A Facile Total Synthesis of All Stereoisomers of Tarchonanthuslactone and Euscapholide from Chiral Epichlorohydrin

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Abstract: A versatile and facile synthetic route to all the stereoisomers of tarchonanthuslactone and euscapholide was developed using epichlorohydrin as the source of all the chiral centers.

Key words: tarchnanthuslactone, euscapholide, epichlorohydrin, diversity, total synthesis

Natural products that contain α,β-unsaturated δ-lactone moiety possess a wide range of biological activities presumably due in part their electrophilic nature as Michael acceptors.[1] While euscapholide (**1d**)[2] that was isolated along with its glucoside from leaves of *Euscaphis japonica* shows the anti-inflammatory activity, its analogue 3,7-dihydroxy-5-octenolide that lacks the Michael acceptor does not show any anti-inflammatory activity.[3] A related natural product, tarchonanthulactone (**4a**)[4] that was isolated from *Tarchonanthustrilobus compositae* shows the antidiabetic activity.[5] Structurally related compounds shown in Figure 1 have interesting biological activities such as anticancer (kurzilactone),[6] antimicobacterial (passifloricin A),[7] and antigerminating activity (cryptocarya diacetate).[8]

Due to these interesting biological activities and subtleties in stereostructures, there have been many reports on the total synthesis of these natural products.[9] The stereoselective syntheses either confirmed or revised initially assigned structures.[10] Diversity-oriented synthesis was also devised to confirm the structures of natural products and to study biological activities of analogues of the natural products.[11] While most synthetic approaches focused on stereoselective synthesis of the natural isomers of these

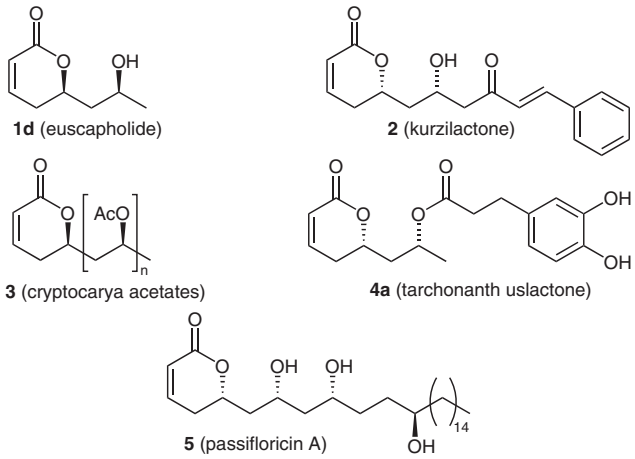
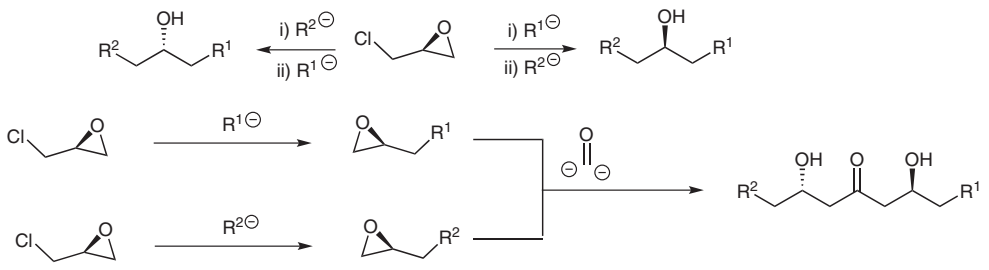


Figure 1

natural products, only a few versatile approaches to these natural products and analogues were reported.[12] Related diversity-oriented synthesis focused on the solid-supported synthesis rather than versatile synthesis. We became interested in devising a practical, versatile, and yet stereoselective route to these natural products and their stereoisomers and decided to utilize epichlorohydrin as the source of chiral alcohols.

Epichlorohydrin could be a versatile source for the synthesis of various polyhydroxylated natural products and their diastereomers since a single stereoisomer of epichlorohydrin can be utilized to generate either isomer of a chiral carbinol center. Depending on the order of nucleophilic addition to epichlorohydrin both *R*- and *S*-isomeric



