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Rearrangement and Nucleophilic Trapping of Bicyclo[4.1.0]hept-2-yl Derived Non-Classical Bicyclobutenium Ions

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Draft

Abstract

Here we describe the synthesis of two specifically labelled carbon-13 isotopologues of *cis*-2-(4-nitrophenoxy)bicyclo[4.1.0]heptane and their solvolysis reactions in trifluoroethanol. By using 1D and 2D ^1H - and ^{13}C -NMR spectroscopy we characterized the pathways for the rearrangement of these isotopologues to give ^{13}C -labelled 4-(2,2,2-trifluoroethoxy)cycloheptene. We show that the initially formed cationic intermediate undergoes a degenerate rearrangement, which does not reach equilibrium before nucleophilic capture of the cation. Moreover, we show that the non-classical carbocation, cyclohept-3-ene(3,1,4-deloc)ylum, gives an approximate 6:1 ratio of the *cis*- to *trans*- diastereomeric 2-(2,2,2-trifluoroethoxy)bicyclo[4.1.0]heptane as reaction intermediates that subsequently solvolyze to the 4-(2,2,2-trifluoroethoxy)cycloheptene product.

Key words

carbenium

rearrangement

bicyclobutenium

carbon-13

NMR

Introduction

Carbohydrates are the major carbon containing biochemical compounds in nature, and are critical components for all living systems. That is, sugar metabolism is central to life and enzymes that add or remove sugar units are found in all kingdoms of life with typically ~2% of genome-encoded proteins possessing this activity.¹ Enzymes that hydrolyze sugars are called glycoside hydrolases (GHs or glycosidases)^{2, 3} and these enzymes, which generally catalyze nucleophilic substitution reactions at the anomeric centre, can be either retaining (product has the same anomeric configuration as the starting material) or inverting.^{4, 5} Bioinformatics has enabled classification these enzymes into over 130 GH families.⁶

Scheme 1 shows the currently accepted mechanism of action for a retaining α -galactoside hydrolase, which involves the formation of a β -galactosyl-enzyme intermediate that undergoes hydrolysis to yield α -galactopyranose as the initial product.

SCHEME 1

STRUCTURES 1–2

Recently, we reported the synthesis of a new family of glycoside hydrolase covalent inhibitors, such as **1**, that were designed as modulators of enzyme activity.^{7–9} These bicyclo[4.1.0]heptyl based mimics of galactopyranosides covalently label an α -galactosidase from a retaining glycoside hydrolase family (GH36) on its catalytic nucleophile (aspartate-327),^{7, 8} a process that presumably involves formation of a non-classical bicyclobutenium ion **2**.^{10, 11} As a result, we are interested in the intrinsic properties of such non-classical carbocations in solution. With regard to the solvolyses of bicyclo[4.1.0]heptan-2-yl compounds, Friedrich and Cooper reported that the perchloric acid catalyzed acetolysis of (2-²H)bicyclo[4.1.0]heptan-2-ol (**3**) gave around 35%

rearranged homoallylic cycloheptenol acetate product (**4r**), irrespective of the stereochemistry of the starting material (Scheme 2).¹²

SCHEME 2.

Based on the results from this study, the authors proposed that the initially formed cation **5** (IUPAC name for delocalized cation cyclohept-3-ene(3,1,4-deloc)ylum-4-d; see insert) can either be trapped by acetic acid to give *cis*- and *trans*-bicyclo[4.1.0]hept-2-yl acetates (**6**) and cyclohept-3-en-1-yl acetate (**4**) or it can undergo a rapid, pseudo-degenerate, rearrangement to give cation **5r** (cyclohept-3-ene(3,1,4-deloc)ylum-1-d). This cation should react with acetic acid in an identical manner to cation **5**. In a separate study, both the *cis*- and *trans*-3,5-dinitrobenzoates of bicyclo[4.1.0]heptan-2-ol were hydrolyzed in aqueous acetone (80:20 v/v acetone:water) to give the diastereomeric bicyclo[4.1.0]heptan-2-ols (*cis*-67%, *trans*-23%) and the homoallylic cyclohept-3-en-1-ol (10% yield) as reaction products.¹³ However, no labelling studies were performed so that the authors were unable to determine if any skeletal rearrangements had occurred during the hydrolysis reaction.

