An Expeditious Access to Enantiomerically Pure *cis*-Dialkyl-Substituted γ- and δ-Lactones

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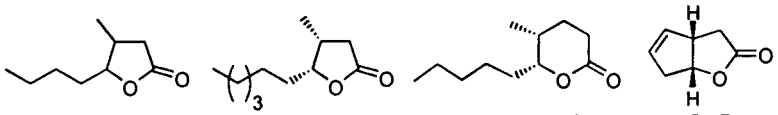
A facile general route to enantiomerically pure 3,4-*cis*-dialkyl-substituted γ-lactones and 4,5-*cis*-dialkyl-substituted δ-lactones by $TiCl_4$-mediated *Evans* asymmetric aldolization as the key step is exemplified by synthesis of *cis*-(3*R*,4*R*)-3-methyldecan-4-olide and (4*R*,5*R*)-aerangis lactone.

Many 3,4-dialkyl substituted γ-lactones have interesting properties. They can be used, *e.g.*, as flavoring agents (see, *e.g.*, [1]), perfume constituents [2], insect propellants [3], bactericides [4], and also as additives for food and drugs [5]. Some of these lactones occur naturally. Whiskey lactones (*cis*/*trans*-3-methyl-4-butyl-γ-lactone (**1**), also known as 'oak lactone'), for instance, represent the main contributors to the flavor of good wine (formed [6] during the traditional wine ageing process in oak barrels) and are, thus, of great (for a review, see [7]) interest to the wine industry. Its 4-hexyl analog *cis*-3-methyldecan-4-olide (**2**) is an odoriferous component of the *Aerangis* species (an orchid native to Kenya and Tanzania) [8]. Compound **2** also occurs [9] in the volatile components of the juices of blood and blond oranges. Similar δ-lactones are also useful as perfume or flavoring agents. Compound **3**, for example, is a perfume and flavoring component that can enhance the ylang-ylang, alpine herb, and creamery notes of various perfume and flavoring compounds [10]. 4-Methyldecan-5-olide (*cis*-**3**; aerangis lactone) is also a major component of the scent of *Aerangis* species.



Efforts to prepare such *cis*-dialkyl-substituted, chiral γ- and δ-lactones were not known (to our knowledge) until the mid-1980s. The reported routes include chiral sulfoxide-induced asymmetric cycloaddition of ketenes [11], asymmetric *Michael* addition of organocopper/Li or *Grignard* reagents to chiral α,β-unsaturated esters [12], ring opening of chiral epoxides [13], chiral-auxiliary-induced asymmetric aldol

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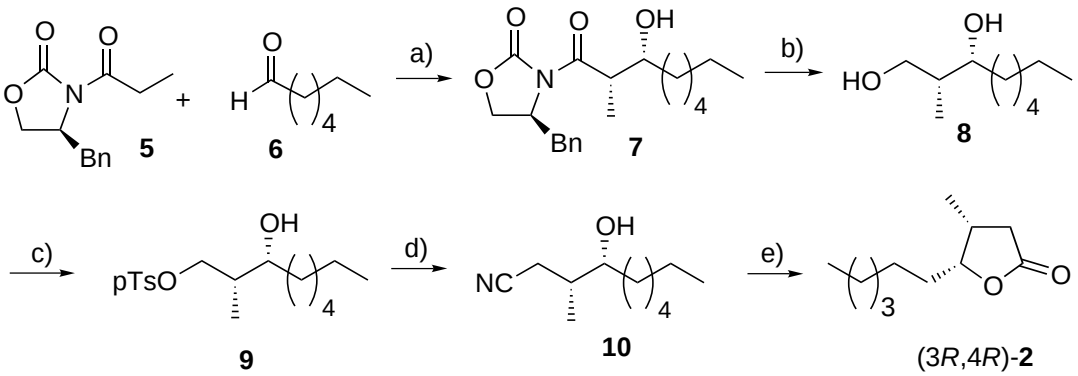
condensations [14][15], utilization of chirons [16][17], and chiral-base-mediated asymmetric *Michael* addition [18]. Among these, the auxiliary approach appears to be the most straightforward method: the two desired stereogenic centers are generated in a single step with a OH group formed simultaneously. However, the two documented syntheses still suffer from some drawbacks. The auxiliaries employed therein (4-methyl-5-phenyloxazolidin-2-one [19] or 10,10-dimethyl-3-thia-4-azatricyclo[5.2.1.$0^{1,5}$]-decane 3,3-dioxide [20]) are more expensive and less easily accessible than those (for a high-yield, low-cost access to oxazolidin-2-ones, see [21]) derived from chiral amino acids. The highly air/water-sensitive and expensive Bu_2BOTf involved in both protocols also represents a major shortcoming. Herein, we wish to report another approach to these targets using a $TiCl_4$-mediated (much less expensive and more readily available than Bu_2BOTf) asymmetric *Evans* [22] aldolization as the key step with oxazolidinones derived from phenylglycine or phenylalanine as auxiliary. The closer approach will be exemplified by syntheses of (3*R*,4*R*)-**2** and (4*R*,5*R*)-**3**.

