Tetrahedron Letters,Vol.25,No.22,pp 2363-2366,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain 

# Carbon-Carbon Bond Formation Using Primary Tosylates Derived From Carbohydrates

Jean-René Pougny

Laboratoire de Biochimie Structurale, E.R.A. 739.
U.E.R. de Sciences Fondamentales et Appliquées, 45046 Orléans Cédex, France.

Summary : Primary tosylates derived from carbohydrates proved to be substrates for direct carbon-carbon bond formation. This procedure is compared to a classical three steps sequence: oxidation-Wittig reaction-hydrogenation.

Many monosaccharides and a large number of their derivatives are easily available and versatile compounds. They prove to be now an important source of chirality for the total synthesis of optically active biological products[1-4]. Carbon-carbon bond formation is frequently involved during a synthetic process and is generally conducted in a three steps sequence : oxidation of an alcohol to the corresponding aldehyde or ketone, Wittig reaction then hydrogenation of the double bond[5].

Despite its wide synthetic importance, the displacement reaction of primary tosylates by lithium dialkyl or dialkenyl cuprates is rarely used in the carbohydrate approach. The formation of new carbon-carbon $\sigma$ -bonds by the coupling of tosylates with lithium dialkylcuprates has been investigated in several laboratories[6-8] and was sometimes applied in the carbohydrate field[9]. While primary tosylates derived from aliphatic[9b] or furanoid[9a,c-e] systems reacted quite well, only one example of the reactivity of a primary tosylate derived from a **pyranoside** was described[10].

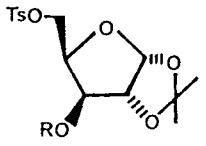
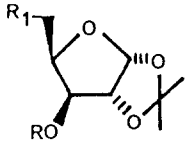
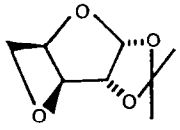
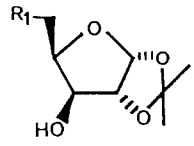
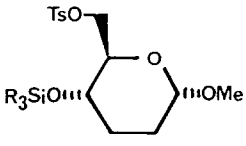
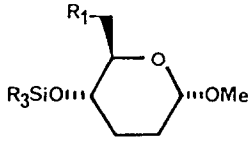
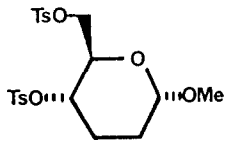
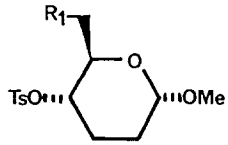
As a part of our program to develop convenient methods for the synthesis of biologically active natural products, we wish to report our results relative to the reactivity of some primary tosylates derived from carbohydrates.

As the table indicates[11], the reaction was improved towards both furanoid and pyranoid derivatives in the presence of either cuprates or Grignard reagents (10% cuprous iodide). One limitation of the reaction was the formation of the primary alcohol resulting from an attack at the sulphur of the tosylate (**entry 1**). The reaction could be conveniently applied to the oxetane **8** (**entries 4 and 5**), protection of the alcohol being assumed by the oxetane ring itself.

This methodology was applied to the 2,3-dideoxy-glycopyranosides. Protection of the secondary alcohol at C-4 could be achieved using a silyl ether protecting group (**entries 6-9**) easily removable in the next step. With the ditosylate **18** (**entry 11**), reaction occured only at the primary position.

Reactivity towards Grignard reagents in the presence of a catalytic amount of cuprous iodide is quite different. While the D-glucofuranose derivatives **4** and **6** (**entries 2 and 3**) afforded

