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An Efficient Synthesis of Chiral Nonracemic Diamines: Application in Asymmetric Synthesis†

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Abstract: A variety of chiral diamines have been synthesized from optically active mandelic acid in an efficient manner. The chiral nonracemic lithium amide base derived from one of the diamines has been used in formal asymmetric synthesis of natural products such as (-)-utenone A and (-)-carbovir.

Recently, we discovered[1] that chiral nonracemic lithium amide base derived from a diamine **4** is an excellent chiral base for enantioselective deprotonation of epoxides.[2] Using this diamine, we were able to synthesize 2-cyclohexene-1-ol in 80% ee and a prostaglandin intermediate in 97% ee.[1,3] O'Brien and Poumellec have used our chiral base chemistry in synthesis of important synthetic intermediates.[4] Similar chiral diamines have been used by others for a variety of enantioselective reactions.[5] The most frequently used synthetic route to these amines starts with phenylglycine and involves N-protection, amide formation and reduction. There is, however, a racemization problem at the coupling step to an amide which has already been studied in detail and the problem has been minimized to a great extent using 1-hydroxybenzotriazole (HOBT) in conjunction with DCC and $CuCl_2$.[1] But, there still remained a need for a flexible synthesis for diamines of the type **4**. To overcome the problems, efforts were made to synthesize these type of diamines from styrene oxide as well as from phenylglycinol.[5c,6] The syntheses are simple and convenient but the drawback is that these involve expensive precursors. In this paper we report a very simple and practical synthesis of a variety of chiral diamines from a cheap and readily available precursor such as O-acetylmandelic acid. In order to extend the scope of the chiral base chemistry further, we report here application of the chiral diamine **4** in formal asymmetric synthesis of two natural products, (-)-utenone A and (-)-carbovir.

As an example, the synthesis of the diamine (*S*)-**4** is described as follows. (*S*)-O-Acetylmandelic acid (5 mmol) was treated with 1.2 equiv. of piperidine and DCC in the presence of 1.2 equiv. of HOBT and $CuCl_2$ in DMF (25 mL) at rt for 24 h. After purification by column chromatography over silica gel, the amide **2** was obtained in 78% yield. The acetate and the amide functionalities of the **2** were reduced in a single pot (LAH, THF, reflux, 8 h) to obtain aminoalcohol **3** in quantitative yield.[7] Without any purification, the aminoalcohol **3** was treated with 3 equivalent of Et_3N and 1.2 equivalent of MsCl in dry ether at 0 °C for 30 min. In the same pot, 2 equivalent of Et_3N followed by 20 equivalent of aq. $MeNH_2$ solution[8] were added and the reaction mixture was stirred at rt for 24 h. Usual work-up and purification over silica gel by column chromatography gave the diamine (*S*)-**4** in 96% yield ($[\alpha]_D$ +97.5° (*c* 2.7, $CHCl_3$); lit.[1] $[\alpha]_D$ -91.6° (*c* 1.8, $CHCl_3$) for *R* isomer]. Similarly, diamine (*R*)-**4** was also synthesized from (*R*)-O-acetylmandelic acid. During the conversion

†This paper is dedicated respectfully to Professor Sukh Dev on the occasion of his 75th birthday.

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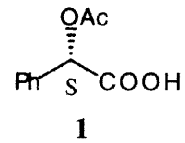
of **3** to **4**, two S_N2 inversion takes place, the first one in the formation of aziridinium ion and the second one is its opening to the final diamine.[9] Thus, the stereochemistry of the precursor is retained in the final product. In order to show versatility of this methodology, we have synthesized a variety of (*S*)-diamines from (*S*)- O-acetylmandelic acid in a high overall yield (Table).



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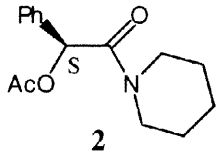

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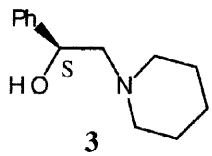

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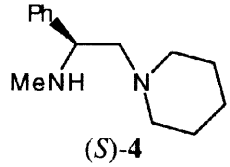
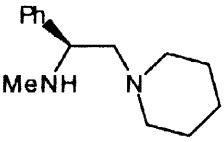
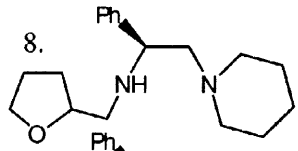
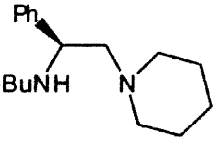
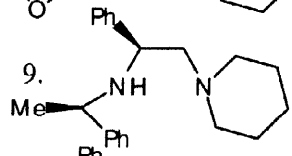
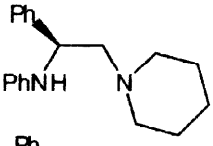
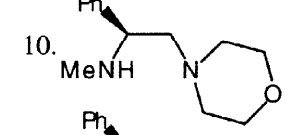
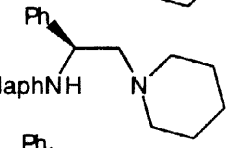
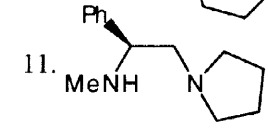
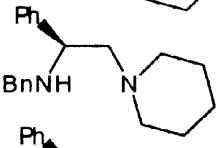
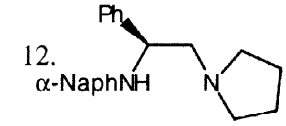
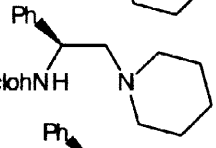
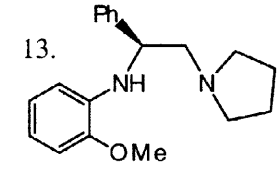
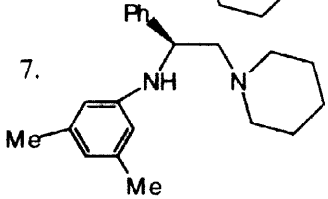


