂ O, 40 °C	88	[27]
30	OMe	H	H	H	2ax	H-mordenite, 80 °C, water/methanol	70	[28]
31	H	H	OBn	H	2ay	NaBO ₂ , H ₂ O, 40 °C	83	[27]
32	H	H	OH	H	2az	DME/xylene, 135 °C	59	[26]
33	<i>i</i> -pentyl	H	OH	H	2ba	DME/xylene, 135 °C	61	[26]

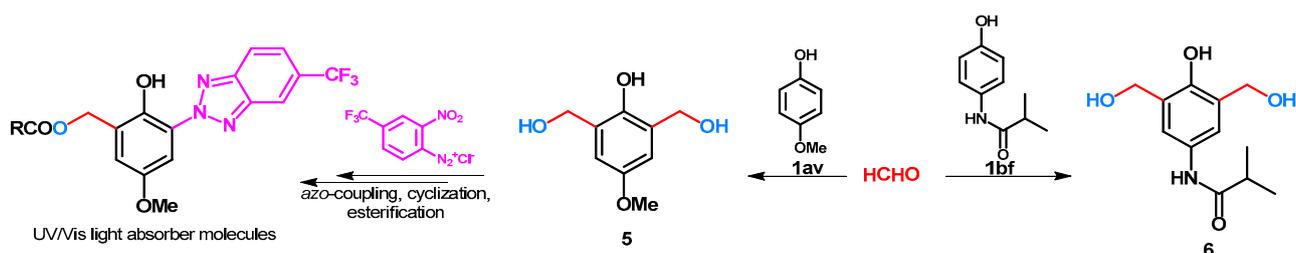
Hydroxymethylation of phenol (**1aa**) and phenolic ketones (**1bb-1be**) was investigated by Goswami et al. [29]. The reactions were conducted at 60–70 °C. It was found that depending on the phenolic substrate:paraformaldehyde ratios, different products could

be isolated. It was also assumed that for the formation of 1,3-dioxane derivatives **4**, the necessary paraformaldehyde ratio depended on the phenol or phenolic ketones (**1**) in question. Starting from **1aa** it was 1:3, from **1bb** and **1bc** 1:7, while from **1be** the ratio was 1:12. It is interesting to note that starting from **1bd**, even by using an extreme excess of paraformaldehyde (1:9), formation of **4bd** was not observed (Scheme 2) [29].



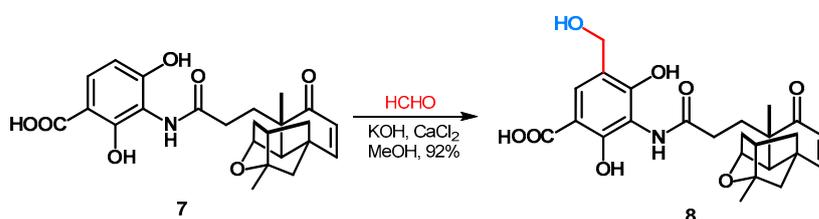
Scheme 2. Divergent hydroxymethylation of phenolic compounds.

The previous syntheses, by using different additives or catalysts, attempted to avoid the dihydroxymethylation of phenols. In some cases, the extra hydroxymethyl function can be further used to build bioactive sidechains. For example, the hydroxymethyl group of compound **5** (Scheme 3) was further transformed to benzotriazole moiety [30], while **6** (Scheme 3) was used as an important crosslinking agent [31].



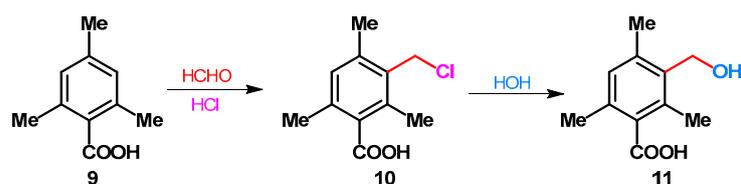
Scheme 3. *Ortho-ortho'* bis-hydroxymethylation of phenol derivatives.

Duan et al. reported the hydroxymethylation of platensimycin (**7**) as an excellent natural-product-derived lead molecule against various gram-positive pathogens. The synthesis was performed in MeOH, by using formaldehyde and inorganic additives KOH and CaCl₂, leading to the formation of **8** in an excellent yield (Scheme 4) [32].



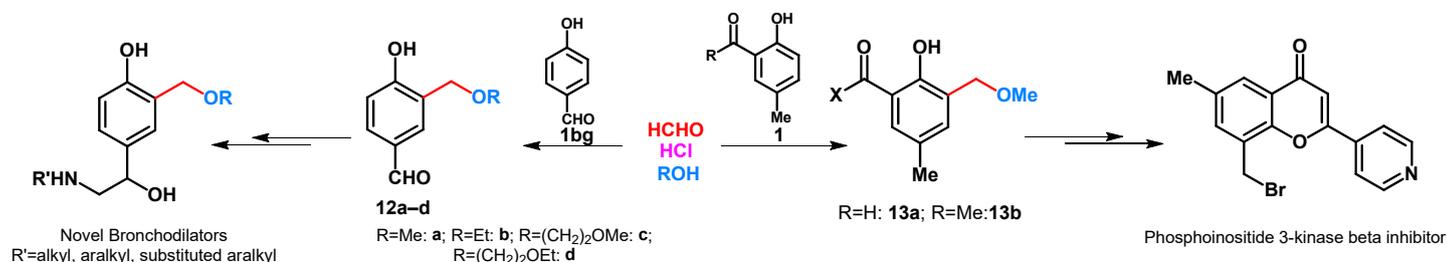
Scheme 4. Hydroxymethylation of platensimycin.

The preparation of 3-hydroxymethyl-2,4,6-trimethylbenzoic acid (**11**) was reported by Stewart. The synthesis included a standard chloromethylation of mesitoic acid (**9**) with formaldehyde in the presence of hydrochloric acid, followed by the rapid hydrolysis of the chloromethyl group during the mildly basic aqueous wash stage incorporated in the work-up procedure (Scheme 5) [33].



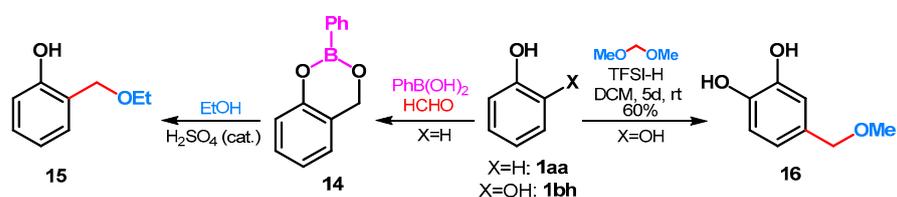
Scheme 5. Chloromethylation and rapid hydrolysis of mesitoic acid.

The synthesis of 4-hydroxy-3-alkoxymethylbenzaldehydes (**12a–d**) was reported by Hirose et al. The role of hydrochloric acid is to form 3-chloromethyl intermediate that reacts immediately with the alcohols applied in the reaction (Scheme 6) [34]. Methoxymethylation of 2-hydroxy-5-methylbenzaldehyde was published by Jorgensen et al. (Scheme 6) [35]. Compound **13a** was then transformed to new potential fibroblast growth factor (FGF) receptor 1 kinase inhibitors. Methoxymethylation of 2-hydroxy-5-methylacetophenone was performed in methanol by using paraformaldehyde in the presence of cc. hydrochloric acid (Scheme 6) [36]. *Ortho*-situated hydroxyl and acetyl functions enabled the building of substituted pyran moiety.



Scheme 6. Alkoxymethylation of hydroxybenzaldehydes and phenolic ketones.

Ortho-selective ethoxymethylation was published by Bélanger et al. [37]. Phenol **1aa** was reacted with formaldehyde in the presence of phenylboronic acid, leading to 1,3,2-benzodioxaborin **14** (Scheme 7). Treatment of **14** with ethanol in the presence of sulphuric acid catalyst gave the desired 2-ethoxymethylphenol **15**. By treatment of 1,2-dihydroxybenzene (**1bh**) with dimethoxymethane in the presence of bistrifluoromethanesulfonimide (TFSI-H), a regioselective Friedel–Crafts alkylation took place and compound **16** was isolated in a yield of 60% (Scheme 7) [5].



Scheme 7. Alkoxymethylation of catechol and phenol with TFSI-H or phenylboronic acid.

The reaction among resorcinol derivatives and flavor-relevant saturated aldehydes was tested by Zomora et al. [38]. As a representative reaction, the synthesis of 4-(1-hydroxypentyl)-2-methyl-benzene-1,3-diol (**17a**) was carried out at 60 °C. It should be mentioned that thanks to the aliphatic alcohol function, the reaction provided different side products, e.g., methoxylated **17a** (Table 2, entry 1), or by water elimination formation of double bond in the side chain. The asymmetric hydroxyalkylation of different phenols was developed by Casiraghi et al. [39]. The reactions were performed in toluene by using chloroacetaldehyde in the presence of chirally modified aluminum chloride derivatives. It was summarized that chiral Lewis acid promoter and the reactants fine-tuned both the regio- and

enantioselectivity of the reaction (Table 2, entries 2–9). Ytterbium(III) trifluoromethanesulfonate ($\text{Yb}(\text{OTf})_3$)-catalyzed electrophilic aromatic substitution of substituted phenols with ethyl-glyoxylate was published by Wang and Zhang [40]. The reactions were performed at rt, and the lowest yield was observed when the starting phenol derivative was bearing tertiary nitrogen (Table 2, entry 13).

Table 2. *ortho*-hydroxyalkylation of substituted phenols with different catalysts.

Entry	R	R ¹	R ²	R ³	R ⁴	Product	Conditions	Yield	Reference
1	Bu	Me	OH	H	H	17a	DME/xylene, 135 °C	66	[38]
2	-CCl ₃	H	H	H	H	17b	Toluene, 4 h, 15 °C	96	[39]
3	-CCl ₃	H	H	Me	H	17c	Toluene, 4 h, 15 °C	97	[39]
4	-CCl ₃	H	H	<i>t</i> -Bu	H	17d	Toluene, 4 h, 15 °C	97	[39]
5	-CCl ₃	Me	H	H	H	17e	Toluene, 4 h, 15 °C	65	[39]
6	-CCl ₃	<i>i</i> -Pr	H	H	H	17f	Toluene, 4 h, 15 °C	78	[39]
7	-CCl ₃	<i>t</i> -Bu	H	H	H	17g	Toluene, 4 h, 15 °C	53	[39]
8	-CCl ₃	Me	H	H	Me	17h	Toluene, 4 h, 15 °C	55	[39]
9	-CCl ₃	Br	H	H	H	17i	Toluene, 4 h, 15 °C	51	[39]
10	-COOEt	H	H	<i>t</i> -Bu	H	17j	$\text{Yb}(\text{OTf})_3/\text{CH}_2\text{Cl}_2$, 10 h, rt	88	[40]
11	-COOEt	H	<i>t</i> -Bu	H	H	17k	$\text{Yb}(\text{OTf})_3/\text{CH}_2\text{Cl}_2$, 10 h, rt	90	[40]
12	-COOEt	H	H	OH	H	17l	$\text{Yb}(\text{OTf})_3/\text{CH}_2\text{Cl}_2$, 10 h, rt	80	[40]
13	-COOEt	H	Et_3N	H	H	17m	$\text{Yb}(\text{OTf})_3/\text{CH}_2\text{Cl}_2$, 10 h, rt	68	[40]
14	-COOEt	H	H	F	H	17n	$\text{Yb}(\text{OTf})_3/\text{CH}_2\text{Cl}_2$, 10 h, rt	81	[40]

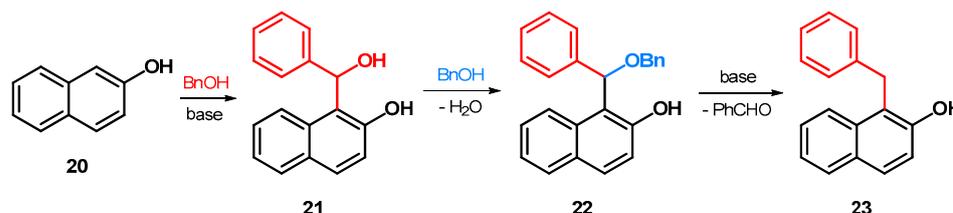
Methoxymethylation of electron-rich monocyclic arenes with formaldehyde-dimethylacetal by using β -Zeolite were performed by Müller et al. First, the method was developed starting from cumol (**18a**) [41], and was then extended to other arenes (**18b–g**) [42]. The structures of methoxymethylated derivatives are summarized in Table 3.

Table 3. β -Zeolite-catalyzed *para*-methoxymethylation of electron-rich benzenes.