Herein, we report the chemical synthesis of two ¹³C-isotopologues of *cis*-2-(4-nitrophenoxy)bicyclo[4.1.0]heptane (**7b** and **7c**) and the NMR characterization of the reaction intermediates along with the thermodynamic product of their solvolysis reactions in trifluoroethanol. We then compare the degree of C-13 scrambling in trifluoroethanol to that reported for deuterium scrambling of the bicyclo[4.1.0]heptyl acetates in acetic acid.

STRUCTURES 7a–7c

Experimental

General procedures and materials

All anhydrous reactions described were performed under an atmosphere of nitrogen using flame-dried glassware. Normal phase flash column chromatography was carried out with 230-400 mesh

silica gel (Silicycle, SiliaFlash® P60). Concentration and removal of trace solvents was done with a Büchi rotary evaporator using a dry ice/acetone condenser and vacuum applied from a Büchi V-500 pump. All reagents and starting materials were purchased from Sigma Aldrich, Alfa Aesar, TCI America or Arcos and were used without further purification. All solvents were purchased from Sigma Aldrich, EMD, Anachemia, Caledon, Fisher or ACP and used without further purification unless specified. Specifically, CH₂Cl₂ was freshly distilled over CaH₂; THF was freshly distilled over Na metal/benzophenone. Cold temperatures were maintained by use of the following conditions: 0 °C, ice-water bath; -78 °C, acetone-dry ice bath. Warm temperatures were achieved using sand baths and heating. Nuclear magnetic resonance (NMR) spectra were recorded using CDCl₃. Chemical shifts (δ) are given in parts per million from tetramethylsilane (δ 0) and were measured relative to the signal of the solvent (¹H NMR: CDCl₃: δ 7.26, ¹³C NMR: CDCl₃: δ 77.16). Coupling constants (*J* values) are given in Hertz (Hz) and are reported to the nearest 0.1 Hz. ¹H NMR spectral data are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br., broad), coupling constants, number of protons. NMR spectra were recorded on a Bruker Avance 600 equipped with a QNP or TCI cryoprobe (600 MHz), Bruker 500 (500 MHz), or Bruker 400 (400 MHz). Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum Two™ Fourier transform spectrometer with neat samples. Only selected, characteristic absorption data are provided for each compound.

***rac*-(1*R*,2*S*,6*S*)-Bicyclo[4.1.0]heptan-2-ol (8)**

To a solution of *rac*-2-cyclohexen-1-ol (1.0 mL, 10.2 mmol) in 100 mL CH₂Cl₂ at 0 °C was charged CH₂I₂ (2.46 mL, 30.6 mmol, 3.0 eq.) followed by diethylzinc (1.0 M in hexanes, 40.8 mL, 40.8 mmol, 4.0 eq.); *Note: diethylzinc is pyrophoric and should be handled with caution.* The resulting cloudy white solution was stirred vigorously for 2 h and then washed with NH₄Cl

(40 mL), NaHCO₃ (40 mL), and brine (40 mL). The organic extract was dried over Na₂SO₄, filtered, and concentrated. Purification by column chromatography (100 % Et₂O), afforded **8** (0.84 g, 7.48 mmol, 73% yield).

***rac*-(1*R*,2*S*,6*S*)-2-(4-nitrophenoxy)-bicyclo[4.1.0]heptane (7a)**

To a cooled (0 °C) solution of alcohol **8** (0.10 g, 0.90 mmol) in DMF (9 mL) was added 1-fluoro-4-nitrobenzene (0.12 mL, 1.1 mmol, 1.2 eq.) and sodium hydride (60% in mineral oil, 0.16 grams, 1.8 mmol, 2.0 eq.). Addition of the sodium hydride resulted in a colour change from yellow to dark green/black. After 1 h, the solution was diluted with Et₂O (5 mL) and was then washed with H₂O (10 mL), NaHCO₃ (10 mL), and brine (10 mL). The organic extract was then dried over Na₂SO₄, filtered, and concentrated. Purification by column chromatography (1:19 / hexanes:EtOAc), afforded **7a** (0.13 g, 0.56 mmol, 62% yield); (600 MHz, CD₃CD₂OD) δ 8.21 (appd, J = 9.3, 2H, H-Ar), 7.14 (m, 2H, H-Ar), 5.07 (appq, J = 5.8, 1H, H-3), 1.89 (m, 1H, H-5a), 1.74–1.66 (m, 2H, H-4a, H-5b), 1.57–1.45 (m, 3H, H-2, H-4b, H-6a), 1.39 (m, 1H, H-6b), 1.22 (m, 1H, H-1), 0.55 (apptd, J = 8.9, 5.0, 1H, H-7a), 0.46 (appq, J = 5.0, 1H, H-7b); ¹³C NMR (151 MHz, CD₃CD₂OD) δ 163.58, 140.86, 125.88, 115.52, 72.81 (C-3), 27.58 (C-4), 22.59 (C-5), 17.60 (C-6), 13.61 (C-2), 12.32 (C-1), 6.19 (C-7).

