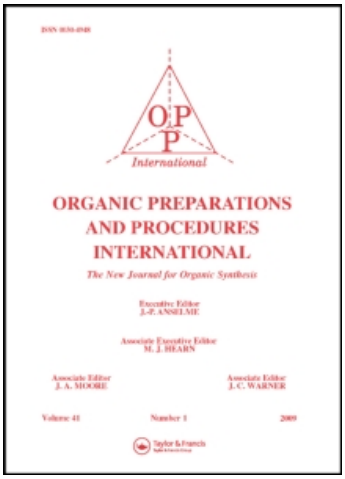

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SYNTHESIS AND ENZYMATIC RESOLUTION OF A CARBOCYCLIC ANALOGUE OF RIBOFURANOSYLAMINE

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SYNTHESIS AND ENZYMATIC RESOLUTION OF A CARBOCYCLIC ANALOGUE OF RIBOFURANOSYLAMINE

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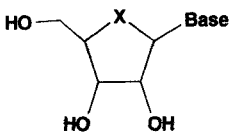
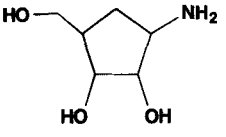
Carbocyclic nucleosides **1** differ from those naturally occurring nucleosides (**2**) in that the furanose ring oxygen atom is replaced by a methylene group. Nucleoside analogues incorporating this change are stable toward metabolic routes that involve cleavage of the bond between the ribofuranose ring and the base.[1] This metabolic stability has been a major impetus for the synthesis of carbocyclic nucleoside analogues. An important intermediate in this effort has been the carbocyclic amine **3**.[1] Many of the previous syntheses of carbocyclic nucleosides were directed toward the preparation of aristeromycin (**4**) from a variety of starting materials. For instance, Borchardt and coworkers[2,3] described the use of ribonic acid-lactone for the synthesis of aristeromycin, while the synthesis by



1 X = CH_2
2 X = O



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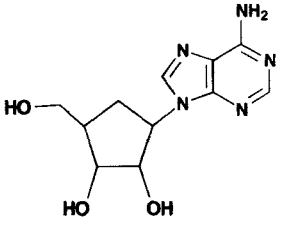

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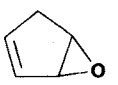
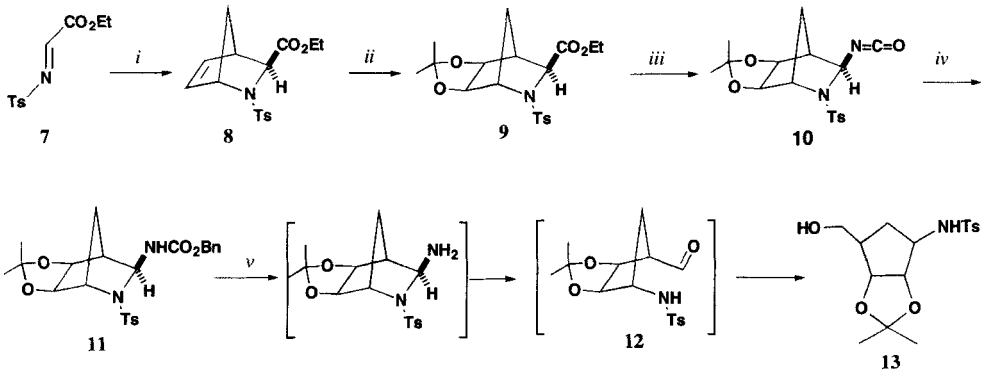


5

Kitagawa and coworkers[4] began with glucose; Trost[5] has described a route from *cis*-1,4-diacetoxycyclopent-2-ene. Other syntheses began with either cyclopentadiene monoepoxide (**5**)[6] or the cyclic lactam (**6**)[7-9] synthesized from cyclopentadiene. The use of Diels-Alder cycloadditions involving cyclopentadiene has been reported by Katagiri[10,11] and others.[12-15] We wished to synthesize both purine and pyrimidine carbocyclic nucleoside analogues, and decided to concentrate on the synthesis of compound **3** as the common intermediate for both classes of compounds.

