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# Enantioselective total synthesis of the polyketide natural product (−)-EI-1941-2: a novel interleukin-1β converting enzyme (ICE) inhibitor

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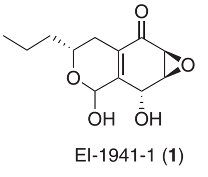
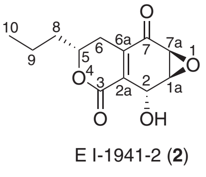
**Abstract**—An enantioselective total synthesis of the novel bioactive epoxyquinone natural product (−)-EI-1941-2, exhibiting promising ICE inhibiting activity, has been accomplished from a readily available chiron derived from the Diels–Alder adduct of cyclopentadiene and *p*-benzoquinone.

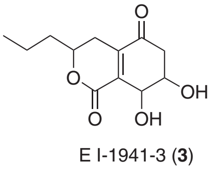
In 2003, Koizumi and co-workers reported the isolation and structure determination of three new microbial metabolites EI-1941-1 (**1**), EI-1941-2 (**2**) and EI-1941-3 (**3**) from the fermentation broth of *Farrowia* sp. E-1941.[1] In the following year, the same group elucidated the stereostructures and absolute configuration of these polyketide based unusual natural products **1**–**3** through high field 2D NMR studies and an X-ray crystal structure determination employing anomalous scattering effects on the *p*-bromobenzoyl derivative of **2**.[2] Besides their structural novelty, polyketides **1** and **2** were found to inhibit selectively human recombinant interleukin-1β (IL-1β) converting enzyme (ICE) activity with $IC_{50}$ values of 0.086 and 0.006 μM, respectively. This was quite a remarkable and promising biological activity profile as ICE, a cysteine protease is involved[3] in the cleavage of the biologically inactive 31 kDa precursor to the biologically active IL-1β, which has been implicated as the mediator in the pathogenesis of rheumatoid arthritis, septic shock, inflammation and other physiological conditions. ICE inhibitors have been suggested as potential anti-inflammatory drug candidates besides other biomedical applications.[4] Thus, E-1941 derived metabolites **1**–**3** are attractive and challenging targets for total synthesis, both on account of their structural features and their novel bioactivity profile and have drawn immediate attention from synthetic chemists.



EI-1941-1 (**1**)



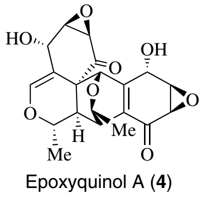
E I-1941-2 (**2**)



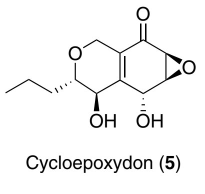
E I-1941-3 (**3**)

The group of Hayashi has recently accomplished the total synthesis of *ent*-EI-1941-2 (**2**).[5] In view of our ongoing interest in the total synthesis of epoxyquinol natural products,[6] we too were drawn to natural products **1**–**3** and in a contemporaneous effort achieved the first total synthesis of natural (−)-EI-1941-2 (**2**), which forms the subject matter of this letter.

The bicyclic framework of natural products **1**–**3** embodies a common epoxyquinone core fused to a pyran ring and bears striking resemblance to the monomeric unit of epoxyquinol A **4** and cycloepoxydon **5**, compounds whose total synthesis, we have delineated recently.[6b,e] In the quest for the target compound **2**, it appeared expedient to explore 6π electron oxy-cyclization protocols on an appropriate derivative to generate the



Epoxyquinol A (**4**)



Cycloepoxydon (**5**)

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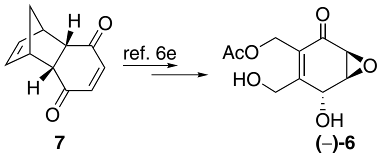
pyranone ring and the requisite bicyclic framework.[7,8] Successful realization of this tactic has culminated in the total synthesis (−)-**2** as detailed below.

