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Homochiral α,β-Unsaturated γ-Lactams: Versatile Templates

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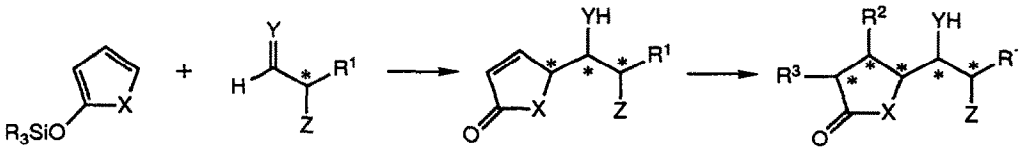
Abstract: *The enantiomerically pure crystalline α,β-unsaturated γ-lactams 4 and 5 have been synthesized by utilizing 2,3-O-isopropylidene-D-glyceraldehyde (3) as chiral source and novel N-tert-butoxycarbonyl-2-(tert-butyldimethylsiloxy)pyrrole (TBSOP) as four carbon homologative reagent. Unsaturated lactam 4 has been selectively elaborated into hydroxylated pyrrolidinones 7, 8, and 11 by stereocontrolled procedures involving conjugate addition of organocuprates, cis-dihydroxylation, and α-alkylation via hydrogenation and enolate formation. The absolute stereochemistries of 4 and 5 have been secured by single crystal X-ray analyses.*

INTRODUCTION

The design and preparation of chiral functional templates to be exploited as divergent precursors of important homochiral targets are prominent issues of the modern organic synthesis.[1] Recently, we have recognized that diastereocontrolled homologation of readily available short units by means of 2-(trimethylsiloxy)furan (TMSOF) producing enantiomerically pure α,β-unsaturated γ-lactones have the decided advantages of large substrate tolerance, high synthetic efficiency, and stereochemical predicability.[2] The development of flexible methodology for stereocontrolled transformation of the lactone moiety of these precursors has enabled synthesis of a variety of acyclic and cyclic compounds including higher-carbon sugars, azasugars, and *C*-glycosyl α-amino acids (Chart 1).[3]

As an extension of this chemistry, we wish now to describe the preparation of two epimeric seven-carbon α,β-unsaturated γ-lactams **4** and **5** using the new nitrogen containing homologation reagent N-*tert*-butoxycarbonyl-2-(*tert*-butyldimethylsiloxy)pyrrole (TBSOP), their X-ray crystal structure determinations, and selected transformations to provide synthetically useful pyrrolidinones of type **7**, **8**, and **11**.

Chart 1

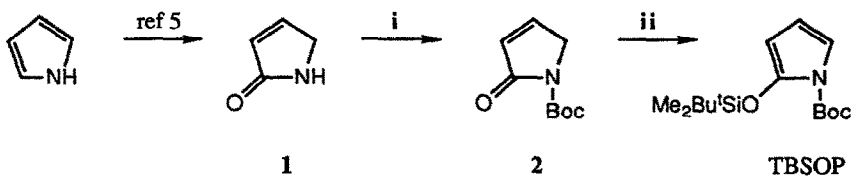


TMSOF: X=O; R_3=Me_3
TBSOP: X=NBoc; R_3=Bu^tMe_2

RESULTS AND DISCUSSION

Synthesis of Templates 4 and 5. Multigram scale preparation of TBSOP was carried out via the reaction steps outlined in Chart 2.[4] Our optimized protocol provided very pure TBSOP as a stable colorless liquid in 66% yield from pyrrol-2(5H)one (**1**). This was quickly prepared from pyrrole as described by Bocchi[5] with minor modification.

Chart 2[a]



1 **2** TBSOP

[a] **Conditions:** i, Boc_2O, DMAP, MeCN, r.t.; ii, TBS-OTf, 2,6-lutidine, CH_2Cl_2, r.t.

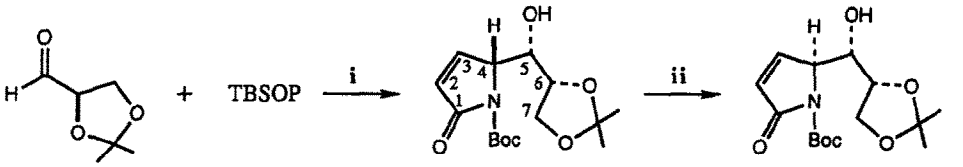
Chain extension of 2,3-*O*-isopropylidene-D-glyceraldehyde (**3**) by four carbon atoms to form the α,β-unsaturated heptenonolactam **4** was accomplished by reaction with TBSOP in diethyl ether in the presence of 1.5 mol equiv of $SnCl_4$ at -80 °C. Much to our delight, crystalline (4*R*, 5*S*, 6*R*)-configurated lactam **4** was formed both in good yield (80%) and excellent diastereoselectivity (≥ 98%) (Chart 3).

The synthesis of the (4*S*, 5*S*, 6*R*)-epimer **5** followed the same epimerization procedure as used for the lactone series,[2,3] starting with **4** using the Et_3N-DMAP system in CH_2Cl_2 at room temperature. This treatment afforded crystalline **5** in 90% yield, accompanied by ca 10% of unconverted **4** which can be recycled.

The 5,6-*erythro* selectivity observed in the homologation of **3** into **4** was expected according to the general sequence via the β-chelation controlled addition of carbon nucleophiles to α,β-dialkoxyaldehydes,[6] whereas the 4,5-*threo* stereoselectivity was rationalized by assuming exclusive *endo* approach of the reaction partners in the addition step.[7]

D-*Arabino*-configurated **4** shows large dextrorotation in $CHCl_3$ (α_D= +197.6°), while its D-*ribo* epimer is levorotatory (α_D= -120.0°). The epimers have similar ^1H and ^{13}C NMR spectra, significant but not diagnostic differences being only observed for the H-4/H-5 coupling constants of 5.7 Hz for **4** and 2.1 Hz for **5**.

Chart 3[a]



3 **4** **5**

[a] **Conditions: i**, $SnCl_4$ (1.5 equiv), CH_2Cl_2, -80°C; **ii**, Et_3N, DMAP, CH_2Cl_2, r.t.

The configurations shown in Chart 3 are only tentative at this point, based on our precedents in the γ-lactone series.[2,3] Happily however, crystals suitable for X-ray analysis were obtained for both compounds, thus allowing exact assignment of the relative and absolute configuration of **4** and **5** (vide infra).