(1-¹³C)Hex-5-enoic acid (9)

A grain of iodine was added to a suspension of magnesium turnings (0.44 g, 18.1 mmol, 1.4 eq.) in THF (35 mL) and this solution was heated to 45 °C and stirred for 30 min, promoting a colour change to light orange. 5-Bromopent-1-ene (2 mL, 16.8 mmol, 1.3 eq.) was then charged dropwise to the solution. After addition of the bromopentene the solution was kept at 45 °C for 90 min until almost all the magnesium had disappeared. The mixture was then cooled to 0 °C and gaseous ¹³CO₂ (99 atom%, ca. 0.32 L, 13.0 mmol) was slowly bubbled through the solution,

which was stirred for a further 30 min. The reaction was then quenched with aqueous HCl (1 M, 10 mL) and then washed with brine (20 mL). The organic extract was then dried with MgSO₄, filtered, and concentrated. Purification by column chromatography (1:3 EtOAc/hexane) afforded labelled carboxylic acid **9** (0.99 g, 8.7 mmol, 67% yield).

(1-¹³C)Hex-5-en-1-ol (10)

To a cooled (0 °C) suspension of LiAlH₄ (0.41 g, 10.7 mmol, 3.0 eq.) in THF (36 mL) was charged with **9** (0.41 g, 3.6 mmol) dropwise. After 10 min, the cooling bath was removed and the reaction was stirred for 2 h. The mixture was then diluted with Et₂O (20 mL) and cooled to 0 °C. This was followed by dropwise charges of water (0.4 mL), 15% aqueous sodium hydroxide (0.4 mL), and water (0.4 mL). The resulting biphasic mixture was warmed to rt, stirred for 15 min, and dried over MgSO₄. The slurry was filtered and the solids were washed with copious Et₂O. The filtrate was then concentrated under reduced pressure. Purification by column chromatography (5:1 v/v pentane:Et₂O), afforded labelled **10** (0.29 grams, 2.9 mmol, 81% yield).

(1-¹³C)Hex-5-enal (11)

To a cooled (−78 °C) solution of DMSO (1.6 mL) in CH₂Cl₂ (23 mL) was charged dropwise oxalyl chloride (1.0 mL, 12.1 mmol) and the mixture was aged for 20 min. A solution of **10** (0.82 g, 8.10 mmol) in CH₂Cl₂ (4 mL) was charged dropwise to the solution and the mixture was aged for 40 min. Et₃N (5.4 mL, 40.3 mmol) was then added dropwise, which prompted a change in appearance to milky white. The resulting mixture was aged for 30 min and then allowed to warm slowly to rt. The crude reaction mixture was washed with NH₄Cl (10 mL), prompting a colour change to pale orange. The aqueous extract was washed with CH₂Cl₂ (5 mL). The pooled organic extracts were then washed with water (2 × 30 mL) and brine (2 × 30 mL). Because of volatility

issues, the organic extract was concentrated to ca. 10 mL and was used as such in the subsequent reaction.

(3-¹³C)Octa-1,7-dien-3-ol (12)

The solution of labelled aldehyde **11** in CH₂Cl₂ (ca. 10 mL) was diluted with THF (20 mL) and then cooled to 0 °C. To this mixture was added dropwise a solution of vinylmagnesium bromide (1.0 M in THF, 8.0 mL, 8.0 mmol). The cooling bath was then removed and the solution was aged for 1 h, followed by quenching with a saturated solution of NH₄Cl (20 mL). The organic extract was dried over MgSO₄ and concentrated. Purification by column chromatography (3:1 v/v hexanes:EtOAc) afforded **12** (0.12 g, 0.95 mmol, 12% yield over two steps).

