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Intramolecular-Prins-cyclization: a novel synthesis of hexahydro-2*H*-furo[3,2-*c*]pyran derivatives

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ABSTRACT

p-Toluenesulfonic acid is found to catalyze the coupling of (*Z*)-hex-3-ene-1,6-diol with a series of aldehydes by means of intramolecular-Prins-cyclization to provide the corresponding hexahydro-2*H*-furo[3,2-*c*]pyran derivatives in good yields with complete cis-selectivity, whereas the coupling of (*E*)-hex-3-ene-1,6-diol with aliphatic aldehydes gave trans-fused bicyclic furopyrans.

The furano- and pyrano[3,2-*c*]pyran skeleton is frequently found in various natural products such as flavonoids, catechins, and pterocarpans (Fig. 1).[1,2] They are generally prepared through *o*-quinonemethides generated in situ from *o*-hydroxybenzaldehydes and alkenols. This method provides a useful access to fused pyranobenzopyrans.[3]

The Prins cyclization is an important transformation to generate a wide range of tetrahydropyrans, usually with net addition of an external nucleophile to the resulting carbocation.[4] Recently, an intramolecular addition of –COOH tethered to a homoallylic alcohol onto the carbocation has been reported to terminate Prins cyclizations.[5] However, the scope of this process has not been explored with a homoallylic alcohol bearing terminal hydroxyl group,[5] hence an efficient and practical methodology for a Prins cyclization would be of importance for natural product synthesis. *p*-TSA is being used as a protic acid for various organic transformations.[6] The mild Brønsted acidity associated with *p*-TSA enhances its use at levels from stoichiometric to catalytic, as a powerful reagent for various organic transformations.[7]

In continuation of our interest on Prins type cyclization and its applications in the total synthesis of natural products,[8] we herein report a novel method for the synthesis of bicyclic furopyrans by means of intramolecular-Prins-cyclization of aldehydes with hex-3-ene-1,6-diol. Initially, we have attempted the coupling of 4-bromobenzaldehyde (**1**) with (*Z*)-hex-3-ene-1,6-diol (*Z*-**2**) in the presence of 10 mol % of *p*-TSA in 1,2-dichloroethane under reflux conditions. The reaction went to completion in 10 h and the product **3c** was obtained in 72% yield with complete cis-selectivity (Scheme 1).

The structure of **3c** was established by NOE experiments. The coupling between H1 and H2 is 3.3 Hz, and this indicates that H2 is in equatorial position. Also the presence of NOE's between H1

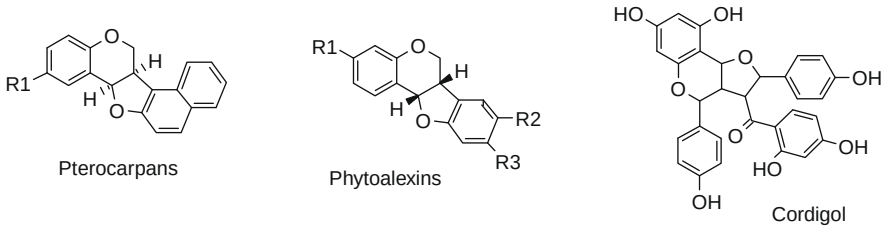

Figure 1. Examples of natural products bearing furano[3,2-*c*]pyran skeleton.

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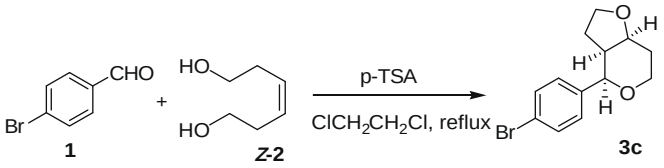


Scheme 1.

