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Tetrahedron 62 (2006) 311–316

Synthesis of (−)-(5*R*,6*S*)-6-acetoxyhexadecanolide based on L-proline-catalyzed asymmetric aldol reactions

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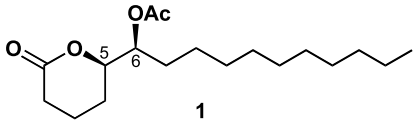
Received 1 June 2005; revised 8 August 2005; accepted 31 August 2005

Available online 3 October 2005

Abstract—A convenient method for proline-catalyzed asymmetric aldol reactions using synthons of straight-chain aliphatic aldehydes, and aldehydes bearing a 1,3-dithiane moiety at the β-position, has been developed. This method was successfully applied to the synthesis of (−)-(5*R*,6*S*)-6-acetoxyhexadecanolide, an oviposition attractant pheromone of the female *Culex* mosquito.

1. Introduction

Recent advances in the field of organocatalytic asymmetric synthesis have provided several new methods for obtaining chiral compounds in an environmentally benign manner.[1] Most attention has been focused on the use of proline due to its ready availability in either L- or D-form and the highly versatile nature of its reactivity.[1,2] In particular, proline-catalyzed asymmetric aldol reactions have been extensively studied from the viewpoint of their synthetic value as well as mechanistic considerations.[1–3] However, there is still a significant limitation on the use of unsubstituted aliphatic aldehydes as an aldol component.[4] Initially, we thought that this problem could be solved by applying a high-pressure technique,[5] but all attempts failed due to the formation of a rather complex mixture. Very recently, Sun et al. reported the use of undecanal itself for asymmetric aldol reactions of this type and applied it in their synthesis of (−)-(5*R*,6*S*)-6-acetoxyhexadecanolide (**1**).[6] This result prompted us to report our independent investigation on the development of new synthons of straight-chain aliphatic aldehydes and their application to the enantioselective synthesis of **1**.[7]



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(−)-(5*R*,6*S*)-6-Acetoxyhexadecanolide (**1**), an oviposition attractant pheromone of the female *Culex* mosquito, has attracted considerable attention from synthetic chemists[8] because of its ability to transmit the West Nile virus.[9] In this lab we reported the short synthesis of this compound based on a chiral triflate technology starting from D-tartrate as the chiral source.[10] In recent years, with the increasing demand for catalytic asymmetric transformations, major studies on the synthesis of **1** have focused on demonstrating of the power of newly discovered techniques.[11] Unfortunately, however, there are no reports on the use of organocatalytic systems to construct this fascinating molecule, except for the recent work of Sun et al.[6] We describe here our own approach using proline-catalyzed asymmetric aldol reactions as a key step along with straight-chain aliphatic aldehyde synthons.

2. Results and discussion

2.1. Model studies for L-proline-catalyzed asymmetric aldol reactions

To survey the possible candidates for straight-chain aliphatic aldehyde synthons, we designed three different types of substrates, that is, thiophenecarboxaldehydes **A** and aldehydes bearing a 1,3-dithiane moiety at the α- or β-position (**B** and **C**), because of the ease at which they are converted to the naked unbranched side chain structures after desulfurization (Fig. 1).[12] Thus, compounds **A** and **B** were chosen as representative aldehydes having no enolizable α-hydrogens, while with **C** it can be expected that the 1,3-dithiane function can act effectively as steric bulk to impede the undesired side reactions.[13]

To confirm the feasibility of our synthetic strategy, we then

Keywords: Proline; Aldol; Aldehydes; Oviposition attractant pheromone.
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doi:10.1016/j.tet.2005.08.111

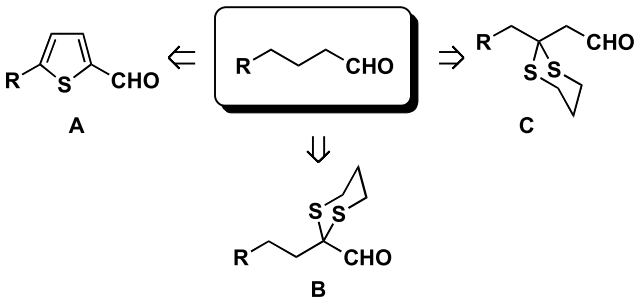


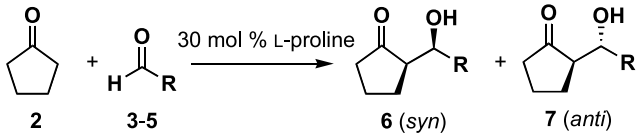
Figure 1. Straight-chain aliphatic aldehyde synthons.

aldehyde carbonyl center (runs 4–6). Fortunately, we found that the use of aldehyde **5** led to the preferential formation of *syn*-adduct **6** with high enantioselectivity (runs 7–9). Apparently, in **5** the β-dithiane functionality exerts a remarkable effect in determining the reaction course with favorable diastereo- and enantioselective control. With these results in hand, we proceeded with the asymmetric synthesis of **1**.