(1-¹³C)Cyclohex-2-en-1-ol (13)

A solution of **12** (0.12 g, 0.95 mmol) in CH₂Cl₂ (5 mL) was degassed 4 times over the course of 2 h by freeze-pump-thaw cycle. Next, Grubbs' 2nd generation catalyst (0.01 g, 0.01 mmol) was charged, prompting a colour change to dark green. The solution was then stirred for 6 h at a bath temperature of 60 °C. Subsequently, the solution was washed with NaHCO₃ (5 mL), NH₄Cl (5 mL), and brine (5 mL), filtered, and the solvent was removed. Purification by column chromatography (3:2 v/v pentanes:Et₂O) afforded **13** (78 mg, 0.79 mmol, 83% yield).

***rac*-(1*R*,2*S*,6*S*)-(2-¹³C)bicyclo[4.1.0]heptan-2-ol (14)**

To a cooled (0 °C) solution of diethyl zinc (1.0 M in hexanes, 2.8 mL, 2.8 mmol, 4.0 eq.) in 4.3 mL CH₂Cl₂ was charged CH₂I₂ (0.17 mL, 2.1 mmol, 3.0 eq.) dropwise (*Note: diethylzinc is pyrophoric and should be handled with caution*). After 20 min, alcohol **13** (70 mg, 0.71 mmol) was charged, and the reaction aged for 24 h. The solution was then washed with NH₄Cl (5 mL), NaHCO₃ (5 mL), and brine (5 mL). Following solvent removal, purification by column chromatography (3:1 / pentanes:EtOAc) afforded bicyclo **14** (44 mg, 0.39 mmol, 55% yield).

***rac*-(1*R*,2*S*,6*S*)-2-(4-nitrophenoxy)-(2-¹³C)bicyclo[4.1.0]heptane (7b)**

To a cooled (0 °C) solution of alcohol **14** (0.044 g, 0.38 mmol) in DMF (4 mL) was charged 1-fluoro-4-nitrobenzene (0.05 mL, 0.46 mmol, 1.2 eq.) followed by sodium hydride (60% in mineral oil, 0.30 grams, 0.76 mmol, 2.0 eq.). The mixture was warmed to room temperature and left to stir for 1 h. The solution was then diluted with Et₂O (5 mL), and washed with H₂O (10 mL), NaHCO₃ (10 mL), and brine (10 mL). The organic extract was then dried over Na₂SO₄, filtered, and concentrated. Purification by column chromatography (1:20 / hexanes:EtOAc), afforded **7b** (28 mg, 0.12 mmol, 32% yield). The NMR spectra for **7b** showed the following notable differences to those for **7a**; (600 MHz, CD₃CD₂OD) δ 5.07 (¹J_{H,¹³C} = 145.1, 1H, H-3), ¹³C NMR (151 MHz, CD₃CD₂OD) δ 27.58 (¹J_{¹³C,¹³C} = 38.6, C-4), 13.61 (¹J_{¹³C,¹³C} = 47.3, C-2).

***rac*-(1*R*,2*S*,6*S*)-(7-¹³C)bicyclo[4.1.0]heptan-2-ol (15)**

To a solution of *rac*-cyclohex-2-en-1-ol (0.15 mL, 1.12 mmol, 1.2 eq.) in CH₂Cl₂ (3.7 mL) was charged (¹³C)-CH₂I₂ (0.075 mL, 0.93 mmol) dropwise, followed by diethyl zinc (1 M in hexane, 1.3 mL, 1.3 mmol, 1.4 eq.). The solution was left to stir for 2 h at room temperature and then washed with NH₄Cl (5 mL), NaHCO₃ (5 mL), and brine (5 mL). The organic extract was dried over Na₂SO₄, filtered, and concentrated. Purification by column chromatography (100 % Et₂O), afforded bicyclo **16** (70 mg, 0.62 mmol, 66% yield).

***rac*-(1*R*,2*S*,6*S*)-2-(4-nitrophenoxy)-(7-¹³C)bicyclo[4.1.0]heptane (7c)**

To a cooled (0 °C) solution of alcohol **15** (0.06g, 0.53 mmol) in DMF (5 mL) was charged 1-fluoro-4-nitrobenzene (0.07 mL, 0.63 mmol, 1.2 eq.), followed by sodium hydride (60% in mineral oil, 0.04 grams, 1.05 mmol, 2.0). The reaction was aged for 3 h. The solution was then washed with NaHCO₃ (5 mL) and brine (5 mL), dried over Na₂SO₄, filtered, and concentrated. Purification by column chromatography (1:20 v/v hexane:EtOAc), affording **7c** (13 mg, 0.06

