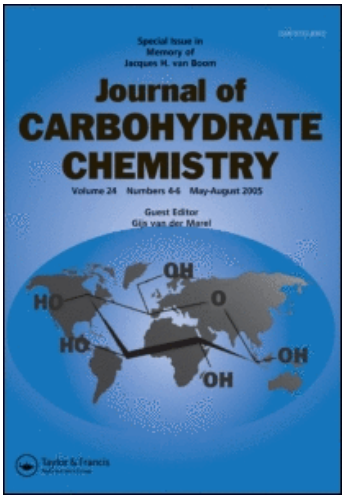

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Resolution of 2,3-Dideoxy-DL-2-Enopyranos-4-Uloses *Via* Chromatographic Separation of their Diastereomeric *O-tert*-Butyloxycarbonyl-L-Alanyl Esters. A Convenient Synthesis of L- and D-Aculose

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RESOLUTION OF 2,3-DIDEOXY-DL-2-ENOPYRANOS-4-ULOSES *VIA* CHROMATOGRAPHIC SEPARATION OF THEIR DIASTEREOMERIC *O-tert*-BUTYLOXYCARBONYL-L-ALANYL ESTERS. A CONVENIENT SYNTHESIS OF L- AND D-ACULOSE[1].

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ABSTRACT

A simple and effective procedure for the resolution of 2,3-dideoxy-DL-2-enopyranos-4-uloses is presented. This procedure is based on column chromatographic separation of their diastereomeric *O*-(*N-tert*-butyloxycarbonyl)-L-alanyl esters, followed by mild acidic cleavage of the ester function. L-Aculose, 2,3,6-trideoxy-L-*glycero*-hex-2-enopyranos-4-ulose, is also prepared in satisfactory yield.

INTRODUCTION

2,3-Dideoxy-DL-2-enopyranos-4-uloses, which are easily prepared by oxidation of 2-furylcarbinols,[2-5] have attracted much attention as precursors of carbohydrates[6] and have been

used as starting materials for the synthesis of a variety of biologically important compounds.[7] In addition, several 5-disubstituted derivatives of the title compounds display interesting antimicrobial and anticoccidial activities.[2,8,9] Recently, stereoselective syntheses of optically pure 2-furylcarbinols, which may lead to optically active 2,3-dideoxy-hex-2-enopyranos-4-uloses have been reported,[10-13] but they usually suffer from limitation in the functionality of C-5.

In this communication we report a simple and effective procedure for the preparation of D- and L-2-enopyranos-4-uloses, which contain a variety of substituents at C-5 position. This prosedure is based on column chromatographic separation of the diastereomeric *O*-(*N*-*tert*-butyloxycarbonyl)-L-alanyl esters of 2-enopyranos-4-uloses.

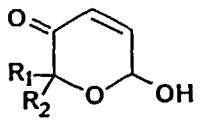
RESULTS AND DISCUSSION

Four 2,3,6-trideoxy-DL-2-enopyranos-4-uloses, namely 5-(*p*-methoxy)phenyl-2,3,6-trideoxy-DL-*glycero*-hex-2-enopyranos-4-ulose (**1a**),[14] 5-(*p*-benzenesulfonyl)phenyl-2,3,6-trideoxy-DL-*glycero*-hex-2-enopyranos-4-ulose (**1b**),[15] 2,3,6-trideoxy-DL-*glycero*-hex-2-enopyranos-4-ulose (**1c**)[3] and 2,3-dideoxy-pent-2-enopyranos-4-ulose (**1d**),[2] were used as starting materials (Scheme 1). Treatment of the above 2-enopyranos-4-uloses with optically pure *N*-*tert*-butyloxycarbonyl-L-alanine (Boc-L-Ala-OH) using the dicyclocarbodiimide (DCC) method in the presence of 4-dimethylaminopyridine (DMAP)[16] gave two diastereomeric esters **2a-d** in high yield. The DCC-DMAP procedure is the method of choice since the mixed carbonic anhydride method[17] gives slightly lower yield. Both procedures afforded only two diastereomeric 1-*O*-(*N*-*tert*-butyloxycarbonyl-L-alanyl)-2-enopyranos-4-uloses which were easily separated on silica gel column (6:4 ether- hexane or 9:1 benzene-ether).