Functionalization Reactions. With the diastereofacial selectivity issue of the homologation of **3** with TBSOP now resolved, we turned to an exploration of routes for stereoselective elaboration of the unsaturated lactam ring of our templates to certain useful pyrrolidinone derivatives. Lactam **4** was available in ample quantities for wide manipulation, with its stereochemistry firmly established by X-ray analysis. It was expected that the vested chirality of **4** would determine completely the setting up of the new chiral centres in the sense depicted in **7**, **8**, and **11** (Chart 4), the reason being that reagent delivery at the developing tetrahedral carbons C-2 and/or C-3 would take the least hindered path (*anti*) with respect to the nearby substituent at C-4.[8]

Compound **4** was first converted to 5-*O*-silyl derivative **6** with TMSCl in pyridine. Treatment of **6** with lithium dimethylcuprate did undergo Michael addition in high yield (84%) to give the 3*R*-isomer **7** only, where the methyl group entered *anti* with respect to the bulky C-4 side-chain.[9]

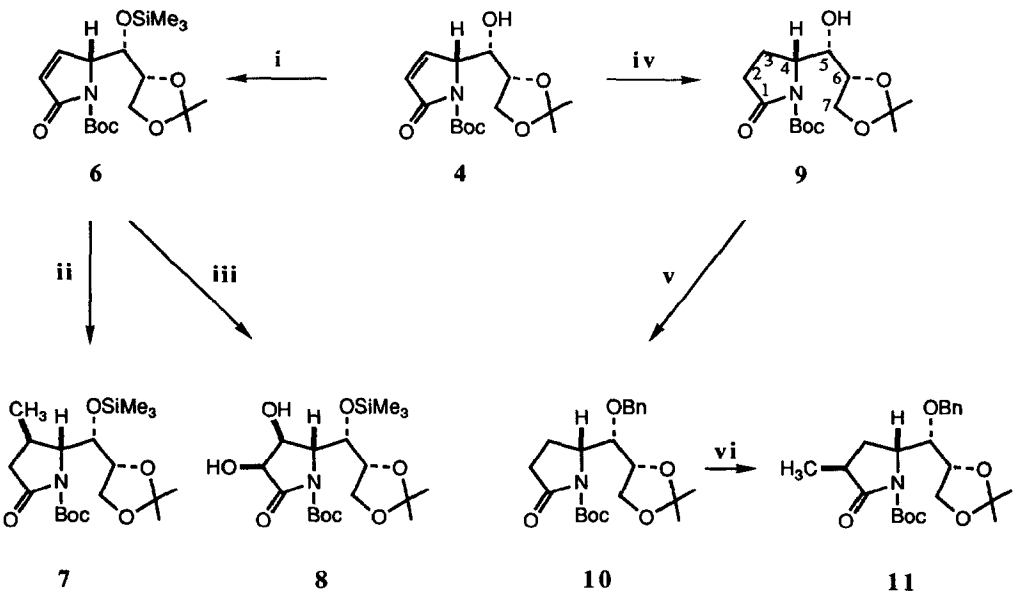
Stereospecific *cis/anti* dihydroxylation of the C-2:C-3 double bond of **6** was cleanly accomplished by using $KMnO_4$ in CH_2Cl_2 under solid-liquid phase-transfer conditions catalyzed by dicyclohexane-18-crown-6 ether.[6] There was obtained D-*glycero*-D-*talo*-configurated pyrrolidinone **8** exclusively (60% yield) bearing five consecutive chiral centres.

Next, compound **4** was converted to saturated lactam **9** by hydrogenation (H_2, Pd/C, NaOAc) which, upon benzylation (BnBr, Ag_2O, THF), was transformed to 5-*O*-benzyl derivative **10**. These mild transformations preserved the integrity of the resident chirality, in particular that of the quite delicate C-4.[10]

The protected saturated lactam **10** provided the opportunity to explore methodology for C-2 functionalization, via enolate formation.[11] Thus, deprotonation of **10** with lithium hexamethyldisilazide (LiHMDS) at -80 °C followed by MeI addition[9] resulted in exclusive formation of 2*S*-methyl derivative **11** in 90% yield.

The configurational assignment of the seven-carbon lactams **7**, **8**, and **11** was straightforward via ^1H and ^{13}C NMR analysis and NOE measurements, in line with similar recent studies.[11,12]

Chart 4[a]



[a] **Conditions: i**, Me_3SiCl, pyridine, r.t.; **ii**, Me_2CuLi, Et_2O, -80°C; **iii**, solid $KMnO_4$, CH_2Cl_2, DCH-18-crown-6, -10°C to r.t.; **iv**, H_2, Pd-C, NaOAc, THF, r.t.; **v**, BnBr, Ag_2O, DMF, r.t.; **vi**, LiHMDS, THF, -80°C then MeI.

In particular, due to the envelope nature of the five-membered ring, diagnostic NOE correlations were observed, including the following: H-4 *vs* C(3) Me and H-2_{eq} *vs* H-3 for **7**; H-2 *vs* H-3, but not H-2 *vs* H-4 for **8**; H-4 *vs* C(2) Me and H-2 *vs* H-3_{ax} for **11.**

X-ray Crystal Structure Analyses. The structures of D-*arabino*-heptenono-1,4-lactam **4** and D-*ribo*-heptenono-1,4-lactam **5** were established by X-ray analyses. Since *R*-glyceraldehyde **3** was the common precurser, incorporated in **4** and **5** as the C(5)-C(6)-C(7) fragment, the absolute configurations were determined as 4*R*, 5*S*, 6*R* for **4** and 4*S*, 5*S*, 6*R* for **5**.

Figures 1 and 2 show ORTEP views of the two isomers in their correct absolute configuration. Details of data collection and processing are given in Table 1, while the final atomic fractional co-ordinates are given in Tables 2 and 3.

In both compounds the lactam rings are nearly planar with a maximum deviation from the mean plane of 0.033Å for C(1) in **4** and of 0.016Å for C(4) in **5**. The bond distances for both molecules are similar and agree with those found in pyrrole rings,[13,14] and also the angles C(4)-N(1)-C(1) of 110.8(2) and 111.7(5)° for **4** and **5** respectively are typical for this moiety bearing an amino-hydrogen atom. In this case the hydrogen atom is substituted by a *tert*-butoxycarbonyl group . The N(1)-C(11)-O(5)-O(6) group is planar and tilted of 14.0(1) in **4** and 11.7(3)° in **5** with respect to the mean plane of the lactam ring.

The C(11)-N(1)-C(1)-O(1) and C(1)-N(1)-C(11)-O(5) systems show some π conjugation, the torsion angles being -14.1(8) and 11.4(1.1)° for the first group and 13.8(6) and -11.2(1.1)° for the second. The sum of the bond angles around the N(1) atom is of 359.1 and 359.5° for the two isomers.

