Pergamon

Tetrahedron Letters 43 (2002) 811–814

TETRAHEDRON LETTERS

TFA-catalyzed trimerization of *R*-(+)-6-methyl-tetrahydro-pyran-2-one

Fabio Fazio and Manfred P. Schneider*

FB 9-Bergische Universität-GH-Wuppertal, D-42097 Wuppertal, Germany

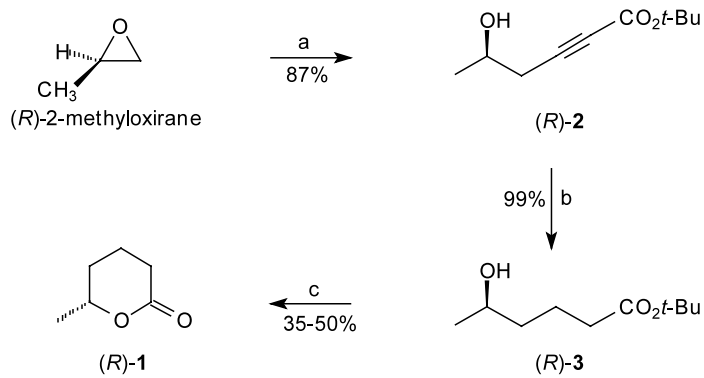
Received 27 June 2001; accepted 22 July 2001

Abstract—The enantiomerically pure (≥98% ee) title compound *R*-(+)-6-methyl-tetrahydro-pyran-2-one (*R*)-**1** in the presence of traces of trifluoroacetic acid (TFA) converts into an equilibrium mixture with its trimer **4** [(*R*)-**1**:**4**=20:80] corresponding to a $\Delta G \cong -0.8$ kcal mol^{-1}. The transformation can be followed by ^{1}H and ^{13}C NMR spectroscopy. The structure of **4** was established by chemical correlation with (*R*)-**1** and its molecular weight determined via its colligative properties.

Some time ago we described a novel synthesis of enantiomerically pure (≥98% ee) 6-alkylsubstituted δ-lactones starting from optically pure alkyloxiranes which, in turn, were obtained via an enzyme assisted route based on the lipase-catalyzed, kinetic resolution of suitable racemic precursors.[1] Using the title compound (*R*)-**1** as an example, the route is summarized in Scheme 1.

Nucleophilic ring opening of (*R*)-2-methyloxirane by the anion of *tert*-butyl propiolate led to *R*-(−)-5-hydroxy-hex-2-ynoic acid *tert*-butyl ester (*R*)-**2**, which was hydrogenated (5% Pd/C, AcOEt, −20°C; 6 h, 99%) quantitatively to the saturated derivative (*R*)-**3** which was in turn cyclized to (*R*)-**1** in the presence of catalytic amounts of trifluoroacetic acid. (*R*)-**1** was isolated by column chromatography on silica gel [Et_2O/*n*-hexane (2/1)] followed by short path distillation (Kugelrohr, 70°C, 10^{-3} mBar) as a white solid (mp 31°C). Although monitoring of the reaction by TLC and GC confirmed quantitative conversion, the yield was only 50%, probably due to the solubility of (*R*)-**1** in the aqueous solution used for work up.

The thus prepared (*R*)-**1**[2] showed a chemical purity of ≥99% (GC analysis) which was further confirmed by the clean and readily interpretable ^{1}H and ^{13}C NMR spectra (Fig. 1A). (*R*)-**1** was optically pure[3] with an optical rotation of $[\alpha]_D^{20} = +36$ (*c* 0.7, $CHCl_3$ stab. with 1% EtOH). Surprisingly and quite unexpectedly we



Scheme 1. (a) *tert*-Butyl propiolate, *n*-BuLi, BF_3–Et_2O, THF, −78°C, 2.5 h; (b) H_2, 5% Pd/C, AcOEt, −20°C, 6 h; (c) TFA, CH_2Cl_2, rt, 24 h.

