Pergamon

Tetrahedron Letters 43 (2002) 1821–1824

TETRAHEDRON LETTERS

Synthesis of α,ω-differently substituted cyclic ethers from carbohydrates by β-fragmentation of alkoxyl radicals

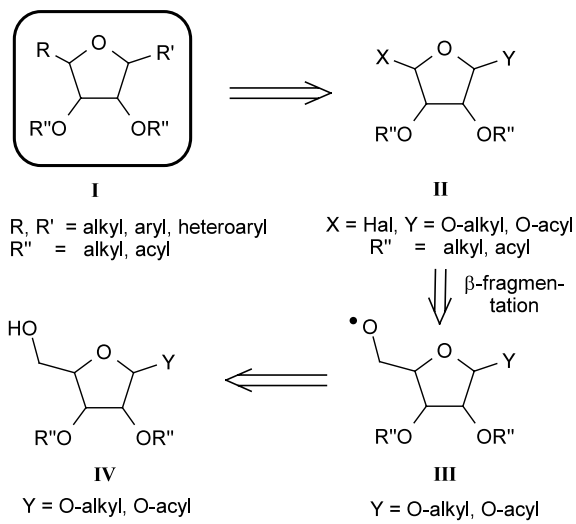
Alicia Boto, Rosendo Hernández* and Ernesto Suárez*

Instituto de Productos Naturales y Agrobiología del C.S.I.C., Carretera de La Esperanza 3, 38206-La Laguna, Tenerife, Spain

Received 19 December 2001; revised 11 January 2002; accepted 16 January 2002

Abstract—The β-fragmentation of alkoxyl radicals derived from easily available carbohydrates is a mild and efficient procedure to obtain unsymmetrical α,ω-disubstituted cyclic ethers.

The synthesis of α,ω-differently substituted cyclic ethers (I) (Scheme 1, R, R′ = alkyl, aryl, heteroaryl) has attracted great interest. This unit is present in many natural products[1] such as antibiotic polyethers,[1a–e] marine toxins,[1b–d] acetogenins,[1f,g] pheromones,[1h] etc., many of which have potent biological activities. Accordingly, different strategies have been developed to synthesize these systems.[2] A direct way to achieve this objective could start from the cyclic aldoses (II), where X and Y are leaving groups which allow the orthogonal introduction of the R and R′ substituents. For instance, using Y = alkoxy or acyloxy group and X = halogen, it would be possible to introduce an R substituent by a radical reaction[3] and an R′ substituent by an ionic one.[4]



Scheme 1. Formation of unsymmetrical cyclic ethers.

Syntheses of the unsymmetrical α-acyloxy (or alkoxy)-ω-haloaldoses (II) are scarce.[5] As a direct, regioselective alternative, we decided to explore the β-fragmentation reaction of alkoxyl radicals (III) (Scheme 1), that could be easily generated by treatment of readily available sugar derivatives (IV) with organohypervalent iodine reagents.[6] This promising strategy could, however, be hampered by side-reactions: once generated, the alkoxyl radicals could evolve either by the desired β-fragmentation, or by other paths such as oxidation to a carbonyl group or the abstraction of a nearby hydrogen.[7] Although primary alkoxyl radicals usually give hydrogen abstraction or oxidation, we expected that in our case the β-fragmentation process would predominate, since the radical resulting from this scission would be stabilized by the α-positioned ring oxygen.[7] The feasibility of this approach and the synthesis of α,ω-disubstituted cyclic ethers is reported herein.

