First Syntheses of Lorneic Acids A and B with Potential PDE5 Inhibition Activity

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Abstract: Two natural products with potential PDE5 inhibition activity, lorneic acids A and B, have been synthesized for the first time in high yield using a chiral amide stereocontrolled addition of aryl lithium to aldehyde as the key step, and the configuration of the chiral benzylic alcohol in lorneic acid B was determined to be *S*.

Key words: lorneic acid A/B, PDE5 inhibitor, asymmetric synthesis, chiral auxiliary, *ortho*-lithiation

Lorneic acids A (**1**) and B (**2**) were found in 2009 from the culture supernatant of an actinomyces strain (NPS554) isolated from a marine sediment sample in Miyazaki Harbor, Japan.[1] The two compounds possess same trialkyl-substituted benzene skeleton just with different functional group in the side chain (Figure 1). Instead of conjugated double bond in **1**, a chiral benzylic hydroxyl group exists in (–)-**2**, which displays optical activity. However, the absolute configuration of the chiral center is still not determined. Compounds **1** and **2** showed significant selective inhibition activity against phosphodiesterase (PDE), particularly PDE5. PDE5 inhibitors are of pharmacological importance in treatment of some diseases such as erectile dysfunctions and pulmonary hypertension.[2] Structure of lorneic acids is relatively rare, and among the known natural products only lorneamides A (**3**) and B (**4**)[3] have the common framework to **1** and **2**. In addition, an evernimicin antibiotic from *Micromonospora carbonaceae* fermentation, Sch 49088, contained a very similar trialkyl-substituted aromatic acid subunit to lorneic acid B.[4] Unusual structure, important bioactivity and natural scarcity make lorneic acids a class of significant targets, yet the synthesis of the compounds has not been reported up to now. Herein we described the first synthesis of **1** and **2** from easily available 4-methylbenzoic acid (**5**).

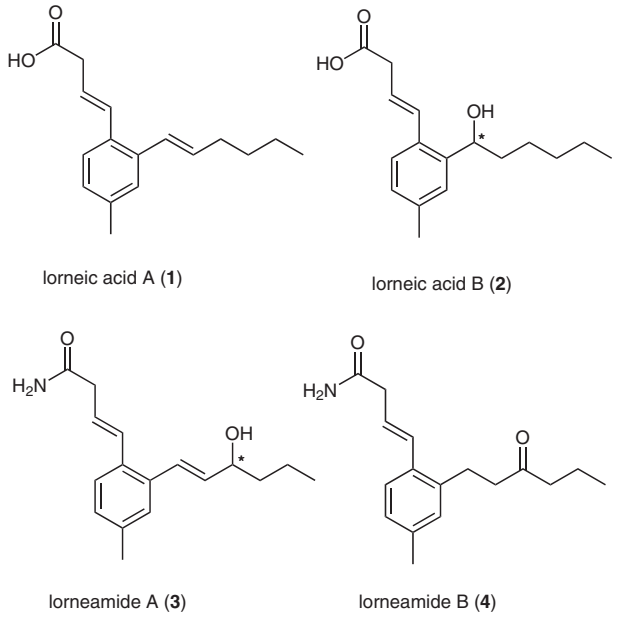
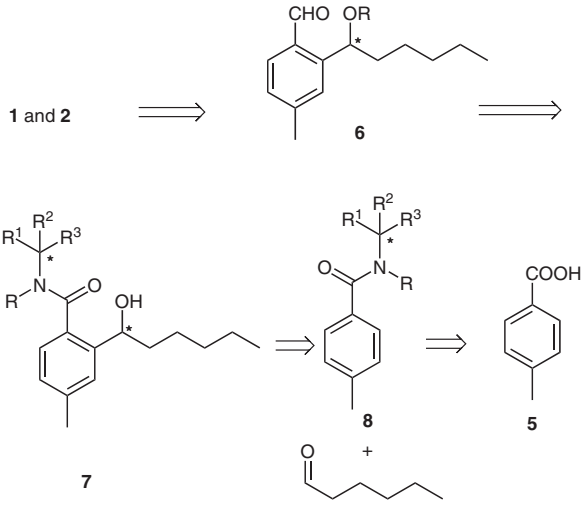