Keywords: chiral δ-lactones; trimerization; trifluoroacetic acid.

* Corresponding author.

0040-4039/02/$ - see front matter
PII: S0040-4039(01)02281-X

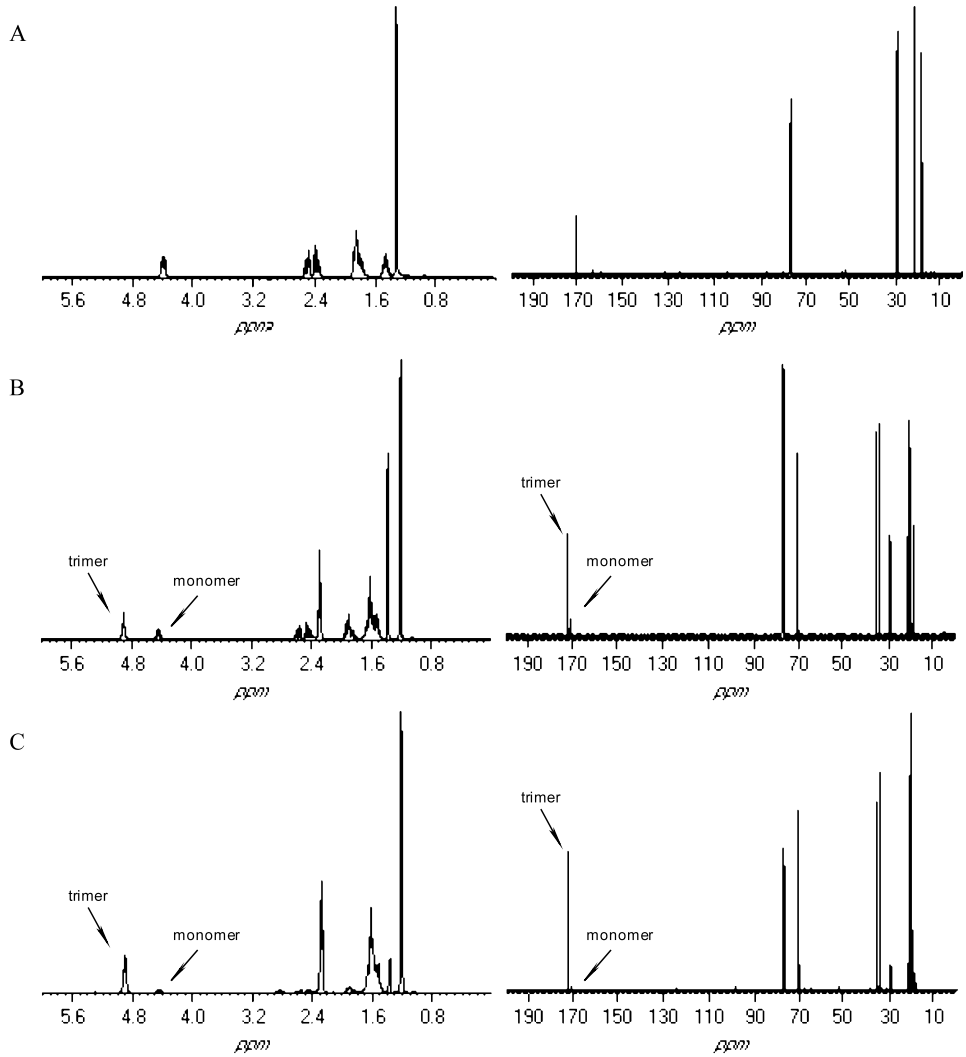
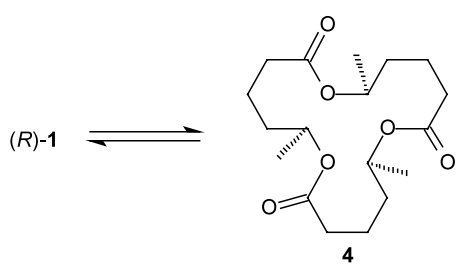