2.2. Total synthesis of (−)-(5*R*,6*S*)-6-acetoxyhexadecanolide (1)

The required aldehyde **11** was readily prepared from ethyl

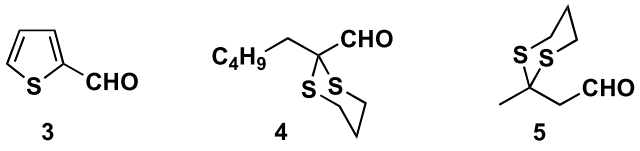
Table 1. L-Proline-catalyzed asymmetric aldol reactions of cyclopentanone (**2**) with aldehydes **3–5**



Run	Aldehyde	Conditions[a]	Yield (%)	dr **6**/**7**[b]	ee (%)[c]	
					6	**7**
1	**3**	DMSO, rt, 30 h[d]	82	48:52	31	34
2	**3**	Solvent-free, rt, 84 h	79	47:53	43	48
3	**3**	Solvent-free, 0.2 GPa, rt, 60 h	77	41:59	15	22
4	**4**	DMSO, rt, 72 h[d]	No reaction			
5	**4**	Solvent-free, rt, 72 h	No reaction			
6	**4**	Solvent-free, 0.2 GPa, rt, 24 h	No reaction			
7	**5**	DMSO, rt, 9 h[d]	75	80:20	93	86
8	**5**	Solvent-free, rt, 6 h	81	80:20	93	85
9	**5**	Solvent-free, 0.2 GPa, rt, 12 h	86	73:27	90	88

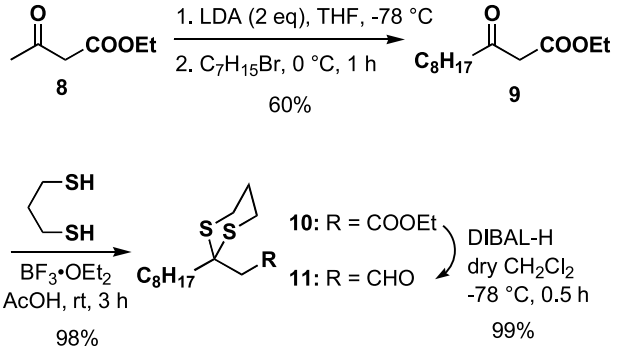
[a] Compound **2**:aldehyde 34:1, except in DMSO (6.5 equiv of **2**).
[b] Determined by ^{1}H NMR.
[c] Determined by chiral HPLC (Chiralpak AD).
[d] Compound **2**:DMSO 1:4 (vol%).

examined the asymmetric aldol reactions of cyclopentanone (**2**) with thiophenecarboxaldehyde **3** (**A**, R=H), aldehydes **4** (**B**, R=C_2H_5) and **5** (**C**, R=H) under the catalysis of L-proline. The starting aldehydes **4** and **5** were prepared from 2-pentyl-1,3-dithiane[14] via well-known lithiation/formylation or by the sequential treatment of ethyl acetoacetate according to the literature procedure.[15]



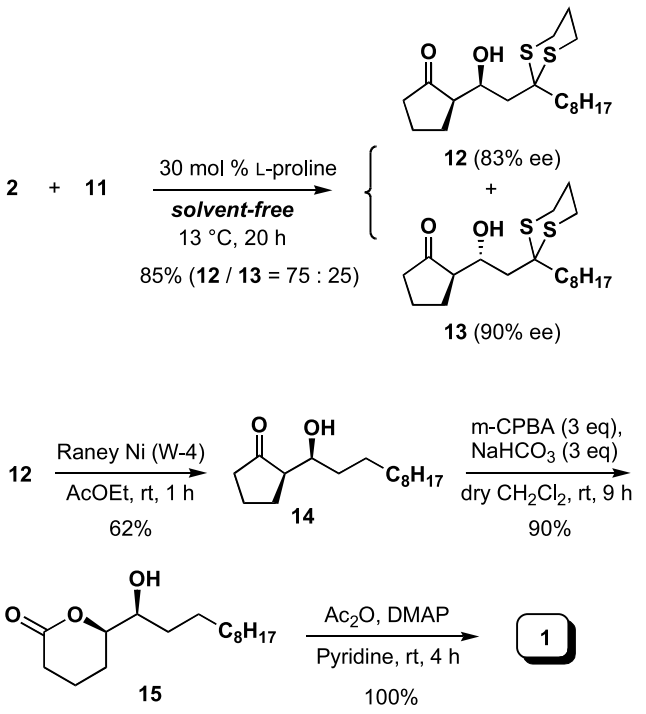
All reactions were examined under three different conditions: (1) in DMSO as a solvent at room temperature; (2) solvent-free at room temperature; and (3) solvent-free at 0.2 GPa pressure and room temperature. As can be seen from the results summarized in Table 1,[16] there is a significant difference in reactivity and stereoselectivity between **3–5**.