mmol, 10% yield). The NMR spectra for **7c** showed the following notable differences to those for **7a**; (600 MHz, CD₃CD₂OD) δ 0.55 ($^1J_{\text{H},^{13}\text{C}} = 162.1$, 1H, H-7a), 0.46 ($^1J_{\text{H},^{13}\text{C}} = 158.5$, H-7b); ^{13}C NMR (151 MHz, CD₃CD₂OD) δ 13.61 ($^1J_{^{13}\text{C},^{13}\text{C}} = 11.9$, C-2), 12.32 ($^1J_{^{13}\text{C},^{13}\text{C}} = 13.9$, C-1).

Determination of intermediate and product structures and ratios by NMR spectroscopy.

NMR spectra, for solvolyses in CF₃CD₂OD at a temperature of 280 K, were acquired on a Bruker AVANCE III HD spectrometer equipped with a QCI cryoprobe operating at 600 MHz for ^1H and 150 MHz for ^{13}C . In a typical experiment, for C-13 containing isotopologues of **7** (~3 mg) was placed in a new 5 mm NMR tube, which was cooled down to $-40\text{ }^\circ\text{C}$ using dry ice. CF₃CD₂OD solvent (550 μL), from a freshly cracked ampule, was added down the wall of the NMR tube. The NMR tube was immediately capped and inserted into the NMR instrument. Manual shimming was performed to obtain optimal Lorentzian peaks and signal to noise ratio. Reactions for carbon-13 labelled compounds were monitored continuously by repetitive acquisition of ^1H NMR, carbon-13 decoupled ^1H NMR, and proton decoupled ^{13}C NMR spectra. When the amount of remaining starting material was judged to be <5%, 1D NOE, COSY and HSQC spectra were acquired in order to assign the stereochemistry of the intermediates. The rearrangement of the intermediates were then followed by $^1\text{H}\{^{13}\text{C}\}$ and $^{13}\text{C}\{^1\text{H}\}$ NMR spectra for approximately 60 mins. The final solvolysis products were characterized by ^1H NMR, $^{13}\text{C}\{^1\text{H}\}$ NMR, COSY and HSQC, after leaving the reaction NMR tube at ambient temperatures overnight, using a Bruker AVANCE II spectrometer equipped with a QNP cryoprobe operating at 600 MHz for ^1H and 150 MHz for ^{13}C .

Results and Discussion

First, we synthesized the parent bicyclo[4.1.0]heptyl analogue (**7a**), using a literature procedure,⁷ and two carbon-13 labelled isotopologues (Schemes 3 and 4).^{7, 8}

SCHEMES 3 and 4

With compounds **7a–c** in hand we decided to modify the ionizing ability of the solvent used in the previous labelling study (AcOH)¹² in order to increase the rate for formation of cationic intermediates, and to use a solvent with a low nucleophilicity (lower the possibility for direct S_N2 reactions). That is, we noted that the ability of acetic acid, based on the Y_{OTs} scale,¹⁴ to promote formation of cations is much less than that for trifluoroethanol [$Y_{\text{OTs}} = 1.80$ (TFE), -0.61 (CH₃CO₂H)], yet acetic acid is a more nucleophilic solvent, $N_{\text{OTs}} = -3.0$ (TFE), -2.35 (CH₃CO₂H).¹⁵

Identification of Intermediates and Products During Solvolysis.

In (1,1-²H₂)2,2,2-trifluoroethan(²H)ol the solvolysis of **7a** occurs rapidly at ambient temperatures. Specifically, we noted that by the time we were able to acquire a ¹H NMR spectrum almost all of **7a** had reacted to be replaced by a complex mixture of intermediates and final product. Moreover, after approximately 1 hour the ¹H NMR spectrum had simplified to that of a single compound 4-[(1,1-²H₂)2,2,2-trifluoroethoxy]cycloheptene (**16a**, Supporting Information Figure S4).