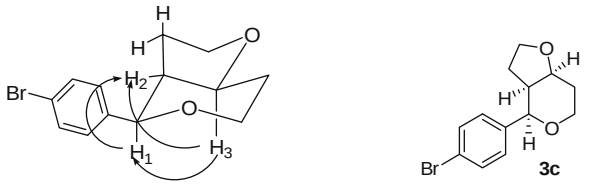


Figure 2. Characteristic NOE's and chemical structure of **3c**.

& H2, H2 & H3, and H1 & H3 confirms the position of protons as shown in Figure 2.

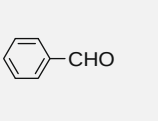
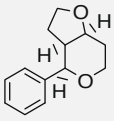
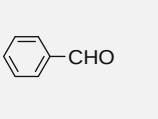
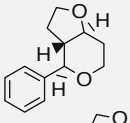
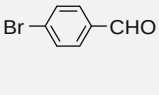
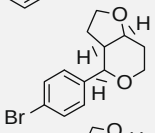
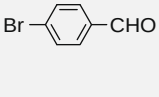
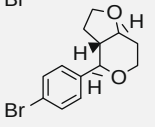
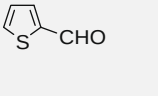
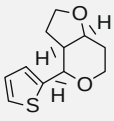
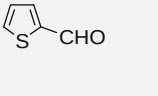
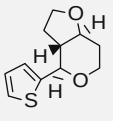
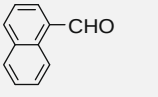
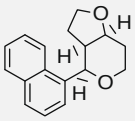
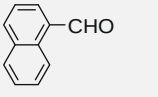
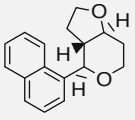
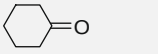
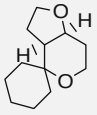
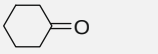
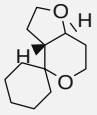
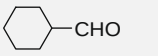
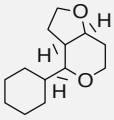
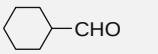
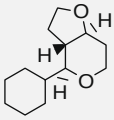
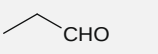
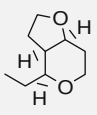
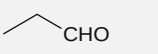
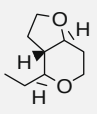
This result prompted us to extend this process for various aldehydes. Interestingly, aromatic aldehydes such as benzaldehyde, thiophene-2-carboxaldehyde, and 2-naphthaldehyde participated well in this reaction (Table 1, entries **a**, **b**, **e**–**h**). In the case of aromatic aldehydes, the desired products were obtained in high yields. Next, we have studied the reactivity of aliphatic aldehydes. However, aliphatic aldehydes gave lower yields than aromatic counter parts (Table 1, entries **k**–**n**). Similarly, ketones such as cyclohexanone also gave lower yields than aromatic aldehydes (Table 1, entries **i** and **j**). To know the effect of cis and trans geometry of the olefin in product distribution, we have attempted the coupling of (*E*)-hex-3-ene-1,6-diol (*E*-**2**) with aromatic aldehydes. Surprisingly, the coupling of (*E*)-hex-3-ene-1,6-diol with *p*-bromobenzaldehyde gave the product as a mixture of *trans*-**3d** and *cis*-**3c** diastereomers. These diastereomers could not be separated by column chromatography. The *cis*–*trans* ratio was determined by ^{1}H NMR spectra of the crude as well as pure product. In all reported cases, the use of (*E*)-hex-3-ene-1,6-diol gave the products in 10:1 ratio. In the case of **3d**, the coupling between H1 and H2 is 9.9 Hz which indicates that H2 is in axial position. Also the absence of NOE's between H1 &H2 and H2 & H3 and the presence of NOE's between H1 and H3 confirm the positions of protons as shown in Figure 3.

The effects of various acid catalysts such as camphorsulfonic acid (CSA) and Amberlyst-15® were studied for this conversion. Of these, *p*-TSA was found to give the best results in terms of yields. The reaction was performed in various solvents such as 1,2-dichloroethane, toluene, tetrahydrofuran, and acetonitrile. Among these, 1,2-dichloroethane was found to give high conversions. This method utilizes easily accessible precursors and inexpensive *p*-TSA. This method is simple and convenient and also provides the desired products in good yields with high stereoselectivity.[9] No improvement in yield was observed either by increasing the reaction time or by catalyst loading.