Thus, thiophenecarboxaldehyde (**3**) gave the desired adducts **6** and **7** in good yields, but diastereo- and enantioselectivity were only moderate under either condition (runs 1–3). Aldehyde **4** was inert under these conditions, indicating severe steric hindrance around the acetoacetate (**8**) after chain elongation[17] as illustrated in Scheme 1. We then proceeded to complete the total synthesis of **1** according to our original idea (Scheme 2).



Scheme 1.

The aldol reaction of **11** with cyclopentanone (**2**, ca. 30 equiv) in the presence of 30 mol% of L-proline under solvent-free conditions at 13 °C for 20 h proceeded quite smoothly to give *syn*- and *anti*-adducts, **12** and **13**, as a 75:25 mixture in a combined yield of 85%.[18,19] The enantiomeric purities of **12** and **13** were determined to be 83 and 90%, respectively, by chiral HPLC analysis (Chiralpak AD, elution with hexane/2-propanol 90:10). After chromatographic separation, careful treatment of the



Scheme 2.

syn-adduct **12** with Raney-Ni (W-4) in ethyl acetate[20] as a solvent gave the desired β-hydroxy ketone **14** in 62% yield as a somewhat unstable product. Therefore, this was immediately subjected to Baeyer–Villiger oxidation by exposure to 3 equiv of *m*-CPBA and 3 equiv of $NaHCO_3$, and the hydroxy-lactone **15** was obtained in 90% yield as a highly crystalline substance. Recrystallization from ether/hexane gave optically pure **15**; mp 67–68 °C, $[\alpha]_D^{20}-12.7$ (*c* 1.0, $CHCl_3$) (lit.[6] mp 66.5–68 °C, $[\alpha]_D-11.0$ (*c* 1.5, $CHCl_3$)), which was finally converted into **1** by acetylation under normal conditions in quantitative yield. This compound, $[\alpha]_D^{21}-36.8$ (*c* 1.55, $CHCl_3$) (lit.[10] $[\alpha]_D^{24}-36.8$ (*c* 1.0, $CHCl_3$)), was identical in all respects to the authentic sample.[10]

3. Conclusions

In conclusion, we have developed a convenient method for the asymmetric aldol reactions of ketones with aldehydes bearing a 1,3-dithiane moiety at the β-position as convenient synthons of straight-chain aliphatic aldehydes. The reaction was successfully applied to the synthesis of **1**. This approach might be useful for preparing a variety of enantiomerically enriched β-hydroxy ketone derivatives, and further studies to extend the scope of this method are now in progress.

4. Experimental

4.1. General

All reactions were performed in an oven-dried glassware under a positive pressure of nitrogen or argon. Air- and moisture-sensitive compounds were introduced via syringe or cannula through a rubber septum. All high-pressure reactions were performed in a piston-cylinder type apparatus (Hikari Koatsu HR-15-B3).

All melting points were measured on Yanagimoto MP-S3 micro-melting point apparatus and were uncorrected. The NMR spectra were recorded on a JEOL LA 400 (400 MHz for ^1H NMR analysis and 100 MHz for ^{13}C NMR analysis). All NMR spectra were taken in $CDCl_3$ solution and were reported in part per millions (δ) downfield from TMS as an internal standard. The infrared spectra were measured with a JASCO FTIR-460plus Fourier Transform Infrared Spectrophotometer and were reported in wavenumbers (cm^{-1}). Optical rotations were measured on a JASCO DIP-370 polarimeter. HPLC analysis was carried out using a Hitachi L-6200 HPLC system.

Thin-layer chromatography (TLC) was conducted by using Merck Kieselgel 60F-254 plates (0.25 mm). For column chromatography, Fuji silicia BW-300 and, for flash chromatography, Merck Kieselgel (230–400 mesh) was employed.