Both diastereomeric esters **2a-c**, derived from the above 2-enopyranos-4-ulose **1a-c** have a *trans* configuration. The configurational assignment has been indicated by the quotient $J_{1,2}/J_{1,3}$ = 1 of vicinal to allylic coupling constants for 5-disubstituted derivatives[15] and by the large $J_{1,2}$ and the small $J_{1,3}$ coupling constants for 5-monosubstituted ones.[3]

Since compounds **1a-d** are moderately stable in acidic or basic media, a selective method for the hydrolysis of the particular ester bond of **2a-c** is needed in order to prevent any decomposition of the products. Investigating several hydrolytic conditions we found that treatment with neat formic acid for 15 min at room temperature gave the best results. Thus, optically active 2-enopyranos-4-uloses were obtained in high yields.

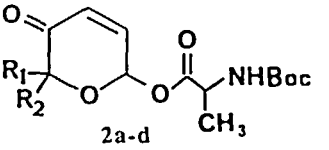
L-Aculose (+)**1c**, 2,3,6-trideoxy-L-*glycero*-hex-2-enopyranos-4-ulose, which is a component of naturally occuring antibiotics[18,19] as well as its enantiomer (-)**1c**, were prepared in satisfactory yields by the described procedure. The absolute configuration of the resolved enantiomers was determined by comparison of their specific rotation with that reported in literature for the natural product.[19] In the case of diastereomeric esters of aculose the rule $R_{f(L\text{-}L)} > R_{f(D\text{-}L)}$ validated for the diastereomeric dipeptides[20] seems to be in agreement.



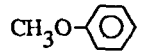
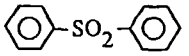
(±) 1a-d

Boc-L-Ala-OH

DCC, DMAP



2a-d

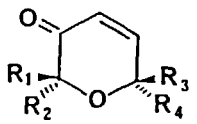
1	R_1	R_2
a		CH_3
b		CH_3
c	H	CH_3
d	H	H

column chromatography | eluent 6:4 ether:hexane or 9:1 benzene:ether

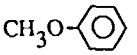
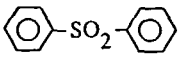
Diastereomer A | Diastereomer B

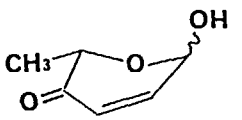
98% HCOOH, room temp., 15 min.

(-)1a-c | (+)1a-c



2

2	R_1	R_2	R_3	R_4
a		CH_3	H	Boc-Ala-O
b		CH_3	H	Boc-Ala-O
c	H	CH_3	Boc-Ala-O	H
d	H	H	Boc-Ala-O	H



(+)1c

SCHEME 1

It should also to be noted that none of the reported methods for stereoselective synthesis of 2-furylcarbinols[10-13] can be applied for the preparation of optically active pentoses from non-carbohydrate precursors. Our procedure applied to **1d**, yields the two diastereomers **2d** in pure form. These products can be used as precursors leading to optically active pentoses.

Achmatowicz and co-workers have shown previously that racemic 2,3-dideoxy-2-enopyranos -4-uloses can be converted stereoselectivelly to sugars of various configurations (*manno, gluco* etc.).[3,21] Our method may be applied for the synthesis of **L**- and **D**- sugars from non-carbohydrate precursors, using 1-*O*-(*N*-*tert*-butyloxycarbonyl-alanyl) derivatives of 2,3-dideoxy-2-enopyranos-4-uloses as key intermediates. Furthermore the resolved compounds will be useful for the synthesis of biologically interesting optically active compounds whose structure-activity relationship can be studied.

