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Aerobic oxidation and EATA-based highly enantioselective synthesis of lamenallenic acid†

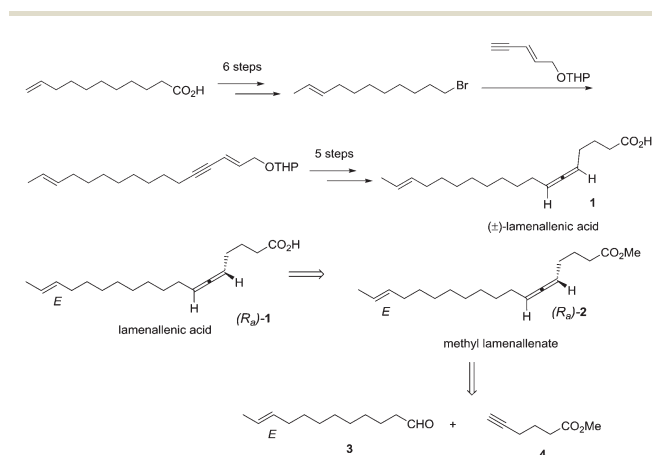
Xingguo Jiang,^a Yufeng Xue^a and Shengming Ma^{*a,b}

By utilizing the recently developed EATA (enantioselective allenylation of terminal alkynes) reaction and the aerobic oxidation of alcohols, lamenallenic acid, a naturally occurring axially chiral allene, has been synthesized with a high ee value and *E/Z* selectivity from methyl 5-hexynoate and (*E*)-10-dodecenal, which could be prepared easily from 1-decyne and 1-pentyne, respectively, with (*S*)- α,α -dimethylprolinol as the chiral source.

Introduction

Currently, about 150 natural products containing an allenic or cumulenenic structure have been isolated and characterized.¹ With a typical structure of 1,3-disubstituted allene, lamenallenic acid was isolated from *Lamium Purpureum* L. (Labiatae) seed oil in 1967.² This molecule contains a *trans* double bond, an axially chiral allene unit, and a free carboxylic acid group (Scheme 1). According to the literature,² the natural product was laevorotatory and the configuration was expected to be R_a

by comparing the specific rotation with (–)-laballenic acid of similar structure, which was previously determined to be R_a by the Landor group.³ Although the structure does not look too complicated, due to the lack of efficient methods for the highly stereoselective construction of the allene unit, in 1972, the Landor group finished the first total synthesis of racemic lamenallenic acid from 10-undecenoic acid and the THP-ether of 4-pentyn-2-enol in 12 steps.⁴ The allenic unit was synthesized by the reaction of 2,14-hexadecadien-4-yn-1-ol and LiAlH_4 . By adding cyclohexylidene- α -D-glucopyranose as the chiral source in this step, (–)-lamenallenic acid was obtained with a very low ee as judged by comparing the specific optical rotation of its (–)-methyl ester ($[\alpha]_D^{20} = -5.8$ ($c = 5.6$, EtOH)) to the reported data for methyl ester of the natural lamenallenic acid ($[\alpha]_D^{25} = -50$ ($c = 0.28$, EtOH) at 589 nm).² Thus, the known synthesis lacks efficiency and high stereoselectivity. Obviously, the challenges for synthesizing the naturally occurring lamenallenic acid are the highly stereoselective construction of the *trans* C–C double bond⁵ and the R_a -axially chiral allene unit.⁶ According to the EATA reaction recently developed by our group,⁷ we reasoned that methyl lamenallenate (R_a)-2 may be synthesized from (*E*)-10-dodecenal 3 and methyl 5-hexynoate 4 (Scheme 1).



Scheme 1 Reported synthesis and our retrosynthetic analysis of lamenallenic acid.

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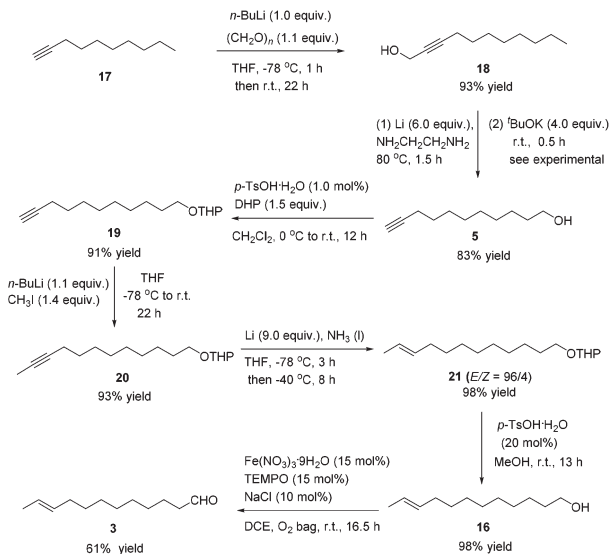
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† Electronic supplementary information (ESI) available: ¹H, ¹³C NMR and HPLC spectra of all the products. See DOI: 10.1039/c6qo00785f

Results and discussion

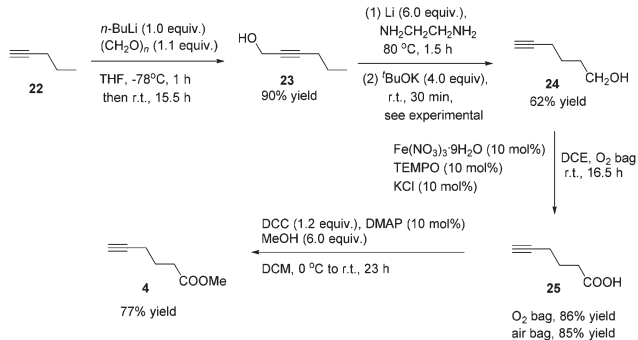
After some unsuccessful initial attempts to construct the C=C double bond with a high *E/Z* ratio involving compounds 6–16 (for details, see the ESI†), we observed that the reduction of 10-dodecyne THP ether 20, which was synthesized from 1-decyne 17 in 4 steps, with Li/NH_3 (1)⁸ gave (*E*)-10-dodecenol THP ether 21 successfully in 98% yield with an *E/Z* ratio of 96/4 (Scheme 2). After deprotection, the *trans* dodec-10-enol 16 underwent an aerobic oxidation reaction using $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}/\text{TEMPO}/\text{NaCl}$ ^{9,10} as catalysts to give *trans* 10-dodecynal 3.



