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# SYNTHESIS OF REGIOISOMERIC NAPHTHO-FURANS *VIA* NAPHTHYLOXYALKANALS

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*A new route to the regioisomeric 2-alkylnaphtho[2,1-b]- and 2-alkylnaphtho[1,2-b]furans via acid-catalyzed cyclization of the corresponding 2-naphthyloxyalkanals under mild conditions over Amberlyst 15 resin has been described. The 2-naphthyloxyalkanals were obtained by palladium-catalyzed reduction of 2-naphthyloxyalkanoyl chlorides.*

**Keywords:** aldehydes, ethers, naphthofurans, cyclization, reduction.

The regioisomeric naphtho[1,2-*b*]-, naphtho[2,1-*b*]-, and naphtho[2,3-*b*]furans are present in many biologically important natural products, mainly belonging to the sesquiterpene class [1]. These products have been isolated from various natural sources such as plants *Liguaria przewalskii* [2], *Trichilia cuneata* [3], *Gossypium barbadens* [4], or fungus *Fusarium oxysporum* [5]. Several synthetic compounds bearing a naphthofuran skeleton are associated with diverse biological activities such as antibacterial [6], antifungal [7], antifertility [8], and antiprotozoan activity against *Trypanosoma cruzi* [9]. Some of nitronaphtho[2,1-*b*]furans have been extensively studied for their mutagenic activities [6, 10] and other naphtho[2,1-*b*]furan derivatives showed a significant anticancer activity against human colon and liver cancer cell lines in the *in vitro* assay [11]. Besides, naphthofurans have potential applications as fluorescent dyes and probes as well as phothosensitizers [12, 13].

A major route for the synthesis of naphthofurans is the intramolecular formation of a furan ring starting with properly substituted α-naphthyloxycarbonyl compounds and their corresponding acetals [14–16]. Polysubstituted naphtho[1,2-*b*]furans were obtained by cyclization of asymmetrically substituted 1-naphthyloxy ketones by heating at high temperature in polyphosphoric acid [17]. Similarly, 2-phenylnaphto[1,2-*b*]furan and 2-phenylnaphto[2,1-*b*]furan were prepared by cyclization of naphthyloxyacetophenone with a strong acid [18]. The regioisomeric naphtho[1,2-*b*]- and -[2,1-*b*]furans were obtained by treating 1- and 2-naphthol and methylsulfinylmethyl ethyl ketone with *p*-toluenesulfonic acid and then desulfurization of 2-alkyl-3-(methyl-thio)naphtho[1,2-*b*]- and -[2,1-*b*]furans with Raney nickel in ethanol [19]. Furthermore, the synthesis of aminonaphtho[1,2-*b*]furan by cyclodehydratation of naphthyloxyamides with phosphorous oxychloride [20] as well as the synthesis of 2-ethylnaphtho[2,1-*b*]furan by cyclization of 2-(1-formyl-2-naphthyloxy)butanoic acid [21] have been described. The modern $Pd^{2+}$-catalyzed oxidative cyclization of 1-allyl-2-naphthol using

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$Cu(OAc)_2$–LiCl as a reoxidant was applied for the synthesis of naphtho[2,1-*b*]furan [22]. The synthesis of naphtho[2,1-*b*]furan through a novel ring transformation reaction of suitably functionalized 2H-pyran-2-ones [1], an annelation of 2-dienylcyclobutenones with both (*E*)- and (*Z*)-diene configurations to naphtho-[1,2-*b*]furans upon heating followed by treating with acid [23], as well as preparation of hydroxynaphtho-[1,2-*b*]furans by interacting naphthoquinone with various nitroenamines [24] have been reported. Cyclized amidino-substituted naphtho[2,1-*b*]furans were prepared in the photochemical dehydrocyclization reaction in ethanol and water from amidinofuryl-substituted phenyl acrylates [25]. Ethyl naphtho[2,1-*b*]furan-2-carboxylate was obtained from 2-hydroxy-1-naphthaldehyde with ethyl chloroacetate and potassium carbonate in DMF by microwave irradiation [7].

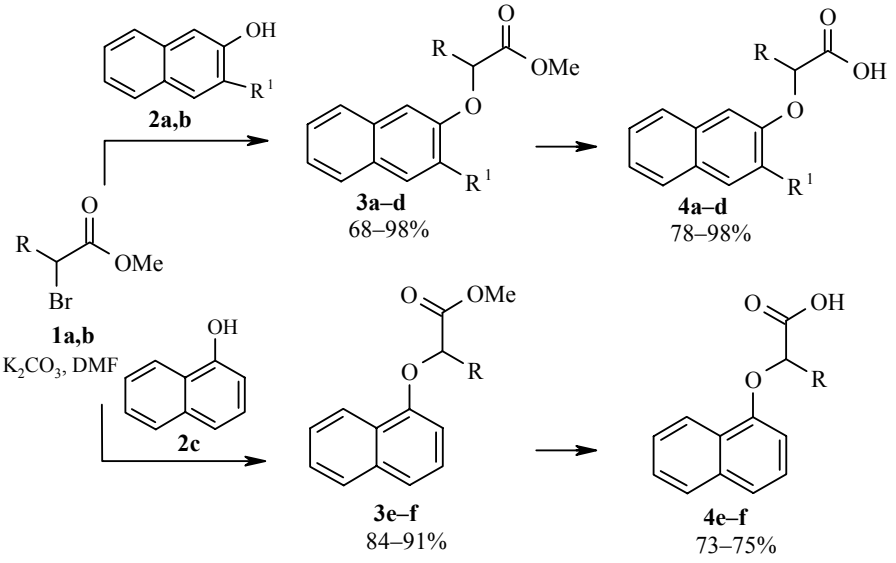
In the preceding paper we showed that acid-catalyzed cyclization of 2-phenoxyalkanals provided a convenient method for the synthesis of 2-alkylbenzo[*b*]furans [26, 27]. In this paper we describe a facile synthesis of regioisomeric naphthofurans by acid-catalyzed dehydrative cyclization of the appropriate naphthyloxyalkanals.

Hitherto, there are two reports in the literature on the synthesis of naphthyloxyalkanals. The first describes preparation of 2-naphthyloxyethanal by condensation of 2-chloro-1,1-diethoxyethane with 2-naphthol in the presence of sodium methylate at 170°C followed by hydrolysis of the acetal with sulfuric acid [28]. The second concerns 2-(1-naphthyloxy)propanals prepared by hydrocarbonylation of naphthyl vinyl ethers over a rhodium catalyst [29].

