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

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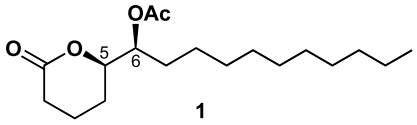
Abstract—A convenient method for proline-catalyzed asymmetric aldol reactions using synthons of straight-chain aliphatic aldehydes, and aldehydes bearing a 1,3-dithiane moiety at the β-position, has been developed. This method was successfully applied to the synthesis of (−)-(5*R*,6*S*)-6-acetoxyhexadecanolide,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

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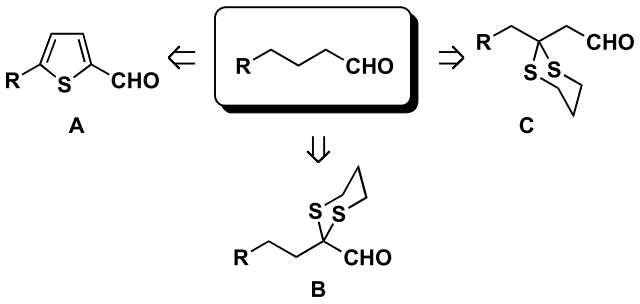


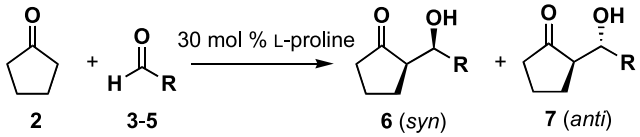
Figure 1. Straight-chain aliphatic aldehyde synthons.

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

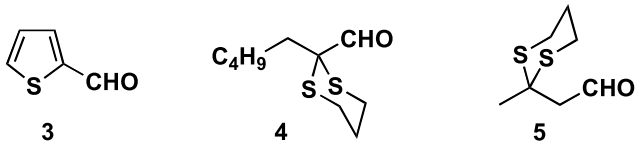
Table 1. L-Proline-catalyzed asymmetric aldol reactions of cyclopentanone (**2**) with aldehydes **3–5**



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

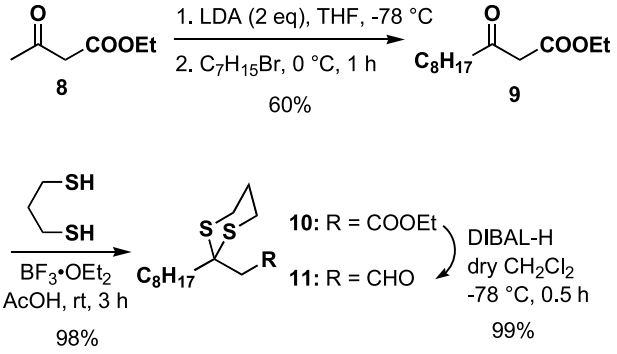
[a] Compound **2**:aldehyde 34:1, except in DMSO (6.5 equiv of **2**).
[b] Determined by ^{1}H NMR.
[c] Determined by chiral HPLC (Chiralpak AD).
[d] Compound **2**:DMSO 1:4 (vol%).

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