Scheme 2 Synthetic route to (*E*)-10-dodecenal **3**.

Methyl 5-hexynoate **4** was then synthesized from 1-pentyne **22** in 4 steps (Scheme 3): 5-hexyn-1-ol **24** was prepared from 1-pentyne **22** through a similar process for the preparation of alkyne **5** from **17**, which was further oxidized to 5-hexynoic acid **25** by applying the $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}/\text{TEMPO}/\text{KCl}$ -catalyzed aerobic oxidation reaction¹¹ resulting in 86% yield with an O_2 bag and in 85% yield with an air bag. The esterification reaction with DCC, DMAP and MeOH in CH_2Cl_2 afforded methyl 5-hexynoate **4** in 77% yield.

We then tested the EATA reaction of the terminal alkyne **4** with *E*-enal **3**: the reaction under the reported conditions⁷ with 20 mol% of CuBr_2 , 1.5 equiv. of alkyne **4**, 1.5 equiv. of aldehyde **3** and 1.0 equiv. of (*S*)-diphenyl prolinol **26** in dioxane at 130 °C successfully afforded 47% yield of methyl lamnallenate (R_a)-**2** with 93% ee. The yield and ee were almost not affected when reducing the amount of aldehyde from 1.5 to 1.1 (entries 1–3, Table 1). With 1.0 equiv. of aldehyde, the yield dropped to 45% (entry 4, Table 1). Increasing the amount of chiral amine (*S*)-**26** to 1.5 equiv. or alkyne to 2.0 equiv. did not significantly improve the yield or ee (entries 5 and 6, Table 1).

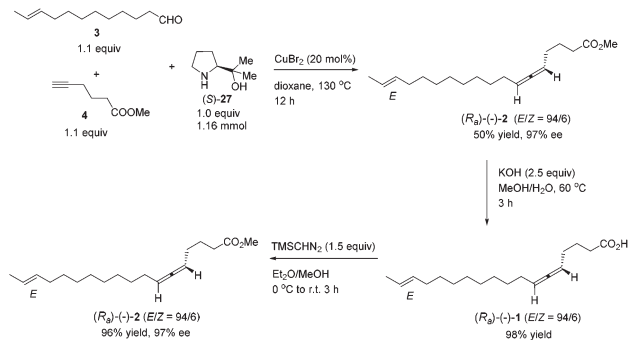
Scheme 3 The synthetic route to methyl 5-hexynoate **4**.Table 1 Optimization of EATA reaction^a

Entry	X	y	z	R	Yield ^b of (<i>R_a</i>)- 2 (%)	ee (%)
1	1.5	1.5	1.0	Ph	52 (47)	93
2	1.5	1.2	1.0	Ph	50 (48)	92
3	1.5	1.1	1.0	Ph	50 (48)	92
4	1.5	1.0	1.0	Ph	48 (45)	92
5	1.5	1.0	1.5	Ph	48 (48)	91
6	2.0	1.1	1.0	Ph	51 (48)	93
7	1.5	1.5	1.0	Me	59 (59)	97
8	1.5	1.1	1.0	Me	57 (56)	97
9	1.2	1.1	1.0	Me	55 (54)	97
10	1.1	1.1	1.0	Me	55 (55)	96

^a The reaction was conducted on the 0.1 mmol scale with 0.02 mmol of CuBr_2 , *x* equiv. of **4**, *y* equiv. of **3** and *z* equiv. of chiral amine in 0.8 mL of dioxane at 130 °C in a sealed tube for 12 h. ^b NMR yield. Isolated yield is given in parentheses.

However, changing the chiral amino alcohol from (*S*)-diphenyl prolinol (*S*)-**26** to (*S*)-dimethyl prolinol (*S*)-**27** increased the yield to 59% and ee to 97% (entry 7, Table 1). The ee remained high when reducing both terminal alkyne **4** and aldehyde **3** to 1.1 equiv. (entries 8–10, Table 1).

By applying 20 mol% of CuBr_2 , 1.1 equiv. of alkyne **4**, 1.1 equiv. of aldehyde **3** and 1.0 equiv. of (*S*)-dimethyl prolinol (*S*)-**27** in dioxane at 130 °C as the standard conditions, the reaction on the 1.16 mmol scale afforded methyl lamnallenate (R_a)-**2** in 50% yield with 97% ee ($[\alpha]_D^{29.3} = -52.8$ ($c = 0.305$, EtOH)) (lit.² $[\alpha]_D^{25} = -50$ ($c = 0.28$, EtOH)) (Scheme 4). KOH was used in MeOH at 60 °C to execute the hydrolysis to produce (–)-lamnallenic acid (R_a)-**1** in 98% yield ($[\alpha]_D^{29.4} = -55.2$ ($c = 0.995$, EtOH), *E/Z* = 94/6). For determination of ee of the synthesized (–)-lamnallenic acid, the prepared acid was subjected to a methylation reaction to reproduce (–)-methyl lamnallenate (R_a)-**2** with 97% ee. Thus, the synthesis of (–)-lamnallenic acid with 97% ee was accomplished.



Scheme 4 Synthesis of (–)-lamnallenic acid.



Conclusions

In conclusion, we finished the highly enantioselective total synthesis of (–)-lamenallenic acid with high optical purity in 9 steps from 1-decyne and 1-pentyne. By applying (*S*)-dimethyl prolinol as the chiral source, the EATA reaction of (*E*)-10-dodecenal and methyl 5-hexynoate, which were prepared from two simple terminal alkynes by routine chemical transformations and iron-catalyzed aerobic oxidation reactions developed by our group, was accomplished with high ee. This has nicely demonstrated the direct tolerance of functional groups such as the C=C bond and carboxylate. Based on our previous report,⁷ the reaction of a terminal alkyne with an aldehyde in the presence of (*S*)-prolinol leads to (*R_a*)-allene; thus, we confirmed the absolute configuration of the allene moiety in natural lamenallenic acid. Compared to the known synthesis, the current synthesis enjoys a high efficiency and high enantioselectivity. Further studies are being pursued in this laboratory.

