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A straightforward stereoselective synthesis of *meso*-, (*S*,*S*)- and (*R*,*R*)-2,6-diaminopimelic acids from *cis*-1,4-diacetoxycyclohept-2-ene

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Abstract—A straightforward synthesis of *meso*-2,6-diaminopimelic acid (DAP) *meso*-**1** was developed from 1,4-diacetoxycyclohept-2-ene (**2**) via an oxidative ring cleavage. Subsequently, an enantio-divergent synthesis of (*S*,*S*)- and (*R*,*R*)-**1** was performed using a homochiral monoacetate **7** available from**2** by enzymatic desymmetrization.

2,6-Diaminopimelic acid (DAP) is a naturally occurring amino acid found in both bacteria and higher plants. It is a symmetrical α,α′-diaminodicarboxylic acid and can therefore exist in three stereoisomeric forms (Fig. 1). *meso*-DAP and (*S*,*S*)-DAP serve as the precursors in the biosynthesis of L-lysine in both bacteria and higher plants and *meso*-DAP is also an essential component of the peptidoglycan of most pathogenic bacteria (Fig. 2). Since DAP is not a constituent of animal tissue and the DAP biosynthetic pathway is absent in mammals, inhibitors of the diaminopimelate pathway have a good chance of displaying low toxicity toward the mammalian host. Inhibition of either DAP biosynthesis or its utilization, therefore, affords an attractive target for antibacterial chemotherapy.[1] In addition, a number of peptidoglycan fragments featuring the DAP residue exhibit antitumor, immunostimulant, and sleep-inducing biological activity.[2] The development of efficient routes to the synthesis of DAP stereoisomers and their analogues has recently been the focus of considerable attention.[3] In general, most of the methodologies described for the synthesis of DAP start from either α-amino acids or chiral glycine templates. In addition, the synthesis of all three stereoisomers of DAP from a common substrate has not been reported. Herein, we describe a convenient synthesis of *meso*-DAP *meso*-**1** and an enantio-divergent synthesis of (*R*,*R*)-, and (*S*,*S*)-DAP as hydrochlorides using 1,4-diacetoxycyclohept-2-ene (**2**) as a common starting material.

Our simple synthetic approach began with the $RuCl_3$-catalyzed oxidative cleavage of 1,4-diacetoxycyclohept-2-ene (**2**),[4] which is readily available from cyclohepta-1,3-diene. Treatment of **2** with catalytic $RuCl_3$ in the presence of $NaIO_4$ in a solution of CH_3CN, CCl_4, and H_2O gave the dicarboxylic acid, which was subjected without isolation to dimethylation with $TMSCHN_2$ to afford the dimethyl ester **3** in 85% yield. Chemoselective hydrolysis of **3** with 0.1 M sodium methoxide in CH_3OH provided the dihydoxide **4** in 71% yield. The diols of **4** were transformed into diazides in a two-step sequence (i, mesylation; ii, azidation) in 72% yield. The azide **5** was reduced with $Pd(OH)_2$-catalyzed hydrogenation in the presence of di-*tert*-butyl dicarbonate (Boc_2O) to give *N*-Boc-DAP dimethylester **6**[5] in 83% yield. Finally, deprotection of **6** with 6 N HCl quantitatively furnished the desired *meso*-DAP as a hydrochloride, which displayed spectroscopic properties consistent with the reported data (Scheme 1).[3g,6]

With the process for synthesis of *meso*-DAP in hand, we turned our attention to an enantio-divergent synthesis of (*R*,*R*)- and (*S*,*S*)-DAP from **2**. An enzymatic asymmetrization of *meso*-diacetate **2** with Novozyme

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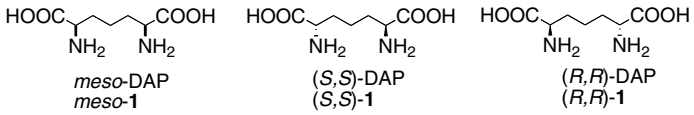


Figure 1. Stereoisomers of diaminopimelic acid (DAP).