Figure 1. ^{1}H and ^{13}C NMR spectra ($CDCl_3$, 400 MHz). (A) Freshly synthesized (*R*)-**1**; (B) product stored at 20°C for 21 days; (C) product stored at 20°C for 35 days.

found, however, that the thus prepared (*R*)-**1** was unstable upon storage in neat form even at low temperatures. This became evident when *crystalline* (*R*)-**1** slowly turned into a *liquid*, the change in physical appearance being accompanied by a change of optical rotation from $[\alpha]_D^{20}=+36$ to $[\alpha]_D^{20}=-7$ (*c* 1.0, $CHCl_3$ stab. with 1% EtOH) for what turned out to be an equilibrium mixture of (*R*)-**1** and a newly formed compound for which we assigned the trimeric structure **4** (Scheme 2).

This trimerization surprisingly turned out to be a very clean transformation, no other oligomers or polymers were observed. It can be conveniently monitored via the corresponding ^{1}H and ^{13}C NMR spectra, which were taken in regular (7 days) intervals. Thus pure (*R*)-**1** (Fig. 1A) having a characteristic multiplet at $\delta=4.39$ ppm in the ^{1}H NMR spectrum (and a signal at $\delta=$ 171.67 ppm for the carbonyl carbon in the ^{13}C NMR) was slowly transformed into (6*R*,12*R*,18*R*)-(−)-6,12,18-trimethyl-1,7,3-trioxa-cyclooctadecane-2,8,14-trione **4**, having a corresponding multiplet at $\delta=4.90$ ppm (three carbonyl carbons at 172.84 ppm in the ^{13}C NMR) (Fig. 1B). After ca. 35 days an equilibrium mixture of (*R*)-**1** and **4** was obtained with a ratio (determined by integration of the ^{1}H NMR signals) of ca. 20:80 (Fig. 1C).

The existence of a true thermodynamic equilibrium was supported by the fact that the same mixture was obtained starting from either pure (*R*)-**1** or **4**.

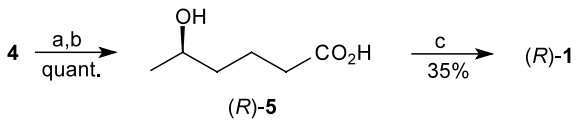


Scheme 2.

Pure **4** was obtained by removal of (*R*)-**1** from the equilibrium mixture by short path distillation (Kugelrohr, 100°C, 10^{-3} mBar). Next to a correct elemental analysis and the obvious similarity of the ^{1}H and ^{13}C NMR spectra of (*R*)-**1** and **4** which allowed a facile interpretation,[4] **4** was chemically correlated with (*R*)-**1**. Hydrolysis of **4** with 2N NaOH in H_2O/THF led to the corresponding sodium salt of *R*-(−)-5-hydroxy-hexanoic acid (*R*)-**5**. After acidification with aqueous conc. HCl and removal of all solvents, the resulting (*R*)-**5** was recyclized to (*R*)-**1** without loss of optical purity (Scheme 3).

Next to proving the molecular constitution of **4** this sequence also allows a regeneration of (*R*)-**1** from the impure mixture.

However, in spite of all this information the correct structure of **4** remained unclear, with other oligomeric structures such as the corresponding dimer or tetramer being obvious options. All of them being symmetric (*n*-fold axes C_n) they would all display six carbon atoms in the ^{13}C NMR. Also, the determination of the molecular weight by various MS techniques (EI, CI, electrospray)[5] proved to be unsuccessful. The thermal instability of **4** led to signals resulting of monomer, dimer and oligomers with unit differences of $m/z = 114$.



Scheme 3. (a) 2N NaOH, THF/H_2O, 0°C–rt, 30 min; (b) conc. HCl, 0°C; (c) TFA, CH_2Cl_2, rt, 24 h.

Thus, the molecular weight of **4** had to be determined the 'old fashioned way' exploiting the colligative properties of this material. Using the freezing point depression in 1,4-dioxane we were able to calculate[6] a molecular weight for **4** of 367.16 (theor. 342.43) (Fig. 2).

