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The Enantiomers of 1β-Adenyl-2α-hydroxy-3β-hydroxymethyl-cyclobutane

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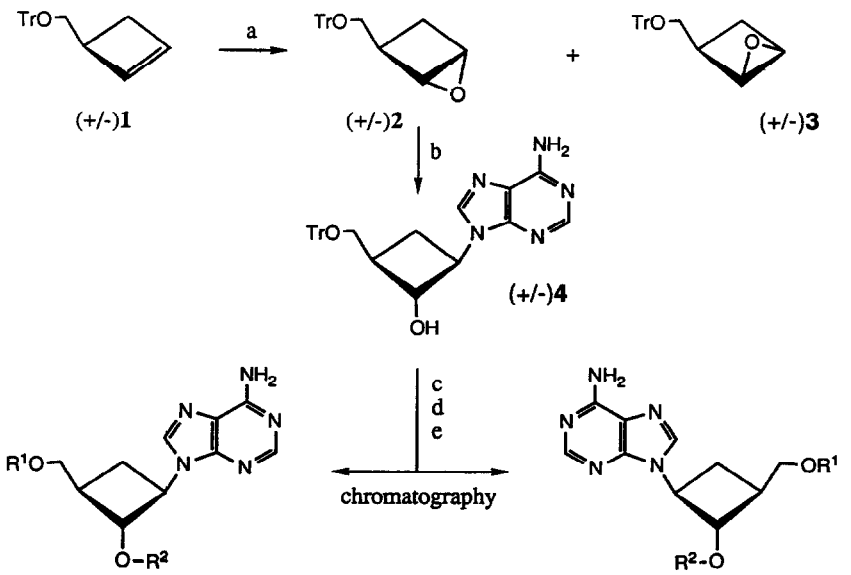
Abstract: The enantiomers of 1β-adenyl-2α-hydroxy-3β-hydroxymethyl-cyclobutane have been separated by chromatography of their 2-(N-BOC-prolyl)-3-trityloxymethyl-derivatives. The (-)-enantiomer has been obtained from 1.2-dihydroxy-3-trityloxymethyl-cyclobutane enriched by acetylation of the racemate with Pseudomonas fluorescens lipase.

Within a program to search for novel nucleotide skeletons with an ability to hybridize with ribo- or deoxyribo-nucleic acids we had a need for the pure enantiomers of carba-nucleoside **4**. Although the synthesis of its racemic form has been reported[1,2] and an enantioselective synthesis has been announced,[3,4] we could not find any description of the pure enantiomers. Here we communicate our experiments towards this goal.

Racemic (+/-)**1**, obtained in an analoguous, modified way to the method reported,[2] was converted to (+/-)**4** (scheme 1). As all attempts to separate the antipodes by chromatography on chiral solid phases failed, we then examined chromatographic separation of the diastereomeric mixtures. The N-Z- or N-BOC-prolyl-esters of (+/-)**4** migrate sufficiently differently on silica gel in hexane/2-propanol = 75:25 to allow their preparative separation. In a representative example 3 g of **5** and **6** were separated on 900 g of silica gel with a 8:2 - mixture of hexane / 2-propanol. Selective removal of N-BOC-proline led to **7** and **8**, subsequent removal of the trityl-group by trifluoroacetic acid in dimethoxyethane gave carba-nucleosides **9** and **10**. Comparison of their optical rotations at different wavelengths with those of (-)-1α-adenyl-3β-hydroxy-4α-hydroxymethyl-cyclopentane[5] led to the indicated assignment of absolute configurations.



f, g: **5** : R^1 = Trityl; R^2 = N-BOC-L-prolyl → **7** : R^1 = Trityl; R^2 = H → **9** : R^1 = H; R^2 = H

