Tetrahedron Letters 51 (2010) 105–108

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Indium-mediated Reformatsky reaction on lactones: preparation of 2-deoxy-2,2′-dimethyl-3-ulosonic acids

Raquel G. Soengas *

Departamento de Química Fundamental, Universidade de A Coruña, 15031 A Coruña, Spain

ARTICLE INFO

Article history:
Received 15 September 2009
Revised 16 October 2009
Accepted 19 October 2009
Available online 23 October 2009

Keywords:
Indium
Reformatsky reaction
Sugar lactones
Ulosonic acids

ABSTRACT

Indium-mediated Reformatsky reactions of simple lactones and aldonolactones with ethyl α-bromoisobutyrate allow the synthesis of the corresponding ketals and ulosonic acid esters, respectively, in good yields.

Carbohydrates have been widely used as starting materials for the synthesis of important small biological molecules and for new biopolymeric materials. In particular, sugar lactones provide short syntheses of novel nucleosides,[1] imino sugars[2] and sugar-derived amino acids.[3] All these targets have unbranched carbon chains, but recent results have indicated that all three classes of such carbon-branched materials give rise to promising biologically active compounds and novel biopolymers. In particular, alkyl-branched sugars could be of great biological interest because the presence of a highly lipophilic region in their sugar skeleton could modify the binding to certain enzymes and thus alter their biological activity.

Some previous work on the Reformatsky reaction of simple and sugar lactones has been reported.[4] However, these reactions proved to be experimentally complex, were subjected to functional group incompatibilites and in some cases only low yields and low regio- and/or stereoselectivity levels were achieved. On the other hand, it has been reported that indium[5] efficiently promotes Reformatsky reactions on aldehydes and ketones.[6] Moreover, it is well known that indium can promote C–C formation reactions in substrates with free hydroxyl groups aqueous media and is therefore a suitable reagent in synthetic carbohydrate chemistry because it avoids the tedious processes required for protection of hydroxy groups in classical carbohydrate chemistry, thus simplifying synthetic applications of carbohydrates that involve organometallic reagents.[7]

As a contribution to this field, we report here preliminary results on a highly efficient indium-mediated Reformatsky reaction between aldonolactones and ethyl α-bromoisobutyrate. This reagent was selected with the aim to open novel opportunities for the access to branched-chain sugars, a class of carbohydrates of great current interest.

We first studied the case of commercially available five-membered lactone **2**. Sonication of mixtures of this compound, indium powder[8] and ethyl α-bromoisobutyrate in DMF and in THF (Table 1) at room temperature for 6 h allowed the racemic mixture of compound **6** to be obtained in 90% and 95% yield, respectively.[9] But when MeOH/H_2O 1:4 and THF/H_2O 1:1 were the solvents, the starting material remained practically unaltered after 12 h (Scheme 1).

Further similar studies with commercially available four-, six- and seven-membered lactones **1**, **3** and **4** (Table 1) carried out in THF for experimental simplicity provided the expected racemic adducts **5** (88% yield), **7** (82% yield) and **8** (92% yield), respectively.

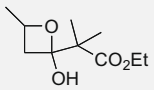
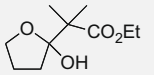
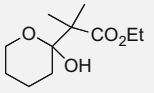
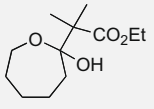
Good to excellent results were achieved and of particular interest is the 88% yield obtained for compound **1** (entry 1), because to date only cuprates[10] and samarium enolates[4c] have allowed four-membered lactone **1** to be transformed into adduct **5** and even then only in moderate and low yields, respectively.

Encouraged by these excellent results we decided to extend the study to the five- and six-membered sugar lactones **9**[11], **10**[12], **11**, **12**[13], **13**[14] and **14**[15], which provided the expected adducts **15**–**20**, respectively, in moderate to good yield (see Table 2) (Scheme 2).