As a result, we decided to acquire spectra during the rearrangement reactions at a lower temperature (280 K) using a 600 MHz NMR spectrometer equipped with a QCI-cryoprobe. Specifically, trifluoroethanolysis of the C7-labelled compound **7c** showed the presence of four ¹³C resonances in the first NMR spectrum acquired after addition of the solvent to **7c** (Supporting Information, Figure S5a). Subsequent spectra accumulated over the course of 60 mins show that the signals at 35.40, 9.74, 8.97, and 7.93 ppm result from **16c**, **17b**, **17a**, and **7c**, respectively (Scheme 5). Moreover, as the reaction progresses the ¹³C signal for the starting material (7.93 ppm) decreases, as those for cyclopropyl intermediates (*cis*- and *trans*-**17**) increase and then decrease until the only signal remaining is for **16c** (Supporting Information, Figure S5c).

SCHEME 5

That the final ^{13}C -NMR spectrum contains a single labelled compound means that the rearrangement of the non-classical carbenium ion intermediates is not being probed by the ^{13}C -labelled **7c**.

In order to address this problem we made ^{13}C -labelled **7b**. Now, trifluoroethanolysis of **7b** showed the presence of seven ^{13}C resonances in the first NMR spectrum acquired after addition of the solvent to **7b** (Supporting Information, Figure S6a). These seven resonances, at 136.92, 82.75, 81.19, 80.25, 76.33, 14.49, and 11.75 ppm result from **16b-1**, **16b-2**, **18** (*cis* and *trans*), **7b**, and **19** (*trans*- and *cis*-), respectively (Scheme 6).

SCHEME 6

Of note, following disappearance of **7b** the four resonances associated with the *cis*- and *trans*-cyclopropyl intermediates are replaced by the two resonances for the C1- and C4-isotopologues of 4-[(1,1- $^2\text{H}_2$)2,2,2-trifluoroethoxy]cycloheptene (Supporting Information, Figure S6).

Stereochemical Assignment of Cyclopropyl Intermediates

In order to assign the diastereomeric selectivity of addition to the carbenium ion intermediate we tried to acquire a 1D NOE spectrum during the solvolysis reaction of **7a**, but we were unsuccessful. We then decided to acquire a HSQC (one bond C–H correlation experiment) during the solvolysis of **7c** (Supporting Information, Figure S7). Clearly, the major cyclopropyl trifluoroethyl ether intermediate ($\delta^{13}\text{C}$ 8.97) shows correlations to two protons, while for the minor isomer ($\delta^{13}\text{C}$ 9.74) we could only identify a single unambiguous correlation to a proton, which had a chemical shift of 0.04 ppm (Supporting Information, Figure S7). Nevertheless, this correlation allows us to assign the major diastereomer to be the *cis*-isomer and the minor as the *trans*-isomer based on literature chemical shifts for the *cis*- and *trans*-isomers of bicyclo[4.1.0]heptan-2-ol^{16, 17} and 2-methoxybicyclo[4.1.0]heptane.¹⁸ We note that the ratio of

diastereomers, based on NMR integrations, is around 5–6:1 in favour of the *cis*-isomer, a ratio that is a slightly larger than that for water capture of the non-classical cation during the hydrolysis of the dinitrobenzoates of bicyclo[4.1.0]heptan-2-ol.¹³

Degree of Skeletal Rearrangement Occurring During the Solvolysis Reactions

If rearrangement of the two pseudo enantiomeric carbenium ions (**20** and **21**), which are present during the solvolysis of **7b** (Scheme 7), is rapid then the amounts of the C1 and C4 isotopic products must be identical. Shown in Figure S9 (Supporting Information) are the vinylic and alkoxy regions of the ¹H NMR spectrum acquired following complete solvolysis of **7b** in CF₃CD₂OD at 280 K to give labelled 4-trifluoroethoxycycloheptenes (**16b-1** and **16b-2**). Integration of both regions shows that the rearranged product is formed in approximately 39 ± 4% [vinylic region gives 0.40/(0.63 + 0.40) and the alkoxy protons show 0.38/(0.38 + 0.59); maximal error is estimated to be 10%]. As noted above, Friedrich and Cooper reported that in acetic acid around 35% rearrangement was observed for a bicyclo[4.1.0]heptyl system (Scheme 2),¹² while we observe approximately 40% rearrangement in the more ionizing and less nucleophilic solvent trifluoroethanol. Clearly, the rearrangement, the presumed mechanism of which is depicted in Scheme 7, has not reached the expected equilibrium of 1:1 for the two delocalized cations. Thus, we conclude that trapping of the initially formed carbenium ion is competitive with rearrangement to the secondary cyclobutenium cation. We note that it is possible that the rearrangement of these high energy intermediates includes dynamic effects that may perturb the bifurcation energy surface for the bicyclo[3.1.1]heptyl carbenium ion.^{19, 20}