Entry	R ¹	R ²	Product	Conditions	Conversion	Reference
1	H	<i>i</i> -Pr	19a	17 h, 80–90 °C	12	[41]
2	H	<i>i</i> -Pr	19a	54 h, 120 °C	46	[42]
3	H	<i>i</i> -Bu	19b	65 h, 75 °C	25	[42]
4	H	<i>t</i> -Bu	19c	90 h, 70 °C	24	[42]
5	H	OMe	19d	6 h, 95 °C	24	[42]
6	OMe	OH	19e	3 h, 95 °C	15	[42]
7	OMe	OMe	19f	64 h, 95 °C	25	[42]
8	H	OH	19g	6 h, 95 °C	24	[42]

2.2. Hydroxy- and Alkoxy-methylation of Phenol-Fused Carbocycles

Regarding alkoxyalkylations of naphthol and its derivatives, the first synthesis concerns such compounds as hydroxylated/alkoxylated bisarylmethylene (BAM) intermediates. In this regard, the reaction of 2-naphthol and benzyl alcohol occurring under high temperature and in the presence of a base—due to which the benzyl alcohol is in situ oxidized to benzaldehyde—yields compound **21**. Subsequently, **21** has been observed to react with the still present benzyl alcohol, yielding compound **22**, which through a base-catalyzed elimination loses benzaldehyde, leaving behind the final benzyl-substituted product **23** (Scheme 8) [43].



Scheme 8. Synthesis of 1-benzyl-2-naphthol (**23**) from 2-naphthol (**20**) and benzyl alcohol.

First synthesis of alkoxyated BAMs concerns the *oxy*-Michael-type addition reaction between aromatic aldehydes (**25a–j**), EtOH and 2-naphthol (**24a**) or 6-hydroxyquinoline (**24b**) assisted by 2,5-dihydroxy-1,4-benzoquinone (**27**) in the presence of HCl. The reaction afforded 1-[ethoxy(aryl)methyl]-2-naphthol (**26a–g**) and 5-[ethoxy(aryl)methyl]-6-hydroxyquinoline (**26h–j**) derivatives at room temperature (Scheme 9, route *a*, Table 4). The importance of **27** was outlined, as without it only xanthene byproducts could be achieved; however, though it was mentioned as catalyst, highest yields could be achieved at additive concentrations (Entries 6 and 7, Table 5) [44].

Table 4. Products and yields of reaction route *a* (check Scheme 9).

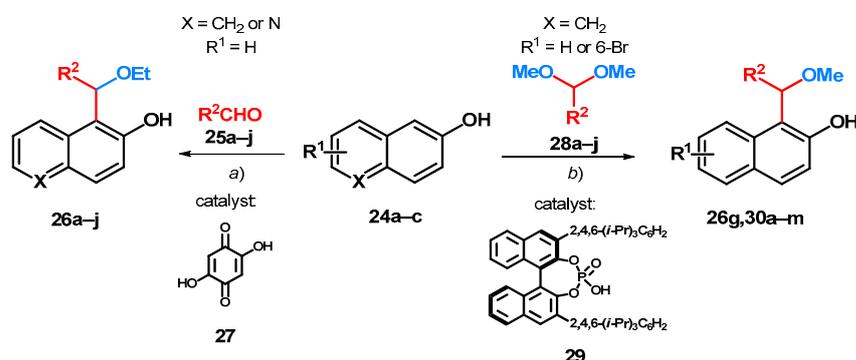
X	R ²	Compound	Yield (%)
CH (24a)	<i>p</i> -NO ₂ C ₆ H ₄ (25a)	26a	86
CH (24a)	<i>m</i> -NO ₂ C ₆ H ₄ (25b)	26b	82
CH (24a)	<i>o</i> -NO ₂ C ₆ H ₄ (25c)	26c	82
CH (24a)	<i>p</i> -MeC ₆ H ₄ (25d)	26d	79
CH (24a)	<i>p</i> -(O-CH ₂ -Ph)C ₆ H ₄ (25e)	26e	81
CH (24a)	<i>p</i> -OMeC ₆ H ₄ (25f)	26f	63
CH (24a)	2-naphthyl (25g)	26g	61
N (24b)	<i>p</i> -BrC ₆ H ₄ (25h)	26h	73
N (24b)	Ph (25i)	26i	71
N (24b)	<i>p</i> -OMeC ₆ H ₄ (25j)	26j	72

Table 5. Catalyst screening of reaction route *a* when X = CH₂ and R² = *p*-OMe-C₆H₄ (check Scheme 9).

Entry	1	2	3	4	6	7
Catalyst (27 , mol%)	5	25	50	750	100	150
Yield of 28f (%)	Trace	21	42	63	86	87

Acetals are widely used in carbon–carbon bond-forming reactions with a variety of nucleophiles for the synthesis of ethers [7,8]. Utilizing different chiral BINOL-based phosphoric acids as Brønsted acid catalysts with acetic acid as additive, the Friedel–Crafts-method synthesis of chiral alkoxyated BAMs from various acetals and naphthols (**24a,b**) was also described. After a thorough screening of solvent, catalyst and additive concentration, the chiral phosphoric acid (*R*)-TRIP (**29**) could efficiently catalyze the asymmetric

Friedel–Crafts reaction of **24a,b** with different aromatic acetals (**28a–j**), affording chiral ethers (**26g,30a–m**) of good enantioselectivity and yield (Scheme 9, Table 6) [6].



Scheme 9. Substituted bisarylmethylene derivatives of 2-naphthol starting from 2-naphthol. (a) EtOH/HCl, 100 mol% **27**, r.t., 24 h; (b) abs. C₂H₄Cl₂, 20 mol% **29**, 20 mol% AcOH, 35 °C.

Table 6. Starting materials, substituents, yields and *ee* for reaction route *b* (check Scheme 9).

24	R ²	Product	Yield (%)	<i>ee</i> (%)
2-naphthol (24a)	Ph (28a)	30a	64	68
2-naphthol (24a)	<i>o</i> -MeC ₆ H ₄ (28b)	30b	58	55
2-naphthol (24a)	<i>m</i> -MeC ₆ H ₄ (28c)	30c	61	71
2-naphthol (24a)	<i>p</i> -MeC ₆ H ₄ (28d)	30d	54	63
2-naphthol (24a)	<i>m</i> -MeOC ₆ H ₄ (28e)	30e	68	63
2-naphthol (24a)	<i>o</i> -ClC ₆ H ₄ (28f)	30f	42	40
2-naphthol (24a)	<i>p</i> -ClC ₆ H ₄ (28g)	30g	55	58
2-naphthol (24a)	<i>p</i> -BrC ₆ H ₄ (28h)	30h	51	33
2-naphthol (24a)	<i>p</i> -FC ₆ H ₄ (28i)	30i	46	50
2-naphthol (24a)	2-naphthyl (28j)	30g	44	66
6-bromo-2-naphthol (24c)	Ph (28a)	30j	57	57
6-bromo-2-naphthol (24c)	<i>m</i> -MeC ₆ H ₄ (28c)	30k	58	66
6-bromo-2-naphthol (24c)	<i>m</i> -MeOC ₆ H ₄ (28e)	30l	54	66
1-naphthol (24c)	Ph (28a)	30m	72	20

It has been previously demonstrated that organic ammonium tribromides (OATB) and in situ generated bromonium ion can be used for C–S bond cleavage in deprotection of dithioacetals [45] and in hydrolysis of 1-thioglycosides [46]. Starting out from the corresponding unsymmetrical sulfides (**31a–g**)—prepared according to literature methods—the synthesis of alkoxyated BAMs (**32a–r**) or hydroxylated 1-benzyl-naphthalen-2-ol (**33s–w**) derivatives could be achieved by utilizing BDMS (bromodimethylsulfonium bromide) and either the corresponding alcohol or water (Table 7) [47].

Table 7. Substituted bisarylmethylene derivatives of 2-naphthol starting out from thioethers. (a) 2 equiv. R³OH, 1 equiv. BDMS, DCM, r.t., 1–2 min. (b) 40 μL H₂O, 1 equiv. BDMS, MeCN, r.t., 5 min.

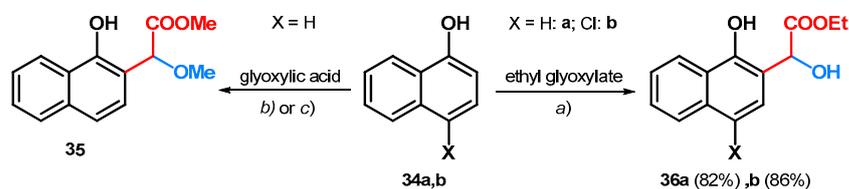
R ¹	R ²	Product	Yield (%)	Method
Ph	Et	32a	94	(a)

Ph	Me	32b	90
Ph	<i>n</i> -Pr	32c	92
Ph	<i>i</i> -Pr	32d	82
Ph	<i>n</i> -Bu	32e	88
Ph	Bn	32f	84
Ph	CH ₂ CH=CH ₂	32g	82
Ph	CH ₂ C≡CH	32h	80
Ph	(CH ₂) ₃ CH=CH ₂	32i	84
Ph	(CH ₂) ₄ Ph	32j	88
Ph	(CH ₂) ₂ OH	32k	81
Ph	(CH ₂) ₈ OH	32l	82
<i>p</i> -NO ₂ -Ph	Me	32m	94
<i>p</i> -NO ₂ -Ph	<i>n</i> -Bu	32n	88
<i>p</i> -F-Ph	Et	32o	94
<i>p</i> -Br-Ph	Me	32p	92
2-C ₁₀ H ₇	Me	32q	88
<i>p</i> -Me-Ph	Et	32r	90
Ph	H	32s	84
<i>p</i> -NO ₂ -Ph	H	32t	88
<i>p</i> -F-Ph	H	32u	86
<i>p</i> -Cl-Ph	H	32v	84
<i>p</i> -Me-Ph	H	32w	82

(b)

Besides aromatic aldehydes, glyoxylic acid and its esters have also been investigated in the alkoxyalkylation of the electron-rich 1- and 2-naphthol systems. Starting out from 1-naphthol (**34a**) and glyoxylic acid, utilizing *tert*-butoxy carbamate or acetamide as catalyst, the methyl 2-methoxyacetate derivative of 1-naphthol (**35**) could be achieved (Scheme 10). Though the syntheses yielded alkoxyated derivatives showing promising catalytic effects in this regard for *tert*-butoxy carbamate and acetamide, the aim of the described work was to synthesize amino acid derivatives through a modified Mannich reaction, thus highlighting the catalysts as unfavorable [48].

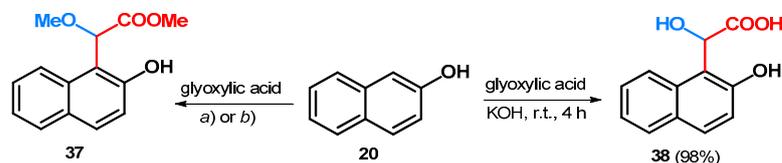
When starting out from ethyl glyoxylate and utilizing ytterbium(III) trifluoromethanesulfonate in DCM beside the previously described phenol derivatives (Scheme 10), 1-naphthol (**34a**) and its 4-chloro derivative (**34b**) gave hydroxyl derivatives (**36a,b**, Scheme 10) [40].



Scheme 10. (a) NH₂Boc, *p*TSA, MeOH, reflux, 98 h, 39%; (b) acetamide, *p*TSA, MeOH, reflux, 72 h, 34%; (c) 5 mol% Yb(OTf)₃ CH₂Cl₂, r.t.

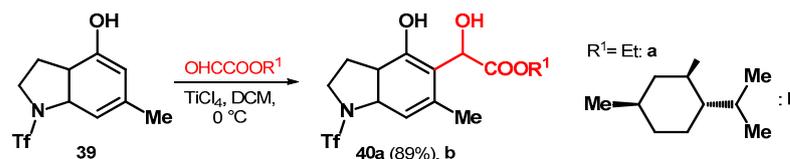
When starting out from 2-naphthol and glyoxylic acid and utilizing the same *tert*-butoxy carbamate or acetamide as catalyst, similar results could be achieved: the methyl 2-methoxyacetate derivative of 2-naphthol (**37**) could be achieved similar to **35** (Scheme 11) [48].

Without the use of such catalysts, applying only KOH, glyoxylic acid condenses with **20**, yielding α -hydroxy- α -(2-hydroxy-1-naphthyl)acetic acid (**38**, Scheme 11). Unfortunately, the acquired enantiomers could not be resolved due to possible racemization under the resolving conditions [49].



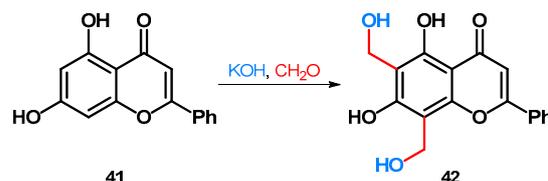
Scheme 11. (a) NH_2Boc , PTSA, MeOH, reflux, 93 h, 38%; (b) acetamide, PTSA, MeOH, reflux, 84 h, 32%.

The previously mentioned glyoxylic acid esters have also been utilized on phenols fused with heterocycles. However, in the case of compound **39**—despite the EDGs on the aromatic ring—titanium catalyst was needed most probably due to the strong inactivating effect of the triflate protecting group on the pyrrolidine moieties' nitrogen. The reaction yielded the ethyl ester derivative **40a** in high yield (89%); however, as far as we know there was no published yield for the relatively more interesting (–)-menthol ester (**40b**, Scheme 12) [50].



Scheme 12. Alkoxyalkylations of pyrrolidine-fused phenol system.