To obtain isomeric 2-(1-naphthyloxy)- and 2-(2-naphthyloxy)alkanals we decided to use the Rosenmund catalytic reduction of the corresponding naphthyloxyalkanoic acid chlorides, e.g., the method applied previously in the synthesis of 2-phenoxyalkanals [26, 27].

The desired 2-(2-naphthyloxy)- (**4a-d**) and 2-(1-naphthyloxy)alkanoic acids (**4e-f**) were prepared as shown in Scheme 1. Williamson ether syntheses were carried out *via* the reaction of the appropriate naphthoxide anion with methyl α-bromoalkanoate in the presence of potassium carbonate in DMF. All ethers **3a-f** were obtained in good yields (68-98%). The basic hydrolysis of **3a-f** gave the desired acids **4a-f** in 73-98% yields.

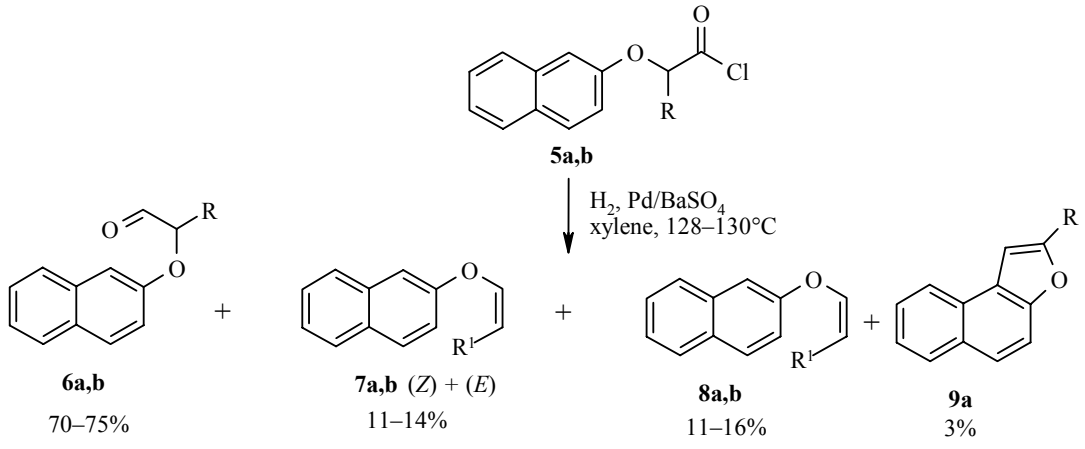
Scheme 1




**1 a** R = Et, **b** R = Bu; **2 a** $R^1$ = H, **b** $R^1$ = CONHPh; **3, 4 a** R = Et, $R^1$ = H; **b** R = Bu, $R^1$ = H; **c** R = Et, $R^1$ = CONHPh; **d** R = Bu, $R^1$ = CONHPh; **e** R= Et; **f** R = Bu

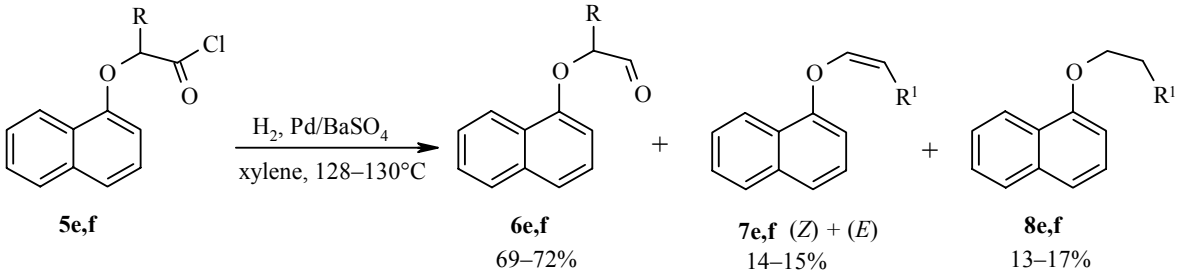
2-Naphthyloxyalkanoyl chlorides **5a-f** were obtained by the reaction of the appropriate acids with thionyl chloride in dry benzene. The solvent and the rest of the thionyl chloride were twice evaporated under vacuum from the crude chlorides, which were directly used for reduction. The reduction was carried out by refluxing acid chlorides in xylene under a hydrogen stream with 5% palladium on barium sulfate as a catalyst and quinoline S as a catalyst deactivator. In the reaction conditions acid chlorides **5a,b** and **5e,f** led to the formation of the corresponding 2-naphthyloxyalkanals (**6a,b** and **6e,f**) as the main products and to a mixture of (*Z*)- and (*E*)-diastereoisomers of naphthyl alkenyl ethers (**7a,b** and **7e,f)** as well as naphthyl alkyl ethers (**8a,b** and **8e,f**) as by-products (Schemes 2 and 3). GC/MS analyses showed that only 2-ethylnaphtho[2,1-*b*]furan (**9a**) was also present in the mixture of the reduction products but in small amounts.

Scheme 2




**5–9 a** R = Et, $R^1$ = Me; **b** R = Bu, $R^1$ = Pr

Scheme 3




**5–9 e** R = Et, $R^1$ = Me; **f** R = Bu, $R^1$ = Pr

TABLE 1. Reduction of Acid Chlorides **5a,b** and **5e,f** under optimal conditions

| Chloride **5** | Yield, %* | | | | |
|---|---|---|---|---|---|
| | Aldehyde **6** | Ether **7** | | Ether **8** | Naphthofuran **9** |
| | | (*Z*) | (*E*) | | |
| **a** | 75 | 3 | 8 | 11 | 3 |
| **b** | 70 | 4 | 10 | 16 | – |
| **e** | 72 | 4 | 11 | 13 | – |
| **f** | 69 | 5 | 9 | 17 | – |