Scheme 1 Versatility of epichlorohydrin

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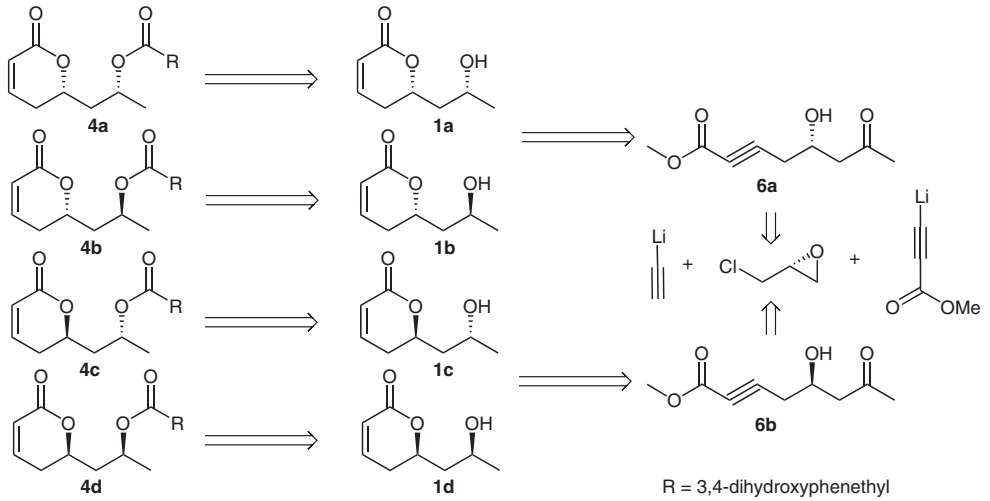


Scheme 2 Synthetic analysis for all diastereomers of tarchonanthuslactone and euscapholide

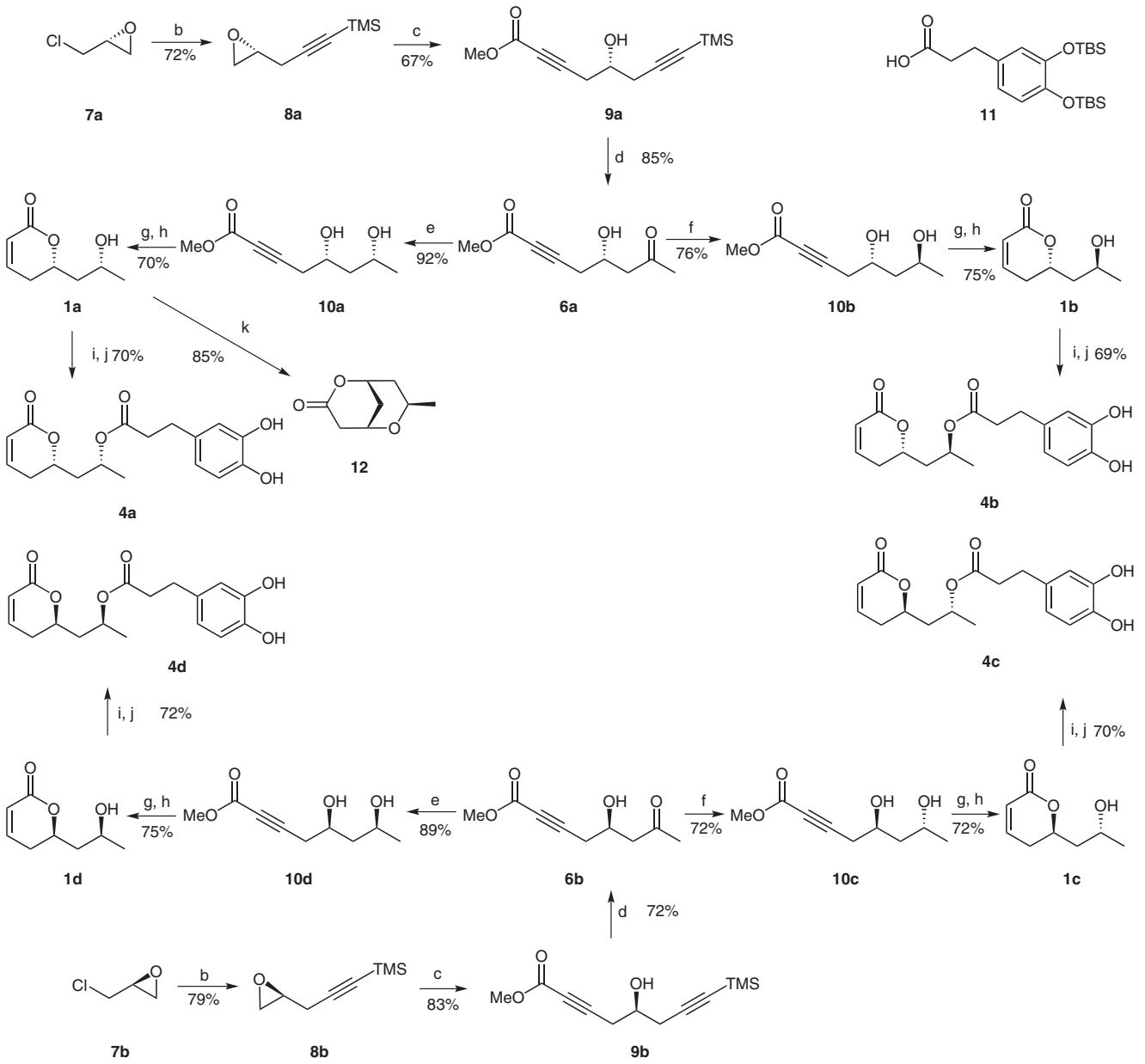
alcohols can be prepared. A carbonyl dianion equivalent like dithiane anion can connect two epichlorohydrin together to produce 1,3,5-triols stereoselectively (Scheme 1) and again depending on the reaction order and subsequent reactions,[13c] all the diastereomers of 1,3,5-triols can be synthesized. Even with this clear advantage of epichlorohydrin in stereoselective synthesis, epichlorohydrins have not been used widely in total synthesis presumably due to scarcity of enantiomerically pure epichlorohydrin.[13] That situation changed recently as enantiomerically pure epichlorohydrin became readily available as Jacobsen's kinetic resolution provided an efficient route to both enantiomers of epichlorohydrin.[14] We envisioned that the polyhydroxylated compounds represented in Figure 1 and their stereoisomers can be synthesized from epichlorohydrin and acyl anion equivalents.

