Pergamon

Tetrahedron Letters, Vol. 38, No. 46, pp. 8081-8084, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10114-9

Stereoselective Radical C-C Bond Forming using Suarez' Protocol: A Non Reductive Process.

Pedro de Armas,*,‡ Fernando García-Tellado,*,‡ José J. Marrero-Tellado,§ Juana Robles‡.

‡Instituto de Productos Naturales y Agrobiología, Consejo Superior de Investigaciones Científicas. §Instituto Universitario de Bioorgánica "Antonio González" Universidad de La Laguna. Astrofísico Francisco Sánchez 3, 38206 La Laguna, Tenerife, Spain.

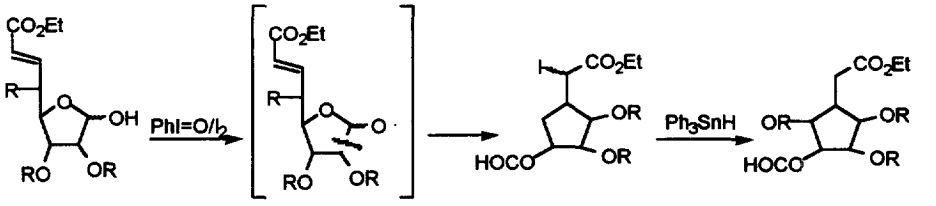
Abstract: Suarez β-fragmentation of carbohydrate lactols induces C-C bond forming, by a non reductive process This tandem β-fragmentation-cyclization reaction of carbohydrate lactol derivatives **1,2,5** produces stereoselective carbocycles **2,4,6** in moderate yield. © 1997 Elsevier Science Ltd.

Radical reactions are now employed routinely by synthetic organic chemists[1]. Special interest has been devoted to the synthesis of carbocycles from carbohydrates.[2]

Most of these reactions are based on tin hydride chemistry. One of the limitations of synthetic sequences based on free radical carbon-carbon bond-forming reactions is that they are generally terminated by hydrogen atom transfer.[3] This means that the cyclization step has to be fast in order to compete with premature hydrogen abstraction. In practice, this can be solved using high dilution conditions or by adding the tin hydride very slowly, to keep its concentration low. Another approach uses less efficient hydrogen donor reagents such as germanium hydride.[3b,c] or tris(trimethylsilyl)silane.[4] Recently Zard[5] and co-workers reported novel radical-chain reactions based on o-alkyltin dithiocarbonates as reagents which eliminate these problems.

We describe here a preliminary result of a different approach to the synthesis of carbocycles via radical chemistry that circumvent these limitations, as illustrated in Scheme1.

Scheme 1



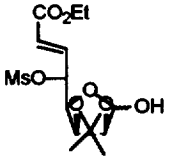
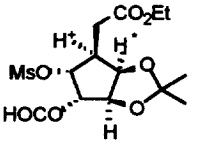
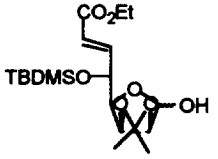
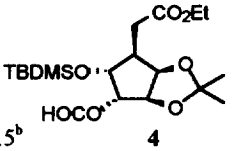
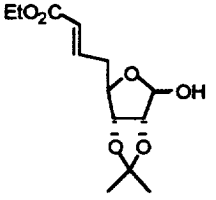
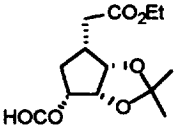
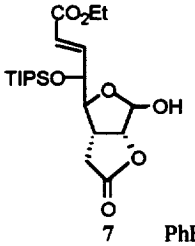
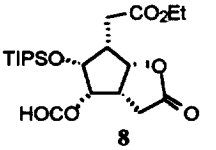
1 **2** **3**

Thus, the carbohydrate lactol derivative 1 undergoes (i) β-fragmentation[6] of the anomeric alkoxy radical generated with hypervalent iodine reagent / I_2 system and (ii) intramolecular trapping of the C2 radical generated in the fragmentation step with a suitably unsaturated ester containing side-chains to give the cyclic iodine **2**.[7] Reduction of the mixture of cyclic iodines provides the cyclopentane derivatives **3**.

The carbohydrate derivatives were treated with iodosylbenzene and iodine in benzene under the conditions specified in Table 1.[8]

As we illustrate this new carbon-carbon bond-forming process generates five membered rings in moderate yield (entry1,4 and 5). However, the cyclization failed with lactone 7 giving several unstable compounds and only traces of the cyclic product. The reaction behavior does not depend on the C2 configuration (compare entry 1 with 5).