Experimental

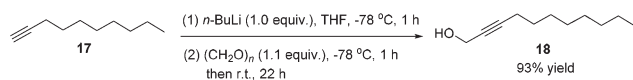
General information

¹H and ¹³C nuclear magnetic resonance spectra were recorded with an instrument operated at 400 MHz for ¹H NMR and 100 MHz for ¹³C NMR spectra. THF and dioxane were dried over sodium wire and distilled freshly before use. DCE was used directly without further treatment unless mentioned otherwise. (*S*)-Dimethyl prolinol (*S*)-27¹² was synthesized by following the reported procedure. Other reagents were used as received without further treatment.

CAUTION: Oxygen in use with combination with organic solvents; remove all ignition sources including sources of sparks, static, or flames since oxygen increases the intensity of any fire. Inhalation of pure oxygen should be avoided as well.

Experimental details and analytical data

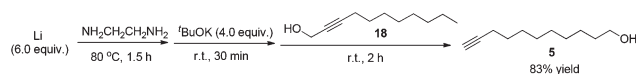
2-Undecyn-1-ol (**18**).¹³



To a 250 mL flame-dried three-necked flask were added **17** (11.6421 g, 95% purity, 80 mmol) and anhydrous THF (80 mL). A solution of *n*-BuLi (2.5 M in hexane, 32.0 mL, 80 mmol) was added dropwise at -78 °C under an Ar atmosphere in 25 min. After 1 h, paraformaldehyde (2.6426 g, 88 mmol) was added into the flask and the resulting mixture was stirred at -78 °C for 1 h. The reaction was then allowed to warm to room temperature naturally and stirred for 22 h. A saturated NH₄Cl aqueous solution (40 mL) was added to quench the reaction. Et₂O (200 mL) and H₂O (100 mL) were added. The organic layer was separated and the aqueous phase was extracted by ethyl ether (60 × 3 mL). The combined organic layer was washed with brine and dried over anhydrous Na₂SO₄. After filtration and evaporation, the residue was purified by chromatography on silica gel (eluent: petroleum ether/ethyl

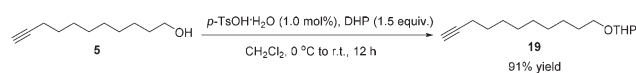
acetate = 20/1 to 5/1) to afford **18**¹³ (12.5673 g, 93%) as an oil: ¹H NMR (400 MHz, CDCl₃) δ 4.28–4.22 (m, 2 H, OCH₂), 2.21 (tt, *J*₁ = 7.0 Hz, *J*₂ = 2.1 Hz, 2 H, C≡CCH₂), 1.87 (brs, 1 H, OH), 1.51 (quint, *J* = 7.2 Hz, 2 H, CH₂), 1.42–1.20 (m, 10 H, 5 × CH₂), 0.88 (t, *J* = 6.8 Hz, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 86.6, 76.7, 51.3, 31.8, 29.14, 29.06, 28.8, 28.6, 22.6, 18.7, 14.0; IR (neat) ν (cm⁻¹) 3336, 2925, 2855, 2289, 2226, 1462, 1376, 1228, 1137, 1012; MS (ESI) *m/z* (%): 191 ((M + Na)⁺).

10-Undecyn-1-ol (**5**).¹⁴



To a 250 mL three-necked flask were added a Li rod (2.0820 g, 300.0 mmol) and NH₂CH₂CH₂NH₂ (200 mL) under an Ar atmosphere. The resulting mixture was stirred for 1.5 h at 80 °C with a preheated oil bath. After being cooled to room temperature naturally, ^tBuOK (22.4435 g, 200.0 mmol) was added and the mixture was stirred for 30 min at room temperature. **18** (8.4130 g, 50.0 mmol) was added dropwise within 5 min. After being stirred at room temperature for 2 h, the reaction mixture was poured into a 1 L beaker containing a mixture of ice and water (200 mL). Et₂O (300 mL) was added to separate the organic layer and the aqueous phase was extracted with ethyl ether (100 × 3 mL). The combined organic layer was washed sequentially with 1 M aqueous HCl (80 mL), a saturated NaHCO₃ aqueous solution (80 mL), and brine. After being dried over anhydrous Na₂SO₄, the mixture was filtered and evaporated. The residue was purified by chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 9/1 to 3/1) to afford **5**¹⁵ (7.0109 g, 83%) as an oil: ¹H NMR (400 MHz, CDCl₃) δ 3.63 (t, *J* = 6.6 Hz, 2 H, OCH₂), 2.18 (td, *J*₁ = 7.1 Hz, *J*₂ = 2.8 Hz, 2 H, C≡CCH₂), 1.94 (t, *J* = 2.6 Hz, 1 H, C≡CH), 1.70–1.48 (m, 5 H, OH + 2 × CH₂), 1.44–1.22 (m, 10 H, 5 × CH₂); ¹³C NMR (100 MHz, CDCl₃) δ 84.7, 68.0, 62.9, 32.7, 29.4, 29.3, 29.0, 28.6, 28.4, 25.6, 18.3; IR (neat) ν (cm⁻¹) 3308, 2928, 2856, 2116, 1462, 1055; MS (ESI) *m/z* (%): 169 (M + H)⁺.