Figure 1



Scheme 1 Synthetic strategy of **1** and **2**

As shown in Scheme 1, aldehyde **6** which is derived from **7** by simple transformation is designed as the intermediate for **1** and **2**. The optically active benzyl alcohol **7** is expected to be formed via *ortho*-lithiation of chiral benzamide **8** followed by stereoselective addition to hexanal. Chiral amide **8** could be obtained from some commercial chiral amines. The secondary amide[5] or tertiary amide[6] functional groups on aryl ring have widely been reported as efficient directors of *ortho* lithiation, and the resulting aryl lithium could participate in diversified reactions.[5–7] Nevertheless, in most cases achiral amides were em-

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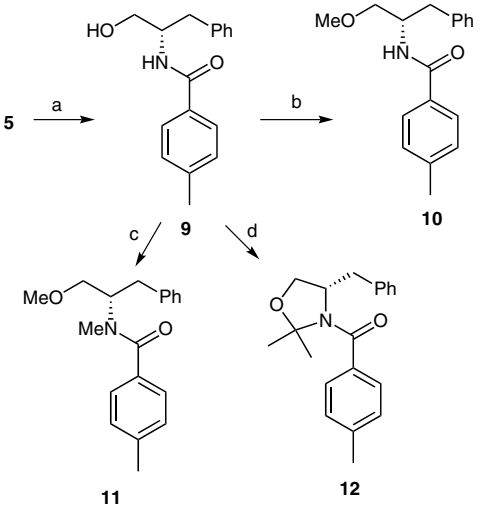
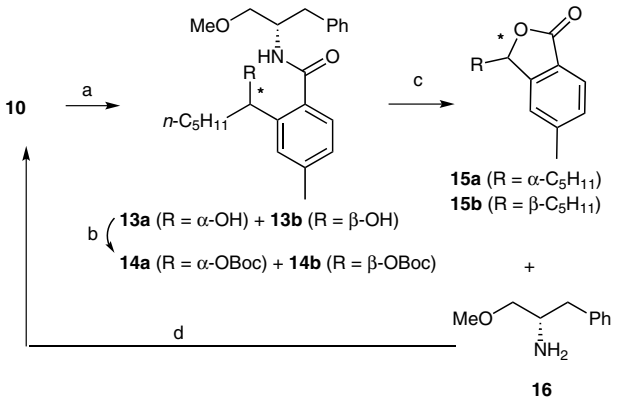
ployed. Only very limited investigation on asymmetric induction of chiral amides in the reactions of the aryl lithium was carried out.[8] We wish to expand this type of asymmetric reactions and apply it to the synthesis of the natural products with chiral benzyl alcohol such as **1** and **2**.

Thus, **5** was converted into the corresponding acyl chloride with $SOCl_2$ and coupled with L-phenylalaninol to provide the desired peptide **9** in high yield (Scheme 2). Peptide **9** was transformed to secondary amide **10** and tertiary amide **11/12** by different modification. Their reactions with hexanal were investigated after treatment of the amides with alkyl lithium. Amides **10** and **11** could not be lithiated by *n*-BuLi, whereas the amide bond of **12** was cleaved to result in 1-*para*-tolylpentan-1-one under same conditions. When the stronger base *t*-BuLi was employed, the reactions of **11** or **12** were quite complex and no desired product was detected. The lithiation of **10** with *t*-BuLi did not work until the temperature was raised to 0 °C from –78 °C. After optimization, treatment of **10** with *t*-BuLi–TMEDA at 0 °C yielded the *ortho*-lithiated species which attacked hexanal to provide the required adducts **13a** and **13b** as two diastereoisomers in 76% total yield (91% based on conversion). Upon treatment of the mixture with Boc_2O the resulting *O*-Boc derivatives **14a** and **14b**,[9] which are easier to isolate on column chromatography, were obtained separately in a ratio of 4.6:1. In 1,4-dioxane containing HCl, pure **14a** and **14b** were converted into enantiomeric lactones **15a** and **15b**, respectively by removal of the *O*-Boc group and subsequent cyclization in one pot, and the excised chiral auxiliary **16** could be recycled to prepare **10** (Scheme 3).