EXPERIMENTAL

General Methods. Melting points were determined with a Buchi micro melting point apparatus and are uncorrected. Specific rotations were determined with a Perkin-Elmer 141 polarimeter using a 10-cm cell. ^{1}H NMR spectra were recorded with a Varian 360 EM (60 MHz) spectrometer in $CDCl_3$ with Me_4Si as an internal reference. ^{13}C NMR spectra were determined with a Varian FT 80A (20 MHz). IR spectra were recorded with a Perkin-Elmer 283B spectrophotometer. Preparative chromatography was performed on silica gel (Merk Art. 13895). Thin layer chromatography (TLC) was conducted on silica gel (Merk Art. 4755).

General Procedure for Preparation of 2a-d. Mixed Anhydride Method. To a stirred solution of *N*-*tert*-butyloxycarbonyl-L-alanine (0.189 g, 1 mmol) in tetrahydrofuran (4 mL) at -15 °C, was added *N*-methylmorpholine (0.11 mL, 1 mmol) followed by isobutyl chlorofomate (0.13 mL, 1 mmol). After 5 min a precooled solution of **1** (1 mmol) in tetrahydrofuran (5 mL) was added. The reaction mixture was stirred for 30 min at -15 °C and for 12 h at room temperature. The solvent was removed in *vacuo* and the residue dissolved in ethyl acetate. The organic phase was washed by 5% aq $NaHCO_3$, H_2O, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on silica gel (1:100) and eluted with 6:4 ether-hexane or 9:1 benzene-ether to give diastereomers A and B (1:1) in 52-60% total yield.

Dicyclohexylcarbodiimide - 4-Dimethylaminopyridine Method. To a stirred solution of *N*-*tert*-butyloxycarbonyl-L-alanine (0.189 g, 1 mmol), 4-dimethylaminopyridine (0.005 g, 0.05 mmol) and **1** (1 mmol) in tetrahydrofuran (3 mL), was added a solution of dicyclohexylcarbodiimide (0.226, 1.2 mmol) in tetrahydrofuran (3 mL) at 0 °C. The reaction mixture was stirred for 5 min at 0 °C and 2 h at room temperature. Precipitated dicyclohexylurea was filtered off and the solvent was removed by evaporation under reduced pressure. The residue was dissolved in dichloromethane (30 mL) and the solution was washed with 0.2 N HCl, H_2O, saturated $NaHCO_3$ solution, H_2O and dried ($MgSO_4$). The solvent was removed by evaporation and the residue was chromatographed as described above to give diastereomers A and B (1:1) in 77-88% total yield.

2a Diastereomer A: R_f (TLC 7:3 hexane-ethyl acetate) 0.52; mp 61 °C; $[\alpha]_D^{25}$ -19.0° (*c* 1.0, ethyl acetate); IR (KBr): 3390 (NH), 1760 (OCO), 1705 (NHCO), 1695 cm^{-1} (=C-C=O) ;^1H NMR: δ 1.3 (s, 12H, CH_3, Boc), 1.5 (d, 3H, J = 7 Hz, CHCH_3), 3.7 (s, 3H, OCH_3), 4.1 (m, 1H, CHCH$_3$), 5.3 (d, 1H, J = 8 Hz, NH), 6.0 (dd, 1H, $J_{1,3}$ = 1.5 Hz, $J_{2,3}$ = 10 Hz, H-3), 6.2 (dd, 1H, $J_{1,2}$ = 1.5 Hz, $J_{1,3}$ = 1.5 Hz, $J_{quotient}$= $J_{1,2}/J_{1,3}$ = 1, H-1), 6.6 (dd, 1H, $J_{1,2}$ = 1.5 Hz, $J_{2,3}$ = 10 Hz, H-2), 7.1 and 6.7 (4H, C_6H_4); ^{13}C NMR δ 195.4 (C-4), 171.9 (OCO), 155.3 (NHCO), 143.5 (C-2), 128.8 (C-3), 87.8 (C-1), 83.7 (C-5), 79.9 [*C*-(CH$_3$)], 54.9 (OCH$_3$), 49.4 (*C*HCH$_3$), 27.0 [C-(*C*H$_3$)], 17.9 (CH*C*H$_3$), 14.1 (CH$_3$).

