The Synthesis of Highly Functionalized Enantiomerically Enriched Cyclohexanes. An Approach to Carba-Sugars and Aminocarba-Sugars.

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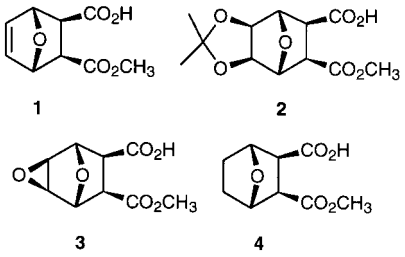
Abstract : Starting from bicyclic hemiesters obtained by enzymatic hydrolysis of *meso* diesters, polyfunctionalized cyclohexanes were prepared with high stereoselectivity in a synthetic strategy of few steps involving a Curtius reaction followed by a retro Michael ring opening reaction and reductions. This sequence offers a versatile approach to the synthesis of various aminocarba-sugars.

Key words: carba-sugars, aminocarba-sugars, functionalized cyclohexanes, furan adducts



The terms pseudo-sugars[1] and carba-sugars[2] refer to carbocyclic analogues of monosaccharides in which the ring oxygen atom is replaced by a methylene group. Owing to their structurally close resemblance to sugars, it has been suggested[3] that carba-sugars might be accepted by enzymes or biological systems in place of true sugars and may thus be excellent glycosidase inhibitors. It is now well established that several glycosidase inhibitors demonstrate promising therapeutic applications in the areas of antibiotic activities, diabetes control or antiviral chemotherapy[4] and, for these reasons, considerable efforts have been directed towards the development of syntheses of carba-sugars and aminocarba-sugars. Different approaches to these compounds in either racemic or enantiomerically pure forms have been devised and include :

– The modification of natural compounds such as carbohydrates[2,5], quinic acid[6] or myo-inositol[7]

– The chemical transformations of microbial metabolites[8]

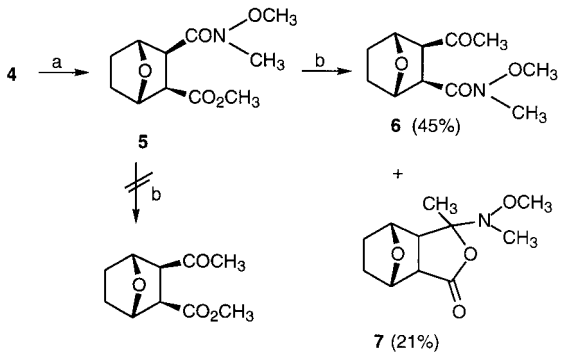
– The ring opening of modified adducts of furan and acrylic acid[2,9]

– The stereoselective conversions of 7-norbornenone [(10)] or dienyl silanes[11]

It occurred to us that hemiesters **1**, **2** or **3**, easily available in enantiomerically-pure form *via* an enzymatic hydrolysis of the corresponding *meso* diesters,[12,13] might be excellent intermediates for the synthesis of carba-sugars or aminocarba-sugars.

In this communication we disclose our preliminary results in this field and describe, starting from **4**, a highly diastereoselective synthesis of the functionalized cyclohexane **12**, a strategy which, when applied to the transformations of norbornane derivatives **1**, **2** or **3** may lead to the synthesis of various 4-amino-4-deoxy carba-sugars. We envisaged that the carboxylic acid group of substrates **1** - **4** could be replaced by a hydroxy- or an amino-group. Then, cleavage of the oxygen bridge under basic conditions[14] would give functionalized cyclohexanes, interesting intermediates for the synthesis of carba-sugars or aminocarba-sugars. The feasibility of this method has been tested starting from the more simple bicyclic compound **4**[15].

It appeared rapidly that substitution of the carboxylic acid group of **4** by a hydroxy or an acetoxy group was more difficult than anticipated and until now we have not found good solution to this modification which is hampered by the proximity of the two functional groups. For example, during our efforts to transform the carboxylic acid into a methyl ketone followed by a Baeyer-Villiger oxidation, we observed side reactions giving a good illustration of this interference (Scheme 1).