To determine the absolute configuration of the new benzylic chiral center, major isomer **15a** from **13a** was converted into both (*S*)- and (*R*)-*O*-methylmendelate derivatives **17** and **18** in a three-step sequence. The proton shift differences between **17** and **18** (upfield ArMe signal



Scheme 2 Preparation of the chiral amides **10**–**12** from **5**. *Reagents and conditions*: (a) $SOCl_2$, Et_3N, CH_2Cl_2, then L-phenylalaninol, r.t., 92%; (b) NaH (1.5 equiv), MeI (1.5 equiv), THF, r.t., 80% (92% based on conversion); (c) NaH (3.0 equiv), MeI (3.0 equiv), THF, r.t., 73%; (d) 2,2-dimethoxypropane, toluene, reflux, 81%.



Scheme 3 Synthesis of the lactone **15**. *Reagents and conditions*: (a) *t*-BuLi, TMEDA, THF, –78 °C, then warm to 0 °C , hexanal, 76%; (b) Boc_2O, DMAP, MeCN, r.t., 80% (**14a**) and 17% (**14b**); (c) HCl, dioxane, 100 °C, 90% of **15a** from **14a** and 86% of **15b** from **14b**; (d) **5**, $SOCl_2$, Et_3N, CH_2Cl_2, r.t., 93%.

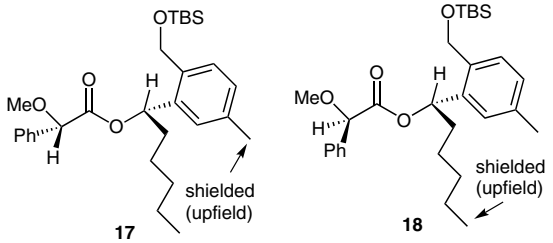
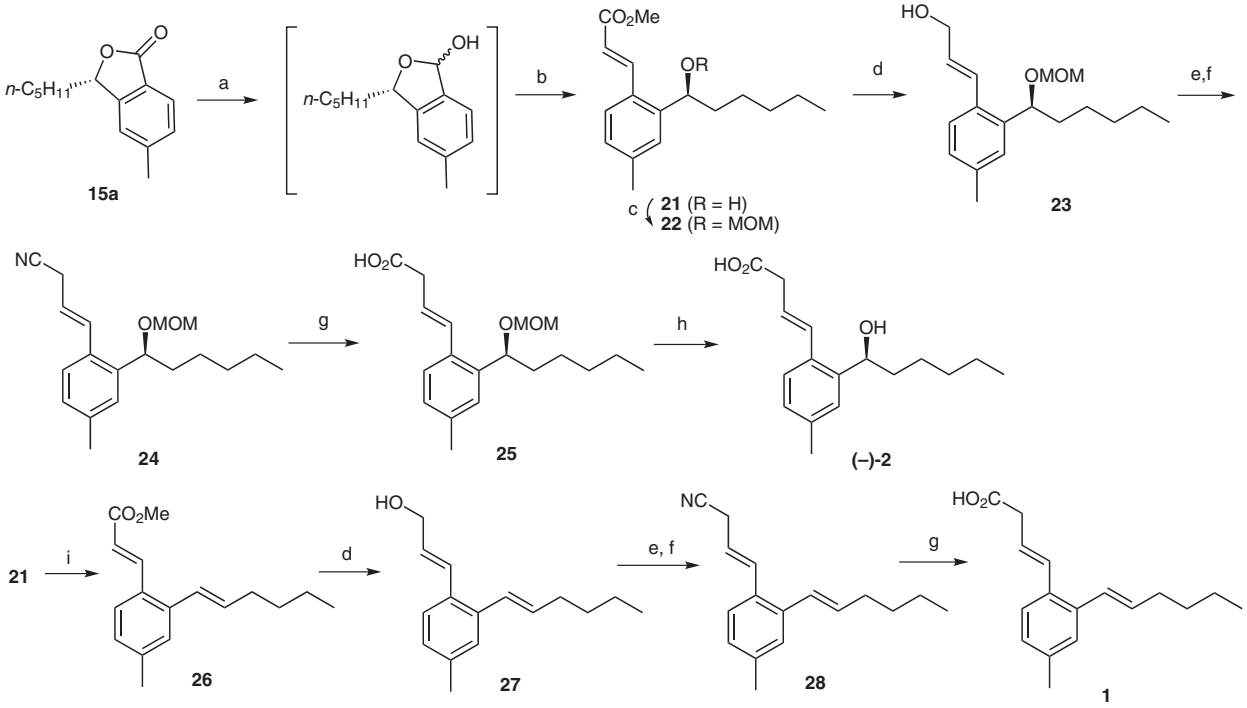