We first attempted to follow the reported procedure for the synthesis of **3** (Scheme 1) exactly as described[15], which began with the reaction of cyclopentadiene and tosylimine **7** to give the cycloadduct **8**. Osmium tetroxide oxidation of **8** gave a diol that was converted to the isopropylidene

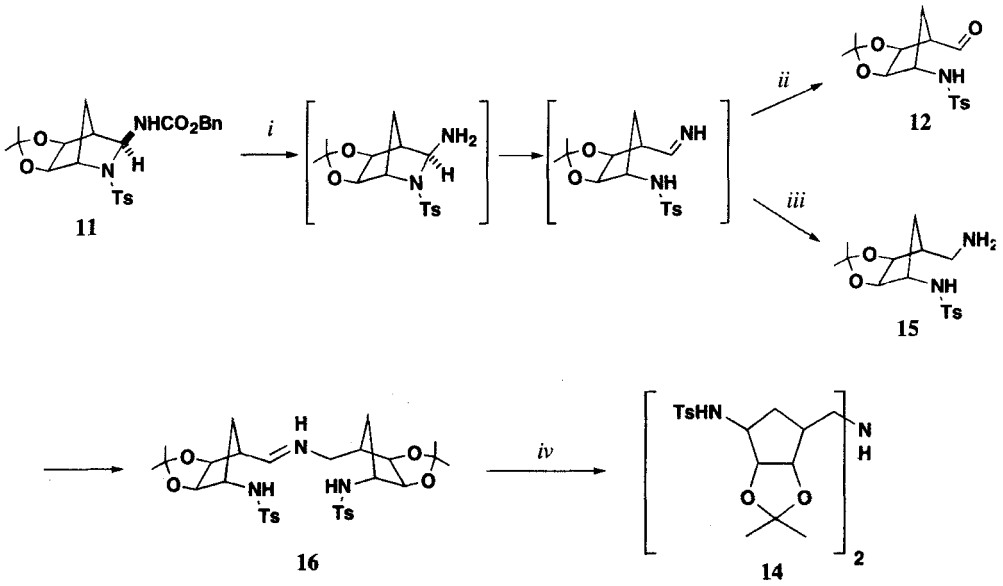
derivative **9**. A Curtius rearrangement converted **9** to the carbamate **11**. Catalytic hydrogenation of this product gave the labile aldehyde **12** which was reduced with sodium borohydride to give the



i) cyclopentadiene, toluene, 90° 18 hrs *ii)* i. OsO_4, NMO; 2,2-dimethoxypropane, acetone, p-TsOH
iii) hydrolysis, followed by diphenylphosphoryl azide, toluene, Δ *iv)* BnOH *v)* i. H_2, Pd/C, EtOH ii. $NaBH_4$

Scheme 1

alcohol **13**. In our hands, the Curtius rearrangement proved troublesome and the sodium borohydride reduction gave varying amounts of a dimeric side-product **14** which lowered the yield of the desired product. This by-product resulted from reduction of the imine **16** formed by condensation of aldehyde **12** and amine **15** (Scheme 2). Since variation of the pH of the reaction mixture did not alleviate the