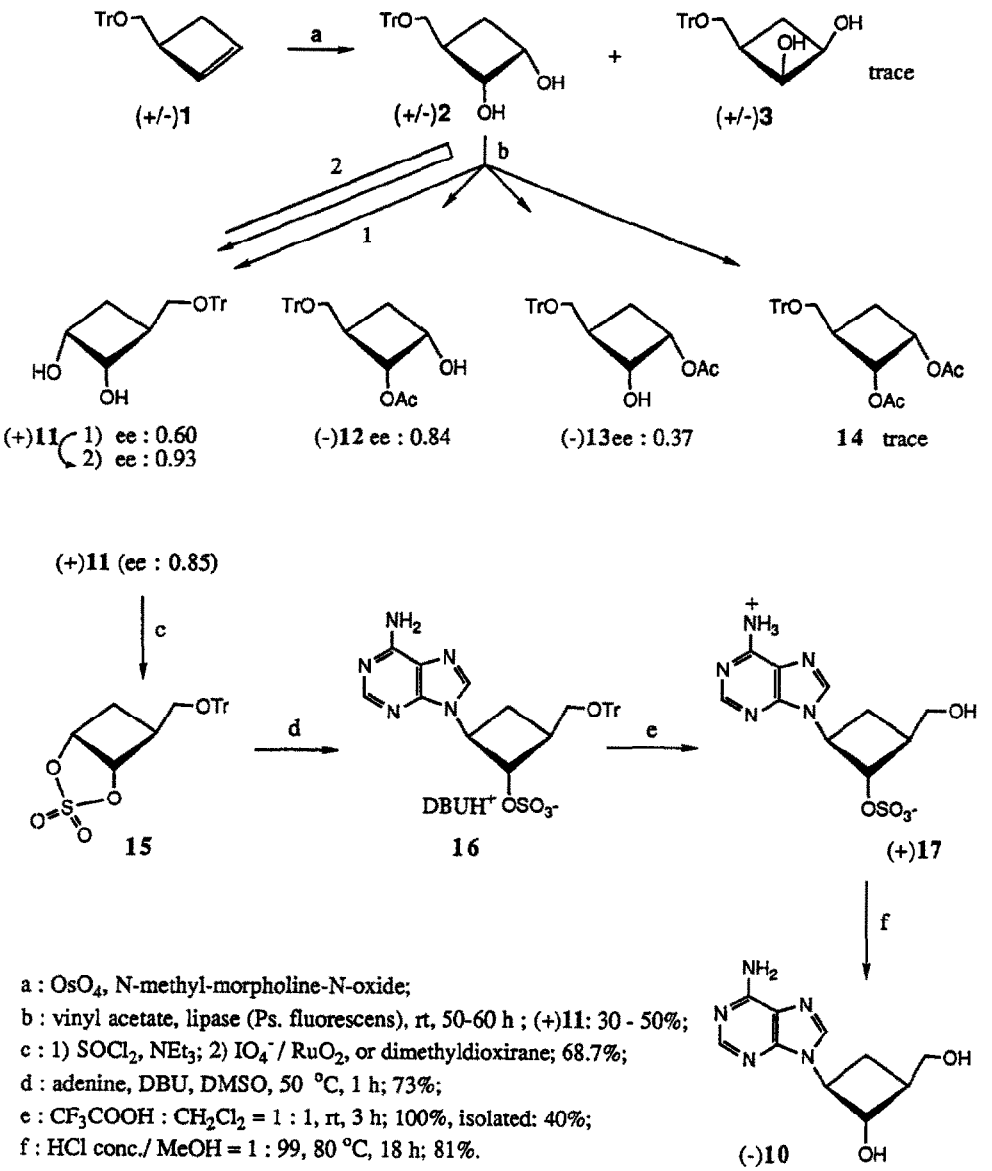
f, g: **6** : R^1 = Trityl; R^2 = N-BOC-L-prolyl → **8** : R^1 = Trityl; R^2 = H → **10** : R^1 = H; R^2 = H

a: dimethyldioxirane / acetone, 0°- 5 °C, 17 h; 65% **2**, 35% **3**; b: adenine / DBU (4 equiv.) DMSO, 110 °C, 19 h; 65%; c: DMF-dimethylacetal, rt, 3 h; 89%; d: N-BOC-Pro, DCCD, N-hydroxy-benzotriazole, 4-dimethylamino-pyridine; 90%; e: acidic resin Merck IV, MeOH, rt, 9 h; 100%; f: 1 M NaOH / MeOH, rt, 20 Min.; 99%; g: $CF_3COOH : H_2O$: dimethoxyethane = 14:14:72, 40 °C, 8 h; 90 %.