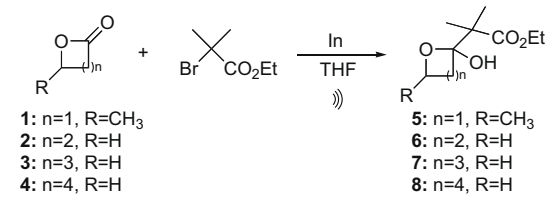
* Tel.: +34 981167000x2207.
E-mail address: rsoengas@udc.es

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.10.092

Table 1
Indium-mediated Reformatsky-type reaction between simple lactones and ethyl α-bromoisobutyrate

Entry	Lactone	Reaction with $BrC(CH)_2CO_2Et$[a]	Yield[b] (%)
1	 **1**	 **5**	88
2	 **2**	 **6**	95
3	 **3**	 **7**	82
4	 **4**	 **8**	92

[a] All reactions conducted according to Ref. 9.
[b] Yields of isolated products.

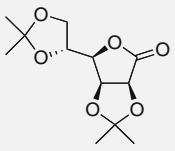
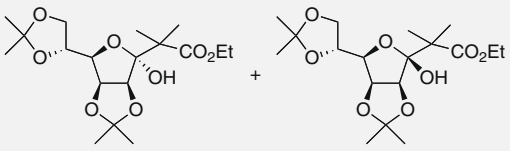
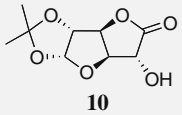
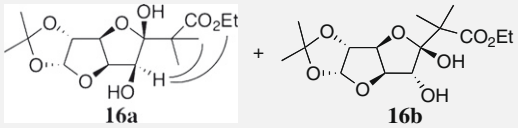
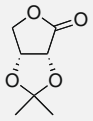
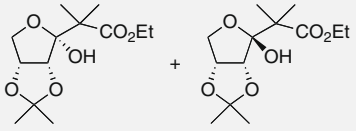
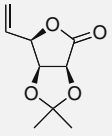
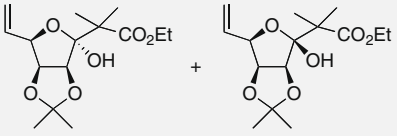
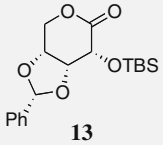
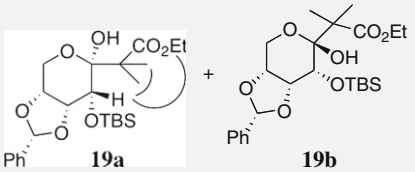
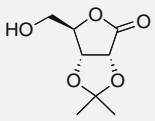
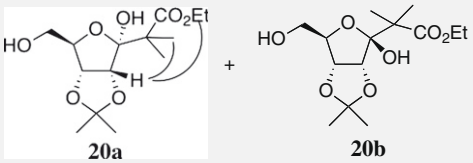


Scheme 1. Reaction of simple lactones and ethyl α-bromoisobutyrate.

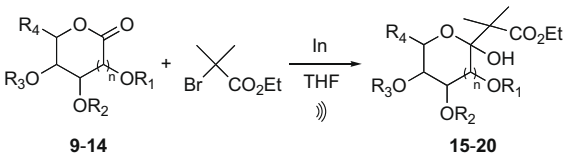
The indium-mediated procedure described here has some clear advantages over previous Reformatsky additions to sugar lactones. For example, as shown in entries 6 and 10, the reaction can be carried out on lactones bearing free hydroxyl groups. Moreover, probably due to the ability of SmI_2 to promote deoxygenation at the C-2 position of sugar lactones,[16] the previously reported SmI_2-mediated Reformatsky reactions on aldonolactones were mostly carried out on 2-deoxygenated substrates. However, our indium procedure overcomes this limitation as it is compatible with the presence of hydroxy and alkoxy substituents at position C-2 of sugar lactones.

Another interesting feature of the indium-mediated procedure is the remarkable chemoselectivity and the mild conditions required. In fact, ethyl isobutyrate readily added to the lactone car-

Table 2
Indium-mediated Reformatsky-type reaction between sugar lactones and ethyl α-bromoisoburyrate

Entry	Lactone	Reaction with $BrC(CH)_2CO_2Et$[a]	Yield[b] (%)	Ratio α:β[c]
5	 **9**	 **15a** **15b**	87	80:20
6	 **10**	 **16a** **16b**	62	100:0
7	 **11**	 **17a** **17b**	78	60:40
8	 **12**	 **18a** **18b**	62	85:15
9	 **13**	 **19a** **19b**	52	100:0
10	 **14**	 **20a** **20b**	72	85:15

[a] All reactions conducted according to Ref. 9.
[b] Yields of isolated products.
[c] Determined by NMR.