(*S*)-**4**

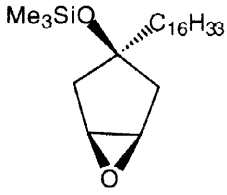
Table: Synthesis of Chiral Nonracemic Diamines from (*S*)-O-acetylmandelic Acid

Entry	Diamines	Yield[a] (%)	$[\alpha]_D$ ($CHCl_3$)	Entry	Diamines	Yield (%)	$[\alpha]_D$ ($CHCl_3$)
1.		75	+ 97.5°[b] (*c* 2.7)	8.		72	+75.7° (*c* 6.0)
2.		75	+ 88.5° (*c* 7.0)	9.		67	+ 134.9° (*c* 7.5)
3.		69	+ 07.2° (*c* 6.5)	10.		69	+ 93.1°[d] (*c* 2.9)
4.		74	+ 31.2° (*c* 7.6)	11.		63	+ 82.5°[e] (*c* 5.5)
5.		63	+ 114.1°[c] (*c* 6.3)	12.		64	- 115.0° (*c* 4.0)
6.		78	+ 93.0° (*c* 7.0)	13.		60	- 28.7° (*c* 3.5)
7.		68	+ 10.1° (*c* 4.5)				

[a]This is the overall isolated yield based on (*S*)-O-acetylmandelic acid. [b]lit.[1] $[\alpha]_D$ -91.6° (*c* 1.8, $CHCl_3$) for *R* enantiomer. [c]lit.[6a] $[\alpha]_D$ -108.6° (*c* 2, $CHCl_3$) for *R* enantiomer. [d]lit.[1] $[\alpha]_D$ -92.0° (*c* 1.2, $CHCl_3$) for *R* enantiomer. [e]lit.[6a] $[\alpha]_D$ -65.4° (*c* 1.2, $CHCl_3$) for *R* enantiomer.

From the table, it is clear that the overall yield in virtually all the cases is very high. In case of piperidine and morpholine diamines (entries 1 to 10), purification of aminoalcohol after LAH redution was not required. However, in case of pyrrolidine diamines (entries 11-13), purification at the aminoalcohol stage was needed.

We further report here the application of both the enatiomers of the chiral diamine **4** in synthesis of important cyclopentanoid intermediates. We carried out enantioselective deprotonation reaction of an epoxide **5** with the base (*R*)-**4** in toluene at 0 °C and obtained **6** in 70% yield and 94% ee [($[\alpha]_D$ -19.1° (*c* 2.22, $CHCl_3$); lit.[10] $[\alpha]_D$ -18.1° (*c* 1.02, $CHCl_3$) for 89% ee]. The **6** is an intermediate[10] in the synthesis of Utenone A **7**[11] which is an antileukemic and considered to be a biosynthetic precursor for other marine natural prducts.[12]



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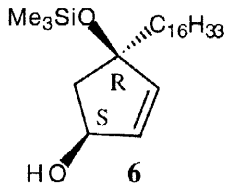
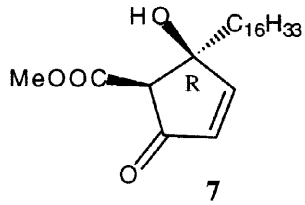
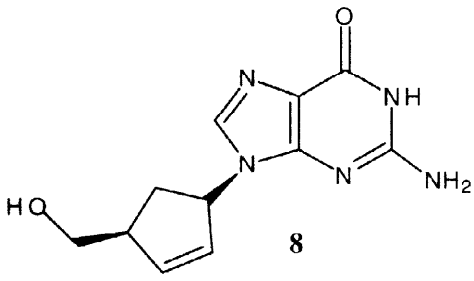


6



7

Similarly, we have extended the application of our chiral base chemistry in the synthesis of (-)-carbovir **8**, an anti-HIV agent. Enantioselective deprotonation of epoxide **9** with (*S*)-**4** in THF gave an intermediate **10** in 20% yield and 80% ee [($[\alpha]_D$ -36.8° (*c* 2.0, $CHCl_3$); lit.[13] $[\alpha]_D$ +33.2° (*c* 0.78, $CHCl_3$)] for 72% ee for (1*S*) isomer].[13,14] The change of solvent to benzene lowered the yield to 14% and enantioselectivity to 40%. The synthetic utility of **10** has already been shown in the literature by converting it into the anti-HIV agent **8**[14b] Since *trans* isomer of the epoxide **9** is also known to be converted into the (-)-carbovir, we studied enantioselective deprotonation of the *trans* epoxide with (*R*)-**4** and could obtain only a poor enantioselectivity (27% ee). This is not surprising to us in view of our previous experience in this area.[1]



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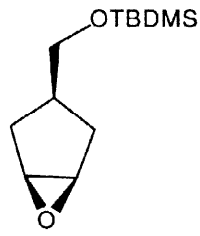

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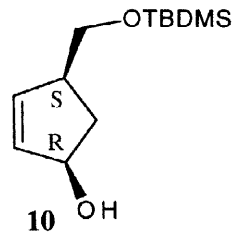

10

In conclusion we have been able to develope a flexible synthesis of chiral nonracemic diamines *via* β-amino alcohols from optically active O-acetylmandelic acid. The methodology can also be used in the synthesis of other chiral diamines as well. We have also shown the application of the chiral bases derived from the diamines **4** by synthesizing important chiral intermediates for natural product synthesis. Further application of chiral diamines in asymmetric synthesis is also underway.[15]

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