As the first example of our synthetic strategy utilizing epichlorohydrin, we devised a synthetic route to tarchonanthuslactone and all diastereomers via euscapholide and its diastereomers. Tarchonanthuslactone and euscapholide have an interesting relationship as they exhibit opposite stereostructures at the chiral centers. To make both natural products efficiently, a versatile asymmetric synthetic route is necessary and epichlorohydrin appeared to be the good starting material for that purpose. The unsaturated lactone ring can be assembled through stereoselective partial reduction of propynoate, and another alcohol can be prepared from corresponding terminal alkyne. This bisalkynyl intermediate **9a** (or **9b**) can be prepared stereoselectively from the chiral epichlorohydrin and two acetylide anions (Scheme 2).

Though all the isomers of euscapholide or tarchonanthuslactone could be synthesized from either isomer of epichlorohydrin, synthesis of tarchonanthuslactone (**4a**) and **4b** started from (*R*)-epichlorohydrin via **1a** and **1b**, respectively, and the synthesis of the other diastereomers of tarchnanthuslactone **4c** and **4d** started from (*S*)-epichlorohydrin via **1c** and euscapholide (**1d**).

Reaction of (*R*)-epichlorohydrin (**7a**) with lithium salt of TMS-acetylene in the presence of $BF_3{\cdot}OEt_2$ produced the halohydrin in 91% yield.[15] The halohydrin was isolated to ensure the stereochemistry of the corresponding epoxide **8a**, since direct conversion of epichlorohydrin into **8a** could lead to ambiguity of stereochemical purity of the epoxide **8a**; that is, a possible direct substitution of chloride by acetylide anion as the outcome of direct substitution would produce the enantiomer of **8a**.[13a] After the epoxide **8a** was obtained from halohydrin, the second acetylide anion, the anion of propynoate was added to **8a** using Yamaguchi conditions[16] to furnish the bisalkynyl ester **9a** in 67% yield.[17]

At this stage we anticipated that the mercury-mediated hydration of the terminal alkyne would be kinetically favorable to conjugated internal alkyne ,though conjugated internal alkyne was reported to be hydrated to the corresponding β-ketoester.[18] Initially, the silyl group of **9a** was deprotected before mercury-mediated hydration reaction to facilitate the selective hydration of the terminal alkyne. To our delight, selective hydration of the terminal alkyne was achieved though the yield was moderate. When the intermediate **9a** was subjected directly to the hydration reaction without deprotection of the silyl group,[19] still the methyl ketone **6a** was obtained selectively in 85% yield. The silyl group of the alkyne might have facilitated the hydration reaction as it would stablilize cationic intermediate.[20] The ketone of **6a** was reduced under chelation control using diethylmethoxyborane and $NaBH_4$ to furnish *syn*-1,3-diol **10a** as a single diastereomer.[21] The partial reduction of alkynoate **10a** using Lindlar catalyst provided the *Z*-olefin in 81% yield.[22] Lactone formation was accomplished using catalytic amount of PTSA in benzene to afford (–)-euscapholide (**1a**)[2] in 86% yield. The spectral data and optical rotation of **1a** matched well with the reported ones. Finally, tarchonanthuslactone was prepared from **1a** in a well-established, two-step sequence. When the ketone of **6a** was reduced by $NaBH(OAc)_3$ through intramolecular delivery of a hydride, *anti*-1,3-