4.1.1. 2-Pentyl-1,3-dithiane-2-carbaldehyde (3). To a stirred solution of 2-pentyl-1,3-dithiane (1.82 g, 9.6 mmol)[14] in dry THF (43 mL) at −78 °C was added *n*-BuLi (7.1 mL, 11.2 mmol; 1.58 M in hexanes) and the mixture was stirred for 2 h. To this light yellow solution was then added dry DMF (0.77 mL, 10 mmol) and the mixture was stirred at −78 °C for 1 h. The mixture was quenched with H_2O and extracted with $CHCl_3$. The combined extracts were dried ($MgSO_4$), concentrated, and purified by silica gel column chromatography (hexane/AcOEt 9:1) to give **3** (1.3 g, 62%) as a colorless oil. R_f 0.47 (hexane/Et_2O 4:1); FTIR (neat) 1715, 1465, 1424; ^1H NMR: 0.88 (3H, t, J= 7.1 Hz), 1.22–1.36 (4H, m), 1.42–1.50 (2H, m), 1.74–1.86 (3H, m), 2.10 (1H, dtt, J=14.2, 4.1, 2.4 Hz), 2.60 (2H, ddd, J=14.6, 4.1, 3.2 Hz), 3.02 (2H, ddd, J=14.6, 12.9, 2.4 Hz); ^{13}C NMR: 13.8, 22.2, 23.4, 24.5, 26.7 (×2), 31.9, 35.9, 58.1, 189.6. Anal. Calcd for $C_{10}H_{18}OS_2$: C, 55.00; H, 8.31. Found: C, 55.08; H, 8.50.

4.2. General procedure for the L-proline-catalyzed asymmetric aldol reactions

Method A (in DMSO at 1 atm and room temperature). A mixture of aldehyde (0.5 mmol), cyclopentanone (**2**, 0.3 mL, 3.4 mmol) and L-proline (17 mg, 0.15 mmol) in dry DMSO (1.2 mL) was stirred at room temperature under Ar. After completion of the reaction, the mixture was quenched with water and the aqueous phase was extracted with $CHCl_3$. The combined extracts were dried ($MgSO_4$), concentrated, and purified by silica gel column chromatography to give the pure *syn*- and *anti*-aldol adducts.

Method B (solvent-free at 1 atm and room temperature). A mixture of aldehyde (0.5 mmol), cyclopentanone (**2**, 1.5 mL, 17.0 mmol) and L-proline (17 mg, 0.15 mmol) was stirred at room temperature under Ar, and then treated as above.

Method C (solvent-free at 0.2 GPa and room temperature). A mixture of aldehyde (0.5 mmol), cyclopentanone (**2**,

1.5 mL, 17.0 mmol) and L-proline (17 mg, 0.15 mmol) was placed in a Teflon reaction vessel, and the mixture was allowed to react at 0.2 GPa and room temperature. After completion of the reaction, the mixture was treated as above.

4.2.1. *syn*-Adduct 6 from 3. Colorless needles; mp 64–67 °C (from Et_2O/hexane); R_f 0.32 (cyclohexane/Et_2O 1:1); $[\alpha]_D^{26}+62.2$ (*c* 1.75, $CHCl_3$; 30% ee); FTIR (KBr): 3366, 1719, 1450, 1401, 1161, 1029; ^{1}H NMR: 1.70–1.83 (1H, m), 1.98–2.10 (3H, m), 2.10–2.22 (1H, m), 2.33–2.41 (1H, m), 2.56 (1H, m), 2.71 (1H, d, $J=5.6$ Hz), 5.50 (1H, dd, $J=5.1$, 3.2 Hz), 6.95–6.99 (2H, m), 7.24 (1H, dd, $J=4.6$, 1.7 Hz); ^{13}C NMR: 20.5, 23.4, 39.1, 55.7, 68.8, 123.9, 124.6, 126.7, 146.3, 220.1. Anal. Calcd for $C_{10}H_{12}O_2S$: C, 61.20; H, 6.16. Found: C, 61.36; H, 6.26.

The ee was determined by chiral HPLC (Chiralpak AD, hexane/2-propanol 90:10, 0.5 mL/min): t_R 17.2 and 19.1 min.

4.2.2. *anti*-Adduct 7 from 3. Colorless oil; R_f 0.25 (cyclohexane/Et_2O 1:1); $[\alpha]_D^{16}-88.2$ (*c* 1.05, $CHCl_3$; 48% ee); FTIR (neat): 3450, 1719, 1449, 1402, 1358, 1222, 1157; ^{1}H NMR: 1.51–1.62 (1H, m), 1.70–1.85 (1H, m), 1.87–2.04 (2H, m), 2.25 (1H, ddd, $J=19.3$, 11.0, 8.8 Hz), 2.40–2.55 (2H, m), 4.65 (1H, s), 5.02 (1H, d, $J=9.3$ Hz), 6.94–6.97 (2H, m), 7.28 (1H, dd, $J=4.9$, 1.4 Hz); ^{13}C NMR: 20.3, 27.0, 38.7, 55.8, 71.3, 124.4, 125.1, 126.4, 145.2, 222.4. Anal. Calcd for $C_{10}H_{12}O_2S$: C, 61.20; H, 6.16. Found: C, 60.88; H, 6.12.