Regarding phenol-fused ring-systems, another interesting reaction concerns the transformation of chrysin, a naturally occurring flavonoid. The reaction conditions specified in the patent were not discoverable, but similar conditions are also discussed later, in the case of indole derivatives in Section 2.3.1.: the flavonoid (**41**) was reacted with a formaldehyde source in the presence of an alkali hydroxide that gave rise to the formation of the methoxymethylated derivative **42** (Scheme 13) [51].

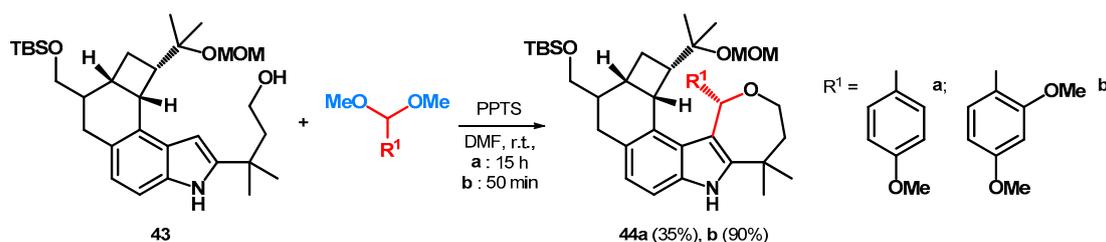


Scheme 13. Synthesis of chrysin-based hydroxymethylene derivative **42**.

2.3. Hydroxy- and Alkoxy-methylation of N-heterocycles

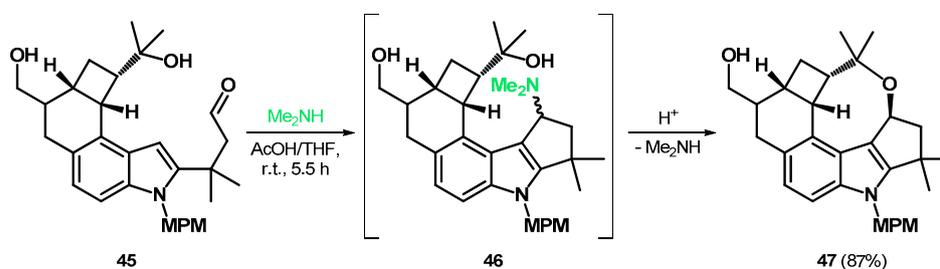
2.3.1. Hydroxy- and Alkoxy-methylation of Indoles

During the development of the total synthesis of penitrem A—a family of tremorgenic mycotoxins isolated from *Penicillium crustosum*—researchers were looking for indole nitrogen protecting groups that would not reduce the reactivity of the indole substructure in a modified Mannich reaction. When trying to build in a methoxylated benzyl protecting group, starting out from the acetal of the corresponding aldehydes under acidic conditions with a free alcoholic group—conditions like what later was exploited as described in Section 2.2. Scheme 9—yielded alkoxyalkylated BAMs **44a,b** (Scheme 14) [52].



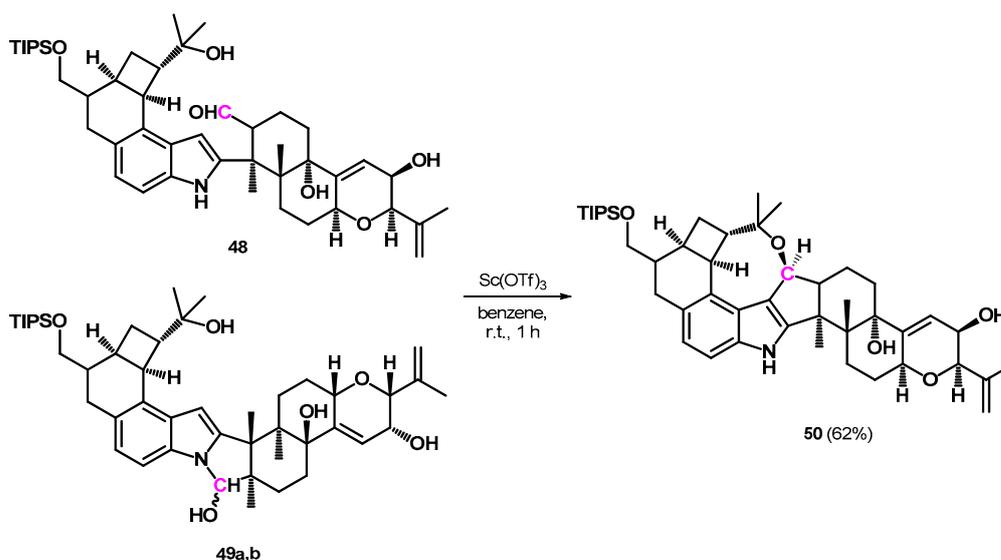
Scheme 14. Unsuccessful protection of indole nitrogen yielding BAMs. PPTS = pyridinium *p*-toluenesulfonate, MOM = methoxymethyl ether.

Later, MPM (*p*-methoxybenzyl) was found to be a sufficient protecting group and the *N*-protected aldehyde 45 was prepared to take part in the aforementioned modified Mannich reaction, yielding the alkoxyalkylated indole-fused oxocine 47 as the final product via intermediate Mannich-base 46 and a tandem Mannich cyclization/gramine fragmentation sequence (Scheme 15). Subsequently, compound 47 was further transformed to give the A–F rings of penitrem with appropriate functionalization [52].



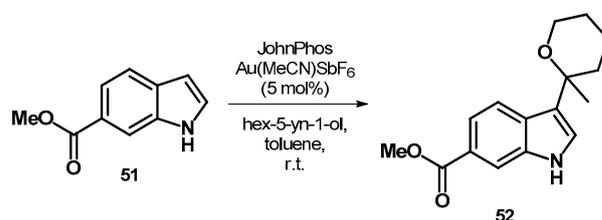
Scheme 15. Tandem Mannich cyclization/gramine fragmentation sequence yielding 47.

The same research group later described the complete total synthesis of the penitrem ring-systems utilizing a different reaction pathway. This reaction also required the building of the oxocine ring condensed—among other rings—on the indole substructure that required no Mannich-type intermediate. Alcohols 48 and 49a,b were synthesized and were tandem-cyclized into the oxocine-condensed ring-system (50) using scandium triflate (Scheme 16) [53].



Scheme 16. Oxidation of three different intermediates (48,49a,b) into 50 by scandium triflate.

Starting out from less functionalized indole derivatives, the first publication describes the synthesis of a novel Nav1.7 sodium channel inhibitor discovery. Compound **52** was synthesized uniquely among the other derivatives described using a gold salt as oxidizer starting out from **51** (Scheme 17). Compound **52** was later transformed; however, the final product had no inhibitory effect [54].



Scheme 17. Synthesis of tetrahydro-2H-pyran-2-yl-indole derivative **52**.

Utilizing similar techniques, two research papers describe the *oxy*-Michael-type modification of indole derivatives (**51,53a–p**) using aromatic aldehydes and methanol in a similar way as discussed previously in Section 2.2, Scheme 9; however, in these cases the acidic catalysts were exchanged to NaOH still yielding BAMs **54aa–xa** (Table 8) [4,55]. It would be interesting to carry out the previously discussed alterations on 2-naphthols with similar conditions.

Table 8. Alkoxyalkylation of indoles (a) 2 equiv. NaOH, 120 °C, 2–24 h; (b) 1.5 equiv. NaOH, 20 °C, 24 h.

Products of synthesis route a									
R ¹	R ²	R ³		Yield (%)	R ¹	R ²	R ³	Yield (%)	
H	H	Me	54aa	89	6-Br	H	Me	54ap	80
2-Ph	H	Me	54ab	90	7-NO ₂	H	Me	54aq	92
4-F	H	Me	54ac	88	H	Ph	Me	54ar	79
4-Cl	H	Me	54ad	82	H	C ₅ H ₄ N	Me	54as	89
4-OMe	H	Me	54ae	82	H	<i>o</i> -NO ₂ C ₆ H ₄	Me	54at	88
4-OCH ₂ Ph	H	Me	54af	84	H	<i>o</i> -MeC ₆ H ₄	Me	54au	87
5-Me	H	Me	54ag	85	H	<i>m</i> -MeC ₆ H ₄	Me	54av	96
5-OMe	H	Me	54ah	81	H	<i>p</i> -MeC ₆ H ₄	Me	54aw	82
5-NO ₂	H	Me	54ai	65	H	<i>m</i> -CHOC ₆ H ₄	Me	54ax	96
5-F	H	Me	54aj	88	H	<i>m</i> -OMeC ₆ H ₄	Me	54ay	79
5-Cl	H	Me	54ak	85	H	<i>p</i> -PhC ₆ H ₄	Me	54az	72
5-Br	H	Me	54al	83	H	<i>p</i> -CNC ₆ H ₄	Me	54ba	89
6-COOCH ₃	H	Me	54am	57	H	2,4-Cl ₂ C ₆ H ₃	Me	54ca	98
6-F	H	Me	54an	81	H	CH ₃ CH ₃ C ₆ H ₃	Me	54da	84
6-Cl	H	Me	54ao	80	H	H	CH ₂ CF ₃	54ea	83
Products of synthesis route b									
R ¹	R ²	R ³		Yield (%)	R ¹	R ²	R ³	Yield (%)	
H	<i>p</i> -CF ₃ C ₆ H ₄	Me	54fa	98	4-Me	<i>p</i> -BrC ₆ H ₄	Me	54pa	89
H	Ph	Me	54ga	96	5-Me	<i>p</i> -BrC ₆ H ₄	Me	54qa	92
H	<i>p</i> -BrC ₆ H ₄	Me	54ha	96	6-Me	<i>p</i> -BrC ₆ H ₄	Me	54ea	94

H	<i>p</i> -ClC ₆ H ₄	Me	54ia	95	7-Me	<i>p</i> -BrC ₆ H ₄	Me	54sa	93
H	<i>p</i> -FC ₆ H ₄	Me	54ja	97	5-Cl	<i>p</i> -BrC ₆ H ₄	Me	54ta	96
H	<i>o</i> -ClC ₆ H ₄	Me	54ka	96	5-Br	<i>p</i> -BrC ₆ H ₄	Me	54ua	98
H	3,4-Cl ₂ C ₆ H ₄	Me	54la	50	5-OMe	<i>p</i> -CF ₃ C ₆ H ₄	Me	54va	96
H	<i>p</i> -NO ₂ C ₆ H ₄	Me	54ma	65	5-CN	<i>p</i> -BrC ₆ H ₄	Me	54wa	42
2-Me	<i>p</i> -BrC ₆ H ₄	Me	54na	96	5-CN	<i>p</i> -CF ₃ C ₆ H ₄	Me	54xa	56
2-Me	<i>p</i> -ClC ₆ H ₄	Me	54oa	93					

Standing out from the transformations discussed previously, a site-selective 1,1-difunctionalization of unactivated alkenes was described that was enabled by cationic palladium catalysis. The scope and limitations of the synthesis were investigated in the case of alkenes comprising alcohols and carboxylic acids (**55a–k**) utilizing palladium(II) acetate and silver hexafluoroantimonate(V) as catalysts yielding **57a–k** (Table 9). It is worth mentioning that for the reaction to take place, directing group **AQ** was necessary and crucial [56].

Table 9. Substituents and yields of final products.

	R ¹	R ²	Compound	Yield (%)		R ¹	R ²	Compound	Yield (%)
	Me	H	57a	55		H	F	57g	46
	H	H	57b	47		Me	H	57h	56 ^a
	H	OMe	57c	56		H	H	57i	54 ^a
	Me	H	57d	58		H	OMe	57j	56 ^a
	Me	OMe	57e	58		Me	H	57k	36
	H	H	57f	56					

^a: MeCN was used as solvent at 80 °C.

Another reaction standing out from the ones discussed previously concerns the synthesis of spiro-pyridoindolone derivatives (**59**). However, one similarity ties it to the transformation discussed in Scheme 17, as the reaction concerns an alkyne moiety reacting with an alcohol—intramolecularly in **58**—in the presence of gold salt catalyst (Table 10) [57].

Table 10. Gold-catalyzed intramolecular alkynol cyclization/hydroindolylolation.