2-(10-Undecyloxy)tetrahydro-2H-pyran (**19**).¹⁶

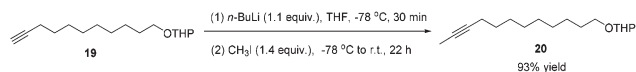


To a 100 mL Schlenk flask were added **5** (1.6815 g, 10.0 mmol) and CH₂Cl₂ (20 mL). *p*-TsOH·H₂O (19.0 mg, 0.1 mmol) and DHP (1.37 mL, *d* = 0.922 g mL⁻¹, 1.2618 g, 15.0 mmol) were added at 0 °C. Then, the resulting mixture was allowed to warm up to room temperature and stirred for 12 h. A saturated NaHCO₃ aqueous solution (5 mL) was added to quench the reaction. Et₂O (50 mL) and H₂O (50 mL) were added. The organic phase was separated and the aqueous phase was extracted with ethyl ether (25 × 3 mL). The combined organic layer was washed with brine and dried over anhydrous Na₂SO₄. After filtration and evaporation, the residue was purified by chromatography on silica gel (eluent: petroleum ether/ethyl ether = 100/1 to 50/1) to afford **19**¹⁶ (2.2915 g, 91%) as an oil: ¹H NMR (400 MHz, CDCl₃) δ 4.60–4.55 (m, 1 H, CH of the THP group), 3.91–3.83 (m, 1 H, one proton of the THP group),



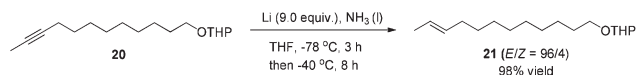
3.77–3.69 (dt, $J_1 = 9.6$ Hz, $J_2 = 7.0$ Hz, 1 H, one proton of OCH₂), 3.54–3.46 (m, 1 H, one proton of the THP group), 3.42–3.34 (dt, $J_1 = 9.6$ Hz, $J_2 = 6.8$ Hz, 1 H, one proton of OCH₂), 2.18 (td, $J_1 = 7.1$ Hz, $J_2 = 2.8$ Hz, 2 H, C≡CCH₂), 1.94 (t, $J = 2.6$ Hz, 1 H, C≡CH), 1.89–1.78 (m, 1 H, one proton of the THP group), 1.76–1.67 (m, 1 H, one proton of the THP group), 1.64–1.47 (m, 8 H, four protons of the THP group + 2 × CH₂), 1.44–1.24 (m, 10 H, 5 × CH₂); ¹³C NMR (100 MHz, CDCl₃) δ 98.8, 84.7, 68.0, 67.6, 62.3, 30.7, 29.7, 29.4, 29.0, 28.7, 28.4, 26.1, 25.4, 19.6, 18.3; IR (neat) ν (cm⁻¹) 3310, 2930, 2856, 2117, 1460, 1350, 1260, 1202, 1121, 1076, 1029; MS (EI) m/z (%): 252 (M⁺, 0.27), 85 (100).

2-(10-Dodecynyloxy)tetrahydro-2H-pyran (20).⁸



To a 250 mL flame-dried three-neck flask were added **19** (2.0210 g, 8.0 mmol) and anhydrous THF (25 mL) under an Ar atmosphere. A solution of *n*-BuLi (2.5 M in hexanes, 3.52 mL, 8.8 mmol) was added dropwise at -78 °C in 5 min. After 30 min, a solution of CH₃I (0.69 mL, $d = 2.3$ g mL⁻¹, 1.5897 g, 11.2 mmol) in anhydrous THF (20 mL) was added dropwise within 10 min at -78 °C. The resulting mixture was allowed to warm up to room temperature naturally and stirred for 22 h. A saturated NH₄Cl aqueous solution (30 mL) was added to quench the reaction. Et₂O (200 mL) and H₂O (100 mL) were added. The organic layer was separated and the aqueous phase was extracted by ethyl ether (50 × 3 mL). The combined organic layer was washed with brine and dried over anhydrous Na₂SO₄. After filtration and evaporation, the residue was purified by chromatography on silica gel (eluent: petroleum ether/ethyl ether = 30/1) to afford **20**⁸ (1.9848 g, 93%) as an oil: ¹H NMR (400 MHz, CDCl₃) δ 4.61–4.54 (m, 1 H, CH of the THP group), 3.92–3.82 (m, 1 H, one proton of the THP group), 3.73 (dt, $J_1 = 9.6$ Hz, $J_2 = 6.9$ Hz, 1 H, one proton of OCH₂), 3.55–3.45 (m, 1 H, one proton of the THP group), 3.38 (dt, $J_1 = 9.6$ Hz, $J_2 = 6.7$ Hz, 1 H, one proton of OCH₂), 2.14–2.07 (m, 2 H, CH₂), 1.88–1.80 (m, 1 H, one proton of the THP group), 1.78 (t, $J = 2.4$ Hz, 3 H, CH₃), 1.76–1.67 (m, 1 H, one proton of the THP group), 1.64–1.42 (m, 8 H, four protons of the THP group + 2 × CH₂), 1.41–1.22 (m, 10 H, 5 × CH₂); ¹³C NMR (100 MHz, CDCl₃) δ 98.8, 79.3, 75.2, 67.6, 62.3, 30.7, 29.7, 29.41, 29.38, 29.1, 29.0, 28.8, 26.2, 25.5, 19.6, 18.7, 3.4; IR (neat) ν (cm⁻¹) 2928, 2856, 1460, 1350, 1260, 1202, 1122, 1076, 1031; MS (EI) m/z (%): 266 (M⁺, 0.94), 85 (100).

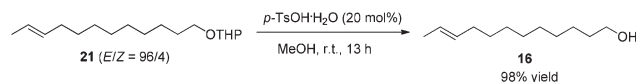
(E)-2-(10-Dodecenyloxy)tetrahydro-2H-pyran (21).



To a 500 mL three-necked flask was introduced NH₃ gas at -78 °C to collect ~150 mL of liquid NH₃. **20** (4.5080 g, 17 mmol), THF (85 mL) and a Li rod (1.0178 g, 153 mmol) were added sequentially at -78 °C. After stirring at -78 °C for 3 h, the resulting mixture was then warmed to -40 °C and stirred for 8 h until the completion of the reaction as moni-