Anal. Calcd for $C_{21}H_{27}NO_7$: C, 62.21; H, 6.71; N, 3.45. Found: C, 62.45; H, 6.54; N, 3.38.

2a Diastereomer B: R_f (TLC 7:3 hexane-ethyl acetate) 0.50; $[\alpha]_D^{25}$ -35.2° (*c* 1.0, ethyl acetate); IR (oil) 3385 (NH), 1765 (OCO), 1705 (NHCO), 1695 cm^{-1} (=C-C=O) ;^1H NMR δ 1.3 (s, 12H, CH_3, Boc), 1.5 (d, 3H, J = 7 Hz, CHCH_3), 3.7 (s, 3H, OCH_3), 4.1 (m, 1H, CHCH$_3$), 5.3 (d, 1H, J = 8 Hz, NH), 6.0 (dd, 1H, $J_{2,3}$ = 10 Hz, $J_{1,3}$ = 1.5 Hz, H-3), 6.1 (dd, 1H, $J_{1,2}$ = 1.5 Hz, $J_{1,3}$ = 1.5 Hz, $J_{quotient}$= $J_{1,2}/J_{1,3}$ = 1, H-1), 6.5 (dd, 1H, $J_{1,2}$ = 1.5 Hz, $J_{2,3}$ = 10 Hz, H-2), 7.1 and 6.7 (4H, C_6H_4); ^{13}C NMR δ 195.3 (C-4), 171.7 (OCO), 155.0 (NHCO), 143.3 (C-2), 128.8 (C-3), 87.8 (C-1), 83.8 (C-5), 79.8 [*C*-(CH$_3$)], 55.1 (OCH$_3$), 49.6 (*C*HCH$_3$), 27.0 [C-(*C*H$_3$)], 17.9 (CH*C*H$_3$), 14.1 (CH$_3$).

Anal. Calcd for $C_{21}H_{27}NO_7$: C, 62.21; H, 6.71; N, 3.45. Found: C, 62.51; H, 6.85; N, 3.32.

2b Diastereomer A: R_f (TLC 7:3 hexane-ethyl acetate) 0.47; mp 48 °C; $[\alpha]_D^{25}$ +33.6° (*c* 1.0, chloroform); IR (KBr) 3385 (NH), 1780 (OCO), 1710 (NHCO), 1700 cm^{-1} (=C-C=O); ^1H NMR δ 1.3 (s, 9H, Boc), 1.4 (d, 3H, J = 7 Hz, CHCH_3), 1.9 (s, 3H, CH_3), 4.0 (m, 1H, CHCH$_3$), 5.0 (d, 1H, J = 7 Hz, NH), 5.9 (dd, 1H, $J_{1,3}$ = 2 Hz, $J_{2,3}$ = 10 Hz, H-3), 6.2 (dd, 1H, $J_{1,3}$ = 2 Hz, $J_{1,2}$ = 2 Hz, $J_{quotient}$ = $J_{1,2}/J_{1,3}$ = 1, H-1), 6.6 (dd, 1H, $J_{1,2}$ = 2 Hz, $J_{2,3}$ = 10 Hz, H-2), 7.6 and 7.1 (9H, C_6H_4, C_6H_5).

Anal. Calcd for $C_{26}H_{29}NO_8S$: C, 60.57; H, 5.67; N, 2.72. Found: C, 60.83; H, 5.48; N, 2.68.