The ee was determined by chiral HPLC (Chiralpak AD, hexane/2-propanol 90:10, 0.5 mL/min): t_R 22.3 and 23.7 min.

4.2.3. *syn*-Adduct 6 from 5. Colorless oil; R_f 0.20 (cyclohexane/AcOEt 2:1); $[\alpha]_D^{18}+61.4$ (*c* 1.40, $CHCl_3$; 82% ee); FTIR (neat): 3449, 1732, 1449, 1421, 1403; ^{1}H NMR: 1.68 (3H, s), 1.69–1.83 (1H, m), 1.83–1.96 (1H, m), 1.97 (1H, dd, $J=15.0$, 1.6 Hz), 2.00–2.20 (6H, m), 2.28–2.36 (1H, m), 2.39 (1H, dd, $J=15.0$, 9.8 Hz), 2.78 (1H, dt, $J=14.4$, 3.2 Hz), 2.80 (1H, dt, $J=14.4$, 3.2 Hz), 2.97 (1H, ddd, $J=14.4$, 5.8, 2.9 Hz), 3.00 (1H, ddd, $J=14.4$, 5.8, 2.9 Hz), 3.21 (1H, d, $J=2.9$ Hz), 4.43 (1H, dd, $J=9.8$, 1.6 Hz); ^{13}C NMR: 20.7, 23.4, 24.6, 26.6, 26.8, 28.5, 39.0, 45.4, 47.6, 54.9, 67.2, 219.8. Anal. Calcd for $C_{12}H_{20}O_2S_2\cdot 1/8H_2O$: C, 54.87; H, 7.77. Found: C, 54.85; H, 7.66.

The ee was determined by chiral HPLC (Chiralpak AD, hexane/2-propanol 80:20, 0.7 mL/min): t_R 12.8 and 13.8 min.

4.2.4. *anti*-Adduct 7 from 5. Colorless oil; R_f 0.24 (cyclohexane/AcOEt 2:1); $[\alpha]_D^{19}-85.8$ (*c* 1.79, $CHCl_3$; 93% ee); FTIR (neat): 3481, 1723, 1448, 1421; ^{1}H NMR: 1.70 (3H, s), 1.68–1.84 (2H, m), 1.85–1.96 (1H, m), 1.98 (1H, d, $J=15.1$ Hz), 1.99–2.12 (2H, m), 2.13–2.27 (3H, m), 2.32–2.39 (1H, m), 2.40 (1H, dd, $J=14.9$, 9.3 Hz), 2.79 (1H, ddd, $J=14.4$, 7.4, 3.4 Hz), 2.81 (1H, ddd, $J=14.4$, 7.4, 3.4 Hz), 2.91 (1H, ddd, $J=14.4$, 9.8, 2.9 Hz), 2.96 (1H, ddd, $J=14.4$, 9.8, 2.9 Hz), 4.06 (1H, br s), 4.13 (1H, m); ^{13}C NMR: 20.5, 24.8, 26.5, 26.7, 26.8, 28.3, 39.0, 45.5, 47.9, 53.9, 69.5, 221.7. Anal. Calcd for $C_{12}H_{20}O_2S_2$: C, 55.35; H, 7.74. Found: C, 55.28; H, 7.98.

The ee was determined by chiral HPLC (Chiralpak AD, hexane/2-propanol 85:15, 0.7 mL/min): t_R 13.4 and 16.4 min.

4.2.5. Ethyl 3-oxoundecanoate (9). To a solution of LDA, prepared from *i*-Pr_2NH (9.12 mL, 65.1 mmol) and *n*-BuLi (44 mL, 65.08 mmol; 1.48 M in hexanes), in dry THF (60 mL) at −78 °C was added dropwise ethyl acetoacetate (3.32 mL, 26.0 mmol) and the mixture was stirred at −78 °C for 1 h. After warming to 0 °C, to this light yellow solution was added dropwise 1-bromoheptane (4.5 mL, 28.64 mmol) and the mixture was stirred at room temperature for 1 h. The mixture was quenched with ice-cold 2 M HCl and extracted with Et_2O. The combined extracts were washed with satd NaCl, dried (Na_2SO_4), concentrated, and purified by silica gel column chromatography (hexane/Et_2O 2:1) to give **9** (3.58 g, 60%) as a colorless oil; R_f 0.47 (hexane/Et_2O 2:1); FTIR (neat): 1747, 1718, 1466, 1234, 1031; ^{1}H NMR: 0.88 (3H, t, $J=7.2$ Hz), 1.27 (9H, m), 1.28 (3H, t, $J=7.3$ Hz), 1.60 (3H, m), 2.53 (2H, t, $J=7.4$ Hz), 3.43 (2H, s), 4.20 (2H, q, $J=7.3$ Hz); ^{13}C NMR: 14.0(5), 14.0(7), 22.6, 23.4, 29.0, 29.1, 29.3, 31.8, 43.0, 49.3, 61.3, 167.3, 203.0. Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.47; H, 10.56.