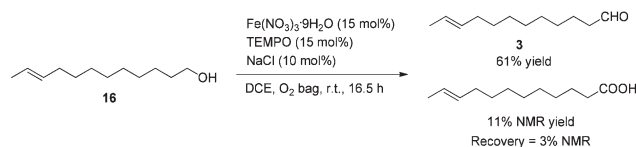
tored by TLC. A saturated NH₄Cl aqueous solution (40 mL) was added to quench the reaction. The flask was opened to air overnight to allow the NH₃ (l) to evaporate. Et₂O (40 mL) and H₂O (20 mL) were added and the organic layer was separated. The aqueous phase was extracted by ethyl ether (30 × 3 mL). The combined organic layer was washed with brine and dried over anhydrous MgSO₄. After filtration and evaporation, the residue was purified by chromatography on silica gel (eluent: petroleum ether/ethyl ether = 50/1) to afford **21**¹⁷ (*E/Z* = 96/4) (4.4510 g, 98%) as an oil: ¹H NMR (400 MHz, CDCl₃) δ 5.47–5.35 (m, 2 H, CH=CH), 4.59–4.56 (m, 1 H, CH of the THP group), 3.91–3.83 (m, 1 H, one proton of the THP group), 3.73 (dt, $J_1 = 10.0$ Hz, $J_2 = 7.0$ Hz, 1 H, one proton of OCH₂), 3.53–3.46 (m, 1 H, one proton of the THP group), 3.38 (dt, $J_1 = 9.6$ Hz, $J_2 = 6.7$ Hz, 1 H, one proton of OCH₂), 2.00–1.91 (m, 2 H, CH₂), 1.88–1.78 (m, 1 H, one proton of the THP group), 1.76–1.68 (m, 1 H, one proton of the THP group), 1.66–1.62 (m, 3 H, CH₃), 1.62–1.46 (m, 6 H, four protons of the THP group + CH₂), 1.40–1.21 (m, 12 H, 6 × CH₂); ¹³C NMR (100 MHz, CDCl₃) δ 131.6, 124.5, 98.8, 67.6, 62.3, 32.6, 30.8, 29.7, 29.6, 29.5, 29.44, 29.43, 29.1, 26.2, 25.5, 19.7, 17.9; IR (neat) ν (cm⁻¹) 2925, 2854, 1458, 1321, 1260, 1202, 1122, 1077, 1030; MS (EI) m/z (%): 268 (M⁺, 0.33), 85 (100). The following signals are discernible for **21** (*Z*): ¹H NMR (400 MHz, CDCl₃) δ 2.07–2.00 (m, 2 H, CH₂).

(E)-10-Dodecen-1-ol (16).



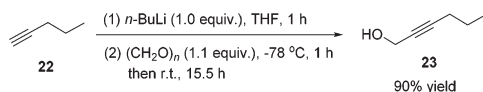
To a 100 mL round bottom flask were added **21** (4.2570 g, 16.0 mmol), *p*-TsOH·H₂O (603.7 mg, 3.2 mmol), and MeOH (32 mL). The reaction was stirred for 13 h until the completion of the reaction as monitored by TLC. A saturated NaHCO₃ aqueous solution (40 mL) was added to quench the reaction. After filtration, MeOH was removed by evaporation. Et₂O (40 mL) and H₂O (20 mL) were added and the organic layer was separated. The aqueous phase was extracted by ethyl ether (30 × 3 mL). The combined organic layer was washed with brine (30 mL) and dried over anhydrous MgSO₄. After filtration and evaporation, the residue was purified by chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 5/1 to 2/1) to afford **16**⁸ (2.8620 g, 98%) as an oil: ¹H NMR (400 MHz, CDCl₃) δ 5.47–5.35 (m, 2 H, CH=CH), 3.62 (t, $J = 6.6$ Hz, 2 H, OCH₂), 1.99–1.92 (m, 2 H, CH₂), 1.80 (brs, 1 H, OH), 1.64 (dd, $J_1 = 3.6$ Hz, $J_2 = 1.2$ Hz, 3 H, CH₃), 1.56 (quint, $J = 7.0$ Hz, 2 H, CH₂), 1.39–1.20 (m, 12 H, 6 × CH₂); ¹³C NMR (100 MHz, CDCl₃) δ 131.6, 124.5, 62.9, 32.7, 32.5, 29.55, 29.53, 29.41, 29.38, 29.1, 25.7, 17.9; IR (neat) ν (cm⁻¹) 3364, 2924, 2854, 1459, 1377, 1056; MS (EI) m/z (%): 184 (M⁺, 0.54), 55 (100).

(E)-10-Dodecenal (3).⁹



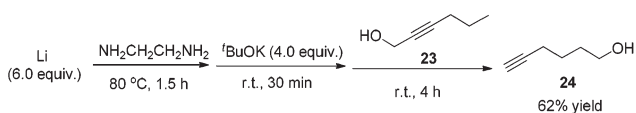
To a 50 mL Schlenk flask were added $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ (145.6 mg, 0.36 mmol), TEMPO (56.5 mg, 0.36 mmol), NaCl (14.1 mg, 0.24 mmol), **16** (442.5 mg, 2.4 mmol), and DCE (9.6 mL) sequentially under the atmosphere of oxygen from a gas bag. The reaction was then carried out at room temperature for 16.5 h. The crude reaction mixture was filtered through a short column of silica gel eluted with ethyl ether (3 × 40 mL). After evaporation, the residue was purified by chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 30/1) to afford **3**¹⁸ (267.2 mg, 61%) as an oil: ¹H NMR (400 MHz, CDCl_3) δ 9.76 (t, J = 1.8 Hz, 1 H, CHO), 5.47–5.35 (m, 2 H, CH=CH), 2.42 (td, J_1 = 7.4 Hz, J_2 = 2.0 Hz, 2 H, CH_2), 1.99–1.90 (m, 2 H, CH=CH CH_2), 1.68–1.58 (m, 5 H, CH_3 + CH_2), 1.38–1.21 (m, 10 H, 5 × CH_2); ¹³C NMR (100 MHz, CDCl_3) δ 203.0, 131.5, 124.6, 43.9, 32.5, 29.5, 29.3, 29.2, 29.1, 29.0, 22.0, 17.9; IR (neat) ν (cm^{-1}) 2925, 2854, 2715, 1727, 1455, 1411, 1013; MS (EI) m/z (%): 182 (M^+ , 0.67), 55 (100).

2-Hexyn-1-ol (**23**).