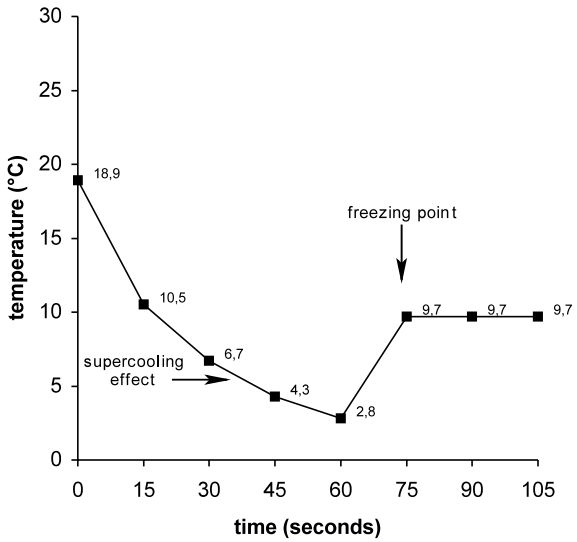
In this formula K_f represents the cryoscopic constant (−4.63 for 1,4-dioxane) and $\Delta T_f = T_{fsolution} - T_{fsolvent}$ is the difference of the freezing points between pure 1,4-dioxane and the under described solution of **4** in the same solvent (see Ref. 6). We found for **4** a MW of 367.16 (theor. 342.43), the error thus was 7.2%.

From the equilibrium constant at 20°C it can be calculated[7] that the trimeric structure **4** is thermodynamically more stable than (*R*)-**1** by a $\Delta G° \cong -0.8$ kcal mol^{-1}, a difference which is clearly sufficient to partially transform (*R*)-**1** into **4**.

It is interesting to speculate why only the trimer, having an 18-membered ring is formed in this transformation so cleanly without any trace of the corresponding dimer, tetramer or other oligomers and polymers.

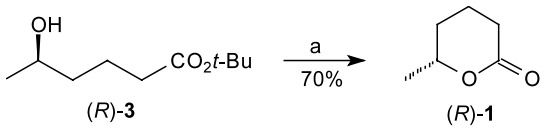
The relative stabilities of lactones having 3–23 ring members had been determined earlier, revealing clearly the higher stability of the 18-membered ring system[8] over the 6- and 12-membered rings (i.e. monomer and dimer). This is in good agreement with our observations and the calculated $\Delta G° \cong -0.8$ kcal mol^{-1}.

With enantiomerically pure δ-lactones being important flavour compounds and thus attractive synthetic targets, we were curious to elucidate the reasons for the surprising trimerization of such a δ-lactone. Clearly, the



$$\text{M.W. of } \mathbf{4} = \frac{(K_f)\,(g_{\,solute})}{\Delta T_f\,(Kg_{\,solvent})} = \frac{-4.63 \times 0.091}{-0.9 \times (1.27 \times 10^{-3})} = 367.16 \quad \text{(theor. 342.43)}$$

Figure 2.



(*R*)-**3** (*R*)-**1**

Scheme 4. (a) *p*-TsOH, toluene, reflux, 1.30 h.

instability of (*R*)-**1** could only be the result of an acid-catalyzed process initiated by the presence of traces of TFA introduced during the cyclization of (*R*)-**3** (Scheme 1). Since δ-lactones are instable towards base, the removal of TFA during workup by extraction with an aqueous Na_2CO_3 solution causes considerably reduced product yields. We therefore initially opted for column chromatography and short path distillation in the hope that the last traces of TFA would be completely removed this way. Evidently this was not the case. If the organic phase during workup is indeed washed with Na_2CO_3, the resulting (*R*)-**1** (isolated in greatly reduced yield of only 35%) is perfectly stable upon storage. The addition of a trace of TFA immediately initiates again the above described trimerization.

Clearly TFA is not the method of choice for the cyclization reaction leading to (*R*)-**1**.