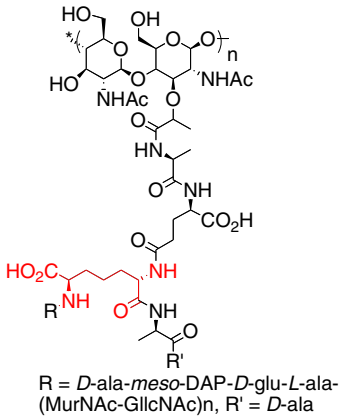
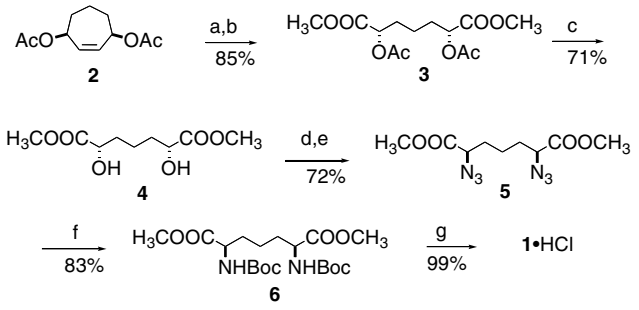


Figure 2. Peptidoglycan of a bacterial cell wall.

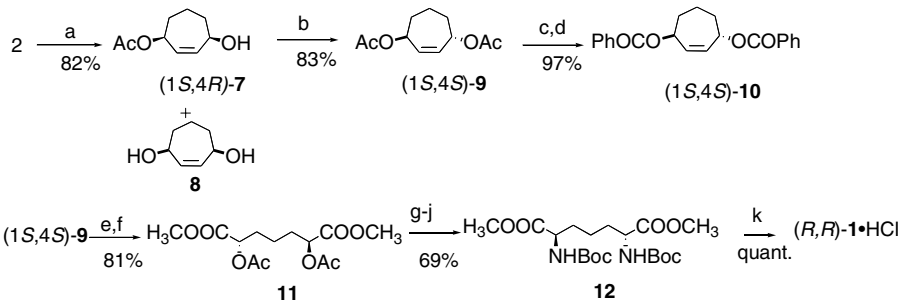


Scheme 1. Reagents and conditions: (a) cat. $RuCl_3$, $NaIO_4$, CCl_4—H_2O—CH_3CN; (b) $TMSCHN_2$, CH_3OH; (c) 0.1 M $NaOCH_3$, CH_3OH; (d) CH_3SO_2Cl, pyridine, CH_2Cl_2; (e) NaN_3, DMF; (f) H_2, cat. $Pd(OH)_2$, Boc_2O, CH_3OH; (g) 6 N HCl.

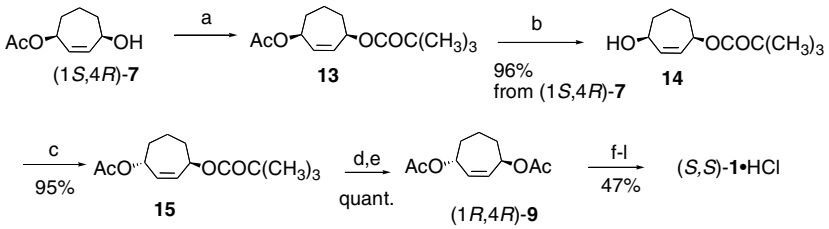
435 in phosphate buffer solution gave a single enantiomer of monoacetate (1*S*,4*R*)-**7**[7] in 81% yield (99% ee) together with the diol **8** (10%). The Mitsunobu reaction of **7** with acetic acid using diisopropyl azodicarboxylate (DIPAD) and triphenylphosphine in THF furnished C_2-symmetric diacetate (1*S*,4*S*)-**9** in 83% yield, which was converted into dibenzoate **10** in a two-step sequence (i, deacetylation; ii, benzoylation). The ee of **10** was determined to be 99% with chiral HPLC. Having a homochiral C_2-symmetric diacetate (1*S*,4*S*)-**9** obtained, an enantio-controlled synthesis of (*R*,*R*)-DAP was accomplished, as shown in Scheme 2 according to a similar procedure described for the synthesis of *meso*-DAP from **2**.[8,9]