Reaction Scheme	R ¹	R ²	Compound	Yield (%)
	5-OMe	H	59a	74
	5-Me	H	59b	80
	5-F	H	59c	86
	5-Cl	H	59d	66
	5-Br	H	59e	73
	5-I	H	59f	77
	6-F	H	59g	90
	6-Cl	H	59h	90
	6-Br	H	59i	76
	4-Br	H	59j	59
	7-Me	H	59k	76
	H	2-Me	59l	75

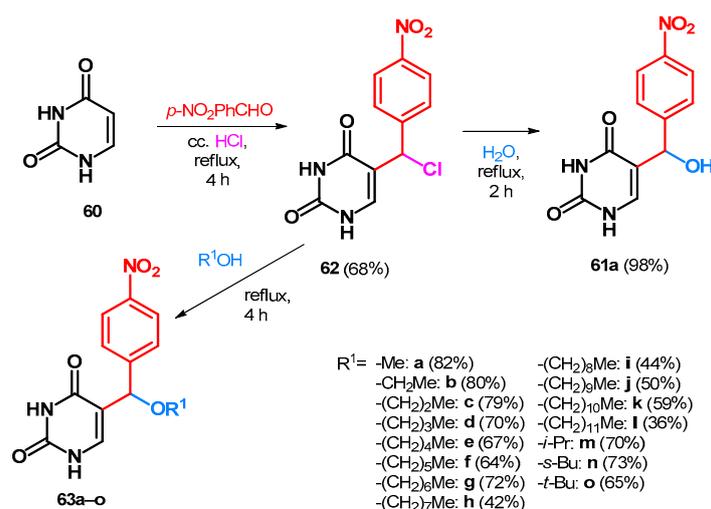
2.3.2. Hydroxy- and Alkoxy-methylation of Uracil

Uracil (**60**) bearing an enamino ketone character was successfully utilized in a hydroxyalkylation reaction using electron-deficient aromatic aldehydes in water. Instead of the more commonly used halogeno derivatives of aromatic aldehydes, the scope and limitations were investigated for *p*-nitrobenzaldehyde with heteroaromatic aldehyde derivatives, showing moderate yields (Table 11) [58].

Table 11. Synthesis and achieved yields of 5-(arylhydroxymethyl)uracil derivatives.

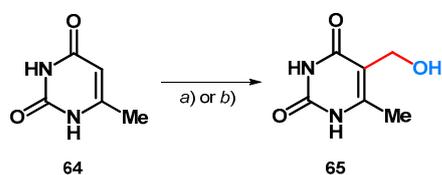
Ar					
Yield (%)	74	66	70	64	82
Compound	61a	61b	61c	61d	61e

Building upon these transformations, Hlavác et al. described the synthesis of **61a** in very similar reaction conditions. However, instead of the hydroxy derivative, first they obtained the chloro derivative (**62**) that had to be further hydrolyzed without the presence of hydrochloric acid. The scope and limitations was also investigated by supplementing water with different aliphatic alcohols, all yielding the alkoxy-methylated BAMs incorporating the uracil moiety (**63a–o**, Scheme 18) [59].



Scheme 18. Synthesis of alkoxy-methylated BAMs incorporating uracil moiety.

Besides aromatic aldehydes, paraformaldehyde was also investigated in the case of 6-methyluracil. The reaction was carried out using KOH as additive, and in both cases the final product was a hydroxymethylated derivative (**65**). However, it is interesting to mention the differences between the two publications: one describes no solvent and a much longer reaction (route *a*) [60], while the other describes the solvent and, despite only a 5 °C difference, half the reaction time and much better yields (route *b*) (Scheme 19) [61]. Both reactions share similarities with the incomplete transformation described in Scheme 13 [51].

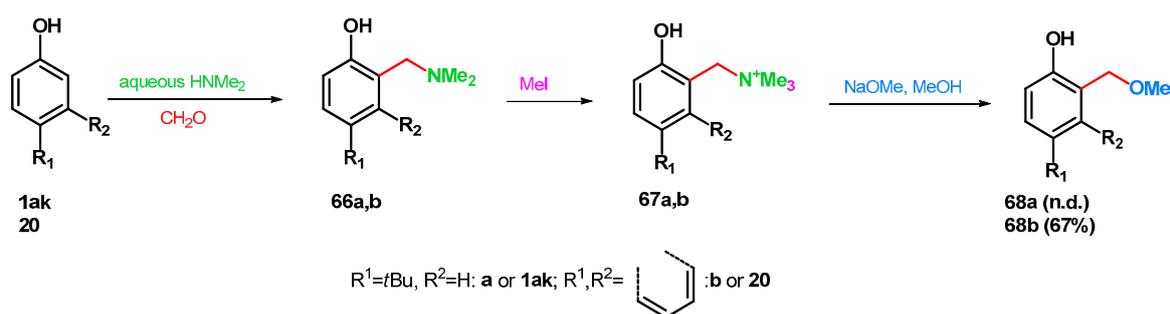


Scheme 19. (*a*) (CH₂O)_n, KOH, 50 °C, 73 h (76%) [60]; (*b*) (CH₂O)_n, KOH, H₂O, 0 °C then 55 °C for 36 h (98%).

3. Hydroxy- and Alkoxyalkylation of Electron-Rich Arenes via Aminoalkyl Intermediates

3.1. Transformations of Phenolic Mannich Bases

Transformations of benzylamines with various nucleophiles have been widely investigated applying conditions on these substances, which favor the *retro*-Mannich degradation yield *ortho*-quinone-methides (*o*QM). As these compounds are prone to rearomatization, nucleophilic attack on the methine group leads to novel molecules bearing benzylalcohol or benzyl-alkyl ether fragments. It was published that by the methylation of compounds **66a,b**, unstable quaternary ammonium species formed (**67a,b**) which are easily transformed to benzyl-methyl ethers **68a,b** under treatment with NaOMe in MeOH [62] (Scheme 20).



Scheme 20. Mannich-subsequent *retro*-Mannich reaction of phenols towards benzyl-methyl ethers.

Based on the findings of Gardner et al., Freccero and his research group in the year 2000 published various transformations of *o*-hydroxybenzyl-trimethylammonium iodide (**69**), testing multiple *N*- (and *S*-) nucleophiles and conditions. UV- and heat-driven eliminative deamination and subsequent nucleophilic addition methods were tested in pH-buffered aqueous solutions [63] (Table 12).

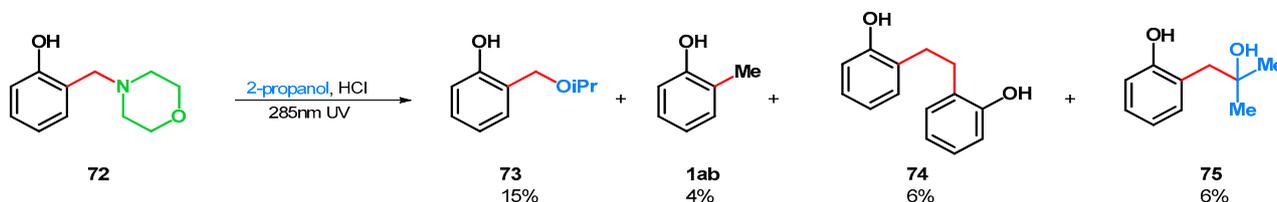
Table 12. Transformations of **69** with amino acids and glutathione as *N*-, *O*- or *S*-nucleophiles.

Product	Condition	NH ₂ R	Yield (%)	Maximal Yield (%) of 2aa
70a	a (pH = 7, 12 h)	glycine	27	70
	b (pH = 7, 2 h)		25	75
70b	a (pH = 6, 15 h)	serine	60	36
	b (pH = 7, 2 h)		9	–
70c,d	a (pH = 5.0, 1 h)	lysine	c: 10 (on ω-NH ₂), d: 30 (on α-NH ₂)	39
	b (pH = 12, 2 h)		c: 16 (on ω-NH ₂), d: 64 (on α-NH ₂)	–
70e, 71a	a (1 h)	tyrosine	e: max. 64 (pH = 10) 71a: max. 18 (pH = 12)	max. 32 (pH = 7)
71b	a (pH = 7, 0.5 h)	glutathione (on thiol)	84	–
	b (pH = 7, 2 h)		86	12

It was proved that in aqueous conditions, not only is the used *N*-nucleophile capable of the addition towards compounds **70a–e**, but the solvent too can act as a nucleophile yielding salicyl alcohol **2aa**. It was found that via thermodeamination, pH = 6–7 favored the formation of compound **2aa**, while higher pH favored **70a–e**. Using photodeaminative methods (UV 254 nm), the ratio of **2aa** rose higher than formerly in most cases (Table 12).

Interestingly, when tyrosine was used, a measurable rate of *O*-alkylation was observed at pH = 10–12 besides the *N*-alkylation.

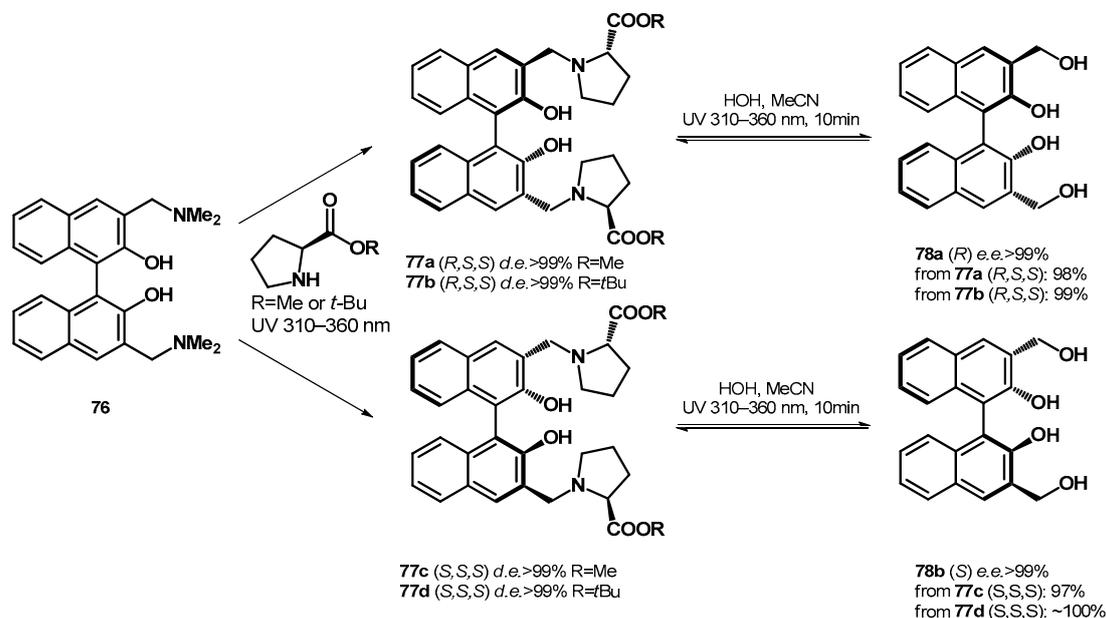
In 1971 H. J. Roth and K. Michel found that the photodeamination-driven transformation can be applied on tertiary amine **72** in 2-propanol-HCl medium, yielding products **1ab**, **73–75** (Scheme 21) [64]. The radical deamination favored the formation of **73**.



Scheme 21. UV-driven *retro*-Mannich reactions of *o*-morpholinomethyl phenol Mannich base.

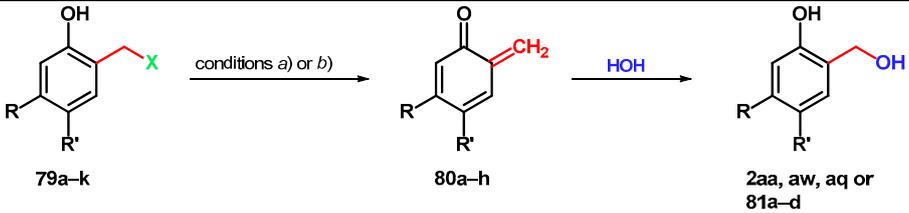
Saito et al. in 1997 published the [65] highly efficient *o*QM formation of dimethylaminomethyl phenols and subsequent transformations toward different acetals. They investigated the *o*QM formation of *o*-hydroxybenzyl alcohols; however, it was found that Mannich bases are much more prone to transformation.

Carrying on the study, Freccero et al. [66] transformed Mannich bases of BINOLs towards L-proline-ester based diastereomers with excellent diastereomeric excess (>99%), which were subsequently transformed to chiral hydroxymethyl derivatives using water/acetonitrile solvent mixture, reaching enantiomeric excess higher than 99%, although they reported the reversibility of the ligand exchange step (**77a–d** and **78a,b**, Scheme 22).



Scheme 22. Enantio- and diastereoselective photochemical synthesis of bis-hydroxymethyl BINOLs.

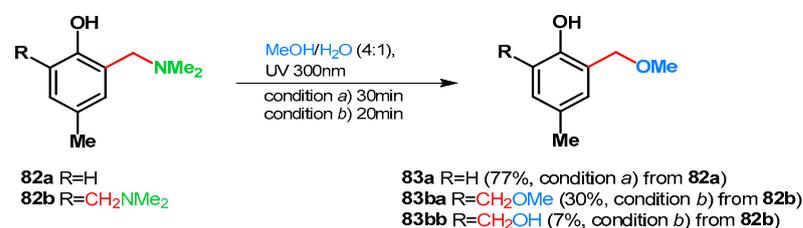
In the same year, they reported that using thermal incubation or flash photolysis tests, electron-donating substituents facilitate the formation of *o*QMs and suppress the rearomative transformation stabilizing the *o*QM. It can be concluded that electron-withdrawing groups suppress the deamination and facilitate the rearomatization. During flash photolysis test, quaternary ammonium compounds had significantly higher quantum yields than the corresponding tertiary amines (Table 13) [67].

Table 13. Thermal- and photochemical degradation of Mannich bases 79a–k.


