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A SYNTHESIS OF (±)-LAEVIGATIN

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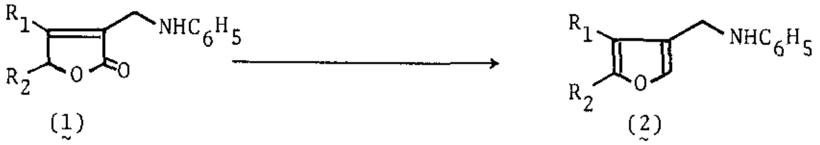
Abstract ——— Reduction of α-anilinomethyl-1,2-butenolides with diisobutylaluminium hydride yielded the corresponding 3-anilinomethylfurans. Hydrogenolysis of 3-anilinomethyl-5,6,7,8-tetrahydro-7-methylbenzo[b]furan over 10 % Pd-C afforded (±)-menthofuran. This synthetic way leading to 3-methylfuran derivatives was applied to a synthesis of (±)-laevigatin starting from 4,7-dimethyl-1-tetralone.

In the previous paper[1], we reported a direct conversion of the epoxides of 1-phenyl-3-vinylazetidin-2-ones to α-anilinomethyl-1,2-butenolides by treatment with methanesulfonic acid in benzene under reflux. Reduction of 1,2-butenolides with diisobutylaluminium hydride (DIBAH) is one of very important conversion in the synthesis of furans[2]. It could be expected that α-anilinomethyl-1,2-butenolides might be easily converted to 3-anilinomethylfurans by the reduction with DIBAH. Furthermore, it is well known that the hydrogenolysis of benzylamines can be often applied to a synthesis of toluene derivatives[3,4,5]. Based upon these two key steps leading to 3-methylfurans, we have investigated a synthesis of (±)-laevigatin. We wish to report the results of our studies.

First, we examined the reduction of α-anilinomethyl-1,2-butenolides (1a-1e)[1] with DIBAH as a model experiment. 1a-1e were treated with DIBAH (20 % hexane solution; 2.2 equiv) in toluene at -78 °C for 1.5 hr and the mixture was decomposed with NH_4Cl aqueous solution at the same temperature. A solution of the crude products[6] in benzene was stirred in the presence of ten folds of silica gel at room temperature for 14 hr to give the corresponding 3-anilinomethylfurans (2a-2e) as an oil in nearly quantitative yield in each of these cases. The products were determined by their spectral data as shown in the Table 1.



a: $R_1=CH_3$, $R_2=H$; b: $R_1=C_6H_5$, $R_2=CH_3$; c: $R_1-R_2=-(CH_2)_4-$;
d: $R_1-R_2=-(CH_2)_2-CH(CH_3)-CH_2-$; e: $R_1-R_2=-(CH_2)_5-$

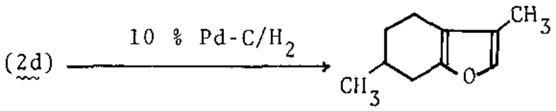
Scheme 1

Table 1. Spectral Data of 3-Anilinomethylfurans (2a-2e)

Compound	Formula	High Res. Mass Spectra m/e (M^+) (Calcd.)	^{1}HNMR (CCl_4)[a] δ
2a	$C_{12}H_{13}NO$	187.100 (187.101)	1.83 (3H, s), 4.00 (2H, s)
2b	$C_{18}H_{17}NO$	263.131 (263.132)	2.28 (3H, s), 4.03 (2H, s)
2c	$C_{15}H_{17}NO$	227.131 (227.129)	1.67-1.93 (4H, m), 2.33-2.67 (4H, m), 3.90 (2H, m)
2d	$C_{16}H_{19}NO$	241.148 (241.147)	1.09 (3H, d, J=6 Hz), 1.67-2.67 (7H, m), 4.00 (2H, s)
2e	$C_{16}H_{19}NO$	241.148 (241.147)	1.60-1.85 (6H, m), 2.33-2.50 (2H, m), 2.62-2.83 (2H, m), 3.95 (2H, s)

[a] Only representative signals are shown.