SCHEME 7

Finally, we comment on the presumed intermediacy of the cyclobutenium ion **22** (Scheme 7). Ever since the observations reported by Roberts and Mazur²¹ that the cyclopropylcarbinyl and

cyclobutyl cations, formed by reaction of aqueous nitrous acid on the corresponding primary amines, give identical ratios of cyclopropylmethanol and cyclobutanol products; cations such as **22** have been invoked in these rearrangement reactions. Recent, high level calculations on the parent $C_4H_7^+$ carbenium ion reported different relative energy levels for the delocalized cyclobutylum and cyclopropylmethylum cations.^{10, 11} In spite of these different conclusions, which likely result from the different basis sets used, both papers report that the energy difference between the two cations is small. Therefore, in the absence of additional information we include the cyclobutylum ion **22** as an intermediate in our proposed mechanism (Scheme 7), although we realize that the rearrangement between **20** and **21** might circumvent this cation.

Supplementary material

Supplementary material is available with this article through the journal Web site at <http://nrcresearchpress.com>. The supplementary material includes 1H and ^{13}C NMR spectra for **7a–c** and **16a**, ^{13}C NMR spectra of the solvolyses of **7b** and **7c**, 1H , $^1H\{^{13}C\}$, and HSQC spectra showing cyclopropyl methylene resonances during reaction of **7c**, and sections of the 1H NMR spectrum for the reaction products of **7b**.

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Structures 1–2**Structures 7a–7c**

SCHEME 1. General Mechanistic Scheme for the Galactosylation Step that Occurs During the Catalytic Cycle of a Retaining α -Galactosidase from GH36.

SCHEME 2. Proposed Mechanistic Scheme for the Rearrangement of Bicyclo[4.1.0]heptan-2-ol in Acetic Acid.

SCHEME 3 Synthesis of (2- ^{13}C)bicyclo[4.1.0]heptan-2-ol (**14**) and its 4-nitrophenyl ether **7b**. a) Mg, ether then $^{13}\text{CO}_2$, 67%; b) LiAlH_4 , THF, 81%; c) $(\text{COCl})_2$, DMSO then Et_3N ; d) vinyl magnesium bromide, ether, 50 °C, 12% (two steps); e) Grubbs' 2nd generation, CH_2Cl_2 , reflux, 83%; f) ZnEt_2 , CH_2I_2 , CH_2Cl_2 , 55%; g) quinuclidine, 4Å mol sieves, 4-nitrofluorobenzene, DMF, rt, 24 h, 32%.

SCHEME 4 Synthesis of (7- ^{13}C)bicyclo[4.1.0]heptan-2-ol (**15**) and its 4-nitrophenyl ether **7c**. a) ZnEt_2 , $^{13}\text{CH}_2\text{I}_2$, CH_2Cl_2 , 66%; b) quinuclidine, 4Å mol sieves, 4-nitrofluorobenzene, DMF, rt, 24 h, 10%.

SCHEME 5. Scheme for the Solvolytic Rearrangement of *rac*-(1*R*,2*S*,6*S*)-2-(4-nitrophenoxy)-(7- ^{13}C)bicyclo[4.1.0] (**7c**) in Trifluoroethanol.

SCHEME 6. Scheme for the Solvolytic Rearrangement of *rac*-(1*R*,2*S*,6*S*)-2-(4-nitrophenoxy)-(3- ^{13}C)bicyclo[4.1.0]heptane (**7b**) in Trifluoroethanol.

SCHEME 7. Presumed Mechanism for the Rearrangement of the two Pseudo-Enantiomeric Non-classical Carbocations Formed During the Trifluoroethanolysis of **7b**.

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Draft

81x41mm (300 x 300 DPI)

7a, C2 = C7 = ^{12}C

7b, C2 = ^{13}C ; C7 = ^{12}C

7c, C2 = ^{12}C ; C7 = ^{13}C

46x42mm (300 x 300 DPI)

167x60mm (300 x 300 DPI)

Draft

143x85mm (300 x 300 DPI)

161x52mm (300 x 300 DPI)

Draft

71x25mm (300 x 300 DPI)

Draft

106x74mm (300 x 300 DPI)

159x94mm (300 x 300 DPI)

92x28mm (300 x 300 DPI)

Draft