Scheme 2. Reaction of aldonolactones and ethyl α-bromoisobutyrate.

bonyl group while other functional groups such as alkenes (entry 8) and acid-sensitive protecting groups like isopropylidene (entries 5–8 and 10), benzylidene ketals (entry 9) and silyl esters (entry 9) remained unaltered.

As far as the selectivity is concerned, excellent results were achieved for lactones **10** and **13** (entries 6 and 9), which gave their respective adducts **16a** and **19a** only, as established by NMR experiments.[17] Lactone **14** (entry 10) gave the anomeric mixture **20a** + **20b**, in which the major component was the thermodynamically favoured anomer **20a**, as determined by NMR experiments.[18] Lactones **9**, **11** and **12** (entries 5, 7 and 8) provided the anomeric mixtures **15a** + **15b**, **17a** + **17b** and **18a** + **19b**, respectively. We assumed that in these cases the major anomers were also the thermodynamically favoured anomers **15a**, **17a** and **18a**. These results are consistent with previous studies on the mechanism of Reformatsky reactions on aldonolactones, which showed that the predominant anomer is always the thermodynamically more stable anomer.[4a,c,e,f] This finding is due either to the substituents at position C-2 acting as directing groups during the addition or to subsequent anomerization to the thermodynamically more stable anomer.

In summary, we have developed a new method for the homologation of lactones. This approach consists of an indium-mediated Reformatsky reaction of aldonolactones with α-bromoisobutyrate. The preliminary results reported here suggest that the process is simpler than previous procedures, which require special reagents, inert conditions and high temperatures. In fact, the milder chemoselective conditions reported here allowed several 2-deoxy-2,2′-dimethyl-3-ulosonates to be obtained with remarkably high levels of stereoselectivity.

These novel branched-chain sugars constitute a new family of ulosonic acids, which are important carbohydrate constituents of cellular and bacterial membranes and are involved in several biological functions.[19] Hence, the 3-ulosonic acid analogues reported should be of interest not only as synthetic intermediates for the preparation of a wide range of branched carbohydrate derivatives but also as potential inhibitors in the biosynthesis of membrane lipopolysaccharides in bacteria.

Evaluation of the biological activity of the unprotected adducts **15**–**20** is currently in progress.

Work is also in progress aimed at extending this promising indium-mediated Reformatsky reaction to other bromoesters. The aim of these studies is to gain access to a pannel of lactone-adducts to be converted into biologically active branched-chain imino sugars and novel biopolymers based on branched-chain heterocyclic amino acids.

Acknowledgments

Financial support from the Spanish Ministry of Science and Innovation (CTQ2008-06493) and the Xunta de Galicia (Isidro Parga Pondal program) is gratefully acknowledged. I would like to thank Professors R. J. Estévez, J. C. Estévez and L. Sarandeses for helpful discussions.

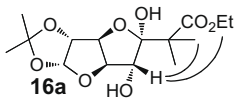
Supplementary data

Supplementary data (specific experimental procedures and ^{1}H and ^{13}C NMR spectra for **16a**, **19a** and **20a + 20b**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.092.