* Relative percentage based on the GC/MS chromatographic area

TABLE 2. Mass Spectra of Compounds **3a-f**, **6a,b,e,f**, **7a,b,e,f**, **8a,b,e,f**, and **9a-e**

| Com-pound | *m/z* ($I_{rel}$, %) |
|---|---|
| **3a** | 244 $[M]^+$ (100), 185 (38), 170 (3),157 (10), 144 (99), 128 (29), 115 (57), 101 (5), 77 (3), 59 (7) |
| **3b** | 272 $[M]^+$ (100), 213 (24), 183 (3), 170 (2), 157 (19), 144 (99), 129 (31), 115 (65), 97 (6), 69 (15), 55 (6) |
| **3c** | 363 $[M]^+$ (46), 304 (4), 271 (11), 243 (94), 211 (22), 171 (100), 155 (5), 142 (19), 128 (6), 115 (27), 93 (8), 73 (8), 59 (4) |
| **3d** | 391 $[M]^+$ (38), 332 (2), 299 (10), 271 (100), 255 (5), 239 (12), 211 (10), 197 (7), 184 (14), 171 (89), 155 (4), 142 (20), 128 (5), 115 (27), 93 (15), 69 (11), 55 (5) |
| **3e** | 244 $[M]^+$ (100), 185 (20), 157 (7), 144 (99), 128 (6), 115 (68), 101 (6), 77 (3), 59 (10) |
| **3f** | 272 $[M]^+$ (100), 213 (12), 183 (1), 170 (5), 157 (8), 144 (99), 129 (9), 115 (58), 97 (7), 83 (1), 69 (12), 55 (5) |
| **6a** | 214 $[M]^+$ (93), 186 (17), 185 (100), 169 (10), 157 (41), 144 (96), 143 (15), 128 (17), 127 (49), 116 (15), 115 (81), 89 (7), 77 (5) |
| **6b** | 242 $[M]^+$ (58), 224 (48), 213 (37), 182 (16), 181 (100), 157 (57), 152 (23), 144 (86), 141 (34), 128 (13), 127 (36), 115 (50), 69 (24) |
| **6e** | 214 $[M]^+$ (70), 196 (7), 185 (56), 181 (10), 157 (10), 144 (100), 143 (21), 127 (24), 116 (27), 115 (71), 89 (6) |
| **6f** | 242 $[M]^+$ (50), 225 (10), 213 (24), 181 (29), 157 (16), 145 (16), 144 (100), 143 (11), 127 (16), 116 (17), 115 (45), 69 (6) |
| **7a** (*E*, *Z*) | 184 $[M]^+$ (100), 169 (16), 155 (28), 144 (49), 142 (6), 141 (26), 128 (29), 127 (15), 116 (12), 115 (54) |
| **7b** (*E*, *Z*) | 212 $[M]^+$ (100), 184 (12), 183 (88), 165 (23), 156 (8), 155 (62), 154 (12), 153 (23), 146 (53), 144 (54), 141 (22), 128 (21), 127 (54), 126 (17), 116 (6), 115 (35), 101 (6), 77 (8) |
| **7e** (*E*, *Z*) | 184 $[M]^+$ (100), 183 (13), 170 (6), 169 (48), 155 (27), 144 (45), 143 (7), 141 (12), 129 (14), 128 (15), 127 (9), 116 (28), 115 (61), 89 (6) |
| **7f** (*E*, *Z*) | 212 $[M]^+$ (100), 184 (7), 183 (53), 169 (18), 165 (23), 156 (5), 155 (40), 154 (7), 153 (14), 145 (6),144 (59), 141 (19), 128 (19), 127 (36), 126 (13), 116 (18), 115 (40), 101 (5), 77 (6) |
| **8a** | 186 $[M]^+$ (45), 145 (13), 144 (100), 126 (7), 116 (8), 115 (30), 89 (4) |
| **8b** | 214 $[M]^+$ (23), 145 (10), 144 (100), 127 (6), 116 (5), 115 (18) |
| **8e** | 186 $[M]^+$ (32), 184 (16), 169 (9), 155 (6), 145 (10), 144 (100), 129 (5), 116 (24), 115 (45), 89 (5) |
| **8f** | 214 $[M]^+$ (24), 145 (11), 144 (100), 127 (5), 116 (13), 115 (23) |
| **9a** | 196 $[M]^+$ (99), 195 (11), 182 (36), 181 (100), 153 (18), 152 (71), 151 (21), 139 (11), 98 (6), 76 (8) |
| **9b** | 224 $[M]^+$ (36), 182 (15), 181 (100), 165 (5), 152 (23), 151 (5) |
| **9c** | 331 $[M]^+$ (100), 274 (21), 259 (3), 245 (62), 217 (19), 197 (24), 184 (11), 170 (54), 155 (3), 142 (34), 127 (16), 114 (22), 91 (3), 77 (7), 63 (2), 50 (1) |
| **9d** | 359 $[M]^+$ (100), 331 (2), 316 (6), 303 (2), 274 (23), 259 (3), 245 (71), 230 (2), 217 (24), 197 (25), 184 (49), 170 (59), 155 (4), 142 (41), 127 (11), 114 (25), 93 (4), 77 (8), 55 (3) |
| **9e** | 196 $[M]^+$ (48), 182 (14), 181 (100), 165 (6), 152 (18), 139 (4), 90 (5), 76 (4) |

The results of our studies show that two simultaneous processes occur on the catalyst surface during the palladium-catalyzed hydrogenation of naphthyloxyalkanoyl chlorides, as was in the case of the reduction of phenoxyalkanoyl chlorides, i.e. hydrogenolysis of C–Cl linkage leading to 2-naphthyloxyalkanal and a bit slower dehydro-decarbonylation (β-elimination of hydrogen and COCl group) giving rise to a naphthyl alkenyl ether. Hydrogenation of this one gives the naphthyl alkyl ether.

The optimization of the reduction parameters, weight ratio of the catalyst and its deactivator to the starting chlorides allowed us to obtain 2-naphthyloxyalkanals in 69-75% yield (Table 1).

All aldehydes **6a-d** were purified by column chromatography (hexane–dichloromethane, 1.5:1) and their structures were established by elemental analyses and spectroscopic methods. Ethers **7a** and **8a** were also isolated, purified, and then analyzed, but the others were analyzed only by GC/MS chromatography.