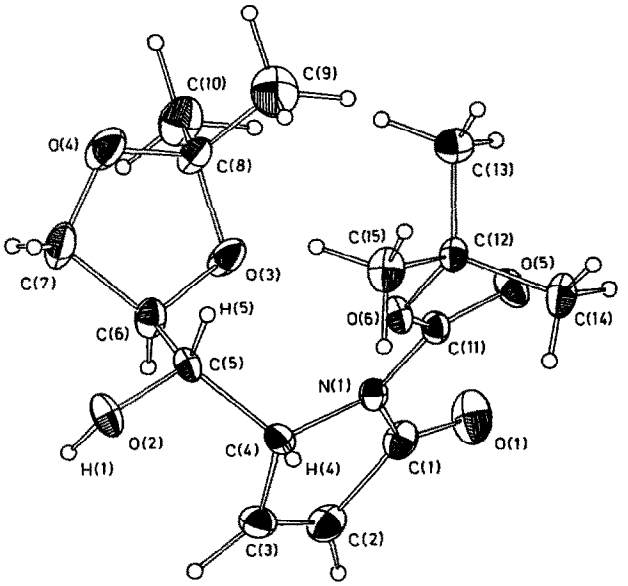


Figure 1. ORTEP view of **4** with thermal ellipsoids at 40% probability. The methyl and methylene hydrogen atoms were generated geometrically for consistency with the drawing of isomer **5**. The O(4) oxygen atom corresponds to the s.o.f. 0.60 (see text)

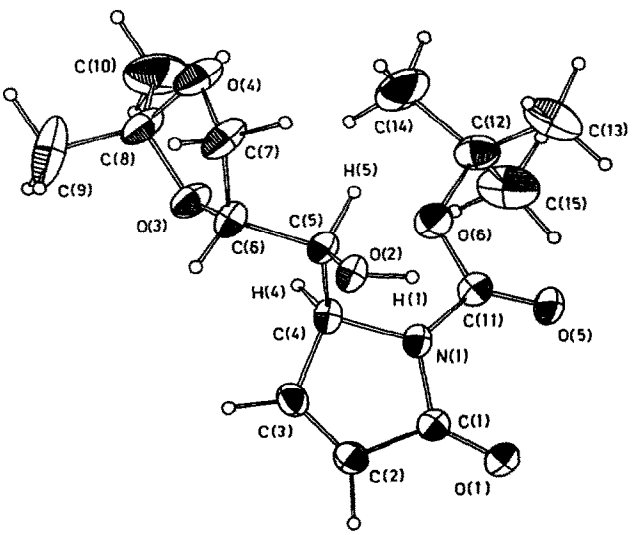


Figure 2. ORTEP view of **5** with thermal ellipsoid at 40% probability

The dioxolane rings are in a pure twist conformation in both isomers (in **4** the twist axis passes through the O(3) atom, in **5** through the C(6) atom; the puckering parameters are q_2= 0.255(8)Å, ϕ_2= 54(1)° in **4**; q_2= 0.418(11)Å, ϕ_2= 90(1)° in **5**).[15] In **5** the alternative ring formed by the O(4') atom corresponding to a 0.40 site occupation factor presents an envelope conformation (q_2= 0.302(15)Å, ϕ_2= -138(2)°). The dihedral angles between the dioxolane and the lactam rings are significantly different: in **4**, 48.0(2)°; in **5**, 84.0(3)°.

Table 1. Experimental data for the crystallographic analyses.

Compound	**4**	**5**
Formula	$C_{15}H_{23}NO_6$	
M	313.4	
Space group	$P6_5$	$P2_12_12_1$
a /Å	9.029(2)	22.327(3)
b /Å	9.029(2)	12.614(2)
c /Å	34.445(4)	6.161(1)
α/°	90.0	90.0
β/°	90.0	90.0
γ/°	120.0	90.0
V/ Å^3	2431.8(8)	1735.1(5)
Z	6	4
Dc/Mg m^{-3}	1.284	1.200
F (000)	1008	672
Crystal size/mm	0.27x0.30x0.58	0.03x0.13x0.33
μ/cm^{-1}	7.90	7.38
θ range/°	3-70	3-70
h range	0-9	0-23
k range	0-11	0-12
l range	0-42	0-7
Standard reflection	5 11 0	12 0 1
No. of measured reflections	4741	1057
No. of unique reflections	1494	845
Conditions for obs.reflections	$I>3\sigma(I)$	$I>3\sigma(I)$
No. of refined parameters.	290	232
R	0.044	0.048
R_w	0.052	0.049
k, *g* in $w = k / [\sigma^2(F_o)+\|g\|(F_o)^2]$	1,0.00404	1,0.00405
Max.,min. height in final ΔF map,eÅ^{-3}	0.16,-0.12	0.16,-0.15

*Data common to both compounds: Cu-Ka radiation (λ=1.54178 Å); Siemens-AED diffractometer; T=293±1K

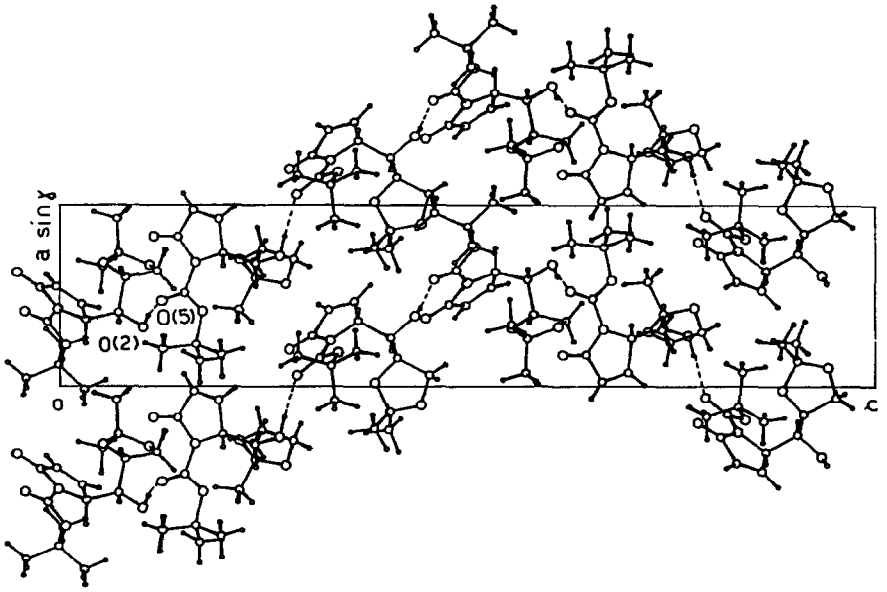


Figure 3. The packing arrangement of **4** on the plane (010), showing helices around the hexad axis.