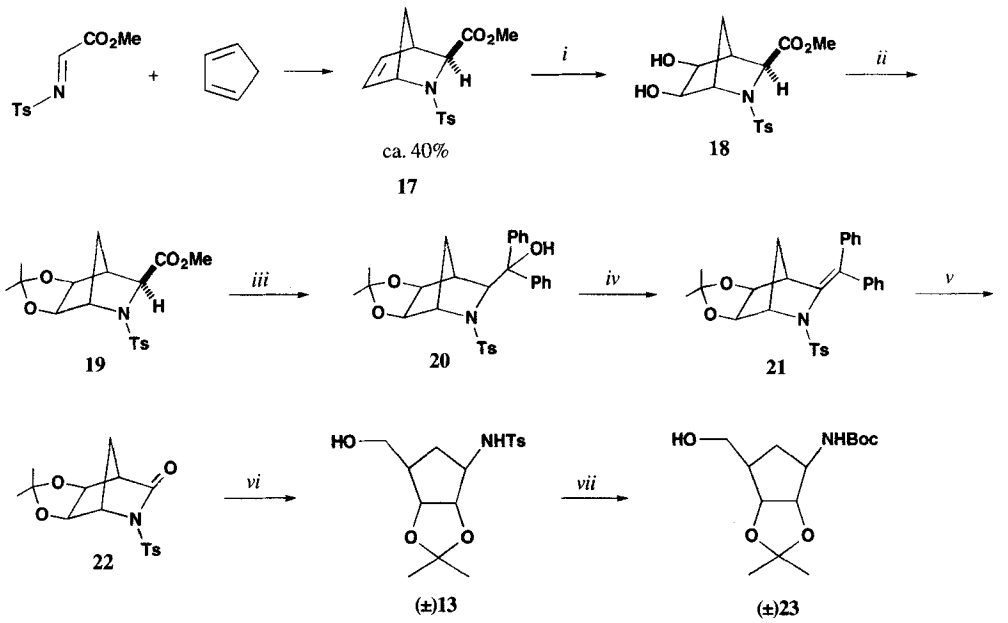


i) H_2, Pd / C *ii)* hydrolysis *iii)* $NaBH_4$ *iv)* $NaBH_4$, ethanol

Scheme 2

problem, a new route was devised. In addition, when the original conditions[15], for the preparation of carbamate **11** were followed (sodium azide under phase-transfer conditions, followed by heating with benzyl alcohol), the only product recovered was the benzyl ester. The present report describes a synthesis of compound **3** in which all intermediates are crystalline. Column chromatography was in large part avoided, resulting in a process suitable for large scale synthesis. We also describe the enzymatic resolution of the key precursor (± **13**).

The new synthesis (Scheme 3) involves a change in the procedure for removal of the carbomethoxy group. Reaction of the carbomethoxy imine[16] and cyclopentadiene afforded the adduct **17** in reasonable yield as a crystalline solid. As before, this material was treated with osmium tetroxide and the diol was converted to the isopropylidene derivative **19**. Reaction of **19** with phenylmagnesium bromide gave the tertiary alcohol **20** which, surprisingly, did not spontaneously dehydrate. Dehydration was effected with trifluoroacetic acid to give olefin **21**. Reaction of **21** with ozone afforded the tosylamide **22**. Reduction of the amide ($LiEt_3BH$) gave the tosyl derivative **13** as before which was deprotected with sodium in liquid ammonia to give the 2', 3'-isopropylidene derivative, isolated as the N-Boc derivative **23**.



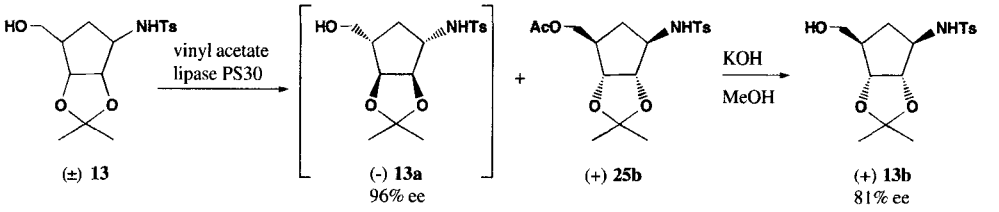
i) OsO_4, NMO *ii*) 2,2-dimethoxypropane, acetone, p-TsOH, 55% *ii*) PhMgBr, Et_2O, 85%
iv) TFA, TFAA, CH_2Cl_2, 90%. *v*) O_3, CH_2Cl_2, MeOH, then DMS. *vi*.) $LiEt_3BH$, THF (81% over 2 steps).
vii) Na, NH_3, THF, then $(BOC)_2O$, 71%.