TABLE 3. $^1$H NMR Spectra ($CDCl_3$/TMS) of Compounds **3a-f**, **4a-f**, **6a,b,e,f, 7a** (*E, Z*), **8a**, and **9a-f**

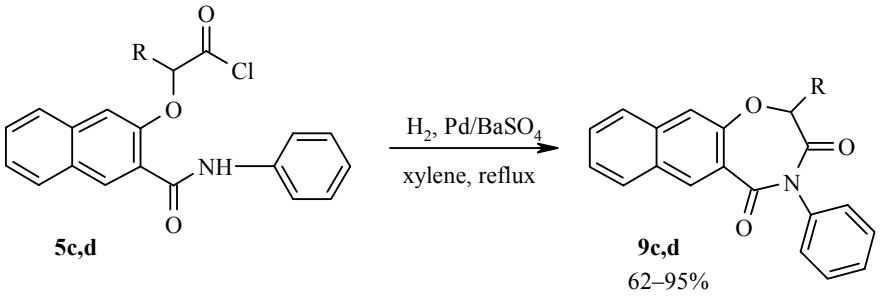
| Com-pound | Chemical shifts, δ, ppm (*J*, Hz) |
|---|---|
| 1 | 2 |
| **3a** | 7.74 (2H, d, *J* = 8.5, Ar); 7.68 (1H, d, *J* = 8.1, Ar); 7.41 (1H, t, *J* = 7.7, Ar); 7.32 (1H, t, *J* = 7.2, Ar); 7.20 (1H, d, *J* = 8.9, Ar); 7.04 (1H, s, Ar); 4.72 (1H, t, *J* = 6.0, CH); 3.74 (3H, s, $OCH_3$); 2.07-2.01 (2H, m, $CH_2$); 1.11 (3H, t, *J* = 7.2, $CH_3$) |
| **3b** | 7.79 (2H, d, *J* = 8.5, Ar); 7.73 (1H, d, *J* = 8.1, Ar); 7.46 (1H, t, *J* = 7.4, Ar); 7.37 (1H, t, *J* = 7.3, Ar); 7.24 (1H, d, *J* = 8.8, Ar); 7.09 (1H, s, Ar); 4.82 (1H, t, *J* = 6.2, CH); 3.78 (3H, s, $OCH_3$); 2.09-2.02 (2H, m, $CH_2$); 1.61-1.54 (2H, m, $CH_2$); 1.48-1.41 (2H, m, $CH_2$); 0.98 (3H, t, *J* = 7.2, $CH_3$) |
| **3c** | 10.24 (1H, s, NH); 8.76 (1H, s, Ar); 7.90 (1H, d, *J* = 8.2, Ar); 7.86-7.84 (2H, m, Ar); 7.70 (1H, d, *J* = 8.3, Ar); 7.51 (1H, t, *J* = 1.2, Ar); 7.42-7.37 (3H, m, Ar); 7.18 (1H, s, Ar); 7.15-7.11 (1H, m, Ar); 5.17 (1H, t, *J* = 5.6, CH); 3.81 (3H, s, $OCH_3$); 2.21-2.13 (2H, m, $CH_2$); 1.11 (3H, t, *J* = 7.46, $CH_3$) |
| **3d** | 10.23 (1H, s, NH); 8.74 (1H, s, Ar); 7.89-7.84 (3H, m, Ar); 7.69 (1H, d, *J* = 8.1, Ar); 7.49 (1H, t, *J* = 7.4, Ar); 7.38 (3H, t, *J* = 7.7, Ar); 7.18 (1H, s, Ar); 7.12 (1H, t, *J* = 7.3, Ar); 5.19 (1H, t, *J* = 5.5, CH); 3.80 (3H, s, $OCH_3$); 2.14-2.08 (2H, m, $CH_2$); 1.51 (2H, q, *J* = 7.5, $CH_2$); 1.36 (2H, q, *J* = 7.3, $CH_2$); 0.87 (3H, t, *J* = 7.2, $CH_3$) |
| **3e** | 8.38-8.35 (1H, m, Ar); 7.77-7.74 (1H, m, Ar); 7.49-7.41 (3H, m, Ar); 7.31-7.27 (1H, m, Ar); 6.64 (1H, d, *J* = 7.7, Ar); 4.75 (1H, t, *J* = 4.1, CH); 3.70 (3H, s, $OCH_3$); 2.15-2.07 (2H, m, $CH_2$); 1.15-1.13 (3H, m, $CH_3$) |
| **3f** | 8.38-8.35 (1H, m, Ar); 7.77-7.73 (1H, m, Ar); 7.51-7.40 (3H, m, Ar); 7.30-7.26 (1H, m, Ar); 6.64 (1H, d, *J* = 7.6, Ar); 4.80 (1H, t, *J* = 4.2, CH); 3.69 (3H, s, $OCH_3$); 2.14-2.03 (2H, m, $CH_2$); 1.61-1.54 (2H, m, $CH_2$); 1.43-1.37 (2H, m, $CH_2$); 0.93 (3H, t, *J* = 7.3, $CH_3$) |
| **4a** | 9.88 (1H, br. s, COOH); 7.75 (2H, d, *J* = 8.5, Ar); 7.69 (1H, d, *J* = 8.1, Ar); 7.42 (1H, t, *J* = 7.6, Ar); 7.34 (1H, t, *J* = 7.1, Ar); 7.21 (1H, t, *J* = 8.9, Ar); 7.08 (1H, s, Ar); 4.75 (1H, t, *J* = 5.8, CH); 2.07 (2H, t, *J* = 6.3, $CH_2$); 1.13 (3H, t, *J* = 7.3, $CH_3$) |
| **4b** | 9.24 (1H, br. s, COOH); 7.75 (2H, d, *J* = 8.4, Ar); 7.69 (1H, d, *J* = 8.1, Ar); 7.42 (1H, t, *J* = 7.6, Ar); 7.34 (1H, t, *J* = 7.1, Ar); 7.20 (1H, t, *J* = 8.7, Ar); 7.07 (1H, s, Ar); 4.78 (1H, t, *J* = 5.9, CH); 2.04-2.01 (2H, m, $CH_2$); 1.58-1.52 (2H, m, $CH_2$); 1.41-1.36 (2H, m, $CH_2$); 0.92 (3H, t, *J* = 7.1, $CH_3$) |