Since (*R*)-**1** is both base labile and soluble in an aqueous environment we now optimized the cyclization procedure by using *p*-TsOH in toluene (Scheme 4). No aqueous workup was required in this case. Considerably improved yields of 70% were obtained and the resulting product is perfectly stable during storage at room temperature.

Although base-catalyzed oligomerization of δ-lactones has already been reported in the literature,[9] this to the best of our knowledge seems to be the first example of an acid (TFA)-catalyzed oligomerization of δ-lactones.

Acknowledgements

We are grateful to the colleagues of Bayer AG, Wuppertal, Germany for the measurement of mass spectra.

References

1. Haase, B.; Schneider, M. P. *Tetrahedron: Asymmetry* **1993**, *4*, 1017.
2. Analyses of (*R*)-**1**: white solid, mp: 31°C; $[\alpha]_D^{20}=+36$ (*c* 0.7, $CHCl_3$ stab. with 1% EtOH); ^1H NMR (400 MHz, $CDCl_3$) δ 4.39 (m, 1H), 2.44 (m, 2H), 1.84 (m, 3H), 1.47 (m, 1H), 1.32 (d, 3H, $J=6.10$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.67, 76.76, 29.47, 29.09, 21.56, 18.40. IR (film, cm^{-1}) 2945, 1720, 1435, 1370, 1230. MS *m*/*z* 114, 99, 70, 55, 42 (100%), 39. Anal. calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 62.52; H, 8.57. GC: column SE-52-CB; pressure: 100 kPa H_2; temperature program: 40°C (5 min), 40–280°C (4°C/min).
3. The determination of the optical purity of (*R*)-**1** was established via GC on chiral support. Column: Lipodex E; pressure: 100 kPa H_2; temperature program: 78°C (42 min), 78–150°C (1.5°C/min); ee ≥98%.
4. Analyses of **4**: high viscous colorless oil; $[\alpha]_D^{20}=-8$ (*c* 0.6, $CHCl_3$ stab. with 1% EtOH); ^1H NMR (400 MHz, $CDCl_3$) δ 4.90 (m, 3H), 2.29 (m, 6H), 1.61 (m, 12H), 1.21 (d, 9H, $J=6.10$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.84, 70.37, 35.23, 34.18, 20.81, 19.87. IR (film, cm^{-1}) 2921, 1701, 1459, 1383. Anal. calcd for $C_{18}H_{30}O_6$: C, 63.14; H, 8.83. Found: C, 62.62; H, 8.59.
5. CI and electrospray MS analyses of **4** were carried out by the Bayer AG, Wuppertal, Germany.
6. Determination of molecular weight of **4** by freezing point depression: 1.27 g of 1,4-dioxane was placed into a test tube (13 cm×1.3 cm) containing a small magnetic stirrer. The test tube was closed with a septum which was previously pierced in order to allow the insertion of a metal contact thermometer with electronic display (0.1°C scale). This apparatus was immersed into a cooling bath maintained at 0°C and the solution was stirred. Every 15 s the temperature was recorded until it became constant for ca. 30 s. This value (10.6°C) was taken as freezing point of pure 1,4-dioxane (a supercooling effect was observed). Then **4** (91 mg) was added carefully to the test tube thereby avoiding any loss of solvent until a homogeneous solution was obtained and the experiment was repeated as above recording the data. The thus obtained freezing point of the solution was +9.7°C. Applying the formula for the calculation of the molecular weight via the freezing point depression of a substance we found a MW of 367.16 (theor. 342.43).
7. $\Delta G°=-RT \ln k=-2.303\ RT \log k$. At 20°C, $k\cong 80/20\cong 4$ and $\Delta G°\cong -1.34 \log 4\cong -0.8$ kcal mol^{-1}.
8. Mandolini, L. *J. Am. Chem. Soc.* **1978**, *100*, 550.
9. Dale, J.; Schwartz, J. E. *Acta Chem. Scand.* **1986**, *B40*, 559.