Scheme 3

Each of the first six steps has been carried out on large (>500g) scale with only slight modification. First, the formation of tosylimine was run under a nitrogen atmosphere, giving a purer product on cycloaddition. Second, the cycloaddition product was found to decompose on recrystalliza-

tion from methanol, but could be purified by trituration with ethanol at ambient temperature. Finally, on a large scale, the osmium reaction did not go on to completion, even when reaction time was extended to 7 days. However, by addition of water at the start of the reaction, completion was attained in two hours.

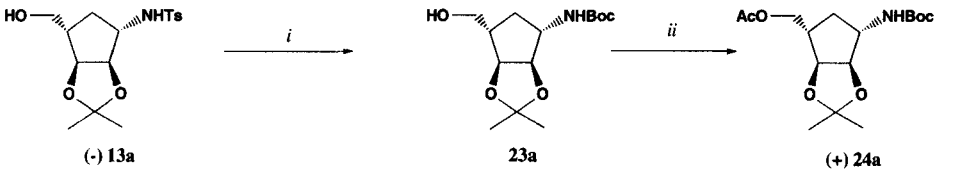
A number of groups, especially those of Ohno[17,18] and Sicsic[19,20] have reported enzymatic resolution of intermediates involved in the synthesis of ribofuranosylamine.[16] We chose to use the intermediate compound **13** (Scheme 4) for the resolution as its tosyl derivative allowed the reaction to



Scheme 4

be monitored by HPLC with a UV detector; monitoring of mixtures containing the Boc compound **23** was unsatisfactory. The procedure of Wang *et al.*[21] using a lipase to effect transesterifications of alcohols with vinyl acetate has been employed successfully in the synthesis of several optically pure pharmaceuticals.[22] The reaction is irreversible as the alcohol product from vinyl acetate rapidly tautomerizes to acetaldehyde, which cannot be re-esterified. A reaction mixture of **13**, vinyl acetate and lipase PS-30 in *t*-butyl methyl ether was monitored by HPLC [Cyclobond I(beta) column]. It was found that one isomer of **13** was only slowly esterified, and after 2 hrs the reaction was ended to give the unreacted material in 37% (out of a possible 50%) yield with an *ee* of 100% after recrystallization. At this point the absolute configuration of the unesterified material was unknown, and we designated this isomer as **13a.** Further, all compounds related to this isomer will be of the "a" series in the following discussion. Products derived from the esterified isomer are designated as belonging to the "b" series.

To determine its absolute configuration, **13a** was converted to **24a** whose absolute configuration is known. As shown in Scheme 5, compound **13a** was converted to the BOC compound **23a**, which was acetylated (Scheme 5) to give compound **24a**.



i) Na, NH_3, THF, then $(Boc)_2O$, THF/H_2O, 50% *ii*) Ac_2O, pyridine, cat. DMAP, 80%.

Scheme 5

The optical rotation of this compound was determined to be +4.6°. Ohno and coworkers[17] reported the value of -4.7° for the isomer that they used in the synthesis of aristeromycin. This indi-

cates that the product needed for carbocyclic nucleoside synthesis is **25b,** the isomer acetylated by lipase PS 30 (Scheme 4). This material was isolated in 63% (out of a possible 50%) yield (material also contains some of the other isomer that accounts for the greater than theoretical yield) with an *ee* of 78%. Hydrolysis of this acetyl ester back to the alcohol gave **13b** in 47% yield with 81% *ee*.

In summary, we describe a new synthesis of carbocyclic ribofuranosylamine. This synthesis gives crystalline intermediates and is amenable to scale-up with few modifications. The resolution of one intermediate is reported. The procedure should be useful in the synthesis of carbocyclic nucleoside analogues.

EXPERIMENTAL SECTION

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by the Marion Merrell Dow Research Institute Analytical Department. NMR spectra were obtained on a Varian VXR-300 or EM-360L spectrometer. Chemical shifts are reported downfield from TMS in spectra obtained in $CDCl_3$ and from DSS in spectra obtained in D_2O. IR spectra were obtained on a Perkin-Elmer 1800 FT IR spectrometer. Thin-layer chromatography (TLC) were developed on Merck silica gel F254 analytical plates, visualized with I_2, UV light, phosphomolybdic acid or $KMnO_4$. For determination of ee, HPLC analysis utilized a Cyclobond I (beta) column with sample concentration of 0.2 mg/mL and a mobile phase of 40/60 MeOH/H_2O (flow rate 0.5 mL/min).

