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AN EFFICIENT AND DIASTEREOSELECTIVE [2+2] CYCLOADDITION: CONVENIENT AND ENANTIOSELECTIVE ROUTE TO *TRANS*-2',3'-DIHYDROXYMETHYLCYCLOBUTANE NUCLEOSIDE ANALOGS

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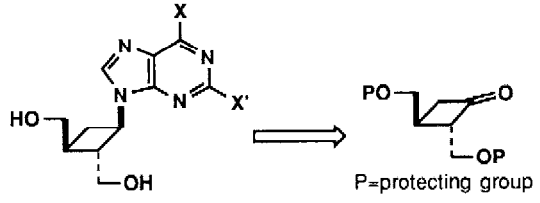
Summary: An efficient route to (2*S*-*trans*)-2,3-bis[(benzoyloxy)methyl]cyclobutanone (**3a**), a key intermediate in the synthesis of cyclobutane nucleoside analogs, via a novel asymmetric [2+2] cycloaddition, is described.

The potent antiviral activities of *trans*-2',3'-dihydroxymethylcyclobutane nucleoside analogs have previously been reported.[1-3] Among the various base analogs, the guanine and adenine derived compounds (**1** and **2**, respectively) exhibit broad spectrum *in vitro* antiherpetic activity. It has also been shown that only the (1*R*)-optical isomers of **1** and **2** possess activity. Several asymmetric syntheses of chiral **1** and **2** *via* the key protected cyclobutanone derivative **3** have recently appeared in the literature.[3-5] Unfortunately, some of these syntheses may be impractical for large scale production due to length, cost, or limited availability of the reagents involved.



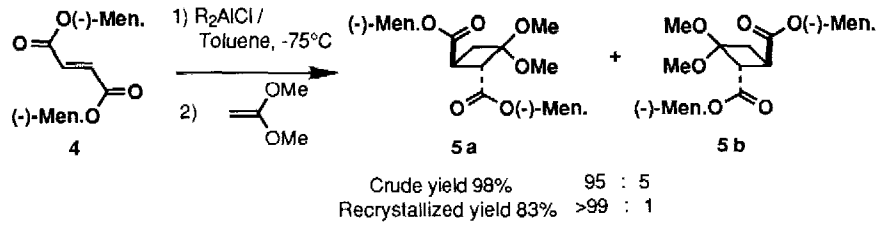
1, X=OH, X'=NH_2
2, X=NH_2, X'=H

3

In our search for a practical approach to chiral **1** and **2**, we considered asymmetric cycloaddition reactions utilizing readily available and inexpensive reagents, as well as recyclable chiral auxiliaries. While the reported options in the case of the [2+2] cycloaddition are limited,[6] the corresponding [4+2] cycloaddition is well precedented. Thus, exceptionally high asymmetric induction has been achieved in the Diels-Alder reaction by the use of dienophiles with two chiral auxiliaries possessing synergistic stereodifferentiating influences.[7,8] As demonstrated by Yamamoto,[8,9] organoaluminum-catalyzed Diels-Alder reactions of dimenthyl fumarate with a variety of dienes afford excellent yields of the corresponding diastereomerically enriched [4+2] cycloadducts. This communication describes a novel, Lewis acid catalyzed,

asymmetric [2+2] cycloaddition between dimethyl ketene acetal and (-)-dimenthyl fumarate (4), and its application to the synthesis of the key intermediate **3** used in the preparation of a variety of antiviral cyclobutyl nucleoside analogs.

Scheme1



Crude yield 98% 95 : 5
Recrystallized yield 83% >99 : 1

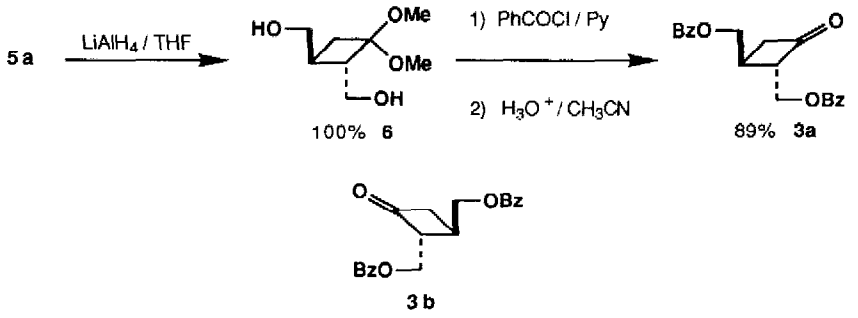
The facial selectivity of (-)- and (+)-dimenthyl fumarates observed in the Diels-Alder reaction[8,10] inspired us to choose the (-)-enantiomer 4 (Aldrich Chemical Company, Inc.). A variety of Lewis acids were employed to facilitate the cycloaddition. Best results were obtained with diethyl- or diisobutylaluminum chloride. Thus, a solution of **4** in toluene at -75°C was treated with 2 equivalents of diethyl- or diisobutylaluminum chloride. The reaction mixture was stirred at -75°C for 10 minutes, followed by the addition of 1.1 equivalent of dimethyl ketene acetal (Scheme 1). After 10 minutes at -75°C, the reaction was carefully quenched at low temperature by addition of small quantities of methanol and aqueous sodium hydroxide, followed by filtration. No aqueous extraction was required as part of the work up.[11] On a 0.25 mole (100 g) scale of (-)-dimenthyl fumarate, this reaction afforded a 98% yield of **5a** in 90% diastereomeric excess. Following a single recrystallization from aqueous methanol, the cycloadduct **5a** was afforded in 83% yield with a diastereomeric excess of >99%.[12,13]