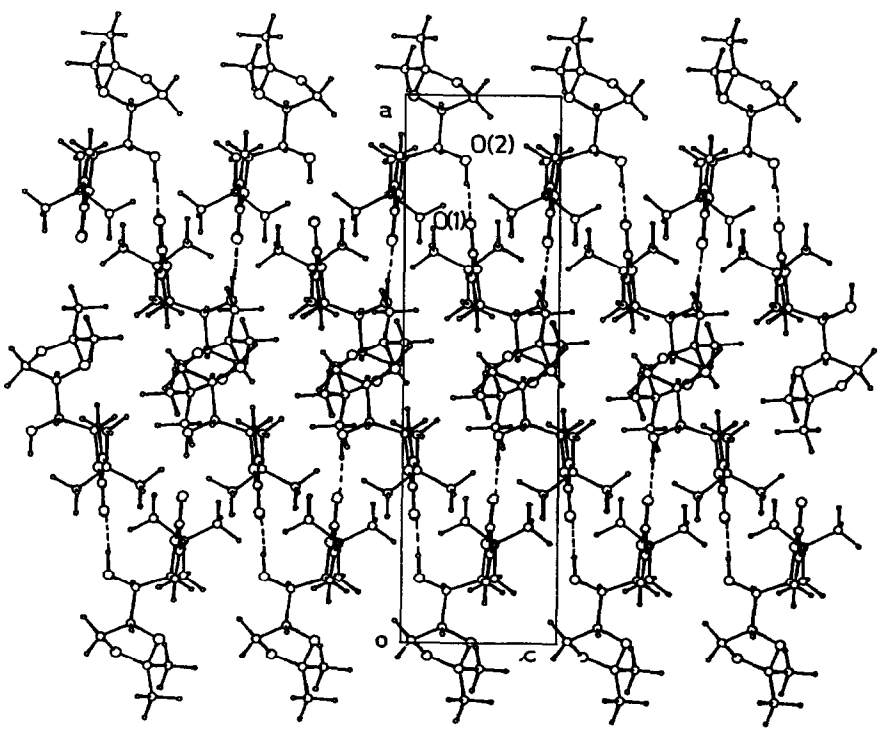


Figure 4. Projection of the isomer **5** on the (010) plane.

Table 2. Atomic fractional co-ordinates for compound **4**.

Atom	*X/a*	*Y/b*	*Z/c*
N(1)	-0.6827(3)	-0.2533(3)	-0.3350(0)
O(1)	-0.8277(6)	-0.2042(7)	-0.3851(2)
O(2)	-0.7184(4)	-0.3897(4)	-0.2311(1)
O(3)	-0.6997(6)	-0.0205(4)	-0.2803(1)
O(4)	-0.5642(8)	0.1046(6)	-0.2235(1)
O(5)	-0.4747(4)	-0.0625(4)	-0.3754(1)
O(6)	-0.4159(3)	-0.1874(3)	-0.3254(1)
C(1)	-0.8266(5)	-0.2810(6)	-0.3565(2)
C(2)	-0.9738(5)	-0.4240(6)	-0.3369(2)
C(3)	-0.9240(5)	-0.4692(5)	-0.3056(2)
C(4)	-0.7338(4)	-0.3643(4)	-0.3009(1)
C(5)	-0.6776(4)	-0.2678(5)	-0.2613(1)
C(6)	-0.7564(6)	-0.1560(6)	-0.2532(1)
C(7)	-0.6988(10)	-0.0629(8)	-0.2140(2)
C(8)	-0.5962(6)	0.1398(6)	-0.2615(2)
C(9)	-0.6864(10)	0.2402(9)	-0.2633(2)
C(10)	-0.4238(9)	0.2340(12)	-0.2809(3)
C(11)	-0.5167(4)	-0.1567(4)	-0.3480(1)
C(12)	-0.2313(4)	-0.1130(5)	-0.3343(1)
C(13)	-0.1410(6)	0.0793(6)	-0.3294(2)
C(14)	-0.2074(7)	-0.1665(8)	-0.3744(2)
C(15)	-0.1754(6)	-0.1932(7)	-0.3030(2)

Table 3. Atomic fractional co-ordinates for compound **5**.

Atom	*X/a*	*Y/b*	*Z/c*
N(1)	-0.1840(2)	-0.0246(4)	-0.0388(9)
O(1)	-0.2666(2)	0.0861(3)	-0.0823(8)
O(2)	-0.1199(2)	0.0119(4)	0.3869(8)
O(3)	-0.0016(2)	-0.0891(4)	0.0542(10)
O(4)	0.0242(6)	-0.1923(12)	0.3311(24)
O(4')	0.0542(8)	-0.1334(20)	0.3595(36)
O(5)	-0.2639(2)	-0.1356(4)	-0.0796(9)
O(6)	-0.1689(2)	-0.1969(3)	-0.0719(10)
C(1)	-0.2134(3)	0.0727(5)	-0.0657(12)
C(2)	-0.1655(3)	0.1536(6)	-0.0654(14)
C(3)	-0.1132(3)	0.1075(6)	-0.0377(12)
C(4)	-0.1183(2)	-0.0105(6)	-0.0115(11)
C(5)	-0.0969(2)	-0.0488(6)	0.2115(12)
C(6)	-0.0295(3)	-0.0405(7)	0.2348(13)
C(7)	-0.0048(3)	-0.1000(8)	0.4318(14)
C(8)	0.0479(4)	-0.1488(8)	0.1272(17)
C(9)	0.1039(4)	-0.0825(16)	0.0934(36)
C(10)	0.0483(6)	-0.2520(9)	-0.0034(29)
C(11)	-0.2115(3)	-0.1225(5)	-0.0636(12)
C(12)	-0.1834(4)	-0.3105(6)	-0.0937(17)
C(13)	-0.2239(7)	-0.3444(8)	0.0976(21)
C(14)	-0.1199(5)	-0.3604(7)	-0.0925(33)
C(15)	-0.2144(6)	-0.3278(8)	-0.3122(18)

The C-O bond distances in these rings are comparable to each other (Tables 4 and 5) and the values fall in the range found in the literature[3,16,17](except those involving the disordered oxygen atom in **5**). In the two compounds the orientation of the O-H group with respect to the dioxolane and lactam rings is shown by the following torsion angles: O(3)-C(6)-C(5)-O(2) = 172.6(4), -173.8(5)°; C(7)-C(6)-C(5)-O(2) = 57.3(6), 69.7(8)°; N(1)-C(4)-C(5)-O(2) = -173.6(3), -65.4(7)°; C(3)-C(4)-C(5)-O(2) = 69.2(5), 46.7(8)° respectively for **4** and **5**.