| **4c** | 10.20 (1H, s, NH); 8.64 (1H, s, COOH); 8.57 (1H, s, Ar); 7.72 (3H, t, *J* = 6.8, Ar); 7.57 (1H, d, *J* = 8.2, Ar); 7.42 (1H, d, *J* = 6.0, Ar); 7.29-7.24 (3H, m, Ar); 7.12 (1H, s, Ar); 7.05 (1H, t, *J* = 7.4, Ar); 5.08 (1H, t, *J* = 5.5, CH); 2.18-2.03 (2H, m, $CH_2$); 1.09-1.02 (3H, m, $CH_3$) |
| **4d** | 10.15 (1H, s, NH); 8.59 (1H, s, COOH); 7.77-7.71 (4H, m, Ar); 7.59 (1H, d, *J* = 8.1, Ar); 7.43 (1H, t, *J* = 7.3, Ar); 7.33-7.27 (3H, m, Ar); 7.14 (1H, s, Ar); 7.08 (1H, t, *J* = 7.1, Ar); 5.08 (1H, broad bond, CH); 2.05 (2H, d, *J* = 6.4, $CH_2$); 1.49 (2H, t, *J* = 6.6, $CH_2$); 1.32 (2H, q, *J* = 7.0, $CH_2$); 0.83 (3H, t, *J* = 7.0, $CH_3$) |
| **4e** | 11.68 (1H, s, COOH); 8.35-8.32 (1H, m, Ar); 7.79-7.76 (1H, m, Ar); 7.49–7.43 (3H, m, Ar); 7.31-7.27 (1H, m, Ar); 6.67 (1H, d, *J* = 7.6, Ar); 4.76 (1H, t, *J* = 6.0, CH); 2.17-2.10 (2H, m, $CH_2$); 1.16 (3H, t, *J* = 7.4, $CH_3$) |
| **4f** | 9.20 (1H, br. s, COOH); 8.34-8.31 (1H, m, Ar); 7.77 (1H, m, Ar); 7.51-7.46 (2H, m, Ar); 7.44 (1H, s, Ar); 7.32 (1H, t, *J* = 8.0, Ar); 6.68 (1H, d, *J* = 7.5, Ar); 4.84-4.81 (1H, m, CH); 2.20-2.08 (2H, m, $CH_2$); 1.66-1.56 (2H, m, $CH_2$); 1.46-1.38 (2H, m, $CH_2$); 0.93 (3H, t, *J* = 7.3, $CH_3$) |
| **6a** | 9.59 (1H, t, *J* = 1.2, CHO); 7.64 (2H, d, *J* = 9.0, Ar); 7.56 (1H, d, *J* = 8.1, Ar); 7.33-7.29 (1H, m, Ar); 7.25-7.21 (1H, m, Ar); 7.11-7.08 (1H, m, Ar); 6.89 (1H, d, *J* = 1.8, Ar); 4.45-4.41 (1H, m, CH); 1.87-1.79 (2H, m, $CH_2$); 0.98 (3H, t, *J* = 7.4, $CH_3$) |
| **6b** | 9.65 (1H, d, *J* = 2.4, CHO); 7.71 (2H, d, *J* = 2.4, Ar); 7.63 (1H, d.d, *J* = 7.6, 0.6, Ar); 7.40-7.36 (1H, m, Ar); 7.32-7.28 (1H, m, Ar); 7.17 (1H, dd, *J* = 6.4, 2.6, Ar); 6.97 (1H, d, *J* = 2.6, Ar); 4.57-4.53 (1H, m, CH); 1.86-1.81 (2H, m, $CH_2$); 1.48-1.46 (2H, m, $CH_2$); 1.36-1.30 (2H, m, $CH_2$); 0.89 (3H, t, *J* = 7.3, $CH_3$) |
| **6e** | 9.65 (1H, s, CHO); 8.35 (1H, t, *J* = 8.0, Ar); 7.75 (1H, s, Ar); 7.47 (2H, s, Ar); 7.41 (1H, d, *J* = 8.2, Ar); 7.23 (1H, d, *J* = 8.0, Ar); 6.56 (1H, d, *J* = 7.6, Ar); 4.53 (1H, t, *J* = 5.4, CH); 2.01-1.93 (2H, m, $CH_2$); 1.09 (3H, t, *J* = 7.4, $CH_3$) |
| **6f** | 9.70 (1H, d, *J* = 3.5, CHO); 8.36-8.33 (1H, m, Ar); 7.81-7.78 (1H, m, Ar); 9.48-7.52 (2H, m, Ar); 7.45 (1H, d, *J* = 8.3, Ar); 7.29 (1H, t, *J* = 6.4, Ar); 6.61 (1H, d, *J* = 7.6, Ar); 4.67-4.63 (1H, m, CH); 2.04-1.92 (2H, m, $CH_2$); 1.60-1.54 (2H, m, $CH_2$); 1.42-1.37 (2H, m, $CH_2$); 0.92 (3H, t, *J* = 7.3, $CH_3$) |