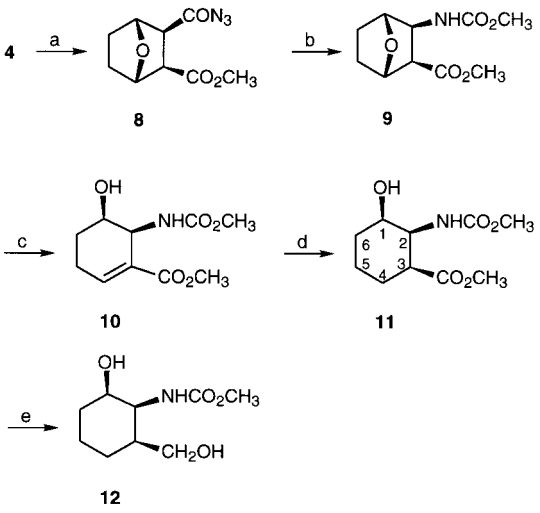


Scheme 1

The amide **5** reacts with methylmagnesium bromide to give the usual chelated intermediate[16] which, upon hydrolysis, does not decompose to the expected methyl ke-

tone but led *via* intramolecular reactions to the keto amide **6** and to the lactone **7**.

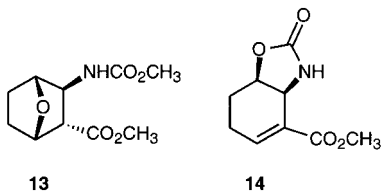
Replacement of the carboxylic acid group by an amino group appears to be more successful and our strategy is outlined in Scheme 2.



a) (i) $ClCO_2Et$, NEt_3, Acetone ; (ii) NaN_3,H_2O. b) Refluxing toluene 3h then addition of MeOH, reflux 2 h, 66% overall yield from **4**.
c) LiHMDS, THF, -10°C, 3h, 53%. d) H_2, 10% Pd/C, CH_3CO_2Et/MeOH, 1/1, 87%. e) $(t\text{-}BuO)_3AlLiH$, THF, 47%

Scheme 2

Enantiomerically pure (ee ≥98%) mono ester **4**, obtained by Pig Liver Esterase - catalyzed hydrolysis of the corresponding *meso* diester,[12] was activated *via* a mixed anhydride[17] and treated with sodium azide[18] to afford the desired acyl azide **8** in quantitative yield. Subsequent rearrangement in refluxing toluene and trapping of the intermediate isocyanate with methanol gave rise to the bicyclic amino compound **9** with excellent stereoselectivity (de > 98%) and enantioselectivity (ee > 95%) as shown by ^1H NMR in the presence of chiral $Eu(hfc)_3$. Basic ring opening of the bicycle **9** proved fairly sensitive to reaction conditions, due to side reactions involving either epimerization of the carbomethoxy group (**9** → **13**) or an intramolecular reaction leading from **10** to the oxazolidinone **14**.



Under the best conditions found (LiHMDS 2.2 equivalents, THF, -10°C, 3 hours) the reaction was clean but the conversion was incomplete and the cyclohexene **10**[19] was formed in 41% yield (53% yield based on recovered **9**). Catalytic hydrogenation of the double bond was performed in the presence of a catalytical amount of 10% Pd(C) under slight pressure (3 bars) of hydrogen at room temperature. The reaction was very slow and only complete after six days to give a unique diastereomer **11**. It is usually assumed that hydrogen adds to the olefin from the least hindered side of the molecule, leading in our case to a *cis*-1,2, *cis*-2,3 configuration. This *cis,cis*-configuration is supported by the small coupling constants ($J_{1,2}$ = 3.9 Hz and $J_{2,3}$ = 5.5 Hz) determined from the ^1H NMR spectrum of **11** by irradiation experiments. Finally, reduction of the carbomethoxy group of the ester was selectively achieved with tri (*tert*-butoxy) lithium aluminum hydride and afforded the cyclohexane **12** in modest yield.

In conclusion a simple and short method for preparing the functionalized cyclohexane **12** has been established. Application of this methodology to the synthesis of various 4-amino, 4-deoxy carba-sugars, starting from compounds **1**, **2** or **3**, are currently underway in our laboratory.