4.2.6. Ethyl (2-octyl-1,3-dithian-2-yl)acetate (10). To a solution of **9** (3.5 g, 15 mmol) in AcOH at room temperature were added $BF_3\cdot Et_2O$ (1 g, 7.05 mmol) and 1,3-propanedithiol (1.8 g, 16.6 mmol) and the mixture was stirred for 3 h. After cooling to 0 °C, the mixture was quenched with H_2O, neutralized with aq $NaHCO_3$, and extracted with CH_2Cl_2. The combined extracts were dried ($MgSO_4$), concentrated, and purified by silica gel column chromatography (hexane/AcOEt 2:1) to give **10** (4.7 g, 98%) as a colorless oil; R_f 0.58 (hexane/AcOEt 2:1); FTIR (neat): 1735, 1185; ^{1}H NMR: 0.88 (3H, t, $J=7.3$ Hz), 1.27 (3H, t, $J=7.1$ Hz), 1.30 (9H, m), 1.55 (3H, m), 1.87 (1H, ddt, $J=14.0$, 11.2, 3.2 Hz), 2.02–2.12 (3H, m), 2.73 (2H, ddd, $J=14.2$, 5.4, 3.4 Hz), 3.04 (2H, ddd, $J=14.2$, 11.2, 2.8 Hz), 3.05 (2H, s), 4.15 (2H, q, $J=7.1$ Hz); ^{13}C NMR: 14.1, 14.2, 22.6, 23.7, 25.0, 26.4 (×2), 29.2, 29.4, 29.7, 31.8, 39.5, 42.7, 50.3, 60.5, 168.9. HRMS calcd for $C_{16}H_{30}O_2S_2$ 318.1687, found 318.1678.

4.2.7. (2-Octyl-1,3-dithian-2-yl)acetaldehyde (11). To a solution of **10** (2.75 g, 8.6 mmol) in dry CH_2Cl_2 (70 mL) at −78 °C was added a solution of DIBAL-H in toluene (1.0 M; 10.8 mL, 10.8 mmol) over 0.5 h and the mixture was placed in a freezer at −78 °C for 0.5 h. The excess of DIBAL-H was quenched with AcOH (0.45 mL) and warmed to room temperature. The mixture was then stirred with satd Rochelle's salt until the suspension disappeared and a clear two-phase solution was obtained. The aqueous phase was extracted with CH_2Cl_2 and the extracts were washed with satd $NaHCO_3$ and satd NaCl, dried (Na_2SO_4), and concentrated. Purification by silica gel column chromatography (hexane/AcOEt 2:1) gave **11** (2.33 g, 99%) as a colorless oil; R_f 0.56 (hexane/AcOEt 2:1); FTIR (neat): 1718, 1465, 1423; ^{1}H NMR: 0.88 (3H, t, $J=7.1$ Hz), 1.27 (10H, m), 1.50 (2H, m), 1.90–2.09 (4H, m),

2.83 (2H, ddd, J=14.6, 6.8, 3.7 Hz), 2.91 (2H, d, J=2.7 Hz), 2.91 (2H, ddd, J=14.6, 9.5, 3.4 Hz), 9.78 (1H, t, J=2.7 Hz); ^{13}C NMR: 13.9, 22.4, 23.8, 24.5, 26.0 (×2), 29.0, 29.1, 29.5, 31.6, 40.2, 49.1, 49.9, 199.53. HRMS calcd for $C_{14}H_{26}OS_2$ 274.1425, found 274.1407.