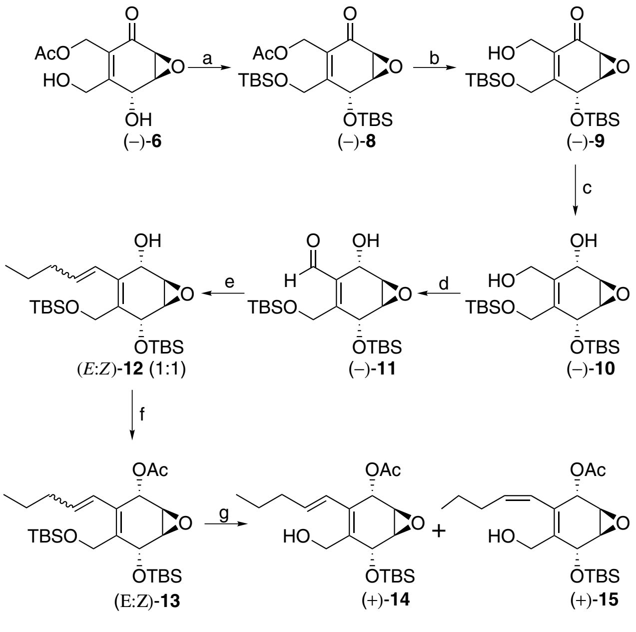
In a related context, we have recently outlined the acquisition of an enantiomerically pure (−)-epoxyquinone **6**, in a short sequence emanating from the abundantly available Diels–Alder adduct **7** of cyclopentadiene and *p*-benzoquinone, involving an enzymatic desymmetrization as the key step, Scheme 1.[6e] The disposition of functionalities and the relative stereochemical array present in **6** together with its ready availability marked it as a suitable starting point for our projected synthesis. To begin with, the C2 α-hydroxyl group in **6**, which has the required configuration present in the natural product and therefore must be retained throughout the synthetic operations, was protected along with the primary hydroxyl group as the di-TBS derivative **8** (Scheme 2).[9] Acetate hydrolysis in **8** led to hydroxyenone **9** which was further reduced to furnish only the α-hydroxy epimer (−)-**10**[9] (Scheme 2). The stereoselectivity in the DIBAL-H reduction of **9** can be attributed to coordination of the reagent with the epoxide and the primary hydroxyl group on the β-face, resulting in hydride delivery from the same face, and has ample precedence.[6e,10] Oxidation of the primary hydroxyl group in **10** was smooth and delivered hydroxyaldehyde (−)-**11**[9] (Scheme 2). Wittig olefination in **11** with the ylide derived from *n*-butyltriphenylphosphonium bromide was nonstereoselective and led to a $\sim$1:1 mixture of *E*:*Z* isomers **12**. Efforts either to improve the *E*:*Z* ratio by altering the reaction condition regime for the Wittig reaction or to enrich the *E*-isomer through photo-equilibration[6b,f] of the *E*:*Z* mixture were not rewarding. Also, the *E*:*Z* stereoisomers **12** were not amenable to clean chromatographic separation. However, conversion of **12** to acetate **13** and chemoselective deprotection of the primary hydroxyl group led to the readily separable (*E*)-**14**[9] and (*Z*)-**15**[9] (Scheme 2).



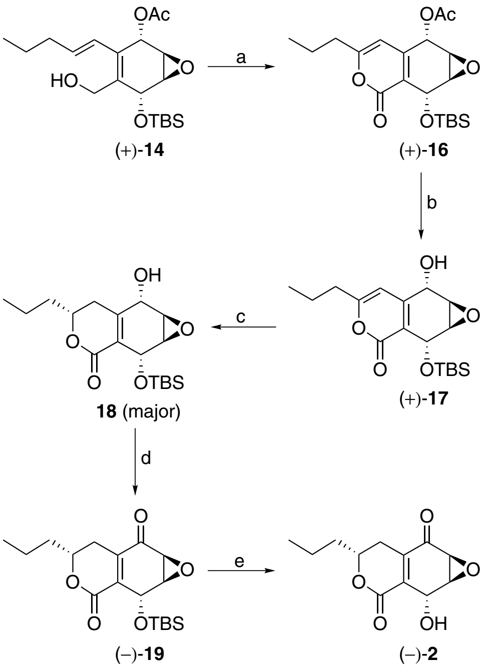
Scheme 1.