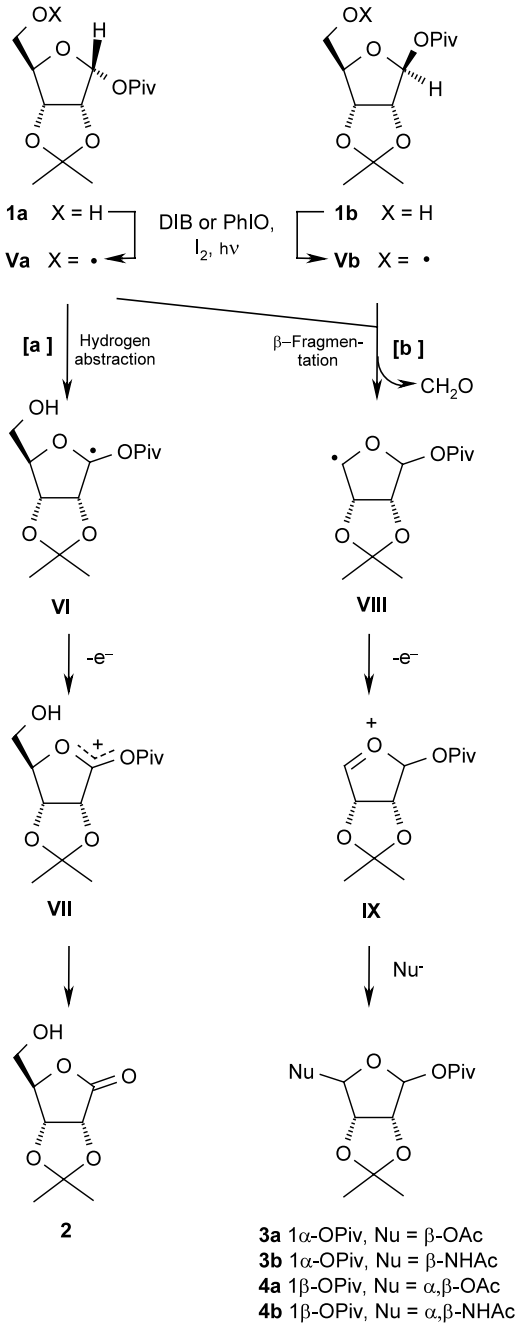
To compare the relative rates of the β-fragmentation process versus the hydrogen abstraction or the oxidation reactions, we studied the reaction of the 1α-pivaloyloxy-ribose derivative **1a** and its 1β-epimer **1b** on treatment with the systems (diacetoxy)iodobenzene (DIB)- or [PhIO]-iodine (Scheme 2).

When the substrate **1a** was treated with DIB-iodine in dichloromethane (Table 1, entry 1), lactone **2**[8] was obtained in 26% yield, along with the diacyloxy derivative **3a** (35% yield).[9] Using acetonitrile as a solvent (entry 2), the major product was the lactone **2** (53%), and a new product was formed, the 4-amido-1-pivaloyl-

Keywords: alkoxyl radical; fragmentation; carbohydrates; diastereoselective synthesis; alditols; cyclic ethers.

* Corresponding author. Fax: 34-922-260135; e-mail: rhernandez@ipna.csic.es

0040-4039/02/$ - see front matter
PII: S0040-4039(02)00123-5



Scheme 2. β-Fragmentation versus hydrogen abstraction processes.

oxyfuranose **3b** (17%).[10] Changing the reagent to PhIO-iodine (entry 3) in acetonitrile, the yield of the amido derivative **3b** was doubled (30%), but the lactone **2** still predominated (54%). In all the cases, only the 4β-isomers **3a** and **3b** were produced.

A plausible mechanism for the formation of these products is shown in Scheme 2. Under treatment with DIB-(or PhIO)-iodine, the alkoxyl radical (Va) was formed, which can evolve in two ways: [1,5]-hydrogen abstraction from C_1 (path a) or the β-fragmentation of the C_4–C_5 bond, giving formaldehyde (path b). The hydrogen abstraction process is favoured here since the C_1–H lies at an appropriate distance (2.3–2.8 Å);[7,11] besides, the resulting radical (VI) is stabilized by the two oxygenated functions at the α-position. The radical (VI) is oxidized afterwards to an oxycarbenium ion (VII)[6,12] by excess reagent, yielding the lactone **2**.

On the other hand, the β-fragmentation process yields a radical intermediate (VIII) which is oxidized to an oxycarbenium ion (IX), which can then be trapped by different nucleophiles: an acetoxy ion from DIB, to yield the 4-acetoxyderivative **3a**, or acetonitrile in a Ritter-type reaction,[13] to give the amido derivative **3b**.

In contrast, when the 1β-pivaloyloxy precursor **1b** was treated with DIB-iodine in dichloromethane (entry 4), no lactone **2** was obtained. The major product was the diacyloxy derivative **4a** (42%) as a separable mixture of the 4β and 4α isomers (4β:4α, 3:1). When the reaction was run in acetonitrile (entry 5), the yield of **4a** decreased (8%), and a new product, the 4-amido-1-pivaloyloxy derivative **4b**, was the major one (60%, separable mixture 4β:4α, 5:1). Rewardingly, when the fragmentation was carried out with PhIO-iodine in acetonitrile (entry 6), the yield of the amidoderivative **4b** was increased (81%, 4β:4α, 5:1).