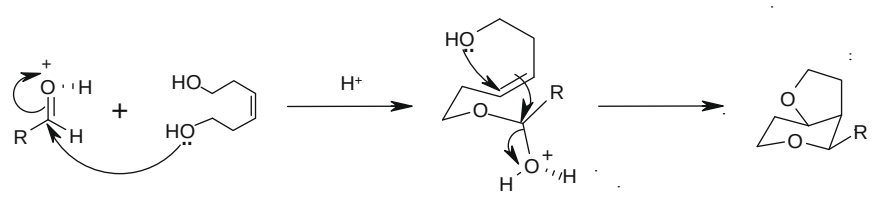
Probably, the reaction proceeds by hemi-acetal formation from aldehyde and homoallylic alcohol. The resulting hemi-acetal may undergo cyclization with olefin followed by the trapping of the resulting carbocation by terminal hydroxyl group leading to the formation of furopyrans (Scheme 2).

In conclusion, we have described an efficient approach for the synthesis of bicyclic hexahydro-2*H*-furopyrans by means of intramolecular-Prins-cyclization. This is an elegant and highly diastereoselective method to accomplish the synthesis of a series of angularly fused furopyrans in a single-step operation. The use of

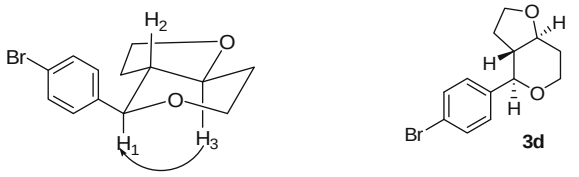
Table 1
p-TSA catalyzed synthesis of 2-substituted furanopyrans

Entry	Olefin	Aldehyde	Product[a]	Time (h)	Yield[b] (%)
a	*Z*			17	54
b	*E*			14	52
c	*Z*			10	72
d	*E*			10	74
e	*Z*			16	71
f	*E*			8.0	43
g	*Z*			10	72
h	*E*			8.0	65
i	*Z*			24	57
j	*E*			17	62
k	*Z*			11	62
l	*E*			7.0	57
m	*Z*			6.0	45
n	*E*			4.0	40

[a] The products were characterized by NMR, IR, and mass spectroscopy.
[b] Yield refers to pure products after chromatography.



Scheme 2.



3d

Figure 3. Characteristic NOE's and chemical structure of **3d**.

p-toluenesulfonic acid makes this method simple, convenient, and economically viable for large scale synthesis.