TABLE : Carbon-carbon bond formation from primary tosylates

| Entry | Substrate | Reagent | Product | Yield[d](%) |
|---|---|---|---|---|
| |  | |  | |
| 1 | 1 R = THP | Cuprate[a](3eq) | 2 R = THP, $R_1$ = Me<br>3 R = THP, $R_1$ = OH | 47<br>40 |
| 2 | 4 R = t.BDMSi | Grignard[b](5eq) | 5 R = t.BDMSi, $R_1$ = 2E,5E-$C_7H_{11}$ | 33 |
| 3 | 6 R = H | Grignard[b](5eq) | 7 R = H, $R_1$ = 2E,5E-$C_7H_{11}$[12,13]<br>$[\alpha]_D$ -18.8 ($CHCl_3$)[12,13] | 21 |
| |  | |  | |
| 4 | 8 | Cuprate[a](3eq) | 9 $R_1$ = Me | 34 |
| 5 | | | 10 $R_1$ = n-$C_7H_{15}$ | 52 |
| |  | |  | |
| 6 | 11 R = Me | Cuprate[c] | 12 R = Me, $R_1$ = Me | 93 |
| 7 | 13 $R_3$ = t.BDPSi | Cuprate[c] | 14 $R_3$ = t.BDPSi, $R_1$ = Me | 84 |
| 8 | | Cuprate[c] | 15 $R_3$ = t.BDPSi, $R_1$ = n-Bu | 22 |
| 9 | 11 R = Me | Cuprate[c] | 16 R = Me, $R_1$ = n-Bu | 40 |
| 10 | 13 $R_3$ = t.BDPSi | Grignard[b] | 17 $R_3$ = t.BDPSi, $R_1$ = Br | 70 |
| |  | |  | |
| 11 | 18 | Cuprate[c] | 19 $R_1$ = Me | 72 |

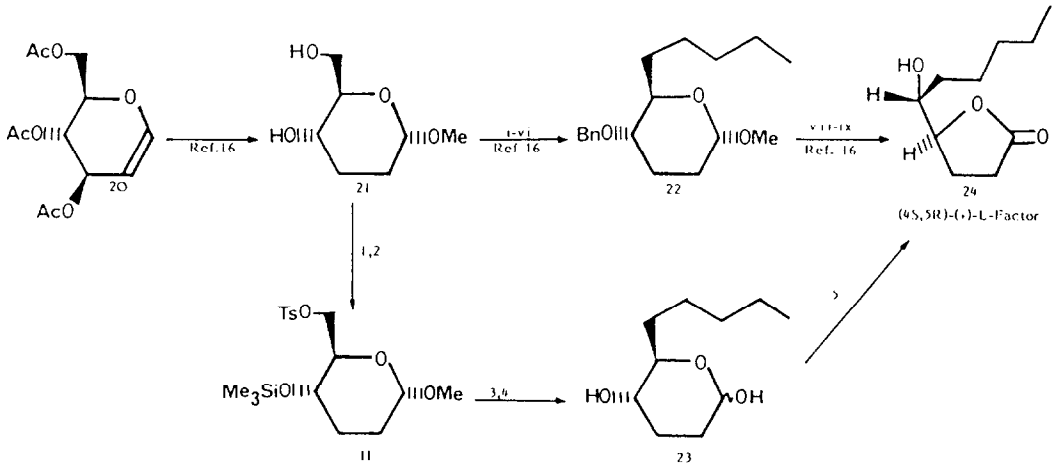
a, Reaction was carried out in dry ether at 0°C; b, Reaction was carried out in dry THF; -78°C (2hr) to RT (24hr); c, 3.5 eq of the dialkyl cuprate were prepared in dry ether (0°C), the solution was cooled to -78°C and a solution of the substrate in dry benzene was added dropwise. After 1hr at -78°C , the mixture was allowed to warm up (2hr at -5°C) and was quenched with saturated aqueous ammonium chloride solution; d, Yields obtained after work up and purification of the products.

the coupling products 5 and 7, compound 13 yielded exclusively the 6-bromo-6-deoxy derivative 17 (entry 10).

The proposed strategy may be an interesting alternative to the classical three steps procedure since primary tosylates are easily obtained as crystalline material in high purity from the corresponding alcohols. On the other hand, oxidation of the primary alcohol position of carbohydrates is generally a complex, low yield reaction. The subsequent Wittig reaction may be complicated by $\alpha,\beta$ elimination and/or epimerization at the $\alpha$ position. Hydrogenation is often inhibited by sulphur and phosphorus by products remaining from these two steps.

Our methodology was improved towards the synthesis of compound 7 (entry 3), a synthetic intermediate described by H.Ohrui[12] (11 steps sequence, overall yield : 24%) and P. Sinaÿ[13] (7 steps sequence, overall yield : 21%) during the course of the synthesis of (+)-Cerulenin from D-glucose. When Grignard reagent[14] (5eq. in dry ether) derived from 2E,5E-heptadienyl chloride was reacted with either compound 4 or 6 (1 eq. in THF solution containing a catalytic amount of cuprous iodide), this one step procedure yielded either compound 5 (33%) or 7 (21%).