2b Diastereomer B: R_f (TLC 7:3 hexane-ethyl acetate) 0.38; $[\alpha]_D^{25}$ -63.4° (*c* 1.1, chloroform); IR (oil) 3380 (NH), 1760 (OCO), 1710 (NHCO), 1690 cm^{-1} (=C-C=O); ^1H NMR δ 1.3 (s, 9H, Boc), 1.4 (d, J = 7 Hz, 3H, CHCH_3), 1.7 (s, 3H, CH_3), 4.0 (m, 1H, CHCH$_3$), 5.0 (d, 1H, J = 7 Hz, NH), 5.9 (dd, 1H, $J_{1,3}$ = 2 Hz, $J_{2,3}$ = 10 Hz, H-3), 6.2 (dd, 1H, $J_{1,3}$ = 2 Hz, $J_{1,2}$ = 2 Hz, $J_{quotient}$= $J_{1,2}/J_{1,3}$ = 1, H-1), 6.6 (dd, 1H, $J_{1,2}$ = 2, $J_{2,3}$ = 10 Hz, H-2), 7.6 and 7.1 (9H, C_6H_4, C_6H_5).

Anal. Calcd for $C_{26}H_{29}NO_8S$: C, 60.57; H, 5.67; N, 2.72. Found: C, 60.72; H, 5.42; N, 2.59.

2c Diastereomer A: R_f (TLC 7:3 hexane-ethyl acetate) 0.57; $[\alpha]_D^{25}$ -77.2° (*c* 1.0, chloroform); IR (oil) 3380 (NH), 1755 (OCO), 1705 (NHCO), 1690 cm^{-1} (=C-C=O); ^1H NMR δ 1.3 (d, 3H, J = 7 Hz, CHCH_3), 1.4 (s, 9H, Boc), 4.3 (dq, 1H, J = 7 Hz, CHCH$_3$), 4.6 (q, 1H, J = 6 Hz, H-5), 5.1 (d, 1H, J = 7 Hz, NH), 6.1 (d, 1H, $J_{2,3}$ = 10 Hz, H-3), 6.4 (d, 1H, $J_{1,2}$ = 3 Hz, H-1), 6.8 (dd, 1H, $J_{1,2}$ = 3 Hz, $J_{2,3}$ = 10 Hz, H-2).

Anal. Calcd for $C_{14}H_{21}NO_6$: C, 56.18; H, 7.07; N, 4.68. Found: C, 56.34; H, 6.94 ; N, 4.58.

2c Diastereomer B: R_f (TLC 7:3 hexane-ethyl acetate) 0.64; mp 172 °C; $[\alpha]_D^{25}$ +79.7° (*c* 1.0, chloroform); IR (KBr) 3380 (NH), 1755 (OCO), 1705 (NHCO), 1700 cm^{-1} (=C-C=O); ^1H NMR δ 1.4 (d, 3H, J = 7 Hz, CHCH_3), 1.5 (s, 9H, Boc), 4.2 (dq, 1H, J = 7 Hz, CHCH$_3$), 4.6 (q,

1H, J = 6 Hz, H-5), 5.3 (d, 1H, J = 7 Hz, NH), 6.2 (d, 1H, $J_{2,3}$ = 10 Hz, H-3), 6.5 (d, 1H, $J_{1,2}$ = 3 Hz, H-1), 6.9 (dd, 1H, $J_{1,2}$ = 3 Hz, $J_{2,3}$ = 10 Hz, H-2).

Anal. Calcd for $C_{14}H_{21}NO_6$: C, 56.18; H, 7.07; N, 4.68. Found: C, 56.28; H, 7.01; N, 4.81.