The first synthesis of **2** in enantiomerically pure forms was reported by *Kitahara* and co-workers in 1999, who employed optically active **4**[3]) as a chiral pool and required eight steps with an overall yield of 7.9% [17]. Our synthesis (*Scheme 1*) started with a $TiCl_4$-mediated *Evans* asymmetric aldol condensation of the known (*S*)-*N*-propionyl-4-benzyl-3-propanoyloxazolidin-2-one (**5**) [23] (prepared from now readily accessible [21] (*S*)-4-benzyloxazolidin-2-one auxiliary and propanoyl chloride without recourse to BuLi) with heptanal (**6**), with *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) as base (see, *e.g.*, [24]). The resulting aldol **7** (*ca.* 80% yield based on the chiral auxiliary) was then converted to diol **8** through direct reduction with aqueous $NaBH_4$ in THF [25]. The yield was significantly higher (*ca.* 80 *vs.* 56%) than the two-step sequence ($LiOH/H_2O_2$ cleavage followed by $LiAlH_4$ reduction) employed for a similar conversion in formal synthesis of serricoring by *Pilli* and *Andrade* [14].

Scheme 1



a) $TiCl_4/TMEDA/CH_2Cl_2$; 80.7%. b) Aq. $NaBH_4$/THF, 79.4%. c) $TsCl/Et_3N/DMAP/CH_2Cl_2$, 84.3% (96.6% based on consumed starting diol). d) NaCN/DMSO; 89.6%. e) *i.* 2N NaOH/EtOH/reflux, *ii.* dilute H_2SO_4/THF, 84.1% (2 steps).

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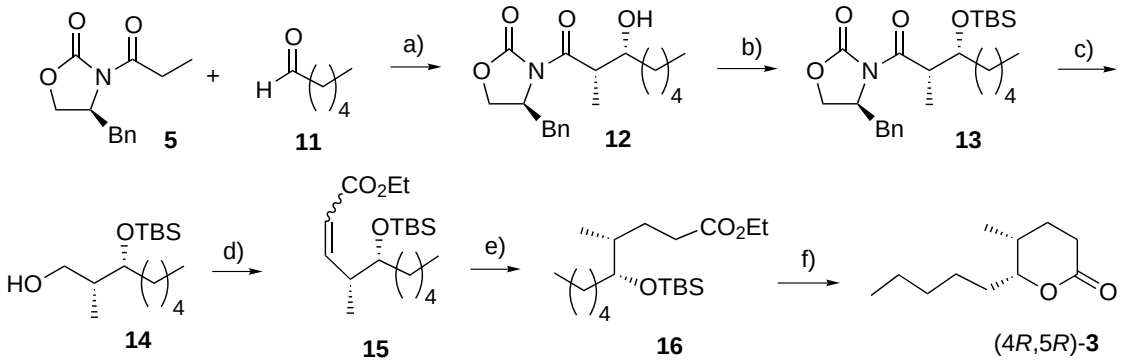
[3]) The compounds (1*S*,5*R*)-**4** and (1*R*,5*S*)-**4** are available from *Aldrich* at $40.0/500 mg and $50.9/1 g, respectively (year 2000/2001 prices)