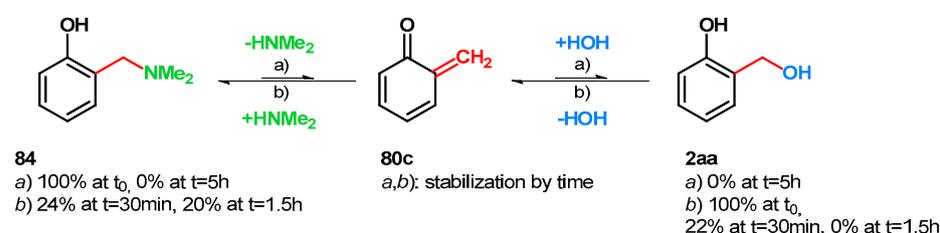
Mannich Base	X	R	R'	Conditions	<i>o</i> QM	<i>o</i> -HO-benzylalcohol
79a	4-morpholinyl	-COOMe	-H	<i>a</i>	80a	81a
79b	4-morpholinyl	-H	-COOMe	<i>a</i>	80b	81b
79c	4-morpholinyl	-H	-H	<i>a</i>	80c	2aa
79d	4-morpholinyl	-H	-OMe	<i>a</i>	80d	2aw
79e	4-morpholinyl	-OMe	-H	<i>a</i>	80e	81c
79f	-N ⁺ Me ₃	-H	-H	<i>b</i>	80c	2aa
79g	-N ⁺ Me ₃	-H	-COOMe	<i>b</i>	80b	81b
79h	-N ⁺ Me ₃	-H	-OMe	<i>b</i>	80d	2aw
79i	-N ⁺ Me ₃	-H	-Cl	<i>b</i>	80f	2aq
79j	-N ⁺ Me ₃	-H	-CN	<i>b</i>	80g	81d
79k	-N ⁺ Me ₃	-H	-CN	<i>b</i>	80h	81e

(a) incubation at 100 °C, (b) laser flash photolysis, 266 nm

Basarić et al. in 2015 also supported this while testing the photodeamination of *p*-cresol-derived tertiary amines and their hydrochlorides via laser flash photolysis at 266 nm. It was found that the quantum yield can be elevated by protonation also. (Scheme 23) [68].

**Scheme 23.** Acid driven photodeamination of tertiary Mannich-base 82a,b.

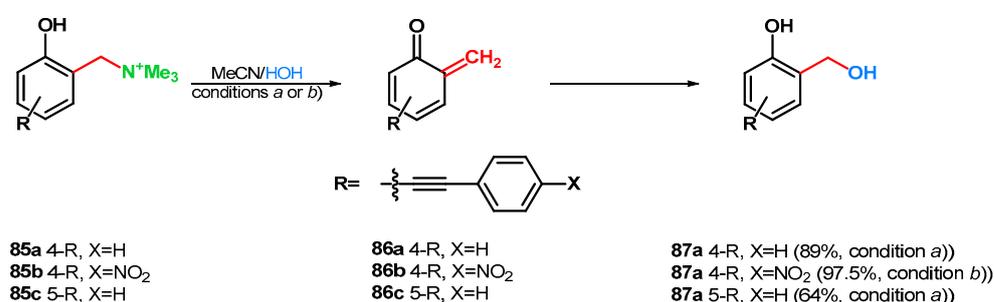
Takaki et al., while synthesizing chromene derivatives starting from Mannich bases or α -substituted salicyl alcohols, tested the equilibrium of compounds **84**, **80c** and **2aa**. (Scheme 24)

**Scheme 24.** Equilibrium between Mannich-base **84** and salicyl alcohol (**2aa**). Conditions: UV 280nm, D₂O/CD₃CN, Ph₂CH₂ (an internal standard); (a) **84** 100% at t_0 , HNMe₂ (40 wt.% in H₂O, ~1 equiv.); (b) **2aa** 100% at t_0 , H₂O (~1 equiv.).

They also found that in contrast to using quaternary benzylammonium salts, treating secondary Mannich-base **84** with water, UV (>280 nm) in D₂O/CD₃CN, no trace of hydrated *o*QM **2aa** was observable (via ¹H-NMR analysis) (condition a); however, starting

from **2aa** and reacting it with HNMe_2 under the same reaction conditions, full conversion was achievable towards **80c** and **84** (condition *b*) [16]. These findings prove the importance of the formation of quaternary ammonium salts of elevated leaving properties regarding *retro*-Mannich transformations. However, elevation of the leaving property of a tertiary amine can be applied through protonation [64,68].

Later, Freccero's research group broadened the investigations in 2016. Various Mannich bases were synthesized from phenols, bearing 4- or 5-arylethynyl substituents for the investigation of the substituent effect on the photogeneration of *o*QM. An aspect of the *o*QM detection was the study of reactivity with water or mercaptoethanol. Overall findings were that the good-leaving quaternary ammonium moiety is needed for a good quantum-yield photolysis, the 5-arylethynyl derivatives showed lower reactivity and that the electron donating substituents fasten the formation of *o*QMs. Three compounds (**85a–c**) were transformed to hydroxymethyl derivatives as test reactions with water-trapping of **86a–c** (Scheme 25) [69].



Scheme 25. Study on substituent effects in correspondence with *o*QM generation condition (a) UV 310nm, 5 min; condition (b) UV 360nm, 450 min.

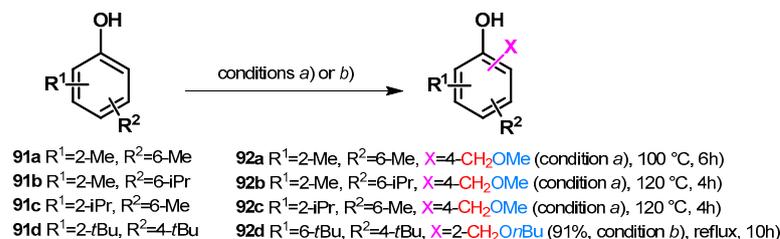
Basarić et al. in 2020 synthesized fluorescent BODIPY-Mannich dyes which, via *o*QM state, can react with the thiol-groups of BSA (bovine serum albumin). The dyes had strong fluorescence that, in the used concentrations, did not affect cells. Based on the previous studies, hydrochlorides of Mannich bases (**88a,b**) were successfully probed for the transformation with methanol, and the photomethanolysis occurred via irradiation (Table 14) [70].

Table 14. Photomethanolysis probe on BODIPY-Mannich dyes

#	Solvent	Wavelength of irradiation			
		254 nm	300 nm	350 nm	visible, cool white
90a	MeOH	decomposed	2	no reaction	
	MeOH/HOH 1:1, pH = 7	68 (16 h)	42 (16 h)	2 (16 h)	<1 (16 h)
	MeOH/HOH 1:1, pH = 9	decomposed	52 (16 h)	8 (16 h)	<1 (16 h)
90b	MeOH	30 (9 h)	12 (12 h)	1 (16 h)	no reaction
	MeOH/HOH 1:1, pH = 7	100 (2 h)	100 (6 h)	21 (16 h)	2 (16 h)
	MeOH/HOH 1:1, pH = 9	94 (4 h)	100 (6 h)	19 (16 h)	2 (16 h)

No data were reported of the summarized isolated yields.

As already stated, polarized *N*-centers favor the *retro*-Mannich transformation towards *o*QMs. Non-UV-driven base and acid catalysis have also been reported to promote such transformations towards *O*-alkylated products. Regarding the synthesis of various chromanecarboxylic acids, the alkoxylation step was reported via the usage of acetic acid additive [71]. However, it was found that a Mannich reaction of disubstituted phenols in alcohols gave alkoxyethylated products while synthesizing antioxidant molecules [72] (Scheme 26).



Scheme 26. One-pot alkoxyethylation of phenols via subsequent Mannich–*retro*-Mannich reactions: condition (a) HNEt₂ (0.14 equiv.), paraformaldehyde (0.87 equiv.), MeOH; condition (b) HN(*n*Bu)₂ (0.10 equiv.), paraformaldehyde (1.7 equiv.), HOAc (0.5 equiv.), *n*BuOH.

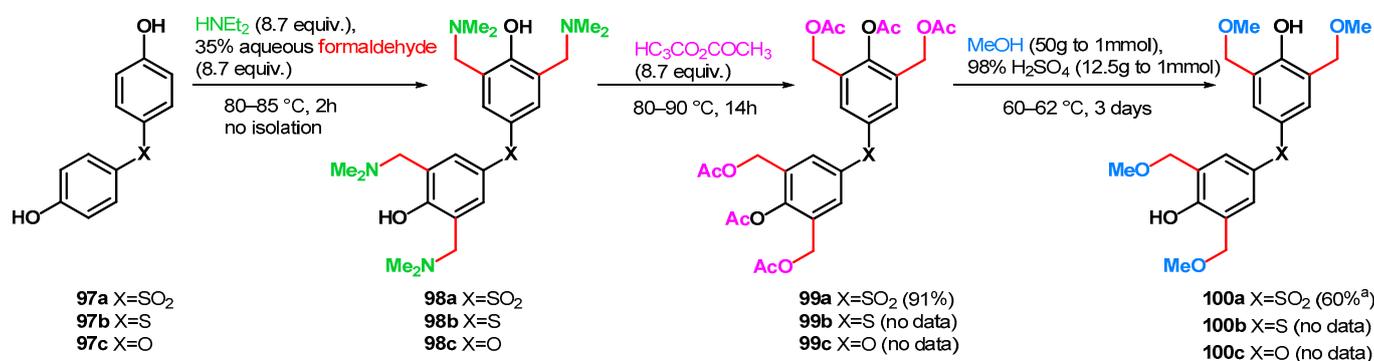
For the alkoxyethylation of substituted (alkyl, halogeno or 2*H*-benzo[*d*][1,2,3]triazol-2-yl) phenols, numerous examples were reported via the treatment of Mannich bases with acetic anhydride and subsequent alkylation with different alcohols. Treating Mannich bases with acetic anhydride yielded *O*-acetyl-*O*-acetyloxyethyl phenols, which under acidic [73] or basic [74] conditions gave the *O*-alkyl products (Table 15). It was found by Crisp and Turner that under mild basic conditions in water, hydroxymethyl derivatives were also able to form, and by the multistep Mannich and subsequent *retro*-Mannich route, in contrast to alkali-mediated hydroxymethylation, higher yields can be achieved (Table 15) [75]. Interestingly, synthesizing benzotriazole derivatives with 2-hydroxyethoxymethyl moieties for step *iii*, 5 equivalents of paraformaldehyde were added. The reason behind this might be that via an in situ acetal formation with ethylene glycol, the formation of bis(benzyloxy)ethylene side-products can be subdued [74].

Table 15. Mannich and subsequent *retro*-Mannich reaction of substituted phenols via acetyloxylation and hydro- or alcoholysis.

Compound	Condition (i)	Compound	Condition (ii)	Compound	Condition (iii)	Compound	Ref.
1aa, 93a–e	<i>i</i>)	72, 82a, 94a–f	<i>ii</i>)	95a–d	<i>iii</i>)	96a–f	
1aa: R ¹ = R ² = H	10 equiv. 40% formaldehyde in water, 10 equiv. 50% aqueous Me ₂ NH, 40 °C, 6 h	82a: 2,4,6-X X = CH ₂ NMe ₂ , R ¹ = R ² = H	10 equiv. Ac ₂ O, 100 °C, 4 h	95a: 2,4,6-X X = CH ₂ OAc, R ¹ = R ² = H	10. equiv. K ₂ CO ₃ , EtOH, 80 °C, 2 h	96a: 2,4,6-X X = CH ₂ OEt	[73]
	2.0 equiv. 38% formaldehyde in water, 0.98 equiv. morpholine, 50 °C, 15 h	72: 2,6-X X = morpholinomethyl, R ¹ = R ² = H (20%)	Ac ₂ O, reflux	95b: 2,6-X X = CH ₂ OAc, R ¹ = R ² = H (57%)	From this step, divergent reaction routes were applied		[75]