2d Diastereomer A: R_f (T L C 7:3 hexane-ethyl acetate) 0.52; $[\alpha]_D^{25}$ +102.0° (*c* 0.7, chloroform); IR (KBr) 3350 (NH), 1750 (OCO), 1705 (NHCO), 1680 cm^{-1}(=C-C=O); ^1H NMR δ 1.4 (m, 12H, Boc, CHC*H*$_3$), 4.2 (d, 1H, J = 16 Hz, H-5e), 4.3 (m, 1H, C*H*CH$_3$), 4.5 (d, 1H, J = 16 Hz, H-5a), 5.0 (d, 1H, J = 7 Hz, NH), 6.3 (d, 1H, $J_{2,3}$ = 10 Hz, H-3), 6.5 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 6.9 (dd, 1H, $J_{1,2}$ = 3.6 Hz, $J_{2,3}$ = 10 Hz, H-2); ^{13}C NMR δ 193.0 (C-4), 172.0 (OCO), 155.0 (NHCO), 141.7 (C-2), 128.9 (C-3), 87.1 (C-1), 80.1 [*C*-(CH$_3$)], 67.2 (C-5), 49.2 (*C*HCH$_3$), 28.2 [C-(*C*H$_3$)], 18.1 (CH*C*H$_3$).

Anal. Calcd for $C_{13}H_{19}NO_6$: C, 54.73; H, 6.71; N, 4.90. Found: C, 54.82; H, 6.59; N, 4.84.

2d Diastereomer B: R_f (TLC 7:3 hexane-ethyl acetate) 0.49; mp 79 °C; $[\alpha]_D^{25}$ -98.0° (*c* 1.0, chloroform); IR (KBr) 3395 (NH), 1750 (OCO), 1705 (NHCO), 1685 cm^{-1} (=C-C=O); ^1H NMR δ 1.4 (m, 12H, Boc, CHC*H*$_3$), 4.2 (d, 1H, J = 16 Hz, H-5e), 4.3 (m, 1H, C*H*CH$_3$), 4.5 (d, 1H, J = 16 Hz, H-5a), 5.0 (d, 1H, J = 7 Hz, NH), 6.3 (d, 1H, $J_{2,3}$ = 10 Hz, H-3), 6.5 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 6.9 (dd, 1H, $J_{1,2}$ = 3.6, $J_{2,3}$ = 10 Hz, H-2); ^{13}C NMR δ 193.1 (C-4), 172.0 (OCO), 154.9 (NHCO), 141.5 (C-2), 128.9 (C-3), 87.4 (C-1), 80.1 [*C*-(CH$_3$)], 67.3 (C-5), 49.3 (*C*HCH$_3$), 28.2 [C-(*C*H$_3$)], 18.1 (CH*C*H$_3$).

Anal. Calcd for $C_{13}H_{19}NO_6$: C, 54.73; H, 6.71; N, 4.90. Found: C, 54.89; H, 6.64; N, 4.65.

General Procedure for Hydrolysis of Esters 2. A solution of **2A** or **2B** (0.2 mmol) in 98% formic acid (0.3 mL) was stirred for 15 min at room temperature. Ethyl acetate (10 mL) and H_2O (10 mL) were added and the organic phase was washed with saturated $NaHCO_3$ solution, H_2O, and dried ($MgSO_4$). The solvent was evaporated to a small volume and the product was isolated by recrystallization from ethyl acetate-hexane or by preparative TLC. Yield 80-85%.

(-)1a: $[\alpha]_D^{25}$ -159.0° (*c* 1.0, chloroform).

(+)1a: $[\alpha]_D^{25}$ +150.8° (*c* 1.0, chloroform).

(-)1b: $[\alpha]_D^{25}$ -59.5° (*c* 1.0, chloroform).

(+)1b: $[\alpha]_D^{25}$ +55.1° (*c* 1.0, chloroform).

2,3,6,-trideoxy-D-glycero-hex-2-enopyranos-4-ulose [(-)1c]: $[\alpha]_D^{25}$ -44.9° (*c* 1.4, chloroform).

2,3,6,-trideoxy-L-glycero-hex-2-enopyranos-4-ulose [(+)1c]: $[\alpha]_D^{25}$ +47.3° (*c* 1.9, chloroform); lit[19] $[\alpha]_D^{20}$ +62.0° (*c* 1.05, chloroform).

IR and NMR data of resolved **1a-c** were in accordance with those reported for racemic mixtures.

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1. This paper is N° 12 in the series **Products from Furans** from these labs. For previous see ref. 7.

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