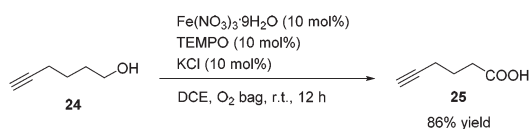
Compound **23** was prepared following the same procedure as preparation of compound **18**. The reaction of **22** (3.9134 g, 98% purity, 56.3 mmol), *n*-BuLi (2.5 M in hexanes, 22.5 mL, 56.3 mmol), and paraformaldehyde (1.9583 g, 95% purity, 61.9 mmol) in anhydrous THF (56 mL) afforded **23**¹⁹ (4.9558 g, 90%) as an oil: ¹H NMR (400 MHz, CDCl_3) δ 4.29–4.23 (m, 2 H, OCH_2), 2.20 (tt, J_1 = 7.2 Hz, J_2 = 2.2 Hz, 2 H, $\text{C}\equiv\text{CCH}_2$), 1.56–1.49 (m, 3 H, CH_2 + OH), 0.98 (t, J = 7.4 Hz, 3 H, CH_3); ¹³C NMR (100 MHz, CDCl_3) δ 86.2, 78.4, 51.1, 21.9, 20.6, 13.4; IR (neat) ν (cm^{-1}) 3329, 2963, 2935, 2872, 2289, 2227, 1457, 1431, 1380, 1338, 1136, 1032, 1003; MS (ESI) m/z (%): 98 (M^+ , 15.61), 83 (100).

5-Hexyn-1-ol (**24**).

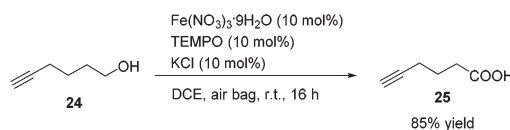


Compound **24** was prepared following the same procedure as preparation of compound **5**. The reaction of the Li rod (417.3 mg, 60.0 mmol), ^tBuOK (4.4892 g, 40.0 mmol), and **23** (981.7 mg, 10.0 mmol) in $\text{NH}_2\text{CH}_2\text{CH}_2\text{NH}_2$ (40 mL) afforded **24**²⁰ (608.8 mg, 62%) as an oil: ¹H NMR (400 MHz, CDCl_3) δ 3.68 (t, J = 6.4 Hz, 2 H, OCH_2), 2.24 (td, J_1 = 6.8 Hz, J_2 = 2.8 Hz, 2 H, $\text{C}\equiv\text{CCH}_2$), 1.97 (t, J = 2.6 Hz, 1 H, $\text{C}\equiv\text{CH}$), 1.74–1.51 (m, 5 H, 2 × CH_2 + OH); ¹³C NMR (100 MHz, CDCl_3) δ 84.2, 68.5, 62.0, 31.5, 24.6, 18.1; IR (neat) ν (cm^{-1}) 3295, 2941, 2868, 2116, 1455, 1434, 1329, 1260, 1161, 1060, 1039; MS (ESI) m/z (%): 98 (M^+ , 4.42), 79 (100).

5-Hexynoic acid (**25**).¹³

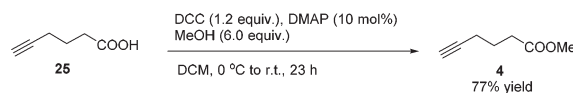


To a Schlenk tube were added $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ (40.6 mg, 0.1 mmol), TEMPO (15.7 mg, 0.1 mmol), KCl (7.7 mg, 0.1 mmol), **24** (97.8 mg, 1.0 mmol), and DCE (4.0 mL) sequentially under the atmosphere of oxygen from a gas bag. The reaction was then carried out at room temperature for 12 h until the completion of the reaction as monitored by TLC (petroleum ether/ethyl acetate = 5/1). The crude reaction mixture was filtered through a short column of silica gel eluted with ethyl ether (3 × 25 mL). After evaporation, the residue was purified by chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 6/1 to 2/1) to afford **25**²¹ (95.9 mg, 86%) as an oil: ¹H NMR (400 MHz, CDCl_3) δ 10.34 (brs, COOH), 2.52 (t, J = 7.4 Hz, 2 H, CH_2), 2.29 (td, J_1 = 7.0 Hz, J_2 = 2.8 Hz, 2 H, $\text{C}\equiv\text{CCH}_2$), 2.00 (t, J = 2.8 Hz, 1 H, $\text{C}\equiv\text{CH}$), 1.86 (quint, J = 7.2 Hz, 2 H, CH_2); ¹³C NMR (100 MHz, CDCl_3) δ 179.7, 83.0, 69.3, 32.5, 23.2, 17.7; IR (neat) ν (cm^{-1}) 3400–2800, 3297, 2118, 1703, 1413, 1242, 1205, 1156, 1052; MS (ESI) m/z (%): 112 (M^+ , 1.68), 70 (100).



To a 100 mL round bottom flask were added $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$ (40.5 mg, 0.1 mmol) and DCE (3.0 mL). TEMPO (15.8 mg, 0.1 mmol), KCl (7.4 mg, 0.1 mmol), **24** (97.5 mg, 1.0 mmol), and DCE (1.0 mL) were then added sequentially. The flask was connected to a gas bag of air with a valve. The reaction was then carried out at room temperature for 16 h until the completion of the reaction as monitored by TLC (petroleum ether/ethyl acetate = 5/1). The crude reaction mixture was filtered through a short column of silica gel eluted with ethyl ether (3 × 25 mL). After evaporation, the residue was purified by chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 6/1 to 2/1) to afford **25**²¹ (94.6 mg, 85%) as an oil: ¹H NMR (400 MHz, CDCl_3) δ 10.41 (brs, 1 H, COOH), 2.52 (t, J = 7.4 Hz, 2 H, CH_2), 2.29 (td, J_1 = 6.9 Hz, J_2 = 2.7 Hz, 2 H, CH_2), 2.00 (t, J = 2.6 Hz, 1 H, $\text{C}\equiv\text{CH}$), 1.86 (quint, J = 7.2 Hz, 2 H, CH_2); ¹³C NMR (100 MHz, CDCl_3) δ 179.7, 83.0, 69.3, 32.6, 23.2, 17.7.

Methyl 5-hexynoate (**4**).