93a: R ¹ = 4-Br, R ² = H	2.2 equiv. 38% formaldehyde in water, 2.2 equiv. morpholine, 80 °C, 6 h, in HOAc	94a: 2,6-X X = morpholino-methyl, R ¹ = 4-Br, R ² = H (82%)	Ac ₂ O (2.2 mL to 1 mol) and HOAc (0.15 to 1 mmol), reflux, 24 h	95c: 2,6-X X = CH ₂ OAc R ¹ = 4-Br, R ² = H (64%)	[75]
94b was synthesized via different reaction route		94b: 2,6-X X = morpholino-methyl, R ¹ = 4-phenylethynyl	Ac ₂ O (11 mL to 1 mmol), HOAc (0.45 to 1 mmol), reflux, 14 h	95d: 2,6-X X = CH ₂ OAc, R ¹ = 4-phenyl ethynyl, R ² = H (75%)	96b: 2,6-X X = CH ₂ OH, R ¹ = 4-phenyl ethynyl, R ² = H (48%)
93b: R ¹ = 2-(2H-benzo[d][1,2,3]triazol-2-yl), R ² = Me		94c: 2-X = CH ₂ NMe ₂ , R ¹ = 2-(2H-benzo[d][1,2,3]triazol-2-yl), R ² = Me		96c: 2-X = CH ₂ O(CH ₂) ₂ OH, R ¹ = 2-(2H-benzo[d][1,2,3]triazol-2-yl), R ² = Me	[74]
93c: R ¹ = 2-(2H-benzo[d][1,2,3]triazol-2-yl), R ² = <i>t</i> -Bu	50% aqueous	94d: 2-X = CH ₂ NMe ₂ , R ¹ = 2-(2H-benzo[d][1,2,3]triazol-2-yl), R ² = <i>t</i> -Bu	cat. KOH, 5 equiv. paraform-	96d: 2-X = CH ₂ O(CH ₂) ₂ OH, R ¹ = 2-(2H-benzo[d][1,2,3]triazol-2-yl), R ² = <i>t</i> -Bu	[74]
93d: R ¹ = 2-(2H-benzo[d][1,2,3]triazol-2-yl), R ² = 1-(2-hydroxy)ethyl	Me ₂ NH, paraformaldehyde	94e: 2-X = CH ₂ NMe ₂ , R ¹ = 2-(2H-benzo[d][1,2,3]triazol-2-yl), R ² = 1-(2-hydroxy)ethyl	aldehyde ethylene glycol, 150 °C, 24 h	96e: 2-X = CH ₂ O(CH ₂) ₂ OH, R ¹ = 2-(2H-benzo[d][1,2,3]triazol-2-yl), R ² = 1-(2-hydroxy)ethyl	[74]
93e: R ¹ = 2-(2H-benzo[d][1,2,3]triazol-2-yl), R ² = 1-(2,2,4,4-tetramethyl)butyl		94f: 2-X = CH ₂ NMe ₂ , R ¹ = 2-(2H-benzo[d][1,2,3]triazol-2-yl), R ² = 1-(2,2,4,4-tetramethyl)butyl		96f: 2-X = CH ₂ O(CH ₂) ₂ OH, R ¹ = 2-(2H-benzo[d][1,2,3]triazol-2-yl), R ² = 1-(2,2,4,4-tetramethyl)butyl	[74]

The method itself can be applied to yield tetrakisalkoxymethylated bisphenols as resin raw materials, which have high storage stability and excellent solvent solubility, heat resistance and optical properties [76]. However, it should be noted that from **97a–c** to **99a–c**, multigram scale reactions (0.3 mol of **97a** yielding 0.275 mol of **99a**) were reported, although from **99a–c** to **100a–c**, the data represent a small-scale (0.8 mmol of **99a**) synthesis (Scheme 27).

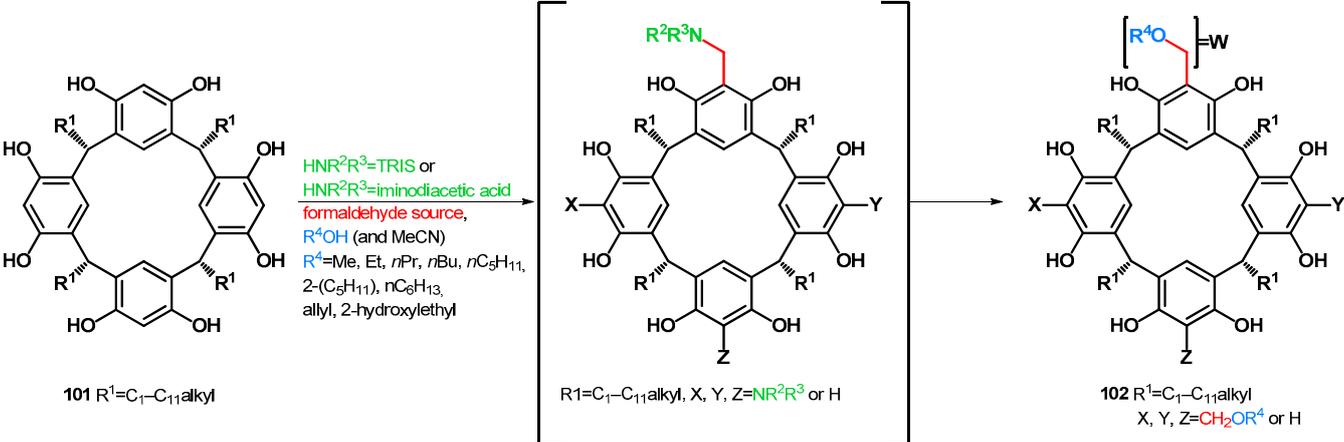


Scheme 27. Methoxymethylation of bisphenols **97a–c** via Mannich–*retro*-Mannich reactions.

Alkoxymethylation methods are studied in correspondence with resorcinarene chemistry. Resorcinarenes, which are versatile building blocks for supramolecular chemistry, have been modified yielding alkoxymethylated products. In 2004, Rissanen,

Shivanyuk et al. conducted the synthesis of tetrakis(alkoxymethyl)resorcinarenes. Testing reaction conditions, it was found that no conversion was observable without using tromethamine, thus hypothesizing an in situ Mannich reaction by which products transform towards the desired alkoxymethylated products (Table 16) [77]. In 2006, Urbaniak et al. carried on the study using iminodiacetic acid as an *N*-nucleophile. Iminodiacetic acid acts as both *N*-nucleophile and an in situ protonating agent, being an optimal additive for the transformation of electron-rich arenes towards their alkoxymethyl derivatives. It was found that a stoichiometric amount of iminodiacetic acid is not necessary, as a 9.4 mol% catalytic amount was sufficient. They proposed a reaction mechanism which involves autoprotonation of the Mannich-type intermediate [78]. Later, selective alkoxymethylation was carried out using iminodiacetic acid catalyst. They reported selectivity driven by the alteration of the reaction time, as shorter reaction times yielded the less-substituted resorcinarenes (Table 16) [79].

Table 16. Alkoxymethylation of resorcinarenes using tromethamine (TRIS) or iminodiacetic acid catalyst.

101	Condition	102	Ref.
 <p>101 $R^1 = C_1-C_{11}$alkyl</p> <p>R^2R^3N</p> <p>R^4OH (and MeCN)</p> <p>$R^4 = Me, Et, nPr, nBu, nC_5H_{11}, 2-(C_5H_{11}), nC_6H_{13}, allyl, 2-hydroxyethyl$</p> <p>102 $R^1 = C_1-C_{11}$alkyl</p> <p>$X, Y, Z = NR^2R^3$ or H</p> <p>$X, Y, Z = CH_2OR^4$ or H</p>			
a: $R^1 = Et$	20 equiv. aqueous formaldehyde	a: $R^1 = Et, X = Y = Z = W = CH_2OEt$ (55%)	[77]
b: $R^1 = C_5H_{11}$	37%, HOAc (0.1 mL to 1 mmol), EtOH (10 mL to 1 mmol), 9 equiv.	b: $R^1 = C_5H_{11}, X = Y = Z = W = CH_2OEt$ (42–69%) ^a	[77]
c: $R^1 = C_{11}H_{23}$	NHR ² R ³ = TRIS, 1 h R.T., 1–2 h reflux	c: $R^1 = C_{11}H_{23}, X = Y = Z = W = CH_2OEt$ (42–69%) ^a	[77]
	5 equiv. aqueous formaldehyde 37%, cat. NHR ² R ³ = iminodiacetic acid (in water) (9.4 mol%), R ⁴ OH as solvent, reflux, 12 h	d: $R^1 = i-Bu, X = Y = Z = W = CH_2OMe$ (79%)	[78]
		e: $R^1 = i-Bu, X = Y = Z = W = CH_2OEt$ (66%)	[78]
		f: $R^1 = i-Bu, X = Y = Z = W = CH_2OnPr$ (64%)	[78]
		g: $R^1 = i-Bu, X = Y = Z = W = CH_2OnBu$ (46%)	[78]
		h: $R^1 = i-Bu, X = Y = Z = W = CH_2OnPe$ (40%)	[78]
		i: $R^1 = i-Bu, X = Y = Z = W = CH_2OnHx$ (28%)	[78]
d: $R^1 = i-Bu$	2 equiv. aqueous formaldehyde 37%, cat. NHR ² R ³ = iminodiacetic acid (10% m/m), R ⁴ OH as solvent, reflux (reaction times separately assigned)	j: $R^1 = i-Bu, X = Y = Z = H, W = CH_2OMe$ (34%, 4 h)	[79]
		k: $R^1 = i-Bu, X = Y = Z = H, W = CH_2OEt$ (39%, 135 min)	[79]
		l: $R^1 = i-Bu, X = Y = Z = H, W = CH_2OnPr$ (39%, 90 min)	[79]
		m: $R^1 = i-Bu, X = Y = Z = H, W = CH_2OAllyl$ (43%, 90 min)	[79]
		n: $R^1 = i-Bu, X = Y = Z = H, W = CH_2O(2-hydroxyethyl)$ (37%, 30 min)	[79]
		o: $R^1 = i-Bu, X = Y = H, X = W = CH_2OnPr$ (14%, 160 min)	[79]

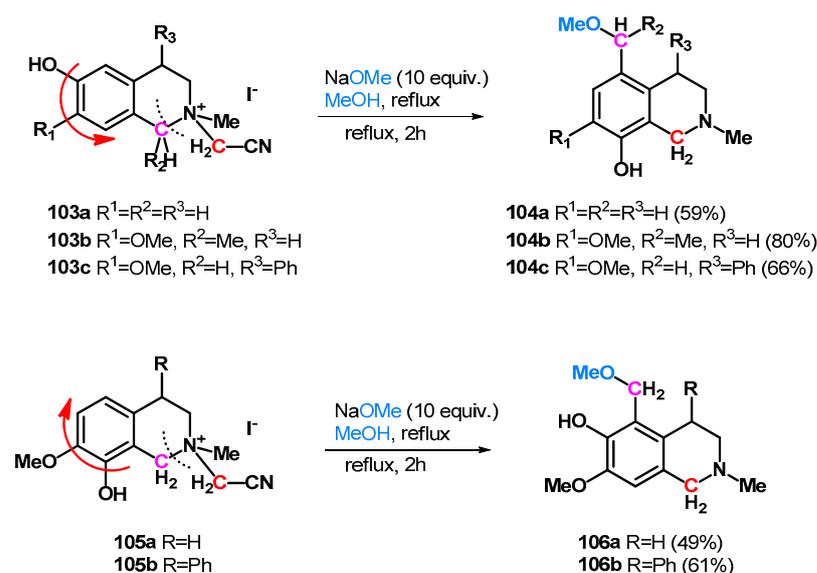
	p: R ¹ = <i>i</i> -Bu, X = Y = H, Z = W = CH ₂ O <i>n</i> Pr (24%, 160 min)	[79]
	q: R ¹ = <i>i</i> -Bu, X = H, Y = Z = W = CH ₂ O <i>n</i> Pr (29%, 180 min)	[79]
	r: R ¹ = <i>i</i> -Bu, X = H, Y = Z = W = CH ₂ Oallyl (30%, 180 min)	[79]
e: R ¹ = <i>n</i> C ₁₁ H ₂₃ 5 equiv. aqueous formaldehyde 37%, cat. NHR ² R ³ = iminodiacetic acid (in water) (9.4 mol%), R ⁴ OH as solvent, reflux, 4 h	s: R ¹ = <i>n</i> C ₁₁ H ₂₃ , X = Y = Z = W = CH ₂ OEt (42%)	[78]
f: R ¹ = Me	t: R ¹ = Me, X = Y = Z = W = CH ₂ OEt (65%)	[78]

^a data were not found in experimental data or supporting info.

3.2. Transformations of Semi-Synthetic Phenols and *N*-heterocycles

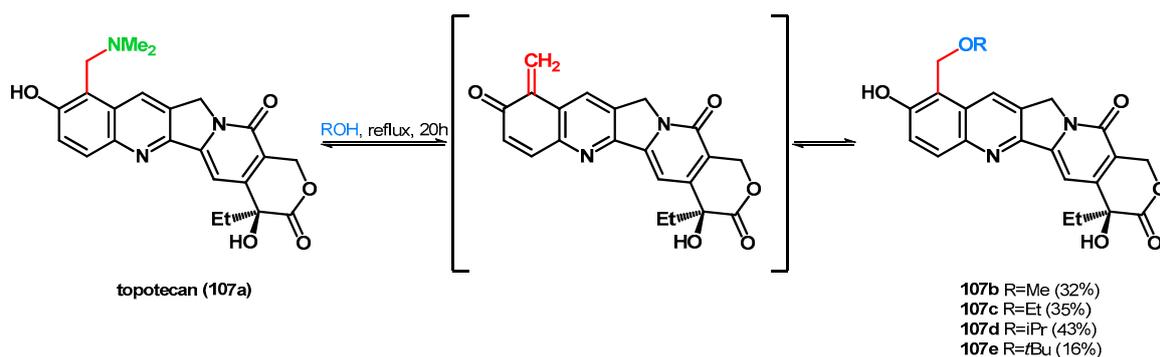
3.2.1. Transformations of Phenol-Fused Molecules

Numerous Mannich–*retro*-Mannich-driven hydroxy- and alkoxy-methylation reactions have been reported in correspondence with hydroxyfunctionalized heterocycles. In 1995, Hara et al. reported the unexpected methoxymethylation side-reaction of tetrahydroisoquinolines (**103a–c**, **105a,b**). The reaction is driven by an intramolecular *retro*-Mannich-type reaction in which *o*- or *p*QM molecules form with simultaneous ring opening and turnover (Scheme 28) [80].