Table 1

Entry	Substrate	Solvent	PhIO (mmol)	I_2 (mmol)	Time (h)	Products	Yield (%)[a]
1	 **1**	PhH	3	1	3[b]	 **2**	40
2		PhH	3	1	5[c]		20
3		PhH	1.5	1	7[d]		11
4	 **3**	PhH	3	1	2.5[b]	 **4**	48
5	 **5**	PhH	3	1	2[b]	 **6**	42
6	 **7**	PhH	3	1	2[b]	 **8**	e

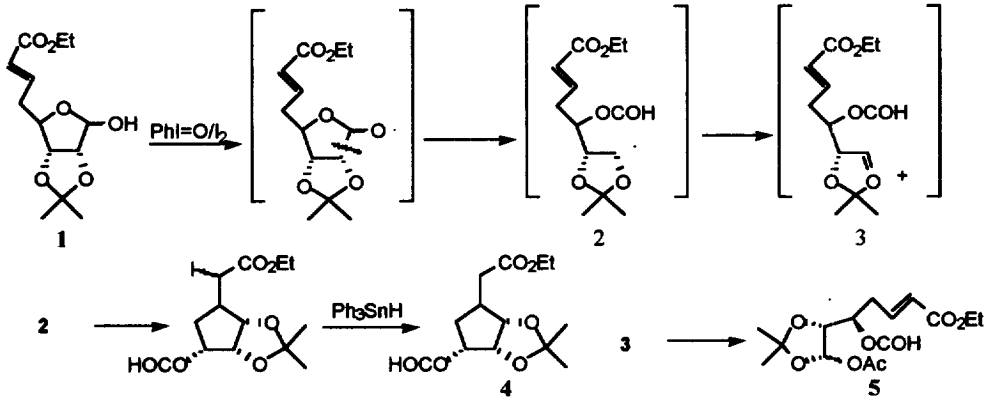
[a] after reduction with Ph_3SnH. [b] reflux. [c] 60 °C. [d] rt. [e] traces.

The stereochemical outcome of this cyclization agrees with a related rationalization embodying a chairlike transition-state model.[9] Only a cis stereoisomer was detected in each case. These isomers show a triplet

(ca 6Hz) for H*. In the case of the other isomer, examination of the model shows that this proton has a dihedral angle of ca 90° to H*.

We explain the moderated yield based on the proposed mechanism (Scheme2).

Scheme 2



On a ribofuranose derivative the C2 radical formed by β-fragmentation of the initially formed anomeric alkoxy radical, is trapped by the side chain unsaturated ester to give (after reduction with Ph_3SnH) the cyclic compound **4**. Also this highly stabilized[10] dioxanyl radical 2 can be oxidised[11] to an oxonium ion 3. If this intermediate cannot revert to the C2 radical in the same way, it will decompose under the reaction condition thus lowering the overall yield. We think that this is our case. As a result, treatment of compound **1** (Scheme2) under the conditions described[8] but in the presence of an external nucleophile (1,5 meq. AcOH or NH_4AcO) give mostly compound **5**[5a] and minor amounts of cyclic compound **4**.

In summary, we have described a new carbon-carbon bond-forming process for the preparation of highly functionalized enantiomerically pure cyclopentanes from readily accessible carbohydrates derivatives. Further studies on the synthetic utility of this method and improvement of the yield by means of less stabilized C2 radicals are in progress.

Acknowledgements. This paper is dedicated to Prof. Y. Kishi on the occasion of his 60th birthday. This work was supported by Spanish DGICYT (PB94-0028). JRC thanks ICI for a predoctoral fellowship. Also the authors thank the Department of Biosíntesis de Productos Naturales for financial support.