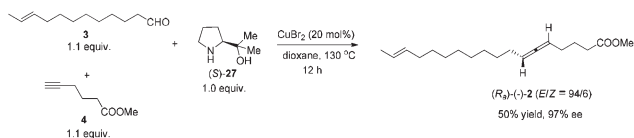


To a round bottom flask were added **25** (1.1163 g, 10.0 mmol)/DCM (5 mL) and DMAP (122.2 mg) sequentially. MeOH (2.43 mL, 0.791 g mL^{-1} , 1.9224 g, 60.0 mmol)/DCM (5 mL), DCC (2.4800 g, 12.0 mmol), and DCM (10 mL) were added sequentially at 0 °C. The resulting mixture was then allowed to warm up to room temperature and stirred for 23 h. The crude reaction mixture was filtered through a short column of silica gel eluted with DCM (3 × 10 mL) and evaporated. H_2O (20 mL) and Et_2O (20 mL) were added and the organic layer was separated. The aqueous phase was extracted by ethyl ether (20 × 3 mL). The combined organic layer was washed with



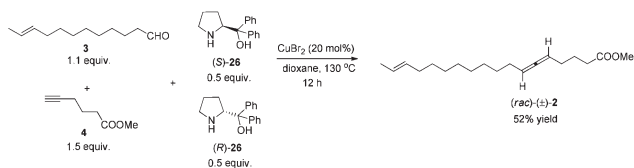
brine and dried over anhydrous MgSO_4 . After filtration and evaporation, the residue was purified *via* chromatography on silica gel (eluent: petroleum ether/ethyl ether = 25/1) to afford **4**²² (967.0 mg, 77%) as an oil: $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 3.69 (s, 3H, OCH_3), 2.47 (t, $J = 7.4$ Hz, 2 H, CH_2), 2.27 (td, $J_1 = 6.9$ Hz, $J_2 = 2.7$ Hz, 2 H, CH_2), 1.98 (t, $J = 2.8$ Hz, 1 H, $\equiv\text{CH}$), 1.86 (quint, $J = 7.2$ Hz, 2 H, CH_2); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 173.5, 83.2, 69.1, 51.6, 32.6, 23.5, 17.8; IR (neat) ν (cm^{-1}) 3295, 2954, 2118, 1736, 1438, 1370, 1318, 1223, 1161, 1058; MS (ESI) m/z (%): 126 (M^+ , 25.52), 82 (100).

Methyl (*R,E*)-5,6,16-octadecatrienoate ((*R*_a)-(–)-2).⁷



To a flame dried Schlenk tube were added CuBr_2 (51.6 mg, 0.23 mmol), (*S*)-27¹² (150.1 mg, 1.16 mmol), **4** (161.6 mg, 1.28 mmol)/dioxane (4.6 mL), and **3** (233.3 mg, 1.28 mmol)/dioxane (4.6 mL) sequentially. The Schlenk tube was then sealed with a screw cap of polytetrafluoroethylene. The resulting mixture was then stirred at 130 °C with a preheated oil bath. After 12 h, the reaction was complete as monitored by TLC (petroleum ether/ethyl acetate = 5/1) and the resulting mixture was diluted with 30 mL of Et_2O and washed with an aqueous solution of hydrochloric acid (3 M, 20 mL). The organic layer was separated and the aqueous phase was extracted with ethyl ether (20 × 2 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4 . After filtration and evaporation, the residue was purified by chromatography on silica gel (eluent: petroleum ether/ethyl ether = 200/1) to afford (*R*_a)-(–)-2^{2,4} (*E/Z* = 94/6) (168.3 mg, 50%) as an oil: 97% ee (HPLC conditions: CHIRALPAK AD-RH (0.46 × 15 cm, 5 μm), $\text{MeCN}/\text{H}_2\text{O} = 62/38$, 0.7 mL min^{-1} , $\lambda = 214$ nm, $t_{\text{R}}(\text{major}) = 48.9$ min, $t_{\text{R}}(\text{minor}) = 60.2$ min); $[\alpha]_{\text{D}}^{29.3} = -52.8$ ($c = 0.305$, EtOH) (lit.² $[\alpha]_{\text{D}}^{25} = -50$ ($c = 0.28$, EtOH)); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 5.47–5.35 (m, 2 H, $\text{CH}=\text{CH}$), 5.13–5.00 (m, 2 H, $\text{CH}=\text{C}=\text{CH}$), 3.67 (s, 3 H, CH_3), 2.36 (t, $J = 7.4$ Hz, 2 H, CH_2), 2.06–1.92 (m, 6 H, 3 × CH_2), 1.74 (quint, $J = 7.4$ Hz, 2 H, CH_2), 1.66–1.62 (m, 3 H, CH_3), 1.43–1.22 (m, 12 H, 6 × CH_2); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 204.0, 174.1, 131.6, 124.5, 91.5, 89.7, 51.5, 33.3, 32.6, 29.6, 29.5, 29.4, 29.18, 29.15, 29.08, 28.9, 28.3, 24.3, 17.9; IR (neat) ν (cm^{-1}) 2924, 2853, 1962, 1741, 1436, 1365, 1313, 1243, 1209, 1154, 1059, 1019, 966, 876; MS (EI) m/z (%): 292 (M^+ , 4.79), 154 (100). The following signals are discernible for (*R*_a)-(–)-2 (*Z*): 1.61–1.59 (m, 3 H, CH_3).

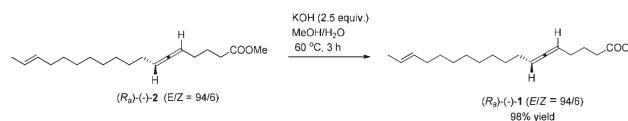
Methyl (*E*)-5,6,16-octadecatrienoate ((*rac*)-(±)-2).⁷



To a flame dried Schlenk tube were added CuBr_2 (18.0 mg, 0.08 mmol), (*S*)-26 (50.8 mg, 0.2 mmol), (*R*)-26 (50.9 mg,