According to our procedure, we propose now a modified synthesis of (4S,5R)-(+)-L-Factor, a proposed autoregulator for anthracycline biosynthesis in Streptomyces[15].




i,TBDPSiCl, Pyr., RT; ii, BnBr, KH, THF, RT; iii, n-$Bu_4N^+F^-$, THF, RT; iv, $(COCl)_2$, DMSO, $CH_2Cl_2$, -78°C (15mn) then $Et_3N$; v, $Ph_3P^+$-n-$C_4H_9Br^-$, n-BuLi, PhMe, -78°C to RT; vi, Raney Ni, MeOH; vii, AcOH-$H_2O$ (4/1), 75°C (90mn); viii, P.C.C., AcONa, 4Å M.S., $CH_2Cl_2$; ix, 10% Pd/C, MeOH.

1, 1.2 eq TsCl, Pyr; RT (65%); 2, $Me_3SiCl$, $(Me_3Si)_2NH$, Pyr., RT (100%); 3, 3.5 eq n-$Bu_2CuLi$, $Et_2O$/PBH (40%); 4, 1N aq. HCl, 2h, RT (80%); 5, $Br_2$, $H_2O$, 10hr, RT (90%).

In our first synthetis[16], L-Factor 24 was obtained in a 9 steps sequence from diol 21. On large scale preparation, steps iv to vi were hazardous (from 19 to 60% yield). Monotosylation of the diol 21 afforded the crystalline monotosylate[17] (65%) which was trimethylsilylated (100%). Carbon-carbon bond coupling occured using lithium di-n-butyl cuprate (entry 9) in 40% yield. Compound 16 was then treated with 1N HCl giving the hemiacetal 23 (80%). Finally, selective oxidation of the hemiacetal in an aqueous bromine solution[18] yielded the 6-C-(n-butyl)-2,3,6-trideoxy-D-erythro-1,4-lactone 24 (90%) identical with the (4S,5R)-(+)-L-Factor previously described[16].

**Experimental:** A typical experimental procedure follows. To a suspension of CuI (2.0g, 10.5 mM, 3.5eq) in dry ether (100 ml) was added dropwise at 0°C under argon MeLi (1.6 M in ether;

21mM, 13ml). The clear solution was cooled to -78°C and compound **11** (1.2g, 3.1mM) in dry benzene solution (30 ml) was added dropwise. After 1 hr at -78°C the mixture was allowed to warm up to -5°C and was stirred for 2 hr at this temperature. Quenching of the reaction mixture with aqueous ammonium chloride solution (50 ml) followed by work up afforded the coupling product **12** as a pure colourless oil (670mg, 93%).

**Acknowledgment:** This research was partially supported by Centre National de la Recherche Scientifique to whom we are grateful. G. Keravis for mass spectrometry is gratefully acknowledged. The author would like to extend his thanks to Pr.P.Sinaÿ for his support and collaboration.

**References**

1. S. Hanessian , Acc.Chem.Res.,12, 159 (1979); in Organic Chemistry Series, Vol.3; Total Synthesis of Natural Products : the "Chiron" Approach, Pergamon Press (1983).

2. D. Seebach, in Modern Synthetic Methods, R. Scheffold; Ed., Otto Salle Verlag, Frankfurt am Main, Germany, 1980, p.91.

3. B. Fraser-Reid and R.C. Anderson, Fortschr.Chem.Org.Naturst., 39,1 (1980); B. Fraser-Reid, Acc.Chem.Res., 8, 192 (1975).

4. A. Vasella, in Modern Synthetic Methods, R. Scheffold, Ed., Otto Salle Verlag, Franckfurt am Main, Germany (1980), p. 173.

5. For typical examples : K. Mori,The synthesis of Insect Pheromones,in Total Synthesis of Natural Products, J. ApSimon, Ed., J. Wiley and Sons, New York (1981), p.1.

6. G.M. Whitesides, W.F. Fisher, Jr., J.San Filippo, Jr., R.W. Bashe, and H.O. House, J.Am.Chem.Soc., 91 ,