Figure 2

at δ = 2.08 ppm in **17** and upfield side-chain Me signal at δ = 0.86 ppm in **18**)[10] indicated *S* configuration of **15a** and hence that of the major isomer **13a** according to Mosher model extended by Trost (Figure 2).[11]

(*S*)-Phthalide **15a** was then employed to explore the subsequent synthesis (Scheme 4). Phthalide **15a** was reduced with DIBAL to afford two inseparable hemiacetal diastereoisomers (1:1), along with trace amount of aldehyde. The olefination of the hemiacetal mixture with the Wittig reagent derived from (2-carboxyethyl)triphenylphosphonium bromide (**19**)[12] would give the target molecule **2** directly. However, no desired product **2** was detected under the attempted conditions varying bases (NaH, BuLi, *t*-BuOK), solvents (DMSO, THF and their mixture) and feeding sequences. So we had to seek an alternative strategy to accomplish the synthesis. Gratifyingly, the hemiacetal mixture was treated with another stabilized ylide **20**, methyl (triphenylphosphoranylidene)acetate,[13] to provide *E*-α,β-unsaturated ester **21** exclusively in 95% yield, which was transformed to MOM ether **22**. Reduction of conjugated ester **22** with DIBAL gave the required alcohol **23**. Iodination of allyl alcohol **23** with I_2 and PPh_3 afforded the crude iodide[14] (without purification), which was converted immediately into allylic cyanide **24** in 74% yield in two steps.[15] Allylic cyanide **24** also was obtained by treatment of the corresponding methanesulfonate from **23** with lowly toxic CuCN[16] with a slight drop in the overall yield (63%). In aqueous KOH solution nitrile **24** was



Scheme 4 Synthesis of **1** and (–)-**2** from **15**. *Reagents and conditions:* (a) DIBAL, toluene, –78 °C, 98%; (b) **20**, toluene, reflux, 95%; (c) MOMCl, DIPEA, CH_2Cl_2, r.t., 95%; (d) DIBAL, toluene, –78 °C , 97% of **23** from **22**, 96% of **27** from **26**; (e) I_2, Ph_3P, CH_2Cl_2; (f) NaCN, MeCN, 74% of **24** from **23** and 65% of **28** from **27** over two steps; (g) KOH, EtOH–H_2O, reflux, 90% of **25** from **24** and 72% of **1** from **28**; (h) HCl, *t*-BuOH, 40 °C, 91%; (i) TsOH, toluene, reflux, 96%.

smoothly hydrolyzed to carboxylic acid **25**, which upon removal of MOM ether afforded the target acid **2**.[17,18] The optical rotation value of the synthetic **2** consistent with that of the reported **2** means that natural (–)-lorneic acid B has *S* configuration.

For the synthesis of **1**, the mixture of **13a** and **13b** was directly cyclized to furnish the mixed enantiomers **15a** and **15b** in 98% yield, which was converted into **21** and its enantiomer following the above way. Elimination of the benzylic alcohol mixture under acidic conditions gave the desired *trans*-olefin **26** as single isomer. Consistent with the route to **2**, **26** was reduced to furnish the alcohol **27**, which was transformed to nitrile **28** via the allylic iodide intermediate in two steps. Finally, hydrolysis of nitrile **28** yielded the target carboxylic acid **1**.[19]