At this stage, the primary hydroxyl group in *E*-isomer (+)-**14** was subjected to oxidation in the recently described milieu[11] of sodium chlorite in the presence of TEMPO and sodium hypochlorite (bleach) to deliver the corresponding carboxylic acid in order to setup a $6\pi$ electrocyclization to generate the pyran ring. In the event, oxidation of (+)-**14**, to our surprise and delight, directly furnished the required bicyclic α-pyrone derivative (+)-**16**[9] (Scheme 3).[7] The yield in this reaction was low and could not be improved further but direct access to (+)-**16** from (+)-**14** in a single pot operation was a welcome augury.

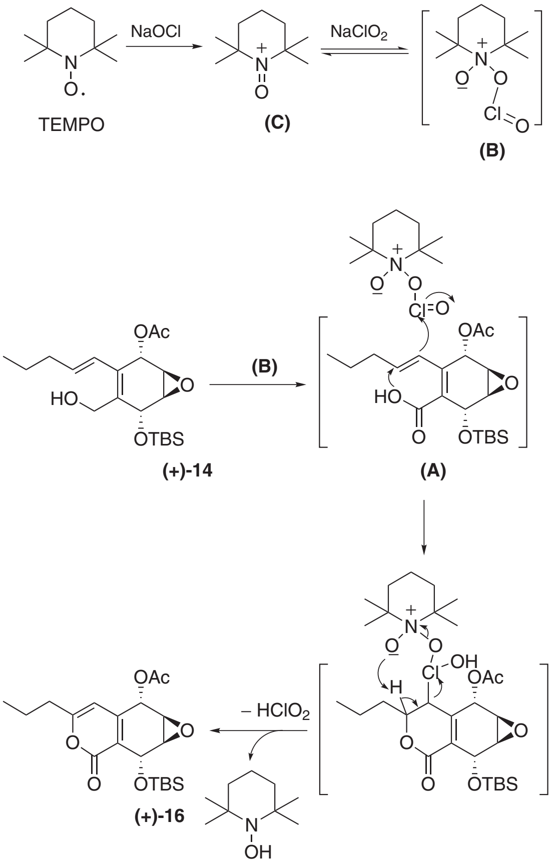
The mechanism of the formation of (+)-**16** from (+)-**14** during the $\mathrm{NaClO_2}$-TEMPO oxidation[11] is not clear, though it is tempting to implicate a $6\pi$ electron cyclization involving a diene carboxylic acid as suggested above (see, Ref. 7) and further oxidation. However,



**Scheme 2.** Reagents and conditions: (a) TBSOTf, 2,6-lutidine, $\mathrm{CH_2Cl_2}$, 0 °C, 30 min, 98%; (b) LiOH, MeOH, 0 °C, 2 h, 85%; (c) DIBAL-H, THF, −78 °C, 30 min, 82%; (d) $\mathrm{MnO_2}$, $\mathrm{CH_2Cl_2}$, rt, 4 h, 79%; (e) $\mathrm{C_4H_9PPh_3Br}$, *t*-BuOK, THF, 0 °C, 1 h, 65%; (f) $\mathrm{Ac_2O}$, pyridine, DMAP, $\mathrm{CH_2Cl_2}$, 0 °C, 2 h, 98%; (g) 5% HF, $\mathrm{CH_3CN}$, 0 °C, 36 h, 80%.



**Scheme 3.** Reagents and conditions: (a) TEMPO, NaOCl, $\mathrm{NaClO_2}$, $\mathrm{NaH_2PO_4}$, cyclopentene, rt, 15 min, 35%; (b) LiOH (0.5 M), DME, 0 °C, 1 h, 70%; (c) 10% Pd–C, $\mathrm{H_2}$, EOAc, rt, 6 h, 94%; (d) $\mathrm{MnO_2}$, $\mathrm{CH_2Cl_2}$, rt, 1 h, 93%; (e) TBAF–AcOH (1:1), THF, rt, 30 min, 90%.