It is clear that in the case of intermediate (Vb) the distance between the alkoxyl radical and the C_1–H is not appropriate for the hydrogen abstraction process, and this intermediate evolves by β-fragmentation to give the 4-acetyloxy or the 4-amido derivatives **4a** and **4b**, respectively.

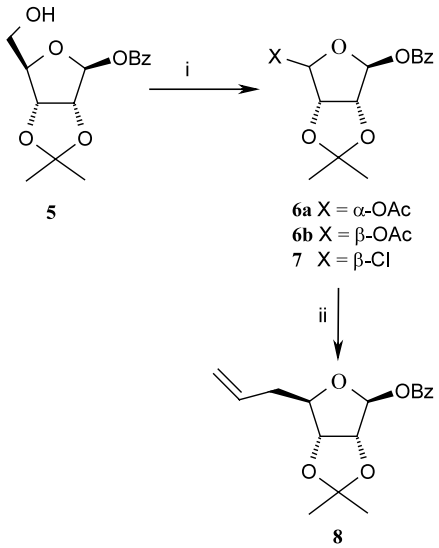
The synthesis of the 1-acyloxy-4-chloro furanoses (II, X = Cl, Scheme 1) was then studied. The 1β-benzoyloxy derivative **5** (Scheme 3) was formed in high yield and

Table 1. Fragmentation of alkoxyl radicals versus hydrogen abstraction in carbohydrates[a]

Entry	Substrate	Reagents	Solvent	Products (yield %, d.r.)[b]
1	**1a**	DIB	CH_2Cl_2	**2** (26), **3a** (35)
2	**1a**	DIB	MeCN	**2** (53), **3a** (7), **3b** (17)
3	**1a**	PhIO	MeCN	**2** (54), **3b** (30)
4	**1b**	DIB	CH_2Cl_2	**4a** (42, 4β:4α, 3:1)
5	**1b**	DIB	MeCN	**4a** (8, 4β:4α, 3:1), **4b** (60, 4β:4α, 5:1)
6	**1b**	PhIO	MeCN	**4b** (81, 4β:4:α, 5:1)

[a] All reactions were performed with DIB or PhIO (2 equiv.) and iodine (1 equiv.) in dry solvents (10 mL per mmol of substrate) under nitrogen at rt, using irradiation with two 80 W tungsten filament lamps for 1 h. Then the reaction mixture was poured into 10% aqueous $Na_2S_2O_3$ and extracted with CH_2Cl_2.

[b] Yields are given for products purified by chromatography on silica gel.



Scheme 3. (i) DIB (2.0 equiv.), ICl (1.0 equiv.), CH_2Cl_2, hv, rt, **6a** (10%), **6b** (11%), **7** (53%); (ii) chloroderivative **7**, $Bu_3SnCH_2CH{=}CH_2$, AIBN, PhH, reflux, 82%.

Table 2. Synthesis of the 1-benzoyloxy-4-chloro furanose **7**[a]

Entry	Reagents (equiv.)	Products (%)[b]
1	DIB (2.0), I_2 (1.0)	**6a** (15), **6b** (33)
2	DIB (2.0), I_2 (1.0), *n*-Bu_4NCl (5.0)	**6a** (16), **6b** (20), **7** (7)
3	$PhICl_2$ (2.0), I_2 (1.0)	Complex mixture
4	DIB (2.0), ICI (1.0)	**6a** (10), **6b** (11), **7** (53)
5	PhIO (2.0), ICl (1.0)	Complex mixture[c]
6	$PhICl_2$ (2.0), ICl (1.0)	Complex mixture

[a] All the reactions were run in dichloromethane, under irradiation of two 80 W tungsten filament lamps for 1 h, at rt.

[b] Yields are given for products purified by chromatography on silica gel.