TABLE 3 (continued)

| 1 | 2 |
|---|---|
| **7a** (*E*) | 8.13-7.35 (7H, m, Ar); 6.68-6.62 (1H, m, CH); 5.11-5.06 (1H, m, CH); 1.92-1.90 (3H, m, $CH_3$) |
| **7a** (*Z*) | 8.13-7.35 (7H, m, Ar); 6.69-6.64 (1H, m, CH); 5.63-5.58 (1H, m, CH); 1.92-1.90 (3H, m, $CH_3$) |
| **8a** | 7.69-7.63 (3H, q, *J* = 15.3, 8.8, Ar); 7.55 (1H, t, *J* = 7.5, Ar); 7.23 (1H, t, *J* = 7.3, Ar); 7.07 (2H, d, *J* = 12.4, Ar); 3.96 (2H, t, *J* = 6.5, $CH_2$); 1.83-1.78 (2H, q, *J* = 14.0, 7.0, $CH_2$); 1.00 (3H, t, *J* = 7.3, $CH_3$) |
| **9a** | 7.98 (1H, d, *J* = 8.2, Ar); 7.84 (1H, d, *J* = 8.1, Ar); 7.55 (2H, s, Ar); 7.47 (1H, t, *J* = 7.5, Ar); 7.38 (1H, t, *J* = 7.2, Ar); 6.74 (1H, s, Ar); 2.85-2.80 (2H, m, $CH_2$); 1.31 (3H, t, *J* = 7.6, $CH_3$) |
| **9b** | 8.03 (1H, d, *J* = 8.0, Ar); 7.88 (1H, d.d, *J* = 6.9, *J* = 0.5, Ar); 7.59 (2H, s, Ar); 7.53-7.49 (1H, m, Ar); 7.44-7.40 (1H, m, Ar); 6.77 (1H, s, Ar); 2.79 (2H, t, *J* = 7.9, $CH_2$); 1.78-1.70 (2H, m, $CH_2$); 1.46-1.37 (2H, m, $CH_2$); 0.96 (3H, t, *J* = 7.4, $CH_3$) |
| **9c** | 8.76 (1H, s, Ar); 7.92 (1H, d, *J* = 8.2, Ar); 7.80 (1H, d, *J* = 8.3, Ar); 7.59 (2H, t, *J* = 7.0, Ar); 7.51-7.40 (4H, m, Ar); 7.22 (2H, d, *J* = 7.9, Ar); 4.58 (1H, t, *J* = 4.2, CH); 2.20-2.08 (2H, m, $CH_2$); 1.19 (3H, t, *J* = 7.3, $CH_3$) |
| **9d** | 8.77 (1H, s, Ar); 7.96-7.23 (10H, m, Ar); 4.67 (1H, broad bond, CH); 2.12-2.01 (2H, m, $CH_2$); 1.71-1.26 (4H, m, $CH_2$); 0.96 (3H, t, *J* = 7.0, $CH_3$) |
| **9e** | 8.26 (1H, d, *J* = 8.3, Ar); 7.88 (1H, d, *J* = 8.2, Ar); 7.60-7.55 (2H, m, Ar); 7.55-7.51 (1H, m, Ar); 7.43-7.39 (1H, m, Ar); 6.47 (1H, s, Ar); 2.91-2.86 (2H, m, $CH_2$); 1.38 (3H, t, *J* = 5.0, $CH_3$) |
| **9f** | 8.26 (1H, d, *J* = 8.3, Ar); 7.89 (1H, d, *J* = 8.2, Ar); 7.61-7.52 (3H, m, Ar); 7.44-7.40 (1H, m, Ar); 6.48 (1H, s, Ar); 2.86 (2H, t, *J* = 7.7, $CH_2$); 1.82-1.74 (2H, m, $CH_2$); 1.48-1.42 (2H, m, $CH_2$); 0.97 (3H, t, *J* = 7.4, $CH_3$) |

In the case of chlorides **5c** and **5d,** no desired aldehydes were obtained by this method. Under the reaction conditions the chlorides underwent intramolecular N-acylation giving naphtho-1,4-oxazepine-3,5-diones **9c** and **9d** (Scheme 4). The same products were obtained when chlorides **5c** and **5d** were heated for several minutes in boiling toluene without palladium.

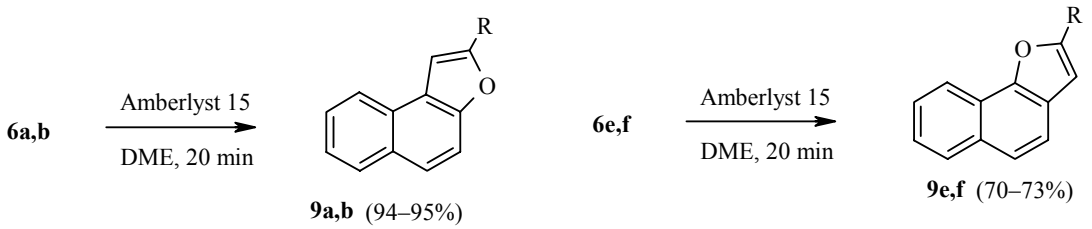
Scheme 4




**5c,d** **9c,d** 62–95%

**5,9 c** R = Et; **d** R = Bu

Scheme 5




**9a,b** (94–95%) **9e,f** (70–73%)

Cyclization of 2-naphthyloxyalkanals was carried out in dimethoxyethane (DME) using Amberlyst 15 resin as a catalyst. The best results and high cyclization yield were achieved when the reaction mixture was heated in boiling DME for 20 min (Scheme 5).

It was found that cyclization of 2-(2-naphthyloxy)alkanals **6a** and **6b** over Amberlyst 15 resin provided only 2-alkylnaphtho[2,1-*b*]furan regioisomer, while the cyclization of model ethyl acetal of 2-naphthoxybutanal **6a** resulted in formation of 2-ethylnaphtho[2,1-*b*]furans as main products and small amounts of 2-ethylnaphtho-[3,2-*b*]furans. The isomeric product was observed when cyclization of compound **6a** was carried out using homogenous sulfuric acid as a catalyst.

A new synthetic method for regioisomeric naphthofurans by cyclization of naphthyloxyalkanals has been developed. The optimum reduction conditions of naphthyloxyalkanoic acid chlorides allowing one to prepare 2-naphthyloxyalkanals with good yields with a minimum of the ethers as by-products were established. The efficient cyclization of 2-naphthyloxyalkanals to 2-alkylnaphthofurans as a green chemistry process carried out under mild conditions over the acidic Amberlyst 15 resin has been presented. The cyclization of naphthyloxyalkanals afforded the desired naphthofurans in excellent yields.

TABLE 4. $^{13}C$ NMR Spectra Data ($CDCl_3$/TMS) of Compounds **3a,b,d,e,f**, **4a-f**, **6a,b,e,f**, and **9a,b,e,f**