A minimum of 2 equivalents of the Lewis acid per equivalent of the fumarate was necessary for successful completion of the reaction. The use of 1 equivalent of Lewis acid at -75°C resulted in isolation of **5a** and **5b** along with unreacted fumarate **4**. Also noteworthy is the observation that when the above reaction was conducted in the absence of a Lewis acid at 80°C, a complex mixture of products, including various decomposition products, was obtained. In addition, the reaction must be performed at temperatures below -60°C to avoid acid catalyzed decomposition of the ketene acetal. When conducted at -40°C, the reaction afforded a *ca.* 57:43 mixture of **5a+5b** : **4** without any noticeable loss of diastereoselectivity by ^{1}H NMR.

Cycloadduct **5a** was reduced with LAH (100% yield) to afford diol **6** which could be efficiently separated from the chiral auxiliary, (-)-menthol, by partitioning between water and heptane, or by chromatography (Scheme 2). Diol **6** was converted to the key intermediate **3a** via benzoylation and ketal hydrolysis (89% yield, two steps). The overall yield of **3a** from

(-)-dimenthyl fumarate (4) was 71% for four steps. The absolute stereochemistry of

Scheme 2



cyclobutanone **3a** was confirmed by chiral HPLC[14] comparison with authentic samples of enantiomerically pure **3a** and **3b**.[3]

In conclusion, we have developed a very efficient and economical route to synthesize chiral *trans*-2',3'-dihydroxymethylcyclobutane nucleoside analogs *via* a novel asymmetric [2+2] cycloaddition. In addition, due to the significance of cyclobutanones as useful synthetic intermediates,[15] the procedure may be of general interest to the synthetic organic community.

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9. The $AlCl_3$, $SnCl_4$ and $TiCl_4$ catalyzed Diels-Alder reactions of dimenthyl fumarate with dienes has previously been reported to give only modest diastereomeric excess (Walborsky, H.M.; Barash, L.; Davis, T.C. *Tetrahedron*, **1963**, *19*, 2333).
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11. The work up procedure involves a sequential dropwise addition of methanol, hexane and 20% aqueous sodium hydroxide at -75° to -40°C. The reaction temperature is then slowly allowed to come to 10°C, followed by the addition of anhydrous magnesium sulfate. The solids are removed by filtration and the filtrates are concentrated *in vacuo*, affording the crude product.
12. The diastereomeric ratio **5a** : **5b** was determined by analytical HPLC (Waters 30 cm X 3.9 mm μPorasil column, 96:4 hexane:ether at 3 mL/minute, using RI and UV (215 nm) detectors).
13. All new compounds have been fully characterized and their spectral data are in accord with proposed structures. **5a**: Melting point 89°C (methanol-water); $[\alpha]_D$ -28.5° (C=1, $CHCl_3$); ^1H NMR ($CDCl_3$, 270 MHz) δ 4.77-4.63 (m, 2H, 2 X -O-CH- of menthyl), 3.52 (d, 1H, J=7.6 Hz, $CH\text{-}CO_2$), 3.31 (s, 3H, methoxy), 3.29 (m, 1H, $CH\text{-}CO_2$), 3.14 (s, 3H, methoxy), 2.58 (dd, 1H, J=12.3, 10.0 Hz, $-CH_2-$ of cyclobutyl), 2.16 (dd, 1H, J=12.3, 8.8 Hz, $-CH_2-$ of cyclobutyl), 2.10-1.92 (m, 3H, menthyl), 1.82 (m, 1H, menthyl), 1.71-1.60 (m, 4H, menthyl), 1.53-1.23 (m, 4H, menthyl), 1.12-0.80 (m, 18 H, menthyl), 0.74 (d, 6H, J=6.5 Hz, menthyl); ^{13}C NMR ($CDCl_3$, 270 MHz) δ 173.04, 168.49, 100.18, 74.90, 74.64, 52.06, 49.53, 48.52, 46.97, 40.92, 40.77, 34.21, 33.37, 31.36, 31.16, 26.29, 25.37, 23.53, 22.89, 21.94, 20.93, 20.65, 16.35, 15.78.
14. Chiral analytical HPLC analyses were carried out with a 25 cm X 4.6 mm Chiralcel OD (Daicel Chemical Industries, Ltd.) column, 96:4:0.2 hexane-isopropanol-ethanol at 3 mL/minute, using a UV detector at 254 nm (retention times of **3a** and **3b** = 7.4 and 8.8 minutes, respectively).
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