References and Notes

1. For leading references see: (a) Hart, D.J. *Science* **1984**, 223, 883. (b) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon: New York, 1986. (c) Curran, D.P. *Synthesis* **1988;** 417; 489. (d) Regitz, M.; Giese, B. Houben-Weyl, *Methoden der Organischen Chemie*; Georg Thieme Verlag: Sttugart, 1989. (e) Motherwell, W.B.; Crich,D. *Free Radical Chain Reactions in Organic Synthesis*; Academic: New York,1992.
2. (a) RajanBabu, T.V. *J. Am. Chem. Soc.* **1987**, 119, 609. (b) Wilcox, C.S; Thomasco, L.M. *J. Org. Chem*, **1985**, 50, 546. (c) Nugent, W.A.; RajanBabu, T.V. *J. Am. Chem. Soc.* **1988**, 110, 8561. (d) RajanBabu,

T.V.; Fukunaga, T.; Reddy, G.S. *J. Am. Soc.* **1989**, 111, 1759. (e) Wilcox, C.S. ; Gaudino, J.J. *J. Am. Soc.* **1986**, 108, 3102. (f) Rajan Babu, T.V. *J.Org. Chem.* **1988**, 53, 4522. (g) Tsang,R.; Fraser-Reid,B. *J. Am. Chem. Soc.* **1986**, 108, 2116. (h) Marco-Contelles,J.; Ruiz-Fernandez,P.; Sanchez,B. *J.Org. Chem.* **1993**, 58, 2894.

3. (a) Wayner, D.D.M.; Abey Chatgilialoglu, C.; Ingold, K.U.; Scaiano, J.C. *J. Am. Soc.* **1981**, 103, 7739. (b) Lusztyh, J.; Maillard, B.; Lindsay, D.A.; Ingold, K.U. *J. Am. Chem. Soc.* **1983**, 105, 3578. (c) Johnston, L.J.; Lusztyk, J.; Wichreyma, A.N.; Beckwith, A.L.J.; Scaiano, J.C.; Ingold, K.V. *J. Am. Chem. Soc.* **1985**, 107, 4594.
4. Chatgilialoglu, C.; Dickhaut, J.; Giese, B. *J. Org. Chem.* **1991**, 56, 6399
5. Boivin, J.; Camara, J.; Zard, Z.S. *J. Am. Chem. Soc.* **1992**, 114, 7909.
6. de Armas, P.; Francisco, C.G.; Suarez, E. Angew. Chem., Int. Ed. Engl. **1992**, 31, 772. (b) de Armas, P.; Francisco, C.G.; Suarez, E. *J. Am. Chem. Soc.* **1993**, 115, 8865. (c) de Armas, P.; Francisco, C.G.; Suarez, E. *Tetrahedron Lett.* **1993**, 34, 7331.
7. In the case of entry 1 (Table 1) the crude reaction mixture was chromatographed on silica gel, although the cyclic iodine was unstable on chromatography we obtained enough amounts to be identified.
8. The following procedure is typical for the synthesis of **2**: a solution of carbohydrate **1** (100 mg, 0.273 mmol) in dry benzene (8 ml) containing iodosylbenzene (180 mg, 0.819 mmol) and iodine (69 mg, 0.273 mmol) was desoxigenated by three cycles of freeze-pump-taw. The solution, under nitrogen, was refluxed for 3h. The reaction mixture was then poured into water and extracted with ether. The organic layer was washed with aqueous sodium thiosulfate and water. To the crude reaction mixture in benzene (3 ml) was added a spatula tip of AIBN and tri-Phenyltin hydride (0.084 ml, 0.33 mmol). This mixture was heated at reflux for 4h. Concentration and purification by flash chromatography (benzene/ethyl acetate 80:20 v/v) gave (40mg, 41%).
9. Curran, D.P.; Rakiewiez, D.M. *Tetrahedron* **1985**, 41, 3943. (b) RajanBabu, T.V.; Fukunaga, T.V; Reddy, G.S. *J. Am. Chem. Soc.* **1989**, 111, 1759.
10. Beckwith, A.L.J.; Pigou, P.E. J. Chem. Soc., Chem. Commun. **1986**, 54, 3140. (b) Curran, D.P.; Chang, C.T. *J. Org. Chem.* **1989**, 54, 3140. (c) Oumar-Mahamat, H.; Moustrou, C.; Surzur, J.M.; Bertran, M.P. *J. Org. Chem.***1989**, 54, 5684. (d) Nagashima, H.; Soki, K.; Ozaki, N.; Wakamatsu, H.; Itoh, K.; Tomo, Y.; Tsuji, J. *J. Org. Chem.* **1990**, 55, 985. (e) Kates, A.; Dombroski, M.A.; Snider, B.B. *J. Org. Chem.* **1990**, 56, 2427. (f) Curran, D.P.; Tamine, J. *J. Org. Chem.* **1991**, 56, 2746.
11. For oxidation of stabilized tertiary radical involved iodine see: ref. 10b.

(*Received in UK* 16 *July* 1997; *accepted* 12 *September* 1997)