[c] The reaction with PhIO was very slow, due to the low solubility of the reagent in CH_2Cl_2, and gave a complex mixture.

stereoselectivity from ribose, and then was treated with DIB or dichloroiodobenzene ($PhICl_2$) and iodine under the conditions listed in Table 2. In all the cases, the reaction was carried out in dichloromethane to avoid the Ritter reaction. The best conditions were obtained when the substrate **5** was treated with DIB and iodine monochloride (ICl) at room temperature (entry 4). A small amount of the two acetates **6a** and **6b**[14] was isolated, but the major product was the desired chloroderivative **7** (53%).[14] The regioselective introduction of a lateral chain at the C_4 position by a radical reaction was attempted next. To our pleasure, when compound **7** was treated with allyltributyltin and catalytic AIBN in benzene, the corresponding allylderivative **8**[14] was obtained exclusively, in 82% yield.

In summary, we have shown the usefulness of the β-fragmentation of primary alkoxyl radicals derived from carbohydrates to synthesize unsymmetrical α,ω-diacyloxy, α-acyloxy-ω-amido and α-acyloxy-ω-chloro aldoses. The α-acyloxy-ω-chloro derivatives are particularly versatile building blocks, which allow the regioselective introduction of lateral chains in the ω-position by a radical reaction. Other substituents could be incorporated afterwards in the α-position by an ionic reaction, according to known procedures.[4] The use of readily available carbohydrates as starting materials would allow the introduction of many functional groups with different stereochemistries onto the ring. The application of this methodology to the synthesis of natural products is underway and will be reported in due course.

Acknowledgements

This work was supported by the Investigation Programmes PB96-1461 and PPQ2000-0728 of the Plan Nacional de Investigación Científica, Desarrollo e Innovación Tecnológica, Dirección General de Investigación, Ministerio de Ciencia y Tecnología, Spain.

References

1. (a) Mann, J. *Nat. Prod. Rep.* **2001**, *18*, 417–430; (b) Faulkner, D. J. *Nat. Prod. Rep.* **2001**, *18*, 1–49; (c) Faulkner, D. J. *Nat. Prod. Rep.* **2000**, *17*, 1–6; (d) Fernández, J. J.; Souto, M. L.; Norte, M. *Nat. Prod. Rep.* **2000**, *17*, 235–246; (e) Murata, M.; Yasumoto, T. *Nat. Prod. Rep.* **2000**, *17*, 293–314; (f) Figadère, B. *Acc. Chem. Res.* **1995**, *28*, 359–365; (g) Hoppe, R.; Scharf, H. D. *Synthesis* **1995**, 1447–1464; (h) Mori, K. *Tetrahedron* **1989**, *45*, 3233–3298.
2. (a) Nicolaou, K. C.; Mitchell, H. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1576–1624; (b) Harmange, J. C.; Figadère, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1711–1754.
3. Keck, G. E.; Yates, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 5831–5833.
4. For a review, see: Schmidt, R. R. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 6, pp. 33–64; (b) for a recent work, see: Pilli, R. A.; Riatto, V. B. *Tetrahedron: Asymmetry* **2000**, *11*, 3675–3686 and references cited therein.
5. (a) Giese, B.; Linker, T. *Synthesis* **1992**, 46–48; (b) Ferrier, R. J.; Tyler, P. C. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2767–2773.
6. For recent reviews on organohypervalent iodine compounds in radical reactions, see: Togo, H.; Katohgi, M. *Synlett* **2001**, 565–581 and references cited therein.
7. For a comprehensive review on the reactivity of alkoxyl radicals, see: Brun, P.; Waegell, B. In *Reactive Intermediates*; Abramovitch, R. A., Ed.; Plenum Press: New York, 1983; Vol. 3, pp. 367–426.
8. Csuk, R.; Kühn, M.; Schöhl, D. *Tetrahedron* **1997**, *53*, 1311–1322.
9. For a previous work from our group where acyloxyaldoses were formed from uronic acids, see: Francisco, C. G.; González, C. C.; Suárez, E. *Tetrahedron*