Scheme 1. Synthesis and separation of (+)**9** and (-)**10**

Table 1. Optical rotation values of diastereomers **5** and **6** and enantiomers **7** - **10**

compound	$[\alpha]_D^{20}$-value	solvent
5	+24.2 ± 2.0	MeOH
6	+43.0 ± 2.0	MeOH
7	+ 3.8 ± 1.8	MeOH
8	- 5.1 ± 1.6	MeOH
9	+29.7 ± 1.0	DMF
10	-28.1 ± 1.0	DMF



Scheme 2. Synthesis of (-)**10**

In a different approach we started from diol **11**, obtained by osmylation of (+/-)**1**. Attempts to osmylate enantioselectively with O-(4-chlorobenzoyl)-dihydro-quinine or O-(4-chlorobenzoyl)-dihydro-quinidine as catalysts were unsuccessful. However, acetylation of (+/-)**11** with lipase from Pseudomonas fluorescens (EC. 3.1.1.3) in vinyl acetate at RT gave a mixture of enriched (+)**11** and the monoacetates **12** and **13** together with a small amount of diacetate **14**. Prolonged reaction (50 - 70 hours) or repeated reaction of isolated unreacted material led to a steady enrichment of (+)**11**[6]. The monoacetates **12** and **13**, however, never exceeded a certain value of enantiomeric excess, probably because of equilibration[7] (scheme 2). For the following steps we used a preparation of (+)**11** with ee = 0.85. Cyclic sulfate **15** was prepared via the thionoester as a nicely crystalline compound, mp. 163 °C, according to the method of Sharpless.[8] Substitution by adenine with DBU in DMSO took place at 50 °C to give the sulfate **16**, which may be easily purified by dilution of the reaction mixture with water, addition of tetrabutylammonium chloride and extraction with chloroform. After removal of the trityl group the zwitterionic **17**, $[\alpha]_D$= +20.5 (H_2O), ee= 0.85, mp.> 230 °C was isolated. Hydrolysis of the sulfate ester gave nucleoside **10** with $[\alpha]_D$= -20 (DMF), or corrected for ee = 0.85: $[\alpha]_D$= -23.5 (DMF).[9] Thus, one can conclude that Pseudomonas lipase acetylates diol (-)**11** preferentially.

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REFERENCES AND NOTES

1. *Europ. Pat. Appl.*, **EPA 0 330 992** (6.9.1989); priority: 29.2.1988, JP 44 553 / 88; Nippon Kayaku Kabushiki Kaisha, Tokyo.
2. Slusarchyk, W. A.; Young, M. G.; Bisacchi, G. S.; Hockstein, D. R.; Zahler, R.; *Tetrahedron Lett.* **1989**, *30* , 6453 - 6456;
   US Pat. **4 918 075** (17.4.1990); E. R. Squibb & Sons, Inc.
3. Nishiyama, Y.; Yamamoto, N.; Yamada, Y.; Daikoku, T.; Ishikawa, Y.; Takahashi, K.; *J. Antibiot.*, **1989**, *42* , 1854 - 1859.
4. Ishikawa, Y.; Narita, A.; Shiozawa, A.; Hayashi, Y.; Narasaka, K.; *J. Chem. Soc., Chem.Commun.*, **1989**, 1919 - 1921.
5. We thank Dr. H. Moser, Central Research, for a sample of this compound.
6. $[\alpha]_D^{20}$= +16 ($CHCl_3$, extrapolated)
7. ee-Values were determined by evaluation of H-NMR signals of acetyl groups of the diacetates in the presence of *(S)* - 1-(9-anthryl)-2.2.2-trifluoro-ethanol.
8. Kim, B. M.; Sharpless, K. B.; *Tetrahedron Lett.*, **1989**, *30* , 655 - 658.
9. New compounds were characterized by NMR- and UV-spectra and by elemental analyses.