2-(4-Toluenesulfonyl)-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylic Acid Methyl Ester (17).- A solution of freshly distilled methyl glyoxalate (528 g, 6.0 mol) (Hoechst) in toluene (4 L) was introduced in a 12 L flask. The solution was stirred under nitrogen during a dropwise addition of 4-toluenesulfonyl isocyanate (1.18 kg, 6.0 mol) (Aldrich). The mixture was heated at reflux for 24 hrs, cooled to 25°, and freshly distilled cyclopentadiene (396 g, 6.0 mol) was added at a rate which maintained a reaction temperature of 25°. The mixture was stirred at ambient temperature for 20 hrs, cooled to 5°, and filtered. The precipitate was washed with four 500 mL portions of ethanol and air dried to give 930 g of crude product. A final slurry with ethanol (2 L) for 30 min gave **17** (840 g, 45%) as a white solid, mp. 81-83°. This material was used without further purification. ^1H NMR ($CDCl_3$): δ 1.4-1.5 (d, 1H, J = 7Hz), 2.0-2.1 (d, 1H, J = 7Hz), 2.45 (s, 3H), 3.3 (s, 1H), 3.5 (s, 1H), 3.75 (s, 3H), 4.6 (s, 1H), 6.1-6.3 (m, 2H), 7.25-7.35 (d, 2H, J = 7.5Hz) and 7.7-7.8 (d, 2H, J = 7.5Hz).

5,6-Dihydroxy-2-(4-toluenesulfonyl)-2-azabicyclo[2.2.1]heptane-3-carboxylic Acid Methyl Ester (18).- A mixture of **17** (480 g, 1.56 mol), N-methylmorpholine N-oxide (210 g, 1.79 mol), acetone (9.6 L), THF (3.3 L) and water (28 mL, 1.56 mol) was stirred at ambient temperature during the dropwise addition of a solution of OsO_4 (4.0 g, 16 mmol) in acetone (300 mL). The mixture was stirred for ca. 2 hrs after the addition was completed, a saturated solution of Na_2SO_3 (1.2 L) was added and stirring was continued for an additional hour. Water (3 L) was added and the organic solvents were removed at 30°/50 torr. The aqueous residue was extracted with CH_2Cl_2 (1 x 4L, 2 x 2L). The combined organic extracts were washed with 1N HCl (4 L), H_2O (4 L) and brine (2.5 L). The organic layer was dried ($MgSO_4$) and concentrated to a volume of 1 L. The residue was diluted with Et_2O (1 L) and solvent was removed (25°/50 torr) until precipitation began. The mixture was treated with

hexane (2 L), filtered and the collected solid was washed with hexane to give 386 g (72%) of **18**, mp. 153-154°.

Anal: Calcd for $C_{15}H_{19}NO_6S$: C, 52.78; H, 5.61; N, 4.10. Found: C, 52.93; H, 5.54; N, 3.96

IR (KBr) 600, 1025, 1058, 1100, 1150, 1207, 1229, 1305, 1315, 1355, 1391, 1752, 2879, 2893 and 3320 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.75-1.95 (m, 3H), 2.4 (s, 3H), 2.65 (s, 1H), 3.65 (s, 3H), 3.85 (s, 1H), 3.95 (s, 1H), 4.0 (d, 1H, J = 7Hz), 4.35 (d, 1H, J = 7Hz), 4.85 (s, 1H), 7.3-7.4 (d, 2H, J = 8Hz) and 7.8-7.9 (d, 2H, J = 8Hz). MS (CI/CH_4) m/z 342 (M + H).