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(19) Procedure for the synthesis of **10** : To a solution of freshly distilled hexamethyldisilazane (890 ml, 4.2 mmol) in dry THF (15 mL) under argon was added at 0°C a solution of *n*-butyllithium (1.6M) in hexane (2.4 mL, 3.85 mmol). The mixture was stirred for 20 minutes and then was added dropwise to a solution of compound **9** (400 mg, 1.75 mmol) in dry THF (20 mL) kept at -10°C under an argon atmosphere. After two hours, brine (5 mL) and a 1M aqueous solution of HCl (10 mL) were added successively at -10°C. The organic layer was separated and the aqueous solution was extracted with ethyl acetate (3x10 mL). The combined organic layers were dried over magnesium sulfate, concentrated in vacuo and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 1/1) to give 163 mg of **10** (41%) as a viscous oil and 93 mg of **9**.
10 : IR (neat) 3315, 1725, 1705, 1655 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 1.53 (m, 1H, H_6), 1.85 (m, 1H, $H_{6'}$), 2.30 (m, 2H, H_5, $H_{5'}$), 3.60 - 3.80 (m, 1H, OH), 3.71 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.86 (m, 1H, H_1), 4.76 (m, 1H, NH), 4.82 (m, 1H, H_2), 7.14 (t, J = 3.6 Hz, 1H, H_4) ; ^{13}C NMR (63 MHz, $CDCl_3$) δ 23.9, 24.8, 48.7, 51.9, 52.4, 69.3, 128.4, 143.7, 158.2, 166.0 ; CIMS (NH_3) m/z (relative intensity): 230 (MH^+, 100), 215 (19), 198 (35) ; $[a]_D^{20}$)) +148 (c 0.92, MeOH). Anal. calcd for $C_{10}H_{15}O_5N$: C, 52.40 ; H, 6.59. Found: C, 52.17, H, 6.56.
Procedure for the synthesis of **11** : A solution of compound **10** (229 mg, 1 mmol) in a mixture of ethyl alcohol (5 mL) and ethylacetate (5 mL) was introduced in to a pressure bottle. After addition of 30 mg of 10% palladium on activated carbon the bottle was filled with hydrogen under 3.3 bar pressure in a Parr hydrogenator. After six days the catalyst was removed by filtration. The filtrate was concentrated and the residue was purified by flash chromatography on silica gel (ethyl acetate/petroleum ether 1/1) to yield 202 mg (87%) of **11**.
11 : IR (neat) 3450, 1720 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ 1.7 (m, 6H), 2.94 (m, 1H, H_3), 3.68 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.85 (m, 1H, H_1), 4.03 (m, 1H, H_2), 5.48 (m, 1H, NH) ; ^{13}C NMR (63 MHz, $CDCl_3$) δ 18.8, 23.9, 29.4, 43.7, 51.8, 52.0, 52.5, 69.5, 157.2, 174.5 ; CIMS (NH_3) m/z (relative intensity): 232 (MH^+, 100), 217 (100), 200 (46) ; $[a]_D^{20}$)) +36 (c 0.99, MeOH). Anal. calcd for $C_{10}H_{17}O_5N$: C, 51.95 ; H, 7.36. Found: C, 51.52, H, 7.61.
Procedure for the synthesis of **12** : To a stirred solution of lithium aluminum hydride (820 mg, 21.5 mmol) in dry THF (20 mL) kept at room temperature under argon was added slowly a solution of *t*-butanol (5 g, 67.5 mmol) in dry THF (20 mL). The mixture was cooled at 0°C and a solution of compound **11** (155 mg, 0.675 mmol) in dry THF (20 mL) was added dropwise. The mixture was stirred at 0°C for 12 hours and a saturated aqueous solution of Na_2SO_4 (10 mL) was added. The organic layer was separated and the organic phase was extracted with ether (3x10 mL) and ethyl acetate (2x10 mL). The combined organic layers were dried over magnesium sulfate and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (ethyl acetate/petroleum ether 8/2) to yield 65 mg (47%) of compound **12**.
12 : IR (neat) 3400, 3320, 1700 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.95 (m, 1H), 1.35 (m, 3H), 1.80 (m, 3H), 2.10 (bs, 1H, OH), 3.45 (m, 2H, CH_2-OH), 3.73 (s, 3H, OCH_3), 3.78 (m, 2H, OH and H_1), 4.20 (m, 1H, H_2), 4.88 (m, 1H, NH) ; ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.9, 24.7, 30.1, 43.5, 54.2, 54.7, 65.2, 73.1, 162.1 ; CIMS (NH_3) m/z (relative intensity): 204 (MH^+, 100). Anal. calcd for $C_9H_{17}O_4N$: C, 53.19 ; H, 8.43. Found: C, 53.59, H,8.54.

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