Scheme 4.

the recent observations of Hayashi and co-workers[5] discount such a process. We propose a tentative mechanism involving tandem oxidations with oxoammonium species as shown below. After the initial oxidation of (+)-**14** to the carboxylic acid **A**,[11] an electrophilic cyclization-elimination, mediated by the oxa-ammonium species **B** (formed from **C** by the addition of $ClO_2^-$), leads to the observed product (+)-**16** (Scheme 4).

The stage was now set to carry forward the key α-pyrone derivative (+)-**16** to complete the synthesis of the natural product. Acetate hydrolysis in (+)-**16** furnished the hydroxyl compound (+)-**17**.[9] Partial catalytic hydrogenation in (+)-**17** proceeded with good stereoselectivity from the β-face, with the hydroxyl and the -OTBS groups sterically shielding the α-face, to furnish **18**,[9] (Scheme 3). $MnO_2$ mediated oxidation of the allylic hydroxyl group in **18** led smoothly to our penultimate compound (−)-**19**.[9] Finally, OTBS deprotection in (−)-**19** with the TBAF–AcOH combination delivered (−)-**2**, which was found to be spectroscopically ($^1$H and $^{13}$C NMR) identical with the natural product. In addition, our synthetic (−)-**2** had $[\alpha]_D^{23}$ −305.9 (*c* 0.34, methanol), similar in sign and magnitude to that exhibited by the natural (−)-**2**, lit.[1] $[\alpha]_D^{23}$ −307.5 (*c* 0.57, methanol).

In summary, we have accomplished the first total synthesis of the novel interleukin-1β (IL-1β) converting enzyme (ICE) inhibitor ( )-EI-1491-2 **2** in its naturally occurring enantiomeric form, from a readily available chiral building block (−)-**6**. A key step in our synthesis was the fortuitous direct oxidation of a dienylic primary alcohol to an α-pyrone moiety.

## Acknowledgements

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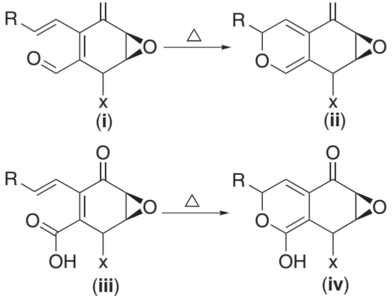
7. In view of the facile 6π electrocyclization of the dienals of the general-type (**i**) leading to (**ii**), observed by us[6a,e] and others[8] in the context of the synthesis of epoxyquinols and related natural products (X = –OH, –OTBS), it was



considered quite plausible that analogous cyclization could also be effected with diene carboxylic acid of the type (**iii**) to furnish (**iv**). Cyclized enol–lactone (**iv**) was well poised for elaboration to the functionality present in the natural products **1**–**3**.