5,6-Isopropylidenedioxy-2-(4-toluenesulfonyl)-2-azabicyclo[2.2.1]heptane-3-carbo-xylic Acid Methyl Ester (19).- A mixture of **18** (435 g, 4.18 mol), acetone (9 L) and 4-methylbenzenesulfonic acid (44.6 g, 0.234 mol) was stirred at ambient temperature for 1 hr and solvent was removed at 30°/50 torr. The residue was dissolved in acetone (3.8 L) and the solution was filtered. The filtrate was diluted with methanol (1.9 L), cooled to 5° and the mixture was filtered. The crystalline product was washed with cold acetone/methanol (1 L, 2:1) and methanol (1 L) to give the product **19** (493 g) as a white solid, mp. 149-151°. The filtrate was evaporated until precipitation began, methanol (750 mL) was added and the mixture was chilled to 5° and filtered to give an additional 113 g of **19** (76% total yield).

Anal. Calcd for $C_{18}H_{23}NO_6S$: C, 56.67; H, 6.08; N, 3.67. Found: C, 56.85; H, 6.12; N, 3.75

IR (KBr) 593, 1019, 1044, 1080, 1094, 1124, 1139, 1159, 1180, 1200, 1233, 1266, 1307, 1329, 1342, 1377, 1385, 1754 and 3027 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.3 (s, 3H), 1.4 (s, 3H), 1.7-1.9 (m, 2H), 2.4 (s, 3H), 2.75 (s, 1H), 3.65 (s, 3H), 3.9 (s, 1H), 3.95 (s, 1H), 4.3-4.35 (d, 1H, J = 7Hz), 4.6-4.65 (d, 1H,J = 7Hz), 7.3-7.35 (d, 2H,J = 8Hz) and 7.8-7.85 (d, 2H, J = 8Hz). MS (CI/CH_4) m/z 382 (M + H)

5,6-Isopropylidenedioxy-2-(4-toluenesulfonyl)-2-azabicyclo[2.2.1]heptane-3-yl]diphenyl-methanol (20).- A solution of **19** (458 g, 1.2 mol) in THF (4 L) was added over 2 hrs to a chilled (0°) solution of phenylmagnesium bromide (870 g, 4.8 mol) in ether (4 L) maintaining the reaction temperature between 0 and 5° and the mixture was stirred overnight at ambient temperature. The mixture was chilled in an ice bath and a saturated solution of NH_4Cl (2L) was slowly added at a rate which maintained the reaction mixture at 25°. Water (1 L) and ether (2 L) were added, the layers were separated and the aqueous layer was extracted with an additional portion (2 L) of ether. The organic extracts were combined, dried ($MgSO_4$) and evaporated. The residue was dissolved in acetone (2 L) and filtered. The filtrate was diluted with methanol (4 L), chilled and filtered to give the product (464 g), mp. 211-213°. A second crop of 68 g was recrystallized to give another 50 g, mp. 211-213° for a combined yield of 85%.

Anal: Calcd for $C_{29}H_{31}NO_5S$: C, 68.99; H, 6.18; N, 2.77. Found: C, 68.81; H, 6.22; N, 2.81

IR (KBr) 704, 1045, 1076, 1091 and 1155 cm^{-1}. ^1H NMR($CDCl_3$): δ 0.90-0.95 (d, 1H, J = 8Hz), 1.3 (s, 3H), 1.4 (s, 3H), 1.4-1.5 (d, 1H, J = 8Hz), 2.4 (s, 1H), 2.42 (s, 3H), 3.1 (s, 1H), 4.1 (s, 1H), 4.4 (s, 1H), 4.45 (d, 1H, J = 7Hz), 4.9 (d, 1H, J = 8Hz) and 6.9-7.5 (m, 14H). MS (CI/CH_4) m/z 506 (M + H).

(±)3-Benzhydrylidene-5,6-isopropylidene-2-(4-toluenesufonyl)-2-azabicyclo[2.2.1]heptane (21).- A mixture of **20** (577 g, 1.14 mol) and CH_2Cl_2 (1.2 L) was chilled to 0° and TFA (264 mL, 3.43 mol)

followed by TFA anhydride (164 mL, 1.16 mol) were added. The cooling bath was removed and a 35° bath was used to elevate the temperature of the reaction mixture to 33° over 10 min. The reaction mixture was poured into a solution of K_2CO_3 (1.2 kg) in H_2O (6 L), the aqueous mixture was stirred for 30 min and the layers were separated. The organic layer was extracted with CH_2Cl_2 (2.5 L), the organic extracts were combined and evaporated. The residue was stirred with methanol (5 L), chilled to 5° and filtered to give the product (548 g, 98%). Recrystallization (CH_2Cl_2/MeOH) gave the product mp. 176-180° in 90% yield.