In the first isomer (**4**) the H(1)···H(5) distance is 2.66Å with H(1)-O(2)-C(5)-H(5) torsion angle of 160.8° presenting therefore an antiperiplanar conformation, while in the second one (**5**) the distance is remarkably shorter, 2.24Å with the corresponding torsion angle of -52.6° (almost in a synclinal conformation). The H(4)···H(5) distances and related torsion angles H(4)-C(4)-C(5)-H(5) are 2.27(8), 2.45(11)Å; 56(5), -54(5)° (synclinal conformation) for **4** and **5** respectively.

In **4** the strong hydrogen bond O(2)-H···O(5)^{I} =2.809(5)Å [I= y-1,-x+y-1,1/6+z] induces the formation of helices around the hexad axis. An interaction C-H···O = 3.295(7)Å and other normal van der Waals contacts join the single helices (Fig.3).

Table 4. Bond distances(Å) and angles(°) for compound **4** with e.s.d.'s in parentheses.

N(1)-C(1)	1.405(6)	N(1)-C(4)	1.461(5)
N(1)-C(11)	1.379(4)	O(1)-C(1)	1.207(8)
O(2)-C(5)	1.424(6)	O(3)-C(6)	1.416(6)
O(3)-C(8)	1.427(5)	O(4)-C(7)	1.425(7)
O(4)-C(8)	1.412(7)	O(5)-C(11)	1.198(6)
O(6)-C(11)	1.328(6)	O(6)-C(12)	1.484(4)
C(1)-C(2)	1.475(6)	C(2)-C(3)	1.310(8)
C(3)-C(4)	1.498(5)	C(4)-C(5)	1.559(6)
C(5)-C(6)	1.523(8)	C(6)-C(7)	1.536(7)
C(8)-C(9)	1.492(12)	C(8)-C(10)	1.506(9)
C(12)-C(13)	1.514(6)	C(12)-C(14)	1.513(7)
C(12)-C(15)	1.519(8)		
C(4)-N(1)-C(11)	124.5(2)	C(1)-N(1)-C(11)	123.9(3)
C(1)-N(1)-C(4)	110.8(3)	C(6)-O(3)-C(8)	110.4(4)
C(7)-O(4)-C(8)	106.8(4)	C(11)-O(6)-C(12)	121.1(3)
N(1)-C(1)-O(1)	126.9(5)	O(1)-C(1)-C(2)	127.9(5)
N(1)-C(1)-C(2)	105.2(4)	C(1)-C(2)-C(3)	110.5(5)
C(2)-C(3)-C(4)	110.8(4)	N(1)-C(4)-C(3)	102.5(3)
C(3)-C(4)-C(5)	113.4(4)	N(1)-C(4)-C(5)	114.6(2)
O(2)-C(5)-C(4)	108.7(3)	C(4)-C(5)-C(6)	113.7(4)
O(2)-C(5)-C(6)	110.6(4)	O(3)-C(6)-C(5)	111.4(4)
C(5)-C(6)-C(7)	112.5(5)	O(3)-C(6)-C(7)	103.2(4)
O(4)-C(7)-C(6)	104.8(5)	O(3)-C(8)-O(4)	107.2(4)
O(4)-C(8)-C(10)	105.5(6)	O(4)-C(8)-C(9)	114.2(5)
O(3)-C(8)-C(10)	109.9(5)	O(3)-C(8)-C(9)	108.6(5)
C(9)-C(8)-C(10)	111.3(6)	O(5)-C(11)-O(6)	127.1(4)
N(1)-C(11)-O(6)	108.6(3)	N(1)-C(11)-O(5)	124.3(4)
O(6)-C(12)-C(15)	101.7(4)	O(6)-C(12)-C(14)	110.5(4)
O(6)-C(12)-C(13)	109.6(4)	C(14)-C(12)-C(15)	111.2(4)
C(13)-C(12)-C(15)	110.6(4)	C(13)-C(12)-C(14)	112.8(4)

In **5** the different conformation of the molecule determines a hydrogen bond between the same alcoholic atom O(2) and the O(1) atom instead of O(5) [O(2)-H···O(1)^{II} = 2.826(6)Å, II=-x-1/2,-y,z+1/2] , in this way ribbons in the c axis direction are formed, kept together through weak interactions C-H···O.

Table 5. Bond distances (Å) and angles (°) for compound **5** with e.s.d.'s in parentheses.

N(1)-C(1)	1.401(8)	N(1)-C(4)	1.489(7)
N(1)-C(11)	1.387(9)	O(1)-C(1)	1.205(8)
O(2)-C(5)	1.421(9)	O(3)-C(6)	1.414(10)
O(3)-C(8)	1.412(11)	O(4)-C(7)	1.469(17)
O(4)-C(8)	1.470(18)	O(4')-C(7)	1.452(21)
O(4')-C(8)	1.451(25)	O(5)-C(11)	1.187(9)
O(6)-C(11)	1.336(8)	O(6)-C(12)	1.476(9)
C(1)-C(2)	1.477(10)	C(2)-C(3)	1.316(10)
C(3)-C(4)	1.501(10)	C(4)-C(5)	1.532(10)
C(5)-C(6)	1.516(8)	C(6)-C(7)	1.530(12)
C(8)-C(9)	1.519(16)	C(8)-C(10)	1.530(17)
C(12)-C(13)	1.546(16)	C(12)-C(14)	1.550(13)
C(12)-C(15)	1.529(15)		
C(4)-N(1)-C(11)	123.6(5)	C(1)-N(1)-C(11)	124.1(5)
C(1)-N(1)-C(4)	111.7(5)	C(6)-O(3)-C(8)	109.0(6)
C(7)-O(4)-C(8)	103(1)	C(7)-O(4')-C(8)	105(1)
C(11)-O(6)-C(12)	122.0(6)	N(1)-C(1)-O(1)	126.4(6)
O(1)-C(1)-C(2)	128.1(6)	N(1)-C(1)-C(2)	105.5(5)
C(1)-C(2)-C(3)	109.7(6)	C(2)-C(3)-C(4)	112.7(6)
N(1)-C(4)-C(3)	100.4(5)	C(3)-C(4)-C(5)	112.7(6)
N(1)-C(4)-C(5)	111.7(5)	O(2)-C(5)-C(4)	113.6(6)
C(4)-C(5)-C(6)	111.8(6)	O(2)-C(5)-C(6)	104.4(6)
O(3)-C(6)-C(5)	109.4(6)	C(5)-C(6)-C(7)	113.6(6)
O(3)-C(6)-C(7)	104.6(6)	O(4')-C(7)-C(6)	103(1)
O(4)-C(7)-C(6)	102.3(9)	O(3)-C(8)-O(4')	109(1)
O(3)-C(8)-O(4)	100.9(8)	O(4')-C(8)-C(10)	129(1)
O(4')-C(8)-C(9)	89(1)	O(4)-C(8)-C(10)	97.7(9)
O(4)-C(8)-C(9)	128(1)	O(3)-C(8)-C(10)	106.9(8)
O(3)-C(8)-C(9)	108(1)	C(9)-C(8)-C(10)	113(1)
O(5)-C(11)-O(6)	126.9(6)	N(1)-C(11)-O(6)	108.4(6)
N(1)-C(11)-O(5)	124.6(6)	O(6)-C(12)-C(15)	108.5(6)
O(6)-C(12)-C(14)	101.2(6)	O(6)-C(12)-C(13)	109.1(7)
C(14)-C(12)-C(15)	111.1(9)	C(13)-C(12)-C(15)	111.5(9)
C(13)-C(12)-C(14)	114.8(9)		