In summary, we have reported the first synthesis of the natural products **1** and (–)-**2** with rare trialkyl-substituted benzene structure. The key benzylic alcohol was efficiently constructed via stereoselective addition of aryl lithium to hexanal under induction of chiral amide. The facile approach should be amenable to the synthesis of both *S*- and *R*-series lorneic acids and their analogues to further SAR studies. We are further seeking the chiral amides with better asymmetric induction by tuning their groups, and their application in the synthesis of more related natural products.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(9) A solution of **10** (0.13 g, 0.45 mmol) in THF (6 mL) was added to a stirred mixture of *t*-BuLi (0.65 mL, 1.03 mmol) and TMEDA (0.15 mL, 0.99 mmol) in THF (2 mL) at –78 °C. The mixture was warmed to 0 °C and stirred for 5 min, then cooled to –78 °C again. To the mixture a solution of hexanal (0.12 mL, 0.99 mmol) in THF (1 mL) was added and stirred at –78 °C for 30 min. Then the mixture was warmed to r.t. and stirred overnight, quenched with sat. NH_4Cl and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography to afford a mixture of **13a** and **13b** (0.13g, 76%). The mixture of **13a** and **13b** (0.13 g, 0.34 mmol) was dissolved in MeCN (9 mL), then DMAP (12 mg, 0.10 mmol) and Boc_2O (0.26 mL, 1.22 mmol) were added, stirred overnight at r.t. After concentration the residue was purified by column chromatography to afford **14a** (0.13 g, 80%) and **14b** (28 mg, 17%). Compound **14a**: $[\alpha]_D^{25}$ –69 (*c* = 1.2, MeOH). IR (neat): 3326, 2929, 2859, 1739, 1655, 1529, 1370, 1280, 1163, 1089, 1026 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.20–7.28 (m, 8 H), 7.09 (d, *J* = 7.9 Hz, 1 H), 5.88 (dd, *J* = 5.8, 8.0 Hz, 1 H), 4.49–4.53 (m, 1 H), 3.49 (dd, *J* = 4.0, 9.5 Hz, 1 H), 3.39 (dd, *J* = 4.8, 9.5 Hz, 1 H), 3.34 (s, 3 H), 2.97 (dd, *J* = 6.9, 13.6 Hz, 1 H), 2.93 (dd, *J* = 7.5, 13.3 Hz, 1 H), 2.35 (s, 3 H), 1.82–1.88 (m, 1 H), 1.68–1.74 (m, 1 H), 1.42 (s, 9 H), 1.23–1.25 (m, 6 H), 0.84 (t, *J* = 6.6, 13.3 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7, 153.6, 140.2, 138.7, 138.2, 133.2, 129.4, 128.6, 128.4, 127.6, 126.4, 126.3, 82.3, 76.4, 72.7, 58.8, 50.7, 37.6, 37.3, 31.5, 27.8, 25.3, 22.4, 21.4, 14.0. HRMS (ESI^+): *m/z* $[M + Na]^+$ calcd for $C_{29}H_{41}NO_5Na$: 506.2882; found: 506.2880. Compound **14b**: $[\alpha]_D^{25}$ –18 (*c* = 0.4, MeOH). IR (neat): 3328, 2928, 2854, 1739, 1657, 1523, 1370, 1278, 1160, 1089, 1025 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.20–7.33 (m, 8 H), 7.09 (d, *J* = 7.6 Hz, 1 H), 5.43 (t, *J* = 7.0, 14.0 Hz, 1 H), 4.53–4.59 (m, 1 H), 3.46 (dd, *J* = 4.0, 9.6 Hz, 1 H), 3.43 (dd, *J* = 5.9, 10.6 Hz, 1 H), 3.37 (s, 3 H), 3.05 (dd, *J* = 6.9, 13.9 Hz, 1 H), 2.95 (dd, *J* = 8.1, 13.8 Hz, 1 H), 2.33 (s, 3 H), 1.55–1.72 (m, 2 H), 1.46 (s, 9 H), 1.10–1.26 (m, 6 H), 0.82 (t, *J* = 6.9, 14.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7, 153.5, 140.2, 138.4, 138.3, 133.2, 129.3, 128.6, 128.4, 127.9, 126.4, 126.1, 82.4, 76.4, 73.3, 59.0, 50.7, 37.3, 37.1, 31.6, 27.8, 24.8, 22.4, 21.4, 14.1. HRMS (ESI^+): *m/z* $[M + Na]^+$ calcd for $C_{29}H_{41}NO_5Na$: 506.2882; found: 506.2877.