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9. *Experimental procedure*: To a solution of diol (58 mg, 0.50 mmol) and *p*-bromobenzaldehyde (138 mg, 0.750 mmol) in anhydrous 1,2-dichloroethane (4 mL) was added *p*-TSA (5 mg, 10 mol %), and it was refluxed for 10 h. The organic layer was washed with brine (4 × 2 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting crude product was purified by column chromatography using ethyl acetate/hexane to afford pure product. The spectral data for products: Compound **3a**: (3a*S*,4*R*,7a*S*)-4-phenylhexahydro-2*H*-furo[3,2-*c*]pyran: liquid, IR (KBr): ν_{max} 2926, 2847, 771 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.1–7.4 (m, 5H), 4.72 (d, *J* = 2.9 Hz, 1H), 4.04–4.33 (m, 2H), 3.92 (dt, *J* = 9.5, 2.9 Hz, 1H), 3.70 (q, *J* = 8.1 Hz, 1H), 3.48 (dt, *J* = 11.7, 3.7 Hz, 1H), 2.38–2.60 (m, 1H), 1.54–2.03 (m, 3H), 1.21–1.41 (m. 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.4, 128.2, 126.9, 125.0, 77.3, 74.9, 66.4, 65.6, 44.4, 28.4, 23.9; MS (APCI): *m*/*z*: 205 $(M+H)^+$; HRMS (APCI) calcd for $C_{13}H_{17}O_2$ $[M+H]^+$: 205.1229, found: 205.1232.
Compound **3b**: (liquid; IR (KBr): ν_{max} 2930, 2855, 1059 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.14–7.36 (m, 5H), 4.23 (ddd, *J* = 11.8, 4.7, 1.5 Hz, 1H), 4.14 (d, *J* = 9.0 Hz, 1H), 3.74–3.95 (m, 2H), 3.52 (dt, *J* = 11.9, 2.3 Hz, 1H), 3.25–3.37 (m, 1H), 2.05–2.15 (m, 1H), 1.5–1.88 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.3, 128.2, 127.7, 126.0, 82.9, 80.7, 66.1, 65.6, 50.3, 32.5, 27.1; MS (APCI): *m*/*z*: 205 $(M+H)^+$; HRMS (APCI) calcd for $C_{13}H_{17}O_2$ $[M+H]^+$: 205.1229, found: 205.1236.
Compound **3c**: (3a*S*,4*R*,7a*S*)-4-(4-bromophenyl)hexahydro-2*H*-furo[3,2-*c*]pyran: liquid; IR (KBr): ν_{max} 2925, 2850, 1062 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.3 Hz, 2H), 7.16 (d, *J* = 8.3 Hz, 2H), 4.68 (d, *J* = 3.3 Hz, 1H), 4.18–4.29 (m, 1H), 4.05–4.16 (m, 1H), 3.92 (dt, *J* = 9.4, 2.5 Hz, 1H), 3.72 (q, *J* = 8.5 Hz, 1H), 3.47 (dt, *J* = 11.8, 2.8 Hz, 1H), 2.40–2.54 (m, 1H), 1,56–1.95 (m, 3H), 1.23–1,38 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.5, 131.2, 126.7, 120.6, 76.5, 74.7, 66.3, 65.5, 44.1, 28.2, 23.7; MS: *m*/*z*: 283 $[M+H]^+$. HRMS (APCI) calcd for $C_{13}H_{16}O_2Br$ $[M+H]^+$: 283.0334, found: 283.0330.
Compound **3d**: liquid; IR (KBr): ν_{max} 2930, 2855, 1063, 771 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.45 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 4.22 (ddd, *J* = 11.7, 5.1, 1.5 Hz, 1H), 4.12 (d, *J* = 9.9 Hz, 1H), 3.68–3.97 (m, 2H), 3.52 (dt, *J* = 12.1, 2.4 Hz,1H), 3.23–3.38 (m, 1H), 2.03–2.18 (m, 1H), 1.42–1.9 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.6, 131.4, 127.8, 121.6, 82.4, 80.8, 66.2, 65.8, 50.4, 32.6, 27.2; MS: *m*/*z*: 283 $[M+H]^+$. HRMS (APCI) calcd for $C_{13}H_{16}O_2Br$ $[M+H]^+$: 283.0334, found: 283.0339.