CONCLUSIONS

In conclusion, this study extends to nitrogen-containing structures the general utility of our C_n+C_4 homologative methodology for the asymmetric synthesis of complex sugars. Using the novel reactant TBSOP, now available in multigram quantity, as four-carbon source, we have synthesized a representative couple of chirally defined seven-carbon unsaturated γ-lactams **4** and **5**. The crystalline nature of these compounds ensured easy purification and permitted unambiguous assignment of their stereostructures by single crystal X-ray analysis. Highly stereoselective elaborations of the unsaturated lactam ring of **4** were also performed, including homoconjugated Michael addition, dihydroxylation, and α-alkylation via hydrogenation and enolization to provide γ-substituted pyrrolidinones **7**, **8**, and **10** of some synthetic value. This methodology and chemistry are being incorporated into synthesis of the pyrrolizidine and indolizidine families of natural products as well as nitrogen-containing sugars.

EXPERIMENTAL SECTION

^1H (300 MHz) and ^{13}C (75.2 MHz) NMR spectra were recorded on a Varian XL 300 instrument (δ in ppm referred to TMS, *J* in Hz). Rotations were measured on a Perkin-Elmer 241 MC. Mp were determined (uncorrected) on a Dr. Tottoli melting point apparatus. Flash chromatography was performed using silica gel 70-230 Mesh purchased from Merck. Kieselgel 60 F_{254} (from Merck) was used for TLC. All the solvents were distilled before use: THF over Na/benzophenone; Et_2O over $LiAlH_4$; CH_2Cl_2 over CaH_2. Elemental analyses were performed by the Microanalytical Laboratory of University of Sassari. All the reactions were performed under an argon atmosphere.

***N*-*tert*-Butoxycarbonyl-2-(*tert*-butyldimethylsiloxy)pyrrole (TBSOP).** This was prepared from pyrrole, via Δ^3-pyrrolinone (**1**) and *N*-*t*-Boc-pyrrolinone (**2**), according to a recently described protocol,[4] on a 10 g scale in 66% yield from **1**.

2,3-*O*-Isopropylidene-D-glyceraldehyde (3). This was prepared from D-mannitol, via the 1,2:5,6-di-*O*-isopropylidene derivative, following a convenient multigram scale preparation.[18]

(4*R*, 5*S*, 6*R*)-*N*-*tert*-Butoxycarbonyl-6,7-*O*-isopropylidene-2,3-dideoxy-hept-2-eno-no-1,4-lactam (4). To a solution of 2,3-*O*-isopropylidene-D-glyceraldehyde (**3**) (1.5 g, 11.5 mmol) in anhydrous Et_2O (70 mL), TBSOP (3.4 g, 11.5 mmol) and $SnCl_4$ (1M in CH_2Cl_2, 17 mL, 17 mmol) were added under argon at -85°C. The mixture was stirred at this temperature for 3 h then a saturated aqueous $NaHCO_3$ solution was added at -85°C and, after ambient temperature was reached, the resulting mixture was extracted with Et_2O (3x30 mL). After drying ($MgSO_4$), the solution was evaporated under reduced pressure and the crude product was crystallized from CH_2Cl_2/hexane: 2.9 g (80%), white solid, mp 138-140 °C; $[\alpha]_D$ +197.59 (*c* 0.83, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.43 (dd, 1H, *J*=6.3, 2.1 Hz, H-3), 6.13 (dd, 1H, *J*=6.3, 1.5 Hz, H-2), 4.81 (dt, 1H, *J*=5.7, 2.4 Hz, H-4), 4.09 (ddd, 1H, *J*=6.0 , 5.7, 3.9 Hz, H-5), 4.01 (q, 1H, *J*=6.0, H-6), 3.94 (dd, 1H, *J*=8.1, 6.0 Hz, H-7a), 3.86 (dd, 1H, *J*=8.1, 6.0 Hz, H-7b), 3.63 (d, 1H, *J*=3.9 Hz, OH), 1.57 (s, 9H, *t*-Bu), 1.37 and 1.32 (2s, each 3H, Me); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 168.90, 150.91, 148.23, 126.94, 109.23, 83.79, 75.63, 72.59, 66.43, 65.57, 27.99, 26.40, 25.08. Anal. Calcd for $C_{15}H_{23}NO_6$: C, 57.15; H, 7.40; N, 4.47. Found: C, 56.93; H, 7.35; N, 4.32.

(4*S*, 5*S*, 6*R*)-*N*-*tert*-Butoxycarbonyl-6,7-*O*-isopropylidene-2,3-dideoxy-hept-2-eno-no-1,4-lactam (5). To a solution of **4** (2.0 g, 6.4 mmol) in CH_2Cl_2 (15 mL) Et_3N (2.0 mL) and N,N-dimethylaminopyridine (200 mg) were added and the mixture was stirred at room temperature overnight. Water (10 mL) was then added and the mixture was extracted with CH_2Cl_2 (3x50 mL). The combined extracts, dried over $MgSO_4$, were avaporated under vacuo and the product purified by flash chromatography on SiO_2 (EtOAc/MeOH 98:2); 1.8 g (90%): white solid; mp 118-120°C; $[\alpha]_D$ -120.0 (*c* 0.8, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (dd, 1H, *J*=6.3, 2.1 Hz, H-3), 6.16 (dd, 1H, *J*=6.3, 2.0 Hz, H-2), 4.97 (q, 1H, *J*=2.1 Hz, H-4), 4.20 (m, 1H, H-6), 4.15 (td, 1H, *J*=6.6, 2.2 Hz, H-5), 4.03 (m, 2H, H_2-7), 3.49 (d, 1H, *J*=6.6 Hz, OH), 1.56 (s, 9H, *t*-Bu), 1.46 and 1.37 (2s, each 3H, Me); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 169.98, 149.67, 147.24, 128.01, 109.90, 83.50, 76.27, 71.40, 67.89, 65.07, 28.07, 26.70, 24.50. Anal. Calcd for: $C_{15}H_{23}NO_6$: C, 57.15; H, 7.40; N, 4.47. Found: C, 57.03; H, 7.30; N, 4.25.