4.2.8. L-Proline-catalyzed asymmetric aldol reaction of cyclopentanone (2) with aldehyde (11). The mixture of **11** (6.82 g, 24.8 mmol), cyclopentanone (**2**, 74.73 mL, 845 mmol) and L-proline (858 mg, 7.45 mmol) was stirred at 13 °C for 20 h under Ar. The mixture was quenched with H_2O and extracted with $CHCl_3$. The combined extracts were dried ($MgSO_4$), concentrated, and purified by silica gel column chromatography (hexane/AcOEt 2:1) to give **12** (5.64 g, 63% yield; 83% ee) and **13** (1.91 g, 22% yield; 90% ee) as a colorless oil, respectively. The ee of these adducts were determined by chiral HPLC (254 nm, flow rate: 0.7 mL/min) carried out with Chiralpak AD (hexane/2-propanol 90:10; product **12** t_R 9.5 and 11.5 min, product **13** t_R 11.7 and 13.3 min).

4.2.9. (2*R*)-2-[(1*S*)-1-Hydroxy-2-(2-octyl-1,3-dithian-2-yl)ethyl]cyclopentanone (12). R_f 0.36 (hexane/AcOEt 2:1); $[\alpha]_D^{22}$ +45.6 (*c* 1.6, $CHCl_3$); FTIR (neat): 3446, 1736, 1457, 1421; ^{1}H NMR: 0.88 (3H, t, J=7.3 Hz), 1.29 (10H, m), 1.41 (1H, m), 1.53 (1H, m), 1.70–1.80 (1H, m), 1.85–2.18 (10H, m), 2.31 (1H, m), 2.37 (1H, dd, J=15.1, 9.8 Hz), 2.73–2.81 (2H, m), 2.93 (1H, ddd, J=13.4, 10.2, 2.9 Hz), 2.99 (1H, ddd, J=13.4, 10.2, 2.9 Hz), 3.34 (1H, d, J=2.7 Hz), 4.42 (1H, d, J=9.5 Hz); ^{13}C NMR: 14.1, 20.7, 22.6, 23.3, 23.9, 24.9, 26.0, 26.4, 29.2, 29.4, 29.8, 31.8, 39.0, 39.7, 42.4, 52.1, 54.9, 66.9, 219.7. Anal. Calcd for $C_{19}H_{34}O_2S_2 \cdot 1/5\ H_2O$: C, 63.00; H, 9.57. Found: C, 62.93; H, 9.38.

4.2.10. (2*R*)-2-[(1*R*)-1-Hydroxy-2-(2-octyl-1,3-dithian-2-yl)ethyl]cyclopentanone (13). R_f 0.38 (hexane/AcOEt 2:1); $[\alpha]_D^{20}$ −70.3 (*c* 0.83, $CHCl_3$); FTIR (neat): 3483, 1722, 1456, 1418; ^{1}H NMR: 0.88 (3H, t, J=7.1 Hz), 1.30 (10H, m), 1.43 (1H, m), 1.55 (1H, m), 1.75–2.10 (8H, m), 2.14–2.26 (3H, m), 2.35 (1H, m), 2.47 (1H, dd, J=15.2, 9.3 Hz), 2.75–2.80 (2H, m), 2.89 (1H, ddd, J=14.0, 9.5, 3.2 Hz), 2.95 (1H, ddd, J=14.0, 9.5, 3.0 Hz), 4.07 (1H, s), 4.14 (1H, dd, J=9.3, 5.6 Hz); ^{13}C NMR: 14.1, 20.6, 22.7, 24.0, 25.1, 26.1, 26.4, 26.7, 29.3, 29.4, 29.8, 31.8, 39.1, 39.3, 42.3, 52.4, 54.0, 69.2, 221.4. Anal. Calcd for $C_{19}H_{34}O_2S_2$: C, 63.64; H, 9.56. Found: C, 63.56; H, 9.31.

4.2.11. (2*R*)-2-[(1*S*)-1-Hydroxyundecyl]cyclopentanone (14). To a solution of **12** (882 mg, 2.46 mmol) in AcOEt (100 mL) was added Raney-Ni (40 g; Aldrich Raney-Ni 2800 was washed successively with H_2O (×3), MeOH (×3), and AcOEt (×3)),[20] and the mixture was stirred at room temperature for 1 h. The insoluble material was removed by filtration and washed thoroughly with AcOEt and MeOH. After evaporation of the solvent, the crude product was purified quickly by silica gel column chromatography ($CHCl_3$/Et_2O 4:1) to give **14** (388 mg, 62%) as a colorless oil; R_f 0.39 ($CHCl_3$/Et_2O 4:1); FTIR (neat): 3419, 1730, 1468, 1454; ^{1}H NMR: 0.88 (3H, t, J=6.8 Hz), 1.26 (16H, s), 1.4–1.6 (2H, m), 1.6–2.0 (3H, m), 2.03–2.15 (3H, m), 2.15–2.24 (1H, m), 2.28–2.36 (1H, m), 4.10 (1H, br); ^{13}C NMR: 14.1, 20.6, 22.7, 22.9, 26.0, 29.3, 29.5, 29.6 (×3), 31.9, 34.8, 39.1, 54.4, 69.7, 221.5.