Scheme 3 *Reagents and conditions:* (a) TMSCCLi, $BF_3{\cdot}Et_2O$, THF; (b) NaOH, CH_2Cl_2; (c) LiCCCOOMe, $BF_3{\cdot}Et_2O$, THF; (d) $HgSO_4$, H_2SO_4, THF, r.t.; (e) $NaBH_4$, Et_2BOMe, THF–MeOH, –78 °C (f) $NaBH(OAc)_3$, MeCN–AcOH (2:1), –40 °C; (g) H_2, Pd/$CaCO_3$, quinoline, benzene, r.t.; (h) PTSA, benzene; (i) **11**, DCC, DMAP, CH_2Cl_2; (j) TBAF, PhCOOH, THF; (k) DBU, CH_2Cl_2.

diol **10b** was obtained selectively in 76% yield. The *anti*-diol **10b** was converted into a diastereomer of tarchnanthuslactone (**4b**) via a diastereomer of euscapholide **1b**. A tetraketide **12**[23] was also synthesized using DBU in dichloromethane. The natural euscapholide (**1d**) and other isomers of tarchonanthuslactone were synthesized from (*S*)-epichlorohydrin following the same synthetic sequence. While these compounds could have been synthesized from (*R*)-epichlorohydrin by simply altering the reaction sequence in the first two epoxide opening steps, we decided to use (*S*)-epichlorohydrin as the starting material to avoid a possible complication with ester group during the second epoxide-opening reaction with lithium acetylide (Scheme 3). Thus, we completed the synthesis of all four diastereomers of tarchonanthuslactone and euscapholide.

In conclusion, we demonstrated that an efficient total synthesis of tarchonanthuslactone and euscapholide along with all of their diastereomers in a nine-step sequence and seven-step sequences, respectively, from enantiomerically pure epichlorohydrins. The current total synthesis is not only the shortest total synthesis of the natural product among the reported synthesis but so versatile that tarchonanthuslactone and euscapholide with opposite stereochemistry at the chiral centers were synthesized through the same reaction sequence. Since the synthetic scheme was simple, straightforward, and versatile, the current synthetic strategy using chiral epichlorohydrin would

readily be applicable to the total synthesis of other natural products along with their stereoisomers.