Anal. Calcd for $C_{29}H_{29}NO_4S$: C, 71.43; H, 5.99; N, 2.87. Found: C, 71.07; H, 6.06; N, 2.78

IR(KBr) 702,734,756,1037,1074,1161 and 1340 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.3 (s, 3H), 1.4 (s, 3H), 1.45 (d, 1H, J = 8Hz), 1.8 (d, 1H, J = 8Hz), 2.4 (s, 3H), 3.25 (s, 1H), 4.3 (d, 1H, J = 7Hz), 4.45 (s, 1H), 4.6 (d, 1H, J = 7Hz) and 7.05-7.4 (m, 14H). MS (CI/CH_4) m/z 488 (M + H).

(±)1-(4-Toluenesulfonyl)amino-4-hydroxymethyl-2,3-isopropylidenedioxycyclopentane (13).- A mixture of **21** (19.2 g, 0.039 mol), CH_2Cl_2 (200 mL) and methanol (10 mL) was chilled to -78° and ozone was added until a blue color formed (40 min). The reaction mixture was purged with nitrogen to expel excess ozone and DMS (4.9 g, 0.079 mol) was added. The reaction mixture was allowed to stand for 18 hrs, then evaporated. The residue was dissolved in THF (150 mL), $LiEt_3BH$ (2 eq) was added and the reaction mixture was stirred for 2 hrs at ambient temperature. Excess reagent was quenched by the addition of MeOH (50 mL), the mixture was diluted with ether (200 mL) and washed with H_2O (100 mL). The organic layer was isolated, dried ($MgSO_4$), evaporated and the residue was purified by flash chromatography (hexane/EtOAc 1:1 → hexane/EtOAc 1:4). The product was dissolved in CH_2Cl_2 (100 mL) and hexane (250 mL) and the mixture was heated on a steam bath until precipitation began. The mixture was removed from the steam bath, slowly cooled to ambient temperature, chilled to 0° and filtered to give 10.8 g (81%) of **13** as a white solid, mp. 108-109°.

Anal: Calcd for $C_{16}H_{23}NO_5S$: C, 56.29; H, 6.79; N, 4.10. Found: C, 56.34; H, 6.72; N, 4.04

IR (KBr) 553, 1049, 1095 and 1159 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.21 (s, 3H), 1.39 (s, 3H), 1.62 (bs, 1H), 2.2-2.3 (brd, 1H), 2.3-2.4 (m, 1H), 2.41 (s, 3H), 2.43 (bs, 1H), 3.6 (m, 1H), 3.7 (m, 1H), 3.8-3.9 (m, 1H), 4.44 (dd, 2H, J_1 = 50.7Hz, J_2 = 5.7Hz), 6.40 (d, 1H, J = 9.4Hz), 7.3 (m, 2H) and 7.8 (m, 2H). MS (CI/CH_4) m/z 342 (M + H).

(±)1-*t*-Butyloxycarbonylamino-4-hydroxymethyl-2,3-isopropylidenedioxy-cyclopentane (23).- Sodium metal was added in portions at -78° to a mixture of **13** (3.02 g, 8.84 mmol), THF (35 mL) and liquid NH_3 (30 mL) until a blue color persisted. Excess sodium was destroyed by addition of ethanol (40 mL) and the mixture was stirred overnight at ambient temperature. The mixture was heated at 60° for 3 hrs to remove any NH_3 which remained, diluted with H_2O (20 mL), di-*t*-butyldicarbonate (5.8 g, 26.5 mmol) was added and the mixture was stirred 72 hrs at ambient temperature. The mixture was diluted with EtOAc (100 mL), and the organic layer was dried and evaporated. The residue was chromatographed (EtOAc/hexane 1:1→3:2) to give the product as an oil which was solidified from CH_2Cl_2/hexane to give a white solid (1.8g, 71%), mp. 95-96°.