Monotosylation of diol **8** was unexpectedly difficult. Initially, we thought that ditosylation might be a major interference and thus tried the protocol of *Martinelli et al.* [26]. The reaction turned out to be very sluggish (with or without Bu_2SnO). Increasing the reactants concentration did not accelerate the reaction but led to drastically reduced yields. At last, much better yields were obtained by running the tosylation at low concentrations. Thus, when the concentration of the starting diol was as low as 0.1M, **9** was formed in *ca.* 84% yield.

The monotosylate **9** was treated with NaCN in DMSO in the presence of a catalytic amount of NaI to give the corresponding nitrile **10** (89.6% yield), which, on hydrolysis in the presence of NaOH, followed by an acid-catalyzed lactonization, resulted in the desired target molecule **2** in 84% yield (from **10**) with all spectroscopic data consistent with those in the literature [17]. The overall yield based on the chiral auxiliary was 40.7%.

Similarly, (4*R*,5*R*)-**3** was synthesized as shown in *Scheme 2*. With hexanal instead of heptanal, the *Evans* aldolization gave aldol **12**. After masking the OH group as (*t*-Bu)Me_2SiO (TBSO), the chiral oxazolidinone auxiliary was removed [27] by $LiBH_4$ in Et_2O containing 1 equiv. of H_2O. A subsequent IBX [28] oxidation, followed by a *Wittig* reaction, afforded **15**, which was then hydrogenated over 10% Pd-C at atmospheric pressure and ambient temperature to give the ester **16** in 95.6% yield. Finally, removal of the (*t*-Bu)Me_2Si protecting group and lactonization were realized in a one-flask manner in the presence of dilute H_2SO_4 in refluxing THF to give the desired δ-lactone (4*R*,5*R*)-3[4]) in 66.8% isolated yield.

Scheme 2



a) $TiCl_4$/TMEDA/CH_2Cl_2; 74.5%. b) TBSOTf/2,6-Lutidine/CH_2Cl_2; 94.1%. c) $LiBH_4$/Et_2O/H_2O; 69%. d) *i.* IBX/DMSO; *ii.* $Ph_3P{=}CHCO_2Et$/THF, 93.3% (2 steps). e) H_2/Pd-C/MeOH; 95.6%. f) Dil. H_2SO_4/THF/reflux; 66.8%.

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[4]) Although *Kitahara* and co-workers [17] claimed that (4*R*,5*R*)-**3** had been synthesized, neither the synthetic route nor any spectroscopic data was disclosed yet. Spectroscopic data for (4*R*,5*R*)-**3**: IR (film): 1735. $[\alpha]_D^{14} = +63.9$ ($c = 0.92$, $CHCl_3$). ^{1}H-NMR: 4.29 (*m*, 1 H); 2.54 (*br. t*, $J = 7.3$, 2 H); 2.30–1.95 (*m*, 2 H); 1.78–1.60 (*m*, 2 H); 1.60–1.40 (*m*, 2 H); 1.40–1.20 (*m*, 5 H); 0.90 (*d*, $J = 7.1$, 3 H); 0.90 (*t*, $J = 6.6$, 3 H). MS: 185 (2, $[M+1]^+$), 167 (0.7), 128 (3), 113 (25), 84 (40), 56 (100), 41 (35)

In brief, we have shown that (3*R*,4*R*)-**2** and (4*R*,5*R*)-**3** are readily accessible *via* a route involving a $TiCl_4$-mediated *Evans* asymmetric aldolization as the key step. Since the alkyl substituents can be easily varied with different acyl oxazolidinones and aldehydes, and as the absolute configuration can be controlled by the chirality in the auxiliary, this approach represents a facile and flexible general route to enantiomerically pure *cis*-disubstituted lactones, which have versatile applications in every-day life, but were not readily accessible up to now.

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