(10) Compound **17**: ^1H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.35 (m, 5 H), 7.13 (d, *J* = 7.7 Hz, 1 H), 6.94 (d, *J* = 7.5 Hz, 1 H), 6.62 (s, 1 H), 5.88 (dd, *J* = 4.2, 9.2 Hz, 1 H), 4.85 (d, *J* = 12.4 Hz, 1 H), 4.78 (s, 1 H), 4.63 (d, *J* = 12.4 Hz, 1 H), 3.39 (s, 3 H), 2.08 (s, 3 H), 1.66–1.85 (m, 2 H), 1.15–1.45 (m, 6 H), 0.90 (s, 9 H), 0.86 (t, *J* = 6.8, 13.4 Hz, 3 H), 0.09 (s, 3 H), 0.05 (s, 3 H). Compound **18**: ^1H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.48 (m, 2 H), 7.30–7.38 (m, 3 H), 7.22 (d, *J* = 7.7 Hz, 1 H), 7.08 (s, 1 H), 7.03 (d, *J* = 7.8 Hz, 1 H), 5.92 (dd, *J* = 4.2, 9.3 Hz, 1 H), 4.90 (d, *J* = 12.4 Hz, 1 H), 4.75 (s, 1 H), 4.67 (d, *J* = 12.4 Hz, 1 H), 3.37 (s, 3 H), 2.29 (s, 3 H), 1.61–1.77 (m, 2 H), 1.01–1.08 (m, 6 H), 0.91 (s, 9 H), 0.78 (t, *J* = 6.5, 13.4 Hz, 3 H), 0.10 (s, 3 H), 0.06 (s, 3 H).

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(17) **Synthesis of (–)-2**: A solution of **25** (35.3 mg, 0.11 mmol) in *t*-BuOH (3 mL) containing concd HCl (0.3 mL) was stirred at 40 °C for 6 h. After cooling, the mixture was extracted with EtOAc. The extract was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography to afford (–)-**2** as a colorless oil (27.7 mg, 91%); $[\alpha]_D^{21}$ –20 (*c* = 0.3, MeOH). IR (neat): 3405, 2928, 2861, 1710, 1613, 1458, 1398, 1206, 1061, 958 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ = 7.32 (d, *J* = 8.0 Hz, 1 H), 7.26 (s, 1 H), 7.01 (d, *J* = 7.7 Hz, 1 H), 6.81 (d, *J* = 15.6 Hz, 1 H), 6.12 (dt, *J* = 7.1, 15.6 Hz, 1 H), 4.94 (t, *J* = 6.5, 13.2 Hz, 1 H), 3.22 (d, *J* = 7.1 Hz, 2 H), 2.32 (s, 3 H), 1.64–1.67 (m, 2 H), 1.30–1.42 (m, 6 H), 0.90 (t, *J* = 6.8, 11.4 Hz, 3 H). ^{13}C NMR (100 MHz, CD_3OD): δ = 175.6, 143.4, 138.4, 133.5, 131.8, 128.8, 127.4, 127.3, 124.8, 71.3, 39.7, 39.2, 32.9, 26.7, 23.7, 21.4, 14.4. HRMS (ESI^+): *m/z* $[M + NH_4]^+$ calcd for $C_{17}H_{28}NO_3$: 294.2064; found: 294.2057.

(18) It is noteworthy that slight concentration-dependent changes in the chemical shifts of the signals of the unsaturated carboxyl acid chain were observed in NMR spectra of **2**, owing to variable aggregation extent via carboxyl group (see Supporting Information).

(19) **Synthesis of 1**: A solution of 28 (91 mg, 0.38 mmol) and KOH (0.31 g) in 30% EtOH–H_2O (5 mL) was stirred for 8 h at 100 °C. After cooling to r.t., the mixture was acidified with 3 M HCl acid to pH 3, and was extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography to afford **1** (70 mg, 72%) as a pale yellow oil. IR (neat): 2958, 2928, 2855, 1709, 1605, 1460, 1222, 1163, 1094, 965 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 7.9 Hz, 1 H), 7.18 (s, 1 H), 6.98 (d, *J* = 8.4 Hz, 1 H), 6.74 (d, *J* = 15.7 Hz, 1 H), 6.59 (d, *J* = 15.6 Hz, 1 H), 6.09 (dt, *J* = 6.9, 15.6 Hz, 1 H), 6.04 (dt, *J* = 7.0, 15.6 Hz, 1 H), 3.28 (d, *J* = 6.9 Hz, 2 H) 2.31 (s, 3 H), 2.23 (q, *J* = 6.8 Hz, 2 H), 1.33–1.48 (m, 4 H), 0.93 (t, *J* = 7.2, 14.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.5, 137.2, 136.0, 133.6, 131.9, 131.5, 127.8, 127.5, 127.0, 126.4, 122.4, 38.8, 33.0, 31.6, 22.3, 21.2, 14.0. HRMS (ESI^+): *m/z* $[M + H]^+$ calcd for $C_{17}H_{23}O_2$: 259.1693; found: 259.1687.