Anal: Calcd for $C_{14}H_{25}NO_5$: C, 58.52; H, 8.77; N, 4.87. Found: C, 58.80; H, 8.94; N, 4.77

IR (KBr) 1167, 1251, 1392 and 1685 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.3 (s, 3H), 1.45 (s, 9H), 1.5 (s, 3H), 1.52-1.55 (m, 1H), 2.2-2.5 (m, 3H), 3.6-3.85 (m, 2H), 3.95-4.05 (m, 1H), 4.35-4.55 (m, 2H)and 5.4-5.6 (bs, 1H). MS (CI/CH_4) m/z 288 (M + H).

Resolution of 13.- To a stirring solution of **13** (925 mg, 2.7 mmol) and vinyl acetate (0.95 mL, 10.3 mmol) in *t*-BuOMe (185 mL) was added lipase PS-30 (930 mg). The suspension was stirred at ambient temperature for 2 hrs, filtered and the filter cake was washed with *t*-BuOMe (20 mL). The solution was evaporated and the residue was chromatographed (EtOAc/Hexane 3:2) to give unreacted alcohol as a crystalline solid (**13a**) (338 mg, 37% yield, 96% ee) and the acetate **24b** (660 mg, 63% yield, 78% ee) as an oil. Recrystallization of **13a** (*t*-BuOMe/Hexane) gave 302 mg (33% yield) of white solid, mp. 126.5-127.5° with 100% ee. OR -10.1° (c = 1.0, $CHCl_3$).

A mixture of the ester **24b** (660 mg, 1.7 mmol), 1N KOH (6.6 mL) and MeOH (4 mL) was heated at 80° for 30 min, the mixture was concentrated on a rotary evaporator at 25° to remove the methanol, and pH of the aqueous mixture was adjusted to 7 with 1N HCl. Extraction of the acidified mixture with EtOAc gave the alcohol **13b** as a yellow solid, which was recrystallized (*t*-BuOMe/Hexane) to give a white solid (275 mg, 47% yield, 81% ee), mp. 123.5-124°. Optical rotation of this material was determined $[\alpha]_D^{20}$= +14.1° (c = 1.1, $CHCl_3$).

(+)4-Acetoxymethyl-1-amino-N-*t*-butyloxycarbonyl-2,3-isopropylidenedioxy–cyclopentane (24a).- A solution of compound **23a** (154 mg, 0.53 mmol) (from reduction of (-)**13a**) (see Scheme IV) and DMAP (10 mg) in pyridine (5 mL) was chilled in an ice bath and acetic anhydride (82 mg, 0.8 mmol) was added. The ice bath was removed and the mixture was stirred for 18 hrs, diluted with CH_2Cl_2 (50 mL) and extracted with 10 mL portions of 1N HCl, and aq. $NaHCO_3$. The solution was dried over Na_2SO_4, filtered and the filtrate was evaporated. The residue was chromatographed (EtOAc/Hexane 1:2) to give the product (140 mg, 80%) as an oil.

Anal: Calcd for $C_{16}H_{27}NO_6$: C, 58.34; H, 8.26; N, 4.25. Found: C, 58.42; H, 8.36; N, 4.23

IR ($CHCl_3$) 606, 662, 756, 870, 916, 968, 1047, 1068, 1167, 1246, 1368, 1456, 1520,1712, 1742, 2937, 2980 and 3352 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.28 (s, 3H), 1.42 (s, 9H), 1.48 (s, 3H), 1.60 (s, 1H), 2.1 (s, 3H), 2.3-2.45 (m, 2H), 3.8-4.0 (m, 1H), 4.12-4.2 (m, 1H), 4.38-4.45 (br s, 2H) and 4.78-4.9 (br s, 1H). MS (CI/CH_4) m/z 330 (M+H). OR $[\alpha]_D^{20}$= +4.6° (c = 0.43, $CHCl_3$).

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