This sample was used immediately for the next reaction.

4.2.12. (5*R*,6*S*)-6-Hydroxy-5-hexadecanolide (15). To a solution of **14** (517 mg, 2.03 mmol) in dry CH_2Cl_2 (30 mL) at 0 °C were added *m*-CPBA (98% activity; 700 mg, 4 mmol) and $NaHCO_3$ (340 mg, 4 mmol), and the mixture was stirred at room temperature for 4 h. To this mixture was added another portion of *m*-CPBA (98% activity; 350 mg, 2 mmol) and $NaHCO_3$ (170 mg, 2 mmol) and the mixture was stirred for 5 h. After completion of the reaction, the excess of *m*-CPBA was quenched with aq $Na_2S_2O_3$. The insoluble material was removed by filtration and washed with CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2. The combined extracts were washed with satd $NaHCO_3$ and satd NaCl, dried ($MgSO_4$), concentrated, and purified by silica gel column chromatography (hexane/AcOEt 1:1) to give **15** (493 mg, 90%) as a colorless solid. Analytically pure **15** was obtained by recrystallization from Et_2O/hexane. Colorless needles; mp 67–68 °C (lit.[6] mp 66.5–68 °C); R_f 0.25 (hexane/AcOEt 1:1); $[\alpha]_D^{20}$ −12.7 (*c* 1.0, $CHCl_3$) (lit.[6] $[\alpha]_D$ −11.0 (*c* 1.5, $CHCl_3$)); FTIR (KBr) 3421, 1714, 1267, 1054; ^{1}H NMR: 0.88 (3H, t, J=7.1 Hz), 1.26 (15H, s), 1.40–1.65 (4H, m), 1.71–2.02 (3H, m), 2.04 (1H, br), 2.45 (1H, ddd, J=17.6, 9.0, 7.1 Hz), 2.61 (1H, ddd, J=17.6, 7.1, 5.6 Hz), 3.83 (1H, m), 4.25 (1H, dt, J=10.7, 3.4 Hz); ^{13}C NMR: 14.1, 18.3, 21.2, 22.7, 25.9, 29.3, 29.5 (×2), 29.6 (×2), 29.8, 31.7, 31.9, 72.4, 83.4, 171.7. Anal. Calcd for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 71.37; H, 11.26.

4.2.13. (5*R*,6*S*)-(−)-6-Acetoxy-5-hexadecanolide (1). The mixture of **15** (310 mg, 1.15 mmol), Ac_2O (0.33 mL, 3.5 mmol) and 4-(dimethylamino)pyridine (42 mg, 0.34 mmol) in dry pyridine (16 mL) was stirred at room temperature. After 4 h, the mixture was quenched with 10 M aq K_2CO_3 and extracted with $CHCl_3$. The combined extracts were dried ($MgSO_4$), concentrated, and purified by silica gel column chromatography (hexane/AcOEt 2:1) to give **1** (352 mg, 100%) as a colorless oil; R_f 0.23 (hexane/AcOEt 2:1); $[\alpha]_D^{21}$ −36.8 (*c* 1.55, $CHCl_3$) (lit.[10] $[\alpha]_D^{24}$ −36.8 (*c* 1.0, $CHCl_3$)); FTIR (neat): 1744, 1466, 1371, 1230; ^{1}H NMR: 0.88 (3H, t, J=6.9 Hz), 1.25 (16H, s), 1.55–1.70 (4H, m), 1.77–2.01 (2H, m), 2.08 (3H, s), 2.46 (1H, ddd, J=17.8, 9.2, 6.8 Hz), 2.60 (1H, dt, J=17.8, 6.4 Hz), 4.35 (1H, ddd, J=11.0, 4.9, 3.4 Hz), 4.98 (1H, dt, J=7.8, 5.1 Hz); ^{13}C NMR: 14.1, 18.3, 21.0, 22.7, 23.5, 25.3, 29.3(0), 29.3(9), 29.4(4), 29.4(8), 29.5(3), 29.5(5), 29.6(1), 31.9, 74.3, 80.5, 170.5, 170.9. Anal. Calcd for $C_{18}H_{32}O_4$: C, 69.19; H, 10.32. Found: C, 69.41; H, 10.51.

Acknowledgements

This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Culture, and Sports, Japan, as well as a Special Research Grant for Green Science from Kochi University. We also thank Prof. Y. Fukuyama of Tokushima Bunri University for MS/HRMS measurements.

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