Compound **3e**: (3a*S*,4*R*,7a*S*)-4-(thiophen-2-yl)hexahydro-2*H*-furo[3,2-*c*]pyran: liquid; IR (KBr): ν_{max} 2926, 2862, 1057, 702 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.23 (d, *J* = 5.8 Hz, 1H), 6.88–7.01 (m, 2H), 4.30 (d, *J* = 10.2 Hz, 1H), 3.73–4.11 (m, 5H), 2.26–2.43 (m, 1H), 1.90–2.15 (m, 3H), 1.57–1.79 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.3, 126.2, 125.2, 75.1, 66.1, 63.5, 44.0, 28.7, 27.5; MS: *m*/*z*: 211 $[M+H]^+$. HRMS (APCI) calcd for $C_{11}H_{15}O_2S$ $[M+H]^+$: 211.0793, found: 211.0801.
Compound **3f**: liquid; IR (KBr): ν_{max} 2930, 2882, 1051, 771 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.19–7.27 (m, 1H), 6.89–6.97 (m, 2H), 4.44 (d, *J* = 9.0 Hz, 1H), 4.21 (ddd, *J* = 6.8, 5.2, 1.5 Hz, 1H), 3.84–3.94 (m, 2H), 3.54 (dt, *J* = 12.0 and 2.2 Hz, 1H), 3.23–3.34 (m, 1H), 2.03–2.13 (m, 1H), 1.55–1.96 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.6, 126.4, 125.0, 124.3, 80.7, 78.7, 66.4, 65.9, 50.8, 32.4, 27.5; MS (APCI): *m*/*z*: 211 $(M+H)^+$; HRMS (APCI) calcd for $C_{11}H_{15}O_2S$ $[M+H]^+$: 211.0793, found: 211.0794.
Compound **3g**: (3a*S*,4*R*,7a*S*)-4-(naphthalene-2-yl)hexahydro-2*H*-furo[3,2-*c*]pyran: liquid; IR (KBr): ν_{max} 2924, 2852, 754 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.71–7.83 (m, 4H), 7.32–7.49 (m, 3H), 4.89 (d, *J* = 3.0 Hz, 1H), 4.24–4.35 (m, 1H), 4.13–4.23 (m, 1H), 3.93 (dt, *J* = 9.8, 3.0 Hz, 1H), 3.71 (q, *J* = 8.3 Hz, 1H), 3.55 (dt, *J* = 12.0, 3.0 Hz, 1H), 2.55–2.70 (m, 1H), 1.85–2.04 (m, 1H), 1.62–1.85 (m, 2H), 1.22–1.37 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.9, 133.2, 132.5, 127.9, 127.8, 127.5, 125.9, 125.5, 123.4, 123.3, 77.1, 74.8, 66.3, 65.6, 44.2, 28.3, 23.9; MS (APCI): *m*/*z*: 255 $(M+H)^+$; HRMS (APCI) calcd for $C_{17}H_{19}O_2$ $[M+H]^+$: 255.1385, found: 255.1385.
Compound **3h**: liquid; IR (KBr): ν_{max} 2927, 2853, 1057, 771 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.70–7.86 (m, 4H), 7.34–7.50 (m, 3H), 4.211–4.36 (m, 2H), 3.76–3.97 (m, 2H), 3.58 (dt, *J* = 12.1, 2.2 Hz, 1H), 3.26–3.44 (m, 1H), 2.06–2.21 (m, 1H), 1.58–1.57 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.9, 133.2, 133.0, 128.1, 127.9, 127.5, 126.0, 125.8, 124.9, 124.1, 83.2, 81.0, 66.3, 65.8, 50.5, 32.7, 27.3; MS (APCI): *m*/*z*: 255 $(M+H)^+$; HRMS (APCI) calcd for $C_{17}H_{19}O_2$ $[M+H]^+$: 255.1385, found: 255.1391.