| Com-pound | Chemical shifts, δ, ppm |
|---|---|
| **3a** | 172.2, 155.8, 134.3, 129.7, 129.3, 127.6, 126.9, 126.4, 123.9, 118.9, 107.6, 77.7, 52.3, 26.2, 9.7 |
| **3b** | 172.5, 155.9, 134.4, 129.8, 129.4, 127.7, 126.9, 126.5, 124.1, 118.9, 107.6, 77.5, 52.3, 32.7, 27.5, 22.4, 14.0 |
| **3d** | 172.0, 163.4, 152.1, 138.9, 135.4, 134.3, 129.0, 128.8, 128.5, 126.4, 125.1, 124.4, 124.0, 120.2, 108.3, 77.5, 52.9, 32.1, 27.0, 22.4, 13.8 |
| **3e** | 172.2, 153.7, 134.6, 127.4, 126.5, 125.7, 125.6, 125.3, 122.2, 121.1, 105.2, 77.8, 52.1, 26.3, 9.8 |
| **3f** | 172.4, 153.7, 134.6, 127.4, 126.5, 125.7, 125.6, 125.3, 122.2, 121.0, 105.1, 76.7, 52.2, 32.7, 27.5, 22.4, 13.9 |
| **4a** | 177.4, 155.5, 134.2, 129.8, 129.4, 127.6, 126.9, 126.5, 124.1, 118.7, 107.8, 26.0, 9.6 |
| **4b** | 177.8, 155.6, 134.2, 129.9, 129.5, 127.7, 126.9, 126.6, 124.2, 118.8, 107.7, 76.0, 32.4, 27.4, 22.3, 13.9 |
| **4c** | 174.4, 164.7, 151.9, 138.1, 136.3, 135.4, 133.8, 129.0, 128.6, 126.4, 125.2, 124.6, 123.9, 120.7, 108.7, 77.8, 25.5, 9.3 |
| **4d** | 175.0, 164.4, 152.2, 138.3, 135.4, 133.7, 129.0, 128.6, 128.5, 126.4, 125.1, 124.4, 124.1, 120.5, 108.7, 77.4, 32.2, 27.1, 22.4, 13.8 |
| **4e** | 178.0, 153.4, 134.6, 127.4, 126.6, 125.6, 125.5, 125.4, 122.1, 121.3, 105.3, 26.2, 9.8 |
| **4f** | 178.0, 153.4, 134.6, 127.4, 126.6, 125.6, 125.5, 125.5, 122.1, 121.3, 105.2, 76.0, 32.5, 27.5, 22.3, 13.9 |
| **6a** | 201.8, 154.5, 133.2, 128.9, 128.3, 126.6, 125.8, 125.6, 123.1, 117.8, 106.8, 81.6, 22.6, 8.1 |
| **6b** | 203.0, 155.7, 134.3, 130.0, 129.4, 127.7, 126.9, 126.7, 124.2, 118.9, 107.9, 81.7, 30.0, 26.9, 22.5, 13.9 |
| **6e** | 203.1, 153.4, 134.8, 127.7, 126.8, 125.6, 122.1, 121.5, 105.7, 99.9, 82.8, 23.9, 9.4 |
| **6f** | 203.2, 153.3, 134.7, 127.4, 126.7, 125.6, 125.5, 121.9, 121.3, 105.5, 81.7, 30.1, 26.9, 22.5, 13.9 |
| **9a** | 159.0, 150.6, 129.1, 127.5, 126.3, 124.7, 122.9, 122.8, 122.6, 122.2, 110.9, 98.9, 20.7, 10.9 |
| **9b** | 159.2, 152.0, 130.4, 128.9, 127.7, 126.1, 124.3, 124.2, 123.9, 123.6, 112.3, 101.0, 30.2, 28.5, 22.6, 14.1 |
| **9e** | 160.2, 149.7, 130.8, 128.3, 126.0, 124.4, 124.3, 122.8, 121.2, 119.7, 119.3, 102.1, 21.9, 12.1 |
| **9f** | 159.0, 149.7, 130.8, 130.8, 128.3, 126.0, 124.4, 122.9, 121.2, 119.7, 119.3, 102.8, 30.1, 28.2, 22.3, 13.8 |

TABLE 5. Elemental Analysis Data for Compounds **3a-f**, **4a-f**, **5a-f**, **6a,b,e,f**, and **9a-f**

| Compound | Empirical formula | Found, % / Calculated, % | | | |
|---|---|---|---|---|---|
| | | C | H | Cl | N |
| **3a** | $C_{15}H_{16}O_3$ | 73.64 / 73.75 | 6.68 / 6.60 | | |
| **3b** | $C_{17}H_{20}O_3$ | 74.85 / 74.97 | 7.46 / 7.40 | | |
| **3c** | $C_{22}H_{21}NO_4$ | 72.63 / 72.71 | 5.93 / 5.82 | | 3.73 / 3.85 |
| **3d** | $C_{24}H_{25}NO_4$ | 73.49 / 73.64 | 6.53 / 6.44 | | 3.37 / 3.58 |
| **3e** | $C_{15}H_{16}O_3$ | 73.67 / 73.75 | 6.65 / 6.60 | | |
| **3f** | $C_{17}H_{20}O_3$ | 74.89 / 74.97 | 7.51 / 7.40 | | |
| **4a** | $C_{14}H_{14}O_3$ | 72.97 / 73.03 | 6.19 / 6.13 | | |
| **4b** | $C_{16}H_{18}O_3$ | 74.31 / 74.39 | 7.11 / 7.02 | | |
| **4c** | $C_{21}H_{19}NO_4$ | 72.03 / 72.19 | 5.61 / 5.48 | | 3.92 / 4.01 |
| **4d** | $C_{23}H_{23}NO_4$ | 73.13 / 73.19 | 6.31 / 6.14 | | 3.65 / 3.71 |
| **4e** | $C_{14}H_{14}O_3$ | 72.95 / 73.03 | 6.18 / 6.13 | | |
| **4f** | $C_{16}H_{18}O_3$ | 74.29 / 74.39 | 7.09 / 7.02 | | |
| **5a** | $C_{14}H_{13}ClO_2$ | 67.46 / 67.61 | 5.34 / 5.27 | 13.99 / 14.26 | |
| **5b** | $C_{16}H_{17}ClO_2$ | 69.38 / 69.44 | 6.34 / 6.19 | 12.52 / 12.81 | |
| **5c** | $C_{21}H_{18}ClNO_3$ | 68.33 / 68.57 | 5.02 / 4.93 | 9.38 / 9.64 | 3.65 / 3.81 |
| **5d** | $C_{23}H_{22}ClNO_3$ | 69.73 / 69.78 | 5.71 / 5.60 | 8.77 / 8.96 | 3.43 / 3.54 |
| **5e** | $C_{14}H_{13}ClO_2$ | 67.52 / 67.61 | 5.41 / 5.27 | 14.02 / 14.26 | |
| **5f** | $C_{16}H_{17}ClO_2$ | 69.23 / 69.44 | 6.31 / 6.19 | 12.63 / 12.81 | |
| **6a** | $C_{14}H_{14}O_2$ | 78.46 / 78.48 | 6.61 / 6.59 | | |
| **6b** | $C_{16}H_{18}O_2$ | 79.29 / 79.31 | 7.52 / 7.49 | | |
| **6e** | $C_{14}H_{14}O_2$ | 78.45 / 78.48 | 6.63 / 6.59 | | |
| **6f** | $C_{16}H_{18}O_2$ | 79.27 / 79.31 | 7.54 / 7.49 | | |
| **9a** | $C_{14}H_{12}O$ | 85.65 / 85.68 | 6.19 / 6.16 | | |
| **9b** | $C_{16}H_{16}O$ | 85.66 / 85.68 | 7.22 / 7.19 | | |
| **9c** | $C_{21}H_{17}NO_3$ | 76.03 / 76.12 | 5.24 / 5.17 | | 4.09 / 4.23 |
| **9d** | $C_{23}H_{21}NO_3$ | 76.75 / 76.86 | 5.98 / 5.89 | | 3.71 / 3.90 |
| **9e** | $C_{14}H_{12}O$ | 85.66 / 85.68 | 6.19 / 6.16 | | |
| **9f** | $C_{16}H_{16}O$ | 85.64 / 85.68 | 7.27 / 7.19 | | |