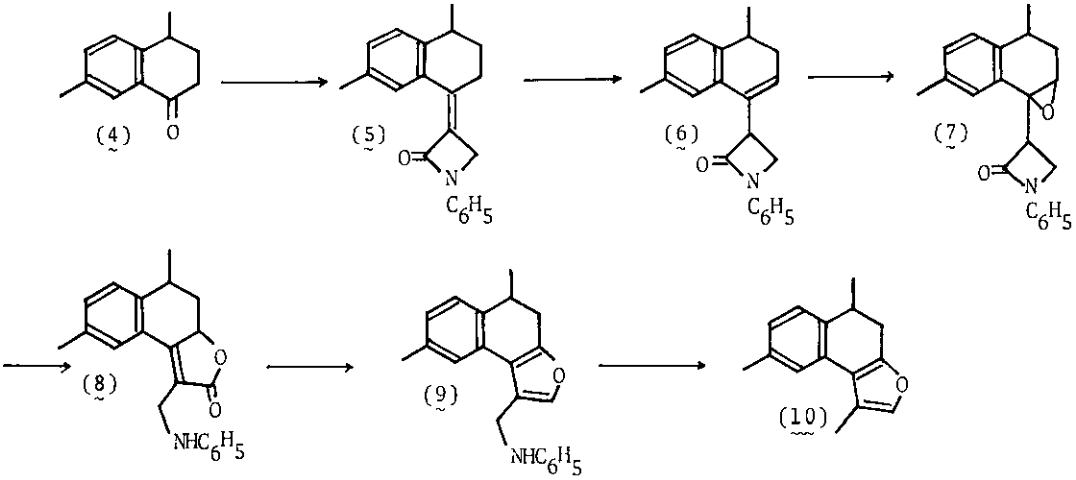
Hydrogenolysis of 2d over 10 % Pd-C in ethanol at 60 °C for 5 hr under atmospheric pressure of hydrogen gave (±)-menthofuran (3, 72 %), the spectral data of which were identical with those of natural menthofuran donated from Dr. Masafu Shinbo, Basic Research Laboratories, The Lion Dentifrice Co. Ltd. (Eq. 1).



(3)

(Eq. 1)

A synthesis of (±)-laevigatin (10) by an application of this 3-methylfuran synthesis was investigated as follows. Condensation of 1-phenyl-2-azetidin-2-one with 4,7-dimethyl-1-tetralone (4)[7] by the method we reported[1] gave the 3-alkylideneazetidin-2-one (5), mp 112-113 °C (benzene-hexane); m/e 303 (M^+), ^{1}HNMR ($CDCl_3$) δ 1.47 (3H, d, J=6 Hz), 2.42 (3H, s), 4.12 (2H, s), 7.08-7.42 (8H, m). Treatment of 5 with lithium diisopropylamide (LDA) in THF at 0 °C for 40 min yielded the isomerized product (6) in quantitative yield as a mixture of stereoisomers. Epoxidation of 6 with m-chloroperbenzoic acid in methylene chloride at room temperature for 14 hr gave the epoxide (7); m/e 319.160 (M^+, Cacld. 319.157 for $C_{21}H_{21}NO_2$). This was, without purification, further treated with methanesulfonic acid in benzene under reflux for 1.5 hr to give the butenolide (8), mp 162-165 °C (benzene-hexane); m/e 319 (M^+), ^{1}HNMR ($CDCl_3$) δ 1.37 (3H, d, J=7 Hz), 1.98 (3H, s), 4.27 (2H, s), 5.17 (1H, m), 6.55-7.46 (8H, m). Reduction of 8 with DIBAH (2.2 equiv) in toluene as in formation of 2 afforded 2-anilinomethyl-4,5-dihydro-5,7-dimethylnaphtho[2,1-b]furan (9) in quantitative yield; m/e 303.163 (M^+, Calcd. 303.162 for $C_{21}H_{21}NO$), ^{1}HNMR (CCl_4) δ 1.23 (3H, d, J=7 Hz), 2.13 (3H, s), 2.43-3.20 (3H, s), 4.30 (2H, s), 6.47-7.29 (9H, m). Hydrogenolysis of 9 over 10 % Pd-C in ethanol at room temperature for 5 hr gave (±)-laevigatin (10, 75 %), ^{1}HNMR (CCl_4) spectrum of which was identical with that of natural laevigatin[8] donated from Professor A. B. de Oliveira.



Scheme 2

As illustrated in the conversion of **1d** to **3** and in the synthesis of (±)-laevigatin from **5**, 3-alkylideneazetidin-2-ones might be useful precursor for preparing some 3-alkylfuran derivatives.

Acknowledgement We are indebted to Professor A. B. de Oliveira, Univerdidate Federal De Minas Gerais, Brasil, for the gift of natural laevigatin and its spectral data. We also thank Dr. Masafu Shinbo, Basic Research Laboratories, The Lion Dentifrice Co. Ltd. for the gift of natural menthofuran.

References and Notes

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