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9. All new compounds were characterized on the basis of IR, $^1$H and $^{13}$C NMR and HRMS data. Spectral data for selected compounds: (−)-**8** $[\alpha]_D^{22}$ −108.4 (*c* 2.02, $CHCl_3$); IR (neat) 1746, 1685, 1472 cm$^{-1}$; $^1$H NMR (300 MHz) ($CDCl_3$): $\delta$ 5.07 (s, 1H), 4.86 (1/2ABq, $J = 11.7$ Hz, 1H), 4.78 (1/2ABq, $J = 12.0$ Hz, 1H), 4.53 (1/2ABq, $J = 13.5$ Hz, 1H), 4.29 (1/2ABq, $J = 13.5$ Hz, 1H), 3.67 (dd, $J = 4.0$, 1.5 Hz, 1H), 3.53 (dd, $J = 3.7$, 1.2 Hz, 1H), 2.02 (s, 3H), 0.90 (s, 9H), 0.89 (s, 9H), 0.19 (s, 3H), 0.17 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H); $^{13}$C NMR (75 MHz) ($CDCl_3$): $\delta$ 193.3, 170.5, 155.5, 126.8, 62.7, 59.0, 56.7, 56.0, 52.6, 25.8, 25.6, 20.7, 18.2, 18.0, −4.3, −4.7, −5.2, −5.4; HRMS (ES): *m/z* for $C_{22}H_{40}O_6Si_2Na$ $[M+Na]^+$, calcd 479.2261, found 479.2270; Compound (−)-**9**: mp = 97 °C; $[\alpha]_D^{24}$ −159.2 (*c* 1.25, $CHCl_3$); IR (neat) 3566, 1685, 1471 cm$^{-1}$; $^1$H NMR (300 MHz) ($CDCl_3$): $\delta$ 4.95 (s, 1H), 4.57 (1/2ABq, $J = 13.8$ Hz, 1H), 4.38–4.32 (m, 2H), 4.27 (1/2ABq, $J = 13.5$ Hz, 1H), 3.66 (dd, $J = 3.7$, 1.5 Hz, 1H), 3.51 (dd, $J = 3.7$, 1.2 Hz, 1H), 2.49 (dd, $J = 7.8$, 6.0 Hz, 1H), 0.91 (s, 9H), 0.90 (s, 9H), 0.20 (s, 3H), 0.18 (s, 3H), 0.11 (s, 3H), 0.09 (s, 3H); $^{13}$C NMR (75 MHz) ($CDCl_3$): $\delta$ 195.6, 152.7, 131.6, 63.6, 59.5, 56.9, 56.4, 52.7, 25.8, 25.6, 18.2, 18.0, −4.2, −4.7, −5.2, −5.3; HRMS (ES): *m/z* for $C_{20}H_{38}O_5Si_2Na$ $[M+Na]^+$, calcd 437.2156, found 437.2133. Anal. for $C_{20}H_{38}O_5Si_2$, calcd C, 57.93; H, 9.24, found C, 56.61; H, 9.16; Compound (−)-**10**: mp = 137 °C; $[\alpha]_D^{23}$ −20.3 (*c* 1.87, $CHCl_3$); IR (neat) 3331, 1472, 1253 cm$^{-1}$; $^1$H NMR (300 MHz) ($CDCl_3$): $\delta$ 4.69 (s, 1H), 4.49 (d, $J = 9.0$ Hz, 1H), 4.41 (1/2ABq, $J = 12.3$ Hz, 1H), 4.30 (dd, $J = 12.3$, 6.9 Hz, 1H), 4.20 (dd, $J = 12.4$, 4.2 Hz, 1H), 4.08 (1/2ABq, $J = 12.3$ Hz, 1H), 3.41–3.40 (m, 1H), 3.26 (br s, 1H), 2.80 (br s, 1H), 2.58 (br s, 1H), 0.91 (s, 9H), 0.89 (s, 9H), 0.19 (s, 3H), 0.16 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H); $^{13}$C NMR (75 MHz) ($CDCl_3$): $\delta$ 134.3, 133.2, 66.1, 64.5, 61.5, 59.8, 52.2, 52.0, 25.8, 25.7, 18.2, 18.0, −4.3, −4.7, −5.2, −5.3; HRMS (ES): *m/z* for $C_{20}H_{40}O_5Si_2Na$ $[M+Na]^+$, calcd 439.2312, found 439.2324. Anal. for $C_{20}H_{40}O_5Si_2$, calcd C, 57.65; H, 9.68, found C, 57.56; H, 9.62; Compound (−)-**11**: $[\alpha]_D^{23}$ −42.6 (*c* 3.45, $CHCl_3$); IR (neat) 3225, 1681, 1471 cm$^{-1}$; $^1$H NMR (400 MHz) ($CDCl_3$): $\delta$ 10.26 (s, 1H), 4.94 (s, 1H), 4.92 (1/2ABq, $J = 15.2$ Hz, 1H), 4.83 (s, 1H), 4.37 (1/2ABq, $J = 15.2$ Hz, 1H), 3.50 (s, 1H), 3.33 (s, 1H), 2.51 (br s, 1H), 0.91 (s, 9H), 0.90 (s, 9H), 0.21 (s, 3H), 0.19 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H); $^{13}$C NMR (75 MHz) ($CDCl_3$): $\delta$ 192.2, 151.7, 132.1, 64.2, 61.1, 59.2, 51.7, 51.5, 25.8, 25.6, 18.2, 17.9, −4.4, −4.7, −5.3; HRMS (ES): *m/z* for $C_{20}H_{38}O_5Si_2Na$ $[M+Na]^+$, calcd 437.2156, found 437.2172; Compound (+)-**14**: $[\alpha]_D^{23}$ +12.9 (*c* 1.01, $CHCl_3$); IR (neat) 3453, 1742, 1472 cm$^{-1}$; $^1$H NMR (300 MHz) ($CDCl_3$): $\delta$ 6.30 (d, $J = 16.2$ Hz, 1H), 5.98 (s, 1H), 5.82–5.72 (m, 1H), 4.73 (s, 1H), 4.32 (1/2ABq, $J = 12.3$ Hz, 1H), 4.23 (1/2ABq, $J = 12.3$ Hz, 1H), 3.36–3.35 (m, 1H), 3.26–3.25 (m, 1H), 2.14–2.06 (m, 2H), 2.09 (s, 3H), 1.66 (br s, 1H), 1.40 (sextet, $J = 7.2$ Hz, 2H), 0.92 (s, 9H), 0.89 (t, $J = 7.5$ Hz, 3H), 0.20 (s, 3H), 0.19 (s, 3H); $^{13}$C NMR (75 MHz) ($CDCl_3$): $\delta$ 170.6, 134.5, 133.4, 127.8, 124.7, 66.0, 64.1, 60.6, 52.2, 50.5, 35.5, 25.7, 22.3, 21.0, 18.0, 13.6, −4.2, −4.5; HRMS (ES): *m/z* for $C_{20}H_{34}O_5SiNa$ $[M+Na]^+$, calcd 405.2073, found 405.2061; Compound (+)-**15**: $[\alpha]_D^{23}$ +105.0 (*c* 0.60, $CHCl_3$); $^1$H NMR (300 MHz) ($CDCl_3$): $\delta$ 5.70–5.63 (m, 2H), 5.55 (s, 1H), 4.85 (s, 1H), 4.25 (1/2ABq, $J = 12.0$ Hz, 1H), 3.99 (1/2ABq, $J = 12.0$ Hz, 1H), 3.32–3.28 (m, 2H), 2.06 (s, 3H), 1.88–1.82 (m, 2H), 1.65 (br s, 1H), 1.46–1.24 (m, 2H), 0.93 (s, 9H), 0.87 (t, $J = 7.5$ Hz, 3H), 0.20 (s, 3H), 0.19 (s, 3H); $^{13}$C NMR (75 MHz) ($CDCl_3$): $\delta$ 170.4, 136.9, 134.2, 126.9, 124.9, 66.8, 63.1, 60.6, 52.7, 50.4, 30.6, 25.7, 22.3, 20.9, 18.0, 13.9, −4.2, −4.9; Compound (+)-**16**: $[\alpha]_D^{23}$ +127.1 (*c* 0.48, $CHCl_3$); IR (neat) 1746, 1723, 1218 cm$^{-1}$; $^1$H NMR (300 MHz) ($CDCl_3$): $\delta$ 5.92 (s, 1H), 5.90 (s, 1H), 5.16 (s, 1H), 3.40 (t, $J = 1.5$ Hz, 2H), 2.43 (dt, $J = 7.8$, 3.0 Hz, 2H), 2.14 (s, 3H), 1.69 (1/2ABq, $J = 7.2$ Hz, 1H), 