Lett. **1997**, *38*, 4141–4144. The purification of the acid precursors was difficult in some cases. In contrast, our substrates are readily synthesized and easily purified.
10. For the sake of clarity, the aldose numbering is retained in the obtained products.
11. (a) Majetich, G.; Wheless, K. *Tetrahedron* **1995**, *51*, 7095–7129 and references cited therein; (b) Francisco, C. G.; Herrera, A. J.; Suárez, E. *Tetrahedron Lett*. **2000**, *41*, 7869–7873.
12. Boto, A.; Hernández, R.; Suárez, E. *Tetrahedron Lett*. **2001**, *42*, 9167–9170 and references cited therein.
13. (a) Bishop, R. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 6, pp. 261–300; (b) Kita, Y.; Shibata, N.; Kawano, N.; Yoshida, N.; Matsumoto, K.; Takebe, Y. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2321–2329.
14. All new compounds were fully characterised by ^{1}H and ^{13}C NMR, IR, MS, HRMS and elemental analysis. The stereochemistry was assigned by ^{1}H and 2D COSY–NOESY NMR. Selected spectroscopic data (IR, ^{1}H NMR, MS and elemental analysis) for compounds **6–8** are given. Compound **6a**: amorphous; IR 1733, 1602, 1585 cm^{-1}; ^{1}H NMR (500 MHz) 1.40 (3H, s), 1.57 (3H, s), 2.17 (3H, s), 4.86 (1H, d, $J=5.8$ Hz), 5.04 (1H, dd, $J=5.4$, 4.5 Hz), 6.26 (1H, d, $J=4.0$ Hz), 6.49 (1H, s), 7.45 (2H, dd, $J=7.9$, 7.6 Hz), 7.60 (1H, dd, $J=7.6$, 7.3 Hz), 8.01 (2H, d, $J=8.0$ Hz); MS (EI) m/z (rel. intensity) 307 (M^{+}–Me, 5), 217 (3), 105 (100), 77 (13). Anal. calcd for $C_{16}H_{18}O_7$: C, 59.62; H, 5.63. Found: C, 59.54; H, 5.42%. Compound **6b**: IR 1735, 1602, 1585 cm^{-1}; ^{1}H NMR (500 MHz) 1.36 (3H, s), 1.53 (3H, s), 1.98 (3H, s), 4.87 (1H, d, $J=5.7$ Hz), 4.94 (1H, d, $J=5.7$ Hz), 6.37 (1H, s), 6.56 (1H, s), 7.46 (2H, dd, $J=7.9$, 7.8 Hz), 7.60 (1H, dd, $J=7.5$, 7.4 Hz), 8.04 (2H, d, $J=8.4$ Hz); MS (EI) m/z (rel. intensity) 307 (M^{+}–Me, 42), 105 (100), 77 (72). Anal. calcd for $C_{16}H_{18}O_7$: C, 59.62; H, 5.63. Found: C, 59.76; H, 5.44%. Compound **7**: IR 1732, 1602, 1585 cm^{-1}; ^{1}H NMR (500 MHz) 1.37 (3H, s), 1.51 (3H, s), 5.04 (1H, d, $J=5.6$ Hz), 5.14 (1H, d, $J=5.6$ Hz), 6.15 (1H, s), 6.60 (1H, s), 7.46 (2H, dd, $J=7.9$, 7.7 Hz), 7.60 (1H, dd, $J=7.5$, 7.3 Hz), 8.08 (2H, d, $J=7.3$ Hz); MS (EI) m/z (rel. intensity) 285/283 (M^{+}–Me, 3.29/10.46), 105 (100). Anal. calcd for $C_{14}H_{15}ClO_5$: C, 56.29; H, 5.06. Found: C, 56.35; H, 5.12%. Compound **8**: IR 3066, 1725, 1643, 1602, 1584 cm^{-1}; ^{1}H NMR (500 MHz) 1.35 (3H, s), 1.53 (3H, s), 2.34 (1H, ddd, $J=15.4$, 8.0, 7.7 Hz), 2.48 (1H, ddd, $J=14.1$, 7.2, 6.4 Hz), 4.41 (1H, dd, $J=7.8$, 7.8 Hz), 4.70 (1H, d, $J=5.8$ Hz), 4.90 (1H, d, $J=5.9$ Hz), 5.07 (1H, dd, $J=17.0$, 1.5 Hz), 5.09 (1H, dd, $J=9.1$, 1.4 Hz), 5.79 (1H, dddd, $J=17.1$, 10.4, 7.0, 6.6 Hz), 6.45 (1H, s), 7.45 (2H, dd, $J=7.9$, 7.7 Hz), 7.58 (1H, dd, $J=7.4$, 7.4 Hz), 8.01 (2H, d, $J=7.1$ Hz); MS (EI) m/z (rel. intensity) 289 (M^{+}–Me, 5), 105 (100). Anal. calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 66.89; H, 6.80%.