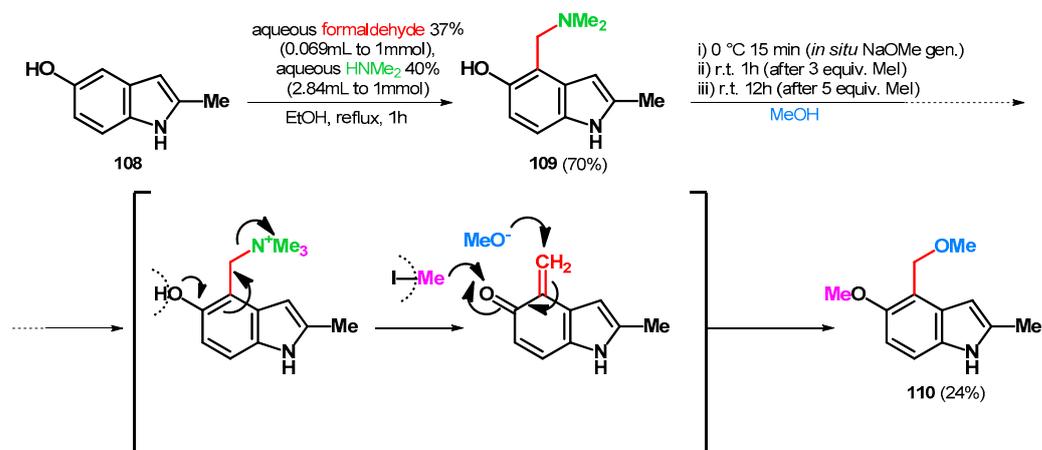
Scheme 28. Intramolecular *retro*-Mannich reaction and ring turnover of tetrahydroisoquinolines **103a–c** and **105a,b** yielding methoxymethyl derivatives.

Zhang et al. performed the alcoholysis of topotecan, the highly water-soluble analogue of 10-hydroxycamptothecine, synthesized via the Mannich reaction [81,82]. The already presented equilibrium was also found between topotecan (**107a**) and compounds **107b–e**, which was explained with the hydrogen bonding ability between the dimethylamino and the phenolic hydroxyl group, thus positively polarizing the nitrogen atom, facilitating the N–C bond cleavage. Compound **106e** showed lower IC₅₀ values than the parent molecule on HepG2 and C26 cell lines, presenting the importance of the N–O swap in pharmaceutical chemistry and drug research (Scheme 29) [83]. Carrying on the study, the same research group broadened the scope of the reaction using thiols and enol-ethers [84].



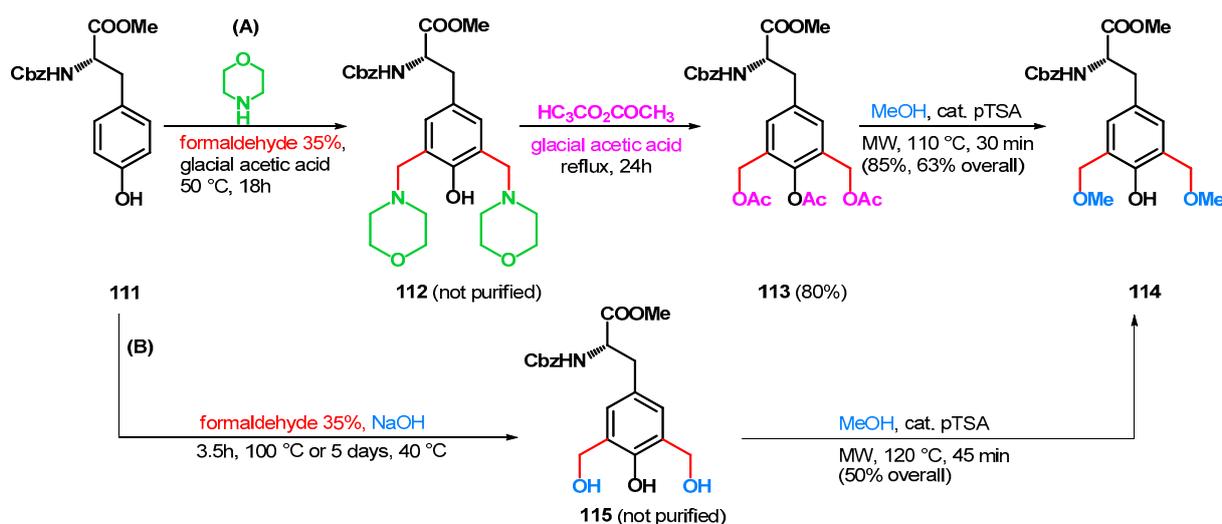
Scheme 29. *retro*-Mannich driven *N*–*O* swap of topotecan (107a), a widely known Mannich base.

Homer and Sperry in 2018 targeted the total synthesis of *Tricholoma* alkaloids [85]. The synthesis started from the Mannich reaction of 5-hydroxy-2-methylindole (108) [86] yielding 109, which was subsequently transformed in one-batch towards 110 with moderate yields (Scheme 30). It is interesting to mention that 6.0 equivalent MeI was added in two portions. It functioned as an *N*-methylating agent [63], facilitating the *retro*-Mannich reaction and also methylating the phenolic hydroxyl group. That compound 110 was isolated with moderate yields might have been caused by the undesired reaction with sodium methoxide and methyl iodide trapping the reagents. The possible product-bearing unmethylated phenolic hydroxyl group was not isolated, as the desired product directly formed in the reaction chamber.



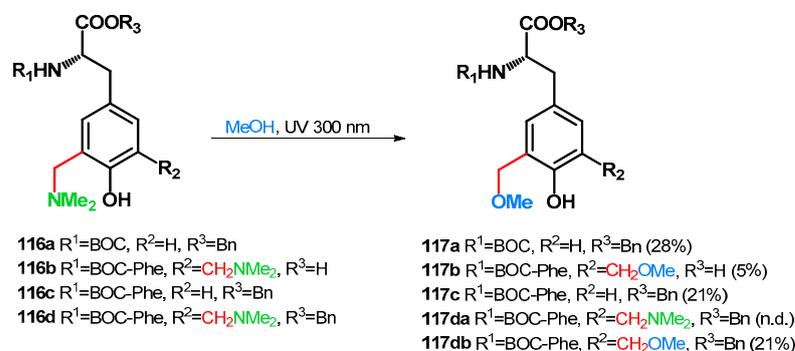
Scheme 30. Total synthesis of tricholoma alkaloid 110 utilizing *N*–*O* swap.

In 2006, Bew et al. reported the synthesis of methylene-bridged (*S*)-tyrosine-phenol dimers. While conducting the syntheses, two methods were described, one exploiting the potential of *retro*-Mannich reactions, the other utilizing inorganic additives while reducing reaction steps. Utilizing pathway **A**, slightly higher yields could be achieved than utilizing **B**, despite the greater number of steps and longer reaction time (Scheme 31) [87].



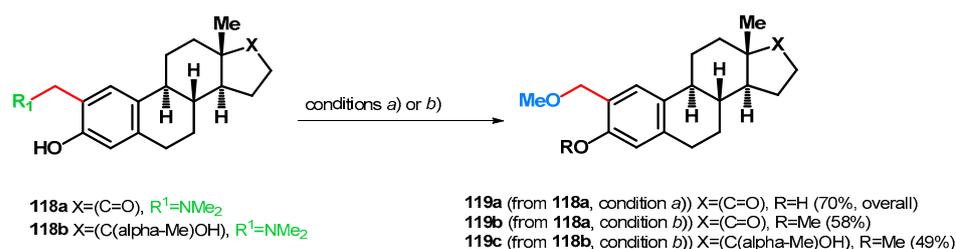
Scheme 31. Synthesis of bis-methoxymethyl compound **114**, a building block for methylene-bridged tyrosine derivatives.

It is worth mentioning, however, that the usage of amino-acid catalysis (i.e., imino-diacetic acid) has not been tested during the study. In 2006, Basarić et al. reported the photochemical transformations of Mannich bases of dipeptides towards methoxymethylated blocks, presenting photoswitchable units for peptide modification and fine-tuning [88]. Bis(dimethylaminomethyl)-derivative **116d** was investigated in the reaction towards **117da,db**. At 30 min reaction time, the ratio was 1:1, running the reaction for a longer time, 68% conversion towards **117db** was achieved (Scheme 32).



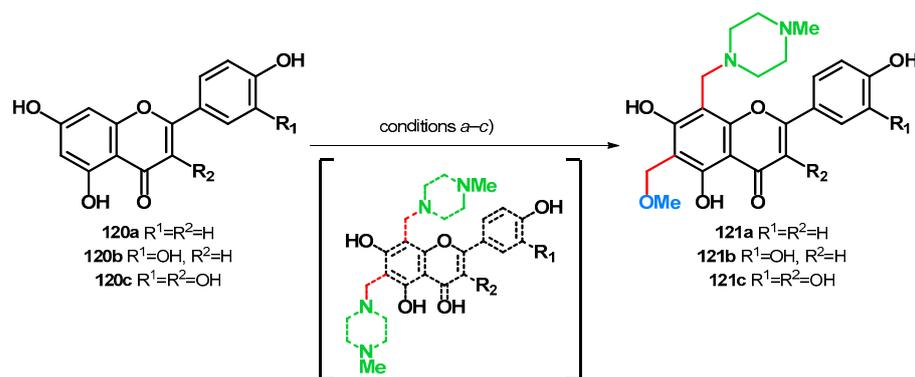
Scheme 32. Photochemical synthesis of methoxymethyl tyrosine derivatives and dipeptides.

In patented literature, two research groups have successfully synthesized 2-methoxymethyl estrone or 2-methoxymethyl-17 α -estradiol derivatives via different reaction routes starting from Mannich bases **118a–c** [89,90]. It was found that the usage of dimethyl sulfate as an initiator of the *retro*-Mannich subreaction (condition *a*), being a more aggressive alkylating agent than methyl iodide, also alkylated the 3-OH group (**119b**). While using MeI (condition *b*), as formerly presented, no *O*-alkylation was observed under the investigated conditions. While the latter findings may be advantageous, designing a one-pot method may cause undesired side-reactions, and this should be taken into consideration when conducting alkylative *retro*-Mannich transformations (Scheme 33).



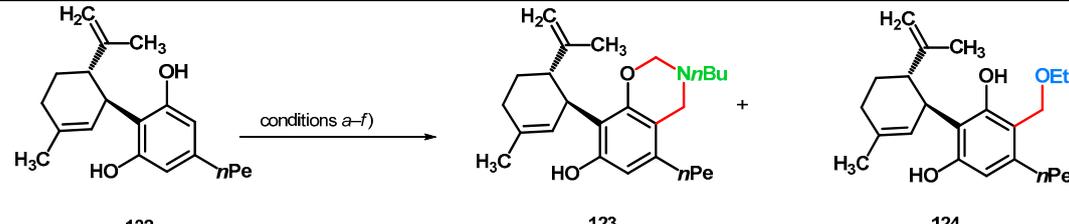
Scheme 33. N–O swap of estrogen-based Mannich bases **118a,b** (a) (i) MeI (26 equiv.), in Et₂O 20h, r.t.; isolated (ii) KOH (excess), MeOH, 3h, reflux [90] (b) MeOH, 17% aqueous KOH (in 2 steps, 12 + 2 weight equiv.), Me₂SO₄ (9–10 molar equiv.), 60 °C, 5 h [89].

In 2016, transformations of apigenin (**120a**), luteolin (**120b**) and quercetin (**120c**) via Mannich reaction were reported [91]. It was found that under the investigated conditions (a–c), running the reaction in MeOH, simultaneous methoxymethylation (at position C–6) and aminomethylation (at position C–8) took place yielding products **121a–c**. Although it has not been investigated, it is noteworthy that a C–6,8 bis-(4-methylpiperazino)methyl derivative is hypothetically possible to form in the reaction mixture. The possible molecules, however, might be prone to transformation towards **121a–c** based on the polarizing properties of the proximal two hydroxyl groups [83] or acidity of the parent molecules themselves [78]; however, the yields have not been reported (Scheme 34).



Scheme 34. Transformation of flavonoids **120a–c** yielding methoxymethyl–morpholinomethyl derivatives: condition (a) MeOH, 2.5 equiv. HCHO, 0.8 equiv. *N*-Me-piperazine, 63 °C, 1 h; condition (b) MeOH, 1.5 equiv. HCHO, 1.5 equiv. *N*-Me-piperazine, 20 °C, 12 h; condition (c) MeOH, 2.0 equiv. HCHO, 1.2 equiv. *N*-Me-piperazine, 46 °C, 6 h.

In 2023, Bereczki et al. synthesized Mannich derivatives of cannabidiol (**122**) in order to enhance their penetrability and/or water solubility [92]. Mannich reaction was an optimal tool; however, conducting the reaction using *n*-butylamine in ethanol, formation of the ethoxymethylated side-product **124**, in addition to **123**, was observed (condition b). The conditions were investigated and optimized, using different solvents (MeOH, 1,4-dioxane) and reaction times. While an *O*-nucleophile alkoxy methylation did not take place in methanol (condition a), neither did it using ethanol at lower temperatures (condition c) or 1,4-dioxane (condition d). The formation of **124** was investigated, and it was found that without an amine component (condition f), the desired product did not form. Under condition e [38], **124** was isolable with moderate yields (Table 17).