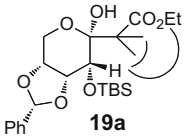
References and notes

1. Watterson, M. P.; Edwards, A. A.; Leach, J. A.; Smith, M. D.; Ichihara, O.; Fleet, G. W. J. *Tetrahedron Lett.* **2003**, *44*, 5853–5857.
2. Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680.
3. Long, D. D.; Smith, M. D.; Martin, A.; Wheatley, J. R.; Watkin, D. G.; Muller, M.; Fleet, G. W. J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1982–1998.
4. (a) Csuk, R.; Glänzer, B. I. *J. Carbohydr. Chem.* **1990**, *9*, 797–807; (b) Grassberger, V.; Berger, A.; Dax, K.; Fechter, M.; Gradnig, G.; Stütz, A. E. *Liebigs Ann. Chem.* **1993**, 379–390; (c) Hanessian, S.; Giraud, C. *Synlett* **1994**, 865–867; (d) Orsini, F.; di Teodoro, E. *Tetrahedron: Asymmetry* **2003**, *14*, 2521–2528; (e) Csuk, R.; Franke, U.; Hu, Z.; Krieger, C. *Tetrahedron* **2003**, *59*, 7887–7895; (f) Cuenca, A. B.; D'Hooge, F.; Gouge, V.; Castelot-Deliencourt, G.; Oulyadi, H.; Leclerc, E.; Jubault, P.; Pannecoucke, X.; Quirion, J.-C. *Synlett* **2005**, *17*, 2627–2630.
5. Araki, S.; Ito, H.; Katsumura, N.; Butsugan, Y. *J. Organomet. Chem.* **1989**, *369*, 291–296.
6. (a) Cintas, P. *Synlett* **1995**, 1087–1096; (b) Podlech, J.; Maier, T. C. *Synthesis* **2003**, 633; (c) Nair, V.; Ros, R.; Jayan, C. N.; Pillai, B. *Tetrahedron* **2004**, *60*, 1959–1982; (d) Babu, S. A.; Yasuda, M.; Shibata, I.; Baba, A. *J. Org. Chem.* **2005**, *70*, 10408–10419.
7. (a) Kim, E.; Gordon, D. M.; Schmid, W.; Whitesides, G. M. *J. Org. Chem.* **1993**, *58*, 5500–5507; (b) Chan, T. H.; Isaac, M. B. *Pure Appl. Chem.* **1996**, *68*, 919–924; (c) Canac, Y.; Levoirier, E.; Lubineau, A. *J. Org. Chem.* **2001**, *66*, 3206–3210; (d) Levoirier, E.; Canac, Y.; Norsikian, S.; Lubineau, A. *Carbohydr. Res.* **2004**, *339*, 2737–2747; (e) Balla, E.; Zamyatina, A.; Hofinger, A.; Kosma, P. *Carbohydr. Res.* **2007**, *342*, 2537–2545; (f) Alcaide, B.; Almendros, P.; Rodríguez-Acebes, R. *J. Org. Chem.* **2002**, *67*, 1925–1928; (g) Chan, t.; Hang, L.; Chao, J. *J. Chem. Soc., Chem. Commun.* **1992**, 747–748.
8. *Typical procedure:* To a suspension of indium powder (0.5 mmol) and ethyl α-bromobutyrate (0.75 mmol) in THF (1 mL) was added the corresponding lactone (0.5 mmol) and the mixture was sonicated for 6 h. The reaction mixture was quenched with saturated aqueous sodium hydrogen carbonate (10 mL) and extracted with ether (3 × 25 mL). The combined organic layers were dried over magnesium sulphate, filtered and evaporated in vacuo. The residue was purified by flash column chromatography in mixtures of ethyl acetate/hexane to obtain the compounds shown in Tables 1 and 2. All the compounds were fully characterized and gave correct high resolution mass spectra. Representative example: ethyl 5,8-anhydro-2-deoxy-4,5:7,8-di-*O*-isopropyliden-2,2-dimethyl-α,β-D-gluco-3,6-furanoso-3-octulosonate: purification of the crude material by flash column chromatography (ethyl acetate/hexane 1:2) afforded