Compound **3i**: (3a′*S*,7a′*S*)-hexahydrospiro[cyclohexane-1,4′-furo[3,2-*c*]pyran: liquid; IR (KBr): ν_{max} 2930, 2857, 1079, 772 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.09–4.21 (m, 1H), 3.88–4.00 (m, 1H), 3.71–3.84 (m, 1H), 3.58–3.69 (m, 1H), 3.50 (dt, *J* = 11.7, 3.7 Hz, 1H), 1.93–2.08 (m, 2H), 1.74–1.87 (m, 1H), 1.18–1.71 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 72.9, 66.1, 57.5, 46.0, 36.0, 34.0, 28.1, 25.7, 21.6, 21.5, 21.4; MS (APCI): *m*/*z*: 197 $(M+H)^+$; HRMS (APCI) calcd for $C_{12}H_{21}O_2$ $[M+H]^+$: 197.1536, found: 197.1543.
Compound **3j**: liquid; IR (KBr): ν_{max} 2929, 2855, 772 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.73–3.90 (m, 3H), 3.30–3.52 (m, 2H), 0.94–2.14 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 76.6, 75.2, 66.1, 59.0, 53.3, 38.5, 33.6, 26.5, 26.0, 24.7, 21.1, 20.4; MS (APCI): *m*/*z*: 197 $(M+H)^+$; HRMS (APCI) calcd for $C_{12}H_{21}O_2$ $[M+H]^+$: 197.1536, found: 197.1531.
Compound **3k**: (3aS,4S,7aS)-4-cyclohexylhexahydro-2*H*-furo[3,2-*c*]pyran: liquid; IR (KBr): ν_{max} 2923, 2850, 771 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 3.74–4.11 (m, 4H), 3.10–3.27 (m, 2H), 2.16–2.31 (m, 1H), 1.88–2.16 (m, 2H), 1.44–1.85 (m, 7H), 1.09–1.43 (m, 4H), 0.78–1.00 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 80.5, 75.2, 66.3, 65.4, 41.0, 40.2, 30.2, 28.7, 28.4, 26.5, 26.0, 25.6, 22.8; MS (APCI): *m*/*z*: 211 $(M+H)^+$; HRMS (APCI) calcd for $C_{13}H_{23}O_2$ $[M+H]^+$: 211.1693, found: 211.1687.
Compound **3l**: liquid; IR (KBr): ν_{max} 2925, 2853, 772 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.01–4.11 (m, 1H), 3.81–3.90 (m, 2H), 3.29 (dt, *J* = 11.9, 2.3 Hz, 1H), 3.05–3.17 (m, 1H), 2.97 (dd, *J* = 9.5, 3.1 Hz, 1H), 1.90–2.04 (m, 2H), 1.05–1.85 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 85.1, 81.5, 66.4, 65.4, 45.9, 42.0, 32.7, 29.5, 27.4, 27.3, 26.5; MS (APCI): *m*/*z*: 211 $(M+H)^+$; HRMS (APCI) calcd for $C_{13}H_{23}O_2$ $[M+H]^+$: 211.1693, found: 211.1701.
Compound **3m**: (3a*R*,4*S*,7a*S*)-4-ethylhexahydro-2*H*-furo[3,2-*c*]pyran: liquid; IR (KBr): ν_{max} 2924, 2854, 772 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.70–4.17 (m, 4H), 3.37–3.50 (m, 1H), 3.26 (dt, *J* = 11.7, 2.9 Hz, 1H), 1.29–2.29 (m, 7H), 0.96 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 77.5, 74.9, 66.4, 65.2, 42.0, 28.7, 27.2, 23.0, 10.2; MS (APCI): *m*/*z*: 157 $(M+H)^+$; HRMS (APCI) calcd for $C_9H_{17}O_2$ $[M+H]^+$: 157.1229, found: 157.1230.
Compound **3n**: liquid; IR (KBr): ν_{max} 2929, 2859, 1030 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 4.07 (ddd, *J* = 6.6, 5.1 and 1.4 Hz, 1H), 3.88 (d, *J* = 5.8 Hz, 1H), 3.84 (d, *J* = 5.1 Hz 1H), 3.32 (dt, *J* = 11.7, 2.2 Hz 1H), 2.98–3.21 (m, 2H), 1.84–2.08 (m, 2H), 1.17–1.75 (m, 5H), 0.96 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 82.1, 81.0, 66.5, 65.4, 48.7, 32.7, 27.6, 27.0, 9.7; MS (APCI): *m*/*z*: 157 $(M+H)^+$; HRMS (APCI) calcd for $C_9H_{17}O_2$ $[M+H]^+$: 157.1229, found: 157.1233.