1.65 (1/2ABq, $J = 7.2$ Hz, 1H), 0.96 (t, $J = 7.5$ Hz, 3H), 0.89 (s, 9H), 0.25 (s, 3H), 0.15 (s, 3H); $^{13}$C NMR (75 MHz) ($CDCl_3$): $\delta$ 170.2, 165.7, 162.5, 143.6, 119.1, 104.4, 65.8, 61.5, 52.5, 49.1, 35.6, 25.7, 20.8, 20.1, 18.0, 13.5, −4.6, −5.1; HRMS (ES): *m/z* for $C_{20}H_{30}O_6SiNa$ $[M+Na]^+$, calcd 417.1709, found 417.1705; Compound (+)-**17**: $[\alpha]_D^{23}$ +103.1 (*c* 0.32, $CH_3OH$); IR (neat) 3438, 1725, 1584 cm$^{-1}$; $^1$H NMR (300 MHz) ($CDCl_3$): $\delta$ 5.97 (s, 1H), 5.25 (d, $J = 2.7$ Hz, 1H), 4.58 (br d, $J = 9.3$ Hz, 1H), 3.54 (t, $J = 3.6$ Hz, 1H), 3.45 (t, $J = 3.0$ Hz, 1H), 2.61 (br d, $J = 11.7$ Hz, 1H), 2.47 (t, $J = 7.2$ Hz, 2H), 1.69 (sextet, $J = 7.5$ Hz, 2H), 0.97 (t, $J = 7.5$ Hz, 3H), 0.88 (s, 9H), 0.27 (s, 3H), 0.15 (s, 3H); $^{13}$C NMR (75 MHz) ($CDCl_3$): $\delta$ 166.8, 162.5, 149.8, 117.1, 104.7, 67.2, 62.7, 51.4, 50.1, 35.7, 25.7, 20.1, 17.9, 13.5, −4.7, −5.1; HRMS (ES): *m/z* for $C_{18}H_{28}O_5SiNa$ $[M+Na]^+$, calcd 375.1604, found 375.1591; Compound (−)-**19**: $[\alpha]_D^{23}$ −110.2 (*c* 0.49, $CH_3OH$); IR (neat) 1726, 1695, 1464 cm$^{-1}$; $^1$H NMR (300 MHz) ($CDCl_3$): $\delta$ 5.18 (br s, 1H), 4.56–4.49 (m, 1H), 3.73 (dd, $J = 3.6$, 1.8 Hz, 1H), 3.59 (d, $J = 3.9$ Hz, 1H), 2.66 (dd, $J = 18.1$, 7.8 Hz, 1H), 2.55 (dd, $J = 18.1$, 4.6 Hz, 1H), 1.85–1.74 (m, 1H), 1.60–1.37 (m, 3H), 0.93 (t, $J = 7.2$ Hz, 3H), 0.87 (s, 9H), 0.26 (s, 3H), 0.16 (s, 3H); $^{13}$C NMR (75 MHz) ($CDCl_3$): $\delta$ 194.4, 163.5, 139.5, 135.8, 77.3, 61.9, 56.4, 52.3, 36.2, 25.7, 25.7, 18.2, 18.1, 13.6, −4.7, −4.8; HRMS (ES): *m/z* for $C_{18}H_{28}O_5SiNa$ $[M+Na]^+$, calcd 375.1604, found 375.1605; Compound (−)-**2**: $[\alpha]_D^{23}$ −305.9 (*c* 0.34, $CH_3OH$); IR (neat) 3446, 1716, 1695, 1417 cm$^{-1}$; $^1$H NMR (300 MHz) ($CD_3CN$):$\delta$ 4.96 (br s, 1H), 4.53–4.44 (m, 1H), 4.07 (br s, 1H), 3.84 (dd, $J = 3.6$, 1.5 Hz, 1H), 3.56 (d, $J = 3.6$ Hz, 1H), 2.52 (dd, $J = 4.5$, 1.2 Hz, 1H), 2.49 (d, $J = 9.0$ Hz, 1H), 1.79–1.55 (m, 2H), 1.52–1.34 (m, 2H), 0.92 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (75 MHz) ($CD_3CN$): $\delta$ 195.5, 165.3, 141.5, 136.7, 78.6, 61.9, 57.3, 53.3, 37.1, 26.8, 18.9, 14.0; HRMS (ES): *m/z* for $C_{12}H_{14}O_5Na$ $[M+Na]^+$, calcd 261.0739, found 261.0735.
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