## EXPERIMENTAL

$^{1}H$ and $^{13}C$ NMR spectra were recorded on a TM Bruker DPX 400 (400 MHz) instrument, solvent $CDCl_3$. Chemical shifts δ are given from TMS (0 ppm) as an internal standard for $^{1}H$ NMR and $CDCl_3$ (77.0 ppm) for $^{13}C$ NMR (100 MHz). Mass spectra were obtained using an Agilent Technologies 6890 N gas chromatograph equipped with a mass detector 5973 Network and 30 m × 0.25 mm capillary column filled with a 0.25 μm film of a 5% MePh silicate. All melting points were determined on a Boetius apparatus and are uncorrected.

Most of the reagents and solvents were purchased in a commercially available grade purity. 1-Naphthol, 2-naphthol, butanoic and hexanoic acids, 3-hydroxynaphthalene-2-carboxylic acid phenylamide, catalyst (5 wt.% $BaSO_4$), and Amberlyst 15 resin were used without further purification. Methyl 2-bromobutanoate **1a** and methyl 2-bromohexanoate **1b** were prepared according to the literature [30]. Benzene, xylene, and DME were dried over sodium, and DMF was dried over type 4A molecular sieves before using.

**Synthesis of 2-(Naphthyloxy)alkanoic Acid Methyl Esters 3a-f (General Method)**. A mixture of naphthol **2a-c** (0.05 mol), methyl 2-bromoalkanoate **1a-b** (0.05 mol), anhydrous potassium carbonate (0.05 mol), and dry DMF (70 ml) was heated at 92–94ºC with stirring for 4 h. Then the solution was poured into ice water and the precipitate was filtered off, washed with water, and dried on air. The crude ester was crystallized from methanol to give compounds **3a**–**f** (Tables 2-5). Yield: compounds **3a** – 98, **3b** – 80, **3c** – 68, **3d** –96, **3e** – 84, **3f –** 91%. Compounds **3a**, mp 55.5-56.5ºC; **3b**,**d-f**, oil products; **3c**, mp 100-103ºC.

**Synthesis of 2-(Naphthyloxy)alkanoic Acids 4a-f (General Method)**. A mixture of ester **3a-f** (0.05 mol) and 10% sodium hydroxide (100 ml) was stirred and heated on a boiling water bath for 4 h. The solution was acidified with 5% hydrochloric acid and the precipitate was isolated. The crude product was purified by activated carbon to give compounds **4a**–**f** (Tables 3–5). Yield: compounds **4a** – 95, **4b** – 78, **4c** – 98, **4d** – 87, **4e** – 75, **4f –** 73%; mp compounds **4a**, 126–127 (Lit. [31] mp 126.5); **4b**, 107–109 (Lit. [32] 108–110); **4c**, 106–111, **4d**, oil product, **4e**, 114-116, **4f**, 98-100ºC.

**Synthesis of 2-(naphthyloxy)alkanoyl chlorides 5a-f (General Method)**. A solution of an anhydrous 2-(naphthyloxy)alkanoic acid **4a-f** (0.02 mol) and thionyl chloride (0.06 mol) in anhydrous benzene (40 ml) was heated at 45-50ºC for 1.5 h and then at 58-60ºC for 3 h. Benzene and an excess of thionyl chloride were evaporated. Then a new portion of anhydrous benzene was added and evaporated again. The crude 2-(naphthyloxy)akanoyl chloride was dried under reduced pressure at room temperature to give oil product **5a-f** (Table 5). Yield: compounds **5a** – 90, **5b** – 98, **5c** – 88, **5d** – 95, **5e** – 78, **5f –** 80%. The crude chlorides were used for reduction without any analyses.

**Reduction of 2-(Naphthyloxy)alkanoyl Chlorides 5a,b,e,f (General Method).** A magnetically stirred mixture of palladium catalyst (5% on barium sulfate, 0.45 g), catalyst poison (quinoline S, 0.2 g), and dry xylene (35 ml) was heated under a hydrogen stream passing at the rate of 2-3 bubbles per second for 20 min. Then it was warmed up to 100ºC and crude compounds **5a,b,e,f** (8 mmol) were added. The mixture was heated at 126-128ºC afterwards. The reaction was monitored by titrating the HCl liberated using 1 M NaOH and was carried out until the chloride conversion was completed (1.5-2 h). The mixture was then cooled and left overnight. The catalyst was filtered off the next day, and the solvent was evaporated. The residual liquid, chromatographically determined, was purified by column chromatography (hexane–dichloromethane, 1.5:1) to give products such as aldehydes **6** and ethers **7, 8** (Tables 1-5).

**Reduction of 2-(3-Phenylcarbamoyl-2-naphthyloxy)alkanoyl Chlorides 5c,d**. Starting with compounds **5c,d** (3 mmol) the same procedure was followed as for compound **5a** to obtain the product, which was crystallized from diethyl ether to give compounds **9c,d** (Tables 2, 3, 5). Yield: **9c** – 95, **9d** – 62%; mp: compounds **9c**, 168-171, **9d**, 91-94ºC.

**Synthesis of 2-alkylnaphthofurans 9a,b,e,f (General Method)**. A solution of compound **6** (4 mmol) and resin Amberlyst 15 (1.36 g) in DME (30 ml) was heated under reflux with stirring for 20 min. The mixture

was cooled and the resin was filtered off. The solvent was evaporated and the residue was purified by column chromatography (hexane–dichloromethane, 1.5:1) to give oil products **9a,b,e,f** (Tables 2-5). Yield: compounds **9a** – 95, **9b** – 94, **9e** – 73, **9f** – 70%.

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