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(17) All new compounds showed satisfactory analytical data for the assigned structure and purity. Spectroscopic Data for Selected Compounds
Compound **1d**: $[\alpha]_D$ +142.8 (*c* 0.55, $CHCl_3$), lit.[2] $[\alpha]^{30}$ +115.5 (*c* 1.52, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.88–6.84 (dt, *J* = 10.1, 3.4 Hz, 1 H), 6.01–5.98 (dt, *J* = 9.8, 1.8 Hz, 1 H), 4.65–4.58 (m, 1 H), 4.09–4.04 (m, 1 H), 2.40–2.37 (m, 2 H), 2.02–1.95 (m, 1 H), 1.77–1.72 (dt, *J* = 12.6, 4.1 Hz, 1 H), 1.23 (d, *J* = 6.3 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.9, 145.1, 121.2, 76.8, 65.2, 43.6, 29.5, 23.7.
Compound **1a**: $[\alpha]_D$ –115.5 (*c* 0.17, $CHCl_3$), lit.[22] $[\alpha]^{25}$ –111 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.89–6.84 (ddd, *J* = 13.9, 6.7, 4.6 Hz, 1 H), 6.01–5.97 (dt, *J* = 9.7, 1.7 Hz, 1 H), 4.65–4.58 (m, 1 H), 4.08–4.03 (m, 2 H), 2.40–2.36 (m, 2 H), 2.07 (br, 1 H), 2.02–1.95 (m, 1 H), 1.76–1.71 (dt, *J* = 12.6, 4.2 Hz, 1 H), 1.23 (d, *J* = 6.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.0, 145.2, 121.2, 76.8, 65.2, 43.5, 29.4, 23.7.
Compound **4a**: $[\alpha]_D$ –76.2 (*c* 0.22, $CHCl_3$), $[\alpha]^{25}$ –76 (*c* 0.6, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.81–6.78 (ddd, *J* = 10.0, 5.0, 2.4 Hz, 1 H), 6.73–6.70 (m, 2 H), 6.59–6.56 (dd, *J* = 8.1, 2.0 Hz, 1 H), 5.99–5.96 (ddd, *J* = 10.0, 3.0, 1.0 Hz, 1 H), 5.05–5.01 (m, 1 H), 4.16 (m, 1 H), 2.81 (t, *J* = 6.5 Hz, 2 H), 2.58 (t, *J* = 7.2 Hz, 2 H), 2.29 (m, 1 H), 2.20 (m, 1 H), 2.04–2.01 (m, 1 H), 1.76–1.70 (m, 1 H), 1.23 (d, *J* = 6.3 Hz, 3 H), 0.95 (s, 9 H), 0.94 (s, 9 H), 0.15 (s, 6 H), 0.14 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7, 165.0, 145.4, 143.9, 142.2, 132.8, 120.9, 120.4, 115.4, 115.2, 75.2, 67.0, 41.0, 35.8, 30.1, 29.0, 20.5.
Compound **4b**: $[\alpha]_D$ –9.5 (*c* 0.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.85–6.81 (m, 1 H), 6.72 (d, *J* = 8.1 Hz, 1 H), 6.66 (d, *J* = 2.0 Hz, 1 H), 6.57–6.55 (dd, *J* = 8.1, 2.1 Hz, 1 H), 6.01–5.97 (ddd, *J* = 11.6, 5.8, 1.9 Hz, 1 H), 5.13–5.09 (m, 1 H), 4.22–4.18 (m, 1 H), 2.84–2.77 (m, 2 H), 2.55 (t, *J* = 6.9 Hz, 2 H), 2.26–2.22 (m, 2 H), 1.89–1.86 (dd, *J* = 9.4, 3.2 Hz, 1 H), 1.81–1.77 (dd, *J* = 9.7, 3.2 Hz, 1 H), 1.22 (d, *J* = 6.3 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.4, 164.8, 145.3, 143.6, 142.6, 132.6, 121.1, 120.4, 115.29, 74.3, 66.9, 41.2, 36.2, 30.3, 29.5, 20.4.
Compound **4c**: $[\alpha]_D$ +9.7 (*c* 0.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.85–6.82 (m, 1 H), 6.74–6.65 (m, 2 H), 6.58–6.54 (dd, *J* = 8.0, 2.0 Hz, 1 H), 6.01–5.97 (ddd, *J* = 11.6, 5.8, 1.8 Hz, 1 H), 5.15–5.08 (m, 1 H), 4.21–4.18 (m, 1 H), 2.82–2.77 (m, 2 H), 2.55 (t, *J* = 6.8 Hz, 2 H), 2.25–2.21 (m, 2 H), 1.89–1.85 (dd, *J* = 9.3, 3.3 Hz, 1 H), 1.81–1.77 (dd, *J* = 9.5, 3.4 Hz, 1 H), 1.22 (d, *J* = 6.3 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5, 164.9, 145.4, 143.6, 142.5, 132.6, 121.0, 120.4, 115.2, 74.4, 66.9, 41.2, 36.1, 30.3, 29.5, 20.4.
Compound **4d**: $[\alpha]_D$ +91.5 (*c* 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.82–6.79 (ddd, *J* = 10.3, 5.4, 2.5 Hz, 1 H), 6.73–6.70 (m, 2 H), 6.58–6.55 (dd, *J* = 8.0, 2.0 Hz, 1 H), 5.99–5.96 (m, 1 H), 5.05–5.01 (m, 1 H), 4.16 (m, 1 H), 2.81 (m, 2 H), 2.58 (t, *J* = 7.2 Hz, 2 H), 2.28 (m, 1 H), 2.20 (m, 1 H), 2.04–2.01 (m, 1 H), 1.76–1.71 (m, 1 H), 1.23 (d, *J* = 6.43 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7, 165.0, 145.5, 143.9, 142.2, 132.8, 120.9, 120.3, 115.4, 75.2, 67.1, 40.9, 35.8, 30.1, 28.9, 20.4. Compound **12**: ^{1}H NMR (400 MHz, C_6D_6–$CDCl_3$, 1:1): δ = 4.36–4.34 (m, 1 H), 3.84 (m, 1 H), 3.63–3.58 (m, 1 H), 2.55–2.51 (br d, *J* = 19.0 Hz, 1 H), 2.30–2.23 (dd, *J* = 19.1, 5.4 Hz, 1 H), 1.64–1.60 (br d, *J* = 13.9 Hz, 1 H), 1.46–1.42 (m, 1 H), 1.31 (m, 1 H), 1.10–1.03 (m, 1 H), 0.91 (d, *J* = 6.0 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.4, 72.9, 65.9, 61.9, 38.6, 36.5, 29.4, 21.4.
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