(4*R*, 5*S*, 6*R*)-*N*-*tert*-Butoxycarbonyl-5-*O*-trimethylsilyl-6,7-*O*-isopropylidene-2,3-dideoxy-hept-2-enono-1,4-lactam (6). To a solution of compound **5** (460 mg, 1.47 mmol) in dry pyridine (8 mL), chlorotrimethylsilane (0.4 mL, 3.15 mol) was added at -30°C under argon and the mixture was stirred at this temperature for 2 h. Water (20 mL) was added and the mixture extracted with CH_2Cl_2 (3x10 mL); the combined extracs were dried over $MgSO_4$ and evaporated under vacuo. The crude mixture was purified by flash chromatography over silica gel (EtOAc/hexane 1:1): 520 mg (91%), colorless oil, $[\alpha]_D$ +156.7 (*c* 1.24, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (dd, 1H, *J*=6.1, 2.2 Hz, H-3), 6.16 (dd, 1H, *J*=6.1, 2.0 Hz, H-2), 4.62 (dt, 1H, *J*=4.9, 1.8 Hz, H-4), 4.54 (t, 1H, *J*=5.0, H-5), 3.72 (m, 3H, H-6 and H_2-7), 1.55 (s, 9H, *t*-Bu), 1.33 and 1.23 (2s, each 3H, Me), 0.19 (s, 9H, $SiMe_3$). Anal. Calcd for $C_{18}H_{31}NO_6Si$: C, 56.08; H, 8.10; N, 3.63. Found: C, 56.17; H, 7.90; N, 3.50.

(3*R*, 4*R*, 5*S*, 6*R*)-*N*-*tert*-Butoxycarbonyl-3-methyl-5-*O*-trimethylsilyl-6,7-*O*-isopropylidene-2,3-dideoxy-heptono-1,4-lactam (7). To a suspension of CuBr·Me_2S (0.27 g, 1.30 mmol) in ether (5 mL) was added a solution of methyl lithium (2.60 mmol) at 0 °C over 5 min. The initial yellow precipitate redissolved to give a pale-yellow colored solution. After cooling the solution to -80 °C **6** (0.10 g, 0.26 mmol) in ether (2 mL) was added, and the reaction stirred for 2 h before being quenched by the cautious addition of satd. ammonium chloride solution. After vigorous extraction to remove copper compounds, the colorless ethereal layer was evaporated to give the crude product. Flash column chromatography (EtOAc/hexane 3:7) gave pure **7** as a colorless oil (70 mg, 67%); $[\alpha]_D$ +33.6 (c 1.28, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.02 (m, 3H, H-5, H-6, H-7a), 3.77 (dd, 1H, *J*=4.5, 0.9 Hz, H-4), 3.72 (dd, 1H, *J*=7.8, 5.4 Hz, H-7b), 2.81 (dd, 1H, *J*=17.7, 8.7 Hz, H-2a), 2.46 (m, 1H, H-3), 2.05 (dd, 1H, *J*=17.7, 0.9 Hz, H-2b), 1.55 (s, 9H, Bu^t), 1.33 and 1.29 (2s, each 3H, Me), 1.13 (d, 3H, *J*=7.2 Hz, Me), 0.17 (s, 9H, $SiMe_3$).Anal. calcd for $C_{19}H_{35}NO_6Si$: C, 56.83; H, 8.79; N, 3.49. Found: C, 56.74; H, 8.84; N, 3.51.

(2*S*, 3*S*, 4*S*, 5*S*, 6*R*)-*N*-*tert*-Butoxycarbonyl-5-*O*-trimethylsilyl-6,7-*O*-isopropylidene-heptono-1,4-lactam (8). To a solution of **6** (517 mg, 1.34 mmol) in CH_2Cl_2 (15 mL) dicyclohexano-18-crown-6-ether (60 mg, 0.16 mmol) and $KMnO_4$ (260 mg, 1.65 mmol) were added at -30°C under stirring. The mixture was stirred at -10°C for 4 h then solid sodium sulfite (450 mg) and water (10 mL) were added and the brown slurry filtered over a celite pad. The filtrates were extracted with CH_2Cl_2 (3x20 mL), dried ($MgSO_4$), evaporated under vacuo, and flash chromatographed over silica gel (EtOAc/hexane 8:2): 280 mg (50%), colorless oil, $[\alpha]_D$ +3.1 (*c* 1.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.62 (bd, 1H, *J*=3.5 Hz, H-2), 4.46 (d, 1H, *J*=4.5 Hz, H-4), 4.42 (bd, 1H, *J*=3.5 Hz, H-3), 4.18 (dd, 1H, *J*=8.3, 4.5 Hz, H-5), 3.89 (dd, 1H, *J*=8.3, 6.4 Hz, H-7a), 3.82 (dd, 1H, *J*=8.3, 5.1 Hz, H-7b), 3.70 (ddd, 1H, *J*=8.4, 6.4, 5.0 Hz, H-6), 3.46 (bs, 2H, OH), 1.39 (s, 9H, *t*-Bu), 1.36 and 1.18 (2s, each 3H, Me), 0.15 (s, 9H, $SiMe_3$); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 173.54, 149.75, 109.96, 83.61, 76.55, 71.12, 69.99, 68.05, 65.96, 65.86, 28.08, 26.40, 25.02, 0.38. Anal. Calcd for: $C_{18}H_{33}NO_8Si$: C, 51.33; H, 7.93; N, 3.34. Found: C, 51.21; H, 7.82; N, 3.31.