The ultimate goal was the synthesis of (*S*,*S*)-DAP. Treatment of (1*S*,4*R*)-**7** with pivaloyl chloride in the presence of pyridine gave pivaloate **13**, which was chemoselectively hydrolyzed to provide the monoester **14** in a two-step 96% yield. The Mitsunobu inversion of **14** afforded *trans*-diacylate **15** (95%), which was quantitatively transformed into a homochiral diacetate (1*R*,4*R*)-**9** via a C_2-symmetric diol in a two-step sequence (i, reductive deprotection with $LiAlH_4$; ii, acetylation). Similarly, (*S*,*S*)-DAP[10] was obtained from (1*R*,4*R*)-**9** as described in Scheme 3.

In conclusion, a concise synthesis of *meso*-, (*S*,*S*)-, and (*R*,*R*)-2,6-diaminopimelic acids **1** as hydrochlorides was accomplished from an achiral *cis*-1,4-diacetoxycyclohept-2-ene (**2**) as a common educt. This procedure can apply to the synthesis of *meso*-DAP homologues such as diaminoadipic acid[11] and diaminosuberic acid.[12] The homochiral monoacetate (1*S*,4*R*)-**7** can be used as a building block for preparation of differently protected DAP analogues[13] for



Scheme 2. Reagents and conditions: (a) Novozyme 435, phosphate buffer; (b) AcOH, PPh_3, $^iPr_2OOCN{=}NCOO^iPr_2$, THF; (c) 0.1 M $NaOCH_3$, CH_3OH; (d) PhCOOH, DCC, DMAP, toluene; (e) cat. $RuCl_3$, $NaIO_4$, CCl_4—H_2O—CH_3CN; (f) $TMSCHN_2$, CH_3OH; (g) 0.1 M $NaOCH_3$, CH_3OH; (h) CH_3SO_2Cl, pyridine, CH_2Cl_2; (i) NaN_3, DMF; (j) H_2, cat. $Pd(OH)_2$, Boc_2O, CH_3OH; (k) 6 N HCl.



Scheme 3. Reagents and conditions: (a) $(CH_3)_3CCOCl$, pyridine; (b) 0.1 M $NaOCH_3$, CH_3OH; (c) AcOH, PPh_3, $^iPr_2OOCN{=}NCOO^iPr_2$, THF; (d) $LiAlH_4$, THF; (e) Ac_2O, pyridine; (f) cat. $RuCl_3$, $NaIO_4$, $CCl_4{-}H_2O{-}CH_3CN$; (g) $TMSCHN_2$, CH_3OH; (h) 0.1 M $NaOCH_3$, CH_3OH; (i) CH_3SO_2Cl, pyridine, CH_2Cl_2; (j) NaN_3, DMF; (k) H_2, cat. $Pd(OH)_2$, Boc_2O, CH_3OH; (l) 6 N HCl.

incorporation into peptides.[14] To accomplish this, further studies are in progress.

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6. For *meso*-**1**. Mp 250–2 °C (dec.); 1H NMR (400 MHz, D_2O) δ: 1.40 (1H, m), 1.54 (1H, m), 1.86 (4H, m), 3.95 (2H, t, $J = 6.6$ Hz). ^{13}C NMR (150 MHz, D_2O) δ: 21.1, 30.2, 53.6, 173.0.
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8. Spectral data of **11** were in accordance with those described by the literature.[3c] $[\alpha]_D^{23}$ −9.7° (*c* 1.00, $CHCl_3$), lit.[3m] $[\alpha]_D$ −8.6° (*c* 0.4, $CHCl_3$).
9. Specific rotation of (*R*,*R*)-**1**. $[\alpha]_D^{23}$ −45.1° (*c* 0.95, 1 N HCl), lit.[3e] (*S*,*S*)-**1**, $[\alpha]_D^{23}$ 42.7° (*c* 1.1, 1 N HCl).
10. Specific rotation of (*S*,*S*)-**1**. $[\alpha]_D^{23}$ 44.7° (*c* 0.95, 1 N HCl), lit.[3m] $[\alpha]_D^{23}$ 44.5° (*c* 0.95, 1 N HCl).
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