0.2 mmol), **4** (75.7 mg, 0.6 mmol)/dioxane (1.6 mL), and **3** (80.2 mg, 0.44 mmol)/dioxane (1.6 mL) sequentially. The Schlenk tube was then sealed with a screw cap of polytetrafluoroethylene. The resulting mixture was then heated at 130 °C with a preheated oil bath. The reaction was complete after 12 h as monitored by TLC (petroleum ether/ethyl acetate = 5/1). After being cooled to room temperature, the resulting mixture was diluted with 15 mL of Et_2O and washed with an aqueous solution of hydrochloric acid (3 M, 10 mL). The organic layer was separated, and the aqueous phase was extracted with ethyl ether (10 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4 . After filtration and evaporation, the residue was purified by chromatography on silica gel (eluent: petroleum ether/ethyl ether = 200/1) to afford (*rac*)-(±)-2⁴ (60.7 mg, 52%) as an oil: $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 5.47–5.35 (m, 2 H, $\text{CH}=\text{CH}$), 5.14–4.99 (m, 2 H, $\text{CH}=\text{C}=\text{CH}$), 3.67 (s, 3 H, CH_3), 2.36 (t, $J = 7.4$ Hz, 2 H, CH_2), 2.06–1.92 (m, 6 H, 3 × CH_2), 1.74 (quint, $J = 7.4$ Hz, 2 H, CH_2), 1.66–1.61 (m, 3 H, CH_3), 1.43–1.22 (m, 12 H, 6 × CH_2); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 204.0, 174.1, 131.7, 124.5, 91.5, 89.8, 51.5, 33.3, 32.6, 29.6, 29.5, 29.4, 29.19, 29.17, 29.1, 28.9, 28.3, 24.3, 17.9; IR (neat) ν (cm^{-1}) 2924, 2853, 1962, 1741, 1436, 1365, 1313, 1242, 1207, 1154, 1060, 1018, 966, 876; MS (EI) m/z (%): 292 (M^+ , 6.07), 80 (100).

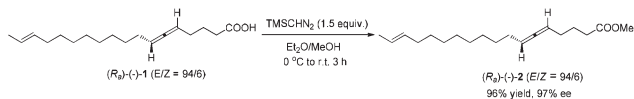
(*R,E*)-5,6,16-Octadecatrienoic acid ((*R*_a)-(–)-1).⁷



To a round bottom flask were added sequentially KOH (56.1 mg, 1.0 mmol), a solvent mixture (2 mL, $\text{MeOH}/\text{H}_2\text{O} = 4/1$ by volume), and (*R*_a)-(–)-2 (117.0 mg, 0.4 mmol)/solvent mixture (2 mL, $\text{MeOH}/\text{H}_2\text{O} = 4/1$ by volume). The resulting mixture was then stirred at 60 °C. The reaction was complete after 3 h as monitored by TLC. HCl (3 M, 0.4 mL) was added dropwise after the mixture was cooled with an ice bath. MeOH was removed by using a rotary evaporator. CH_2Cl_2 (30 mL) and water (20 mL) were added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (10 mL × 3). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4 . After filtration and evaporation, the residue was purified by chromatography on silica gel to afford (*R*_a)-(–)-1^{2,4} (*E/Z* = 94/6) (109.3 mg, 98%) (eluent: petroleum ether/ethyl acetate = 10/1 to 2/1) as an oil: $[\alpha]_{\text{D}}^{29.4} = -55.2$ ($c = 0.995$, EtOH); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 10.93 (brs, 1 H, COOH), 5.47–5.34 (m, 2 H, $\text{CH}=\text{CH}$), 5.14–5.00 (m, 2 H, $\text{CH}=\text{C}=\text{CH}$), 2.40 (t, $J = 7.4$ Hz, 2 H, CH_2), 2.08–1.92 (m, 6 H, 3 × CH_2), 1.75 (quint, $J = 7.4$ Hz, 2 H, CH_2), 1.66–1.62 (m, 3 H, CH_3), 1.43–1.21 (m, 12 H, 6 × CH_2); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 204.0, 180.3, 131.7, 124.5, 91.6, 89.6, 33.3, 32.6, 29.6, 29.5, 29.4, 29.18, 29.16, 29.1, 28.9, 28.2, 23.9, 17.9; IR (neat) ν (cm^{-1}) 3500–2500, 2923, 2853, 1962, 1707, 1438, 1413, 1287, 1240, 1204, 1158, 1056, 964, 875; MS (EI) m/z (%): 278 (M^+ , 1.17), 140 (100). The following signals are discernible for (*R*_a)-(–)-1 (*Z*): 1.61–1.58 (m, 3 H, CH_3).



ee determination: by the synthesis of methyl (*R_a*)-(-)-2.¹¹



To a round bottom flask were added (*R_a*)-(-)-1 (55.8 mg, 0.2 mmol) and a solvent mixture (5 mL, Et₂O/MeOH = 4/1 by volume). TMSCHN₂ (2 M in hexane, 0.15 mL, 0.3 mmol) was added dropwise at 0 °C. The reaction mixture was then warmed up to room temperature naturally. When the reaction was complete as monitored by TLC after 3 h, the solvent was evaporated under vacuum, and the residue was purified by chromatography on silica gel to afford (*R_a*)-(-)-2^{2,4} ($E/Z = 94/6$) (56.2 mg, 96%) (eluent: petroleum ether/ethyl ether = 150/1) as an oil: 97% ee (HPLC conditions: CHIRALPAK AD-RH (0.46 × 15 cm, 5 μm), MeCN/H₂O = 62/38, 0.7 mL min⁻¹, λ = 214 nm, t_R (major) = 47.1 min, t_R (minor) = 60.0 min); [α]_D^{29.4} = -52.1 ($c = 0.315$, EtOH) (lit.² [α]_D²⁵ = -50 ($c = 0.28$, EtOH)); ¹H NMR (400 MHz, CDCl₃) δ 5.47–5.34 (m, 2 H, CH=CH), 5.13–5.00 (m, 2 H, CH=C=CH), 3.67 (s, 3 H, CH₃), 2.36 (t, $J = 7.6$ Hz, 2 H, CH₂), 2.06–1.91 (m, 6 H, 3 × CH₂), 1.74 (quint, $J = 7.2$ Hz, 2 H, CH₂), 1.67–1.61 (m, 3 H, CH₃), 1.44–1.20 (m, 12 H, 6 × CH₂); ¹³C NMR (100 MHz, CDCl₃) δ 204.0, 174.0, 131.6, 124.5, 91.4, 89.7, 51.4, 33.3, 32.6, 29.6, 29.5, 29.4, 29.2, 29.14, 29.06, 28.9, 28.3, 24.3, 17.9. The following signals are discernible for (*R_a*)-(-)-1 (Z): 1.61–1.58 (m, 3 H, CH₃).

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