a single anomer (**16a**) (0.10 g, 62%) as a clear oil. $[\alpha]_D^{29}$ −6.2 (*c* 1.2 in $CHCl_3$). ^{1}H NMR ($CDCl_3$, ppm): 1.26 (t, 3H, *J* = 4.3 Hz, $-OCH_2CH_3$); 1.25, 1.29, 1.31 (3 × s, 12H, 4 × CH_3); 3.33 (d, 1H, –OH); 4.17 (dd, 2H, *J* = 4.3 Hz, $-OCH_2CH_3$); 4.51 (d, 1H, *J* = 2.9 Hz, H-5); 4.65 (d, 1H, *J* = 2.1 Hz, H-7); 4.79–4.81 (m, 1H, H-6); 5.38 (s, 1H, H-4); 6.03 (d, 1H, *J* = 2.1 Hz, H-8). ^{13}C NMR ($CDCl_3$, ppm): 14.11 ($-OCH_2CH_3$); 20.05, 22.03, 27.22, 27.69 (4 × CH_3); 48.55, 49.65 (C-2); 61.71 ($-OCH_2CH_3$); 72.49, 81.80, 83.22, 86.70 (C-4, C-5, C-6, C-7); 105.36 (C-3), 107.37 (C-8), 113.19 ($-C(CH_3)_2$); 177.84 (C=O). MS (ESI, *m*/*z* %): 239.13 (24, $[M+Na]^+$); 199.13 (54, $[M-H_2O+H]^+$). HRMS for $C_{11}H_{20}O_4Na$ ($[M+Na]^+$) calculated 239.1253. Found: 239.1250.
9. Similarly to previous studies on indium-mediated Reformatsky reactions, it is reasonable to postulate that the ulosonic acids are formed by nucleophilic addition of indium sesquihalide $(EtO_2C(CH_3)_2C)_3In_2Br_3$ to the lactone. Tussa, L.; Lebreton, C.; Mosset, P. *Chem Eur. J.* **1997**, *3*, 1064–1070.
10. Pommier, A.; Pons, J.-M. *Synthesis* **1993**, 441–459.
11. Luzzio, F. A.. In *The Oxidation of Alcohols by Modified Oxochromium(IV)-Amine Reagents, Organic Reactions*; Hoboken: N.J., United States, 1998; Vol. 53.
12. Bayshal, B. P.; Hak Fun, C.; Fellows, L. E.; Fleet, G. W. J. *Tetrahedron* **1987**, *43*, 415–422.
13. Banda, G.; Chakravarthy, I. E. *Tetrahedron: Asymm.* **2006**, *17*, 1684–1687.
14. Lefeber, D. J.; Steunenberg, P.; Vliengenthart, J. F. G.; Kamerling, J. P. *Tetrahedron: Asymmetry* **2005**, *16*, 507–511.
15. Obtained from selective deprotection of the primary hydroxyl group by treatment with PPTS in EtOH at 50 °C of the corresponding 5-*O*-(1-methoxy-1-methyl-ethoxymetyl) derivative, prepared as described in the literature: Hanessian, S.; Stephane, M.; Machaalani, R.; Huang, G.; Pierron, J.; Loiseleur, O. *Tetrahedron* **2006**, *62*, 5201–5214.
16. (a) Chiara, J. L.; Cabri, W.; Hanessian, S. *Tetrahedron. Lett.* **1991**, *32*, 1125–1128; (b) Hanessian, S.; Girard, C.; Chiara, J. L. *Tetrahedron. Lett.* **1992**, *33*, 573–576; (c) Girard, C.; Hanessian, S. *Synlett* **1994**, 861–862; (d) Girard, C.; Hanessian, S. *Synlett* **1994**, 863–864.

17. *Compound* **16a**: NOE between H-4 and the CH_3 in C-2 and between H-4 and the ethyl group. *Compound* **19a**: NOE between H-4/H-5 and the CH_3 in C-2 and between H-4/H-5 and the ethyl group.

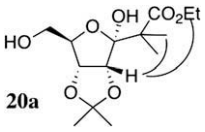


16a



19a

18. *Compound* **20a**: NOE between H-4 and the CH_3 in C-2 and between H-4 and the ethyl group.



20a

19. (a) Ogura, H.; Hosegawa, A.; Suami, T. *Carbohydrates, Synthetic Methods and Applications in Medicinal Chemistry*; VCH: Cambridge, Basel, 1992; (b) Unger, F. M. *Adv. Carbohydr. Chem. Biochem.* **1981**, *38*, 323–388; (c) Schauer, R. *Adv. Carbohydr. Chem. Biochem.* **1982**, *40*, 131–234.