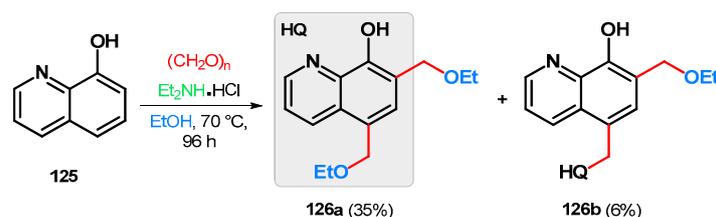
Table 17. Mannich-type modifications of (–)-cannabidiol under different conditions.


conditions		123(%)	124(%)
(a)	3.0 equiv. 36% aqueous formaldehyde, 3.0 equiv. NH ₂ nBu, MeOH, room temperature, 7 days	89	–
(b)	3.0 equiv. 36% aqueous formaldehyde, 3.0 equiv. NH ₂ nBu, EtOH, reflux, 20 h	64	21
(c)	3.0 equiv. 36% aqueous formaldehyde, 3.0 equiv. NH ₂ nBu, EtOH, reflux, 6 h then 45 °C, 18 h overnight	~100	0
(d)	3.0 equiv. 36% aqueous formaldehyde, 3.0 equiv. NH ₂ nBu, 1,4-dioxane, reflux, 6 h then 50 °C, 18 h overnight	60	–
(e)	3.0 equiv. 36% aqueous formaldehyde, 3.0 equiv. NEt ₃ , EtOH, reflux, 2 days (reflux, 6 h then 45 °C, 16 h overnight)	–	30
(f)	3.0 equiv. 36% aqueous formaldehyde, EtOH, 3 days (reflux, 6 h then 45 °C, 16 h overnight)	–	0 ^a

^a bisarylmethane-type side product formed.

The information that an equilibrium was found [16] between alkoxyethyl and aminomethyl phenolic compounds, and that product **124** did not form at lower temperatures, suggests that the mentioned equilibrium can be shifted towards the alkoxyethyl compounds by raising temperature. It is notable that higher temperatures might be able to facilitate proton exchange and thus the polarization of the proximal Mannich-N-atom.

Modified Mannich reaction of 8-hydroxyquinoline, a widely cited bioactive agent [93–97] (**125**), was reported using diethylamine hydrochloride and paraformaldehyde; however, the isolated products were not identified as Mannich bases. The reaction was carried out in ethanol that most probably served as an O-nucleophile on the intermediate Mannich base and exchanged the diethylamino function giving 5,7-bis(ethoxymethyl)quinolin-8-ol (**126a**) as a major product. A dimer (**126b**) was also isolated, formation of which is hypothesized via a *para*-quinone-methide intermediate (Scheme 35) [98].

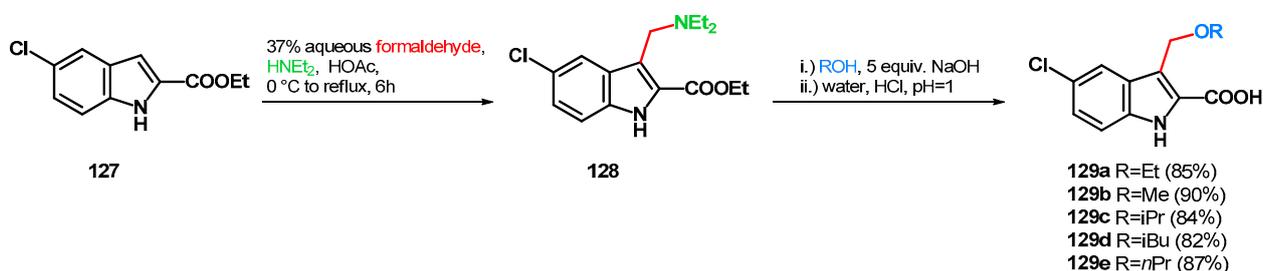
**Scheme 35.** Synthesis of 8-hydroxyquinoline-derived ethoxymethylene derivatives **126a** and **b**.

Taking the aforementioned information into consideration, a hypothetical reason behind the formation of **126a** can be the in situ protonating ability of the diethylamine hydrochloride, thus constituting the driving force of the *retro*-Mannich substep. This is supported by the fact that by utilizing methylene bromide as a methylene source with diethylamine base, the previously targeted diethylaminomethyl-derived 8-hydroxyquinolines were able to be successfully isolated.

3.2.2. Transformations of N-heterocycles

In 2016, Youssif et al. synthesized antiproliferative 3-alkoxymethyl or 3-phenyl indole-2-carboxamides, which showed good activity on MCF7 and HCT116 cell lines (Scheme 36) [99]. In 2022, they carried on the study, synthesizing 2,3-dihydropyrazino

[1,2-*a*]indole-1,4-dione derivatives, which showed activity on BRAF^{V600E} and EGFR [100]. It is worth mentioning that in correspondence with both articles, *retro*-Mannich and subsequent alkoxylation reactions were utilized in order to yield the desired products.



Scheme 36. Design of 3-alkoxymethyl indole-2-carboxylic acid antiproliferative agents.

Transformation of **128** towards **129a–e** was conducted in the corresponding alcohols and NaOH with excellent yields. *Retro*-Mannich reaction was reported using both acid and base catalysis in correspondence with the synthesis of indole-based triarylmethanes. The base catalysis is promoted by the deprotonation of the indole and its subsequent demethylation at position C–3 [101]. Note, however, that in the case of **129a–e**, theoretically the proximal carboxylic function could act as an autoprotinating agent if the reaction mixture reaches neutral pH and ester function is hydrolyzed while the aminomethyl moiety is still intact. Also, the *retro*-Mannich reaction can be conducted under acidic conditions present during work-up.

The C–3-alkoxymethyl transformations of kynurenic acid ethyl ester (**130**) were reported by Szatmári et al. [102]. Kynurenic acid being an endogenous neuroprotective agent [103–111] of prosperous research, its skeleton has been fine-tuned via the Mannich reaction [112–117]. It was found that utilizing secondary amino acid nucleophiles and paraformaldehyde in ethanol, the substrate did not undergo aminomethylation. The isolated product was compound **131a**. Based on previous research, an expansive study was conducted focusing on the optimization of the reaction conditions in order to yield different C–3-alkoxyalkylated kynurenic acid derivatives. Additives triethylamine, NaOEt, pTSA and HOAc did not facilitate the formation of **131a**. Most probably in the case of the electron-deficient arenes (such as **130**), the alkoxyalkylation reaction could be conducted via the Mannich–*retro*-Mannich route with better conversions.

As a next step for secondary amines, their corresponding acetate salts or amino acid derivatives along with various ampholytic additives were tested in the reaction in order to investigate the simultaneous amino- and alkoxyalkylation (Table 18).

Table 18. C–3 alkoxyalkylation of kynurenic acid ethyl ester (**130**) via organic additives.

Conditions		Conversion, Reaction Time (and Isolated Yield)	
HNR ² R ³	Equivalence	R ¹ OH	131
	1.0	Ethanol	0%

Conditions		Conversion, Reaction Time (and Isolated Yield)	
HNR ² R ³	Equivalence	R ¹ OH	132
	1.0	Ethanol	a: 75% (60 h)

Conditions		Conversion, Reaction Time (and Isolated Yield)	
HNR ² R ³	Equivalence	R ¹ OH	131
	1.0	Ethanol	0%

Conditions		Conversion, Reaction Time (and Isolated Yield)	
HNR ² R ³	Equivalence	R ¹ OH	131
	1.0	Ethanol	0%

Conditions		Conversion, Reaction Time (and Isolated Yield)	
HNR ² R ³	Equivalence	R ¹ OH	131
	1.0	Ethanol	0%

Conditions		Conversion, Reaction Time (and Isolated Yield)	
HNR ² R ³	Equivalence	R ¹ OH	131
	1.0	Ethanol	0%

Conditions		Conversion, Reaction Time (and Isolated Yield)	
HNR ² R ³	Equivalence	R ¹ OH	131
	1.0	Ethanol	0%

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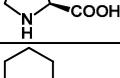
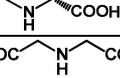
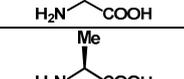
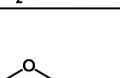
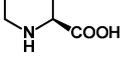
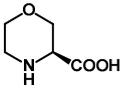
Conditions		Conversion, Reaction Time (and Isolated Yield)	
HNR ² R ³	Equivalence	R ¹ OH	131
	1.0	Ethanol	0%

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Conditions		Conversion, Reaction Time (and Isolated Yield)	
HNR ² R ³	Equivalence	R ¹ OH	131

	1.0	Ethanol	0%	b : 98% (60 h)
	1.0	Ethanol	a : 4% (8 h)	c : 92% (60 h)
	1.0	Ethanol	a : 3% (1–3 h)	a : 56% (28 h)
	1.0	Ethanol	a : 5% (1–5 h)	b : 34% (20 h)
	1.0	Ethanol	a : 20% (9 h)	c : 60% (9 h)
	1.0	Ethanol	a : 5% (6 h)	0%
	1.0	Ethanol	a : 15% (22 h)	0%
	1.0	Ethanol	a : 15% (60 h)	0%
	1.0	Ethanol	0%	d : isolated 44% (88 h)
	1.0	Ethanol	0%	e : isolated 9% (95 h)
	0.1	Ethanol	a : 6% (24 h)	0%
	0.5	Ethanol	a : 39% (40 h, isolated 33%)	0%
	1.0	Ethanol	a : 25% (22 h)	0%
	2.0	Ethanol	a : 48% (40 h)	0%
	0.5	2-Propanol	b : 21% (26 h, isolated 16%)	0%

It was reported that the low basicity of the nucleophile facilitates the reaction, but it was proposed that using morpholine-based additives, the O-atom of the nucleophile might be able to coordinate the solvent, thus elevating the conversion towards **131a,b**. The optimal equivalence was found to be 0.5, able to subdue side-reactions.

The scope of the reaction was investigated using different aldehydes, although no conversion was observed. However, using different alcohols, isopropyl derivative **131b** was isolated. The transesterification and C-3-isopropoxymethylation were found to run simultaneously. Similarly to what was previously reported [92], the desired product did not form using methanol, neither did it using tertiary butanol, which was proposed as being an excessively bulky O-nucleophile.

However, the mechanism of the Mannich–*retro*-Mannich-driven alkoxy-methylation has been previously proposed [78]. The authors in that case reported indirect proof of the mechanism via the esterification of compound **132c** with ethanol, which instantaneously transformed towards **131a** under the investigated conditions.

4. Conclusions and Outlook

The main footsteps of the former years' research concerning hydroxy- and alkoxy-alkylation of electron-rich arenes have been reviewed. First, the focus was pointed towards the direct alkoxy- or hydroxyalkylation of phenols, phenolic ketones and phenol-fused carbo- and heterocycles regarding their hydroxy-functionalized benzene ring, utilizing various catalysts such as sodium metaborate, zeolites as well as homogenous acid and base catalysts. Regioselective hydroxyalkylation has been also successfully conducted. Reviewing the corresponding syntheses, various alkylene sources have been used, such as aldehydes, acetals or, in some cases, dehydrated analogues of oxo-compounds, and alkynes functioned as appropriate substrates.

In the second part of this review, alkoxy- and hydroxyalkylation via *retro*-Mannich reaction was in focus. The widely used Mannich-reaction, being a versatile tool for C–C bonding, yielded benzylic-type amines using various bioactive compounds (indoles, amino acids and small peptides, cannabinoids, flavonoids, anti-proliferative alkaloids or small heterocycles) as substrates. The Mannich bases already bearing the aminoalkyl moieties were reported to transform towards quinone methides, which compounds subsequently underwent reactions with *O*-nucleophiles. For the quinone methide generation, several methods were grouped, such as photodeamination, *N*-overalkylation, using acid catalysis and *N*–*O* swap via acetyloxylation and subsequent hydro- or alcoholysis. Heterocyclic compounds bearing pyrrol-type nitrogen atoms were reported to undergo such reactions via base catalysis. One-pot methods were also presented in this review, examining the potential of amino-acid catalysis or the driving force of intramolecular proton transfer.

Research focusing on novel C–C bonding formation techniques using water or various alcohols as nucleophiles has already been widely published; however, the recent progress of the field proves its impact.

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Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

BAM	bisarylmethylene
BINOL	1,1'-bi-2-naphthol
BDMS	bromodimethylsulfonium bromide
BODIPY	dipyrrrometheneboron difluoride
BPR	boron-modified phenolic resin
BSA	bovine serum albumin
DCM	dichloromethane
EDG	electron donating group
MOM	methoxymethyl
MPM	<i>p</i> -methoxybenzyl
PPTS	pyridinium <i>p</i> -toluenesulfonate
<i>p</i> TSA	<i>p</i> -toluenesulfonic acid
QM	quinone methide
(<i>R</i>)-TRIP	(<i>R</i>)-3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate
TBSO	<i>tert</i> -butyl-dimethylsilyloxy
TRIS	tris(hydroxymethyl)aminomethane, tromethamine

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