(4*R*, 5*S*, 6*R*)-*N*-*tert*-Butoxycarbonyl-6,7-*O*-isopropylidene-2,3-dideoxy-heptono-1,4-lactam (9). A solution of **4** (1.42 g, 4.54 mmol) in THF (50 mL) was hydrogenated in the presence of 10% Pd on carbon (150 mg) and NaOAc (200 mg) at room temperature for 24 h. After the catalyst was filtered, the solution was evaporated and the crude product was purified by flash chromatography on silica gel (AcOEt/hexane 8/2): 1.31 g (92%), white solid, mp 99-103°C; $[\alpha]_D$ +59.24 (*c* 1.26, $CHCl_3$); ^1H NMR

(300 MHz, $CDCl_3$) δ 4.31 (ddd, 1H, *J*=5.7, 5.4, 3.9 Hz, H-4), 4.05 (m, 2H, H-7a and H-7b), 3.97 (ddd, 1H, *J*=5.5, 4.8, 1.2 Hz, H-6), 3.69 (q, 1H, *J*=5.7 Hz, H-5), 3.54 (d, 1H, *J*=6.3 Hz, OH), 2.71 (dt, 1H, *J*=17.1, 10.5 Hz, H-2a), 2.32 (ddd, 1H, *J*=17.7, 6.0, 4.8 Hz, H-2b), 2.10 (m, 2H, H-3a and H-3b), 1.48 (s, 9H, But), 1.36 (s, 3H, Me), 1.30 (s, 3H, Me); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 174.52, 151.73, 109.39, 83.60, 77.74, 74.48, 66.80, 60.36, 31.96, 27.99, 26.56, 25.07, 21.71. Anal. Calcd. for $C_{15}H_{25}NO_6$: C, 57.13; H, 7.99; N, 4.44. Found C, 57.26; H, 8.15; N, 4.59.

(4*R*, 5*S*, 6*R*)-*N*-*tert*-Butoxycarbonyl-5-*O*-benzyl-6,7-*O*-isopropylidene-2,3-dideoxy-heptono-1,4-lactam (10). To a solution of **9** (1.21 g, 3.84 mmol) in DMF (16 mL), Ag_2O (1.5 g, 19.2 mmol) and BnBr (2.28 mL, 19.2 mmol) were added under stirring at room temperature. After being stirred for 5 h, the mixture was filtered on a celite pad and the pad washed with acetone (3x5 mL) and Et_2O (3x5 mL). The solution was concentrated under vacuo then purified by flash chromatography on silica gel (AcOEt/hexane 6:4): 1.37 g (88%), colorless oil, $[\alpha]_D$ -18.6 (*c* 0.7, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 5H, CH_2Ph), 5.18 (d, 1H, *J*=14.4 Hz, 1/2 CH_2Ph), 4.84 (dd, 1H, *J*=7.8, 4.5 Hz, H-5), 4.14 (dt, 1H, *J*=7.8, 6.3 Hz, H-6), 4.05 (dd, 1H, *J*=8.4, 6.0 Hz, H-7a), 3.98 (d, 1H, J=14.4 Hz, 1/2 CH_2Ph), 3.80 (dd, 1H, *J*=8.4, 5.7 Hz, H-7b), 3.70 (ddd, 1H, *J*=7.2, 4.2, 2.4 Hz, H-4), 2.57 (dt, 1H, *J*=16.2, 10.8 Hz, H-2a), 2.32 (ddd, 1H, *J*=17.0,8.7, 3.3 Hz, H-2b), 2.08 (m, 2H, H-3a and H-3b), 1.48 (s, 9H, But), 1.39 (s, 3H, Me), 1.34 (s, 3H, Me); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 175.90, 152.78, 136.75, 128.55, 128.36, 127.49, 110.02, 83.22, 74.02, 67.15, 56.89, 45.64, 29.91, 27.66, 26.50, 25.25, 22.09. Anal. Calcd. for $C_{22}H_{31}NO_6$: C, 65.15; H, 7.71; N, 3.46. Found: C, 65.21; H, 7.90; N, 3.64.

(2*S*, 4*R*, 5*S*, 6*R*)-*N*-*tert*-Butoxycarbonyl-2-methyl-5-*O*-benzyl-6,7-*O*-isopropylidene-2,3-dideoxy-heptono-1,4-lactam (11). To a stirring solution of **10** (53 mg, 0.13 mmol) in THF (2 mL) under an argon atmosphere at -80 °C was added lithium hexamethyldisilazide (0.21 mmol). The resulting solution was stirred at -80 °C for 1 h, followed by addition of methyl iodide (20 mg, 0.14 mmol). The reaction was allowed to stir for 1 h at -80 °C, then allowed to warm to room temperature over a period of 1 h. The reaction mixture was then added to ether followed by extraction with water and brine, and then dried over magnesium sulphate. The product was then purified by flash column chromatography on silic agel (EtOAc/hexane 1:1) giving a colorless oil (7 mg, 13%): $[\alpha]_D$ -75.43 (c 0.35, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (m, 5H, CH_2Ph), 5.18 (d, 1H, *J*=14.4 Hz, 1/2 CH_2Ph), 4.83 (dd, 1H, *J*=8.1, 4.8 Hz), 4.13 (m, 1H), 4.05 (m, 1H), 3.98 (d, 1H, *J*=14.4 Hz, 1/2 CH_2Ph), 3.79 (dd, 1H, *J*=8.4, 5.7 Hz, H-7a), 3.57 (dd, 1H, *J*=8.1, 4.8 Hz, H-7b), 2.68 (m, 1H, H-2), 2.22 (dd, 1H, *J*=13.5, 8.7 Hz, H-3a), 1.62 (m, 1H, H-3b), 1.48 (s, 9H, But), 1.39 and 1.35 (2s, each 3H, Me), 1.20 (d, 3H, 6.9 Hz, Me). Anal. calcd for $C_{23}H_{33}NO_6$: C, 65.85; H, 7.93; N, 3.34. Found: C, 65.91; H, 7.87; N, 3.42.

Structure Determination. The intensity data were collected in the ω-2θ step scanning mode on a Siemens AED three circle diffractometer under the control of a General Automation Jumbo 220 Computer using Ni-filtered Cu Kα radiation for both compounds. The intensity of a standard reflection was monitored after every 50 measurements and showed good stability of the crystal and the electronics. The intensity data were corrected for Lorentz and polarization but no correction for absorption was applied because of the size of the crystals used. The structures were solved by direct methods (SHELX-86)[19] for **4** and using SIR[20] program for **5**. Both structures were refined by full matrix least-squares cycles using SHELX-76[21] system of computer programs. In compound **4** all hydrogen atoms were located from a difference synthesis and refined

in the last cycle of refinement. In compound **5** five reflections, which suffered errors during data reduction, were removed. The oxygen atom O(4) of the dioxolane ring is disordered and statistically distributed in two positions with s.o.f. 0.6 and 0.4 respectively (deduced from the electron density map). The hydrogen atoms were located from a Fourier difference synthesis and isotropically refined except those bonded to methyl carbons and to methylene C(7) because of the large thermal motion of the parent carbon. Scattering factors for C,H,N and O were taken from ref. 22. All calculations were performed on a Gould 6040 Powernode Computer of the Centro di Studio per la Strutturistica Diffrattometrica del C.N.R. (Parma), using PARST[23] program for the geometrical description of the structure and ORTEP[24] and PLUTO[25] for the structure drawings.[26]

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26. Table listing structure factors, hydrogen positional parameters and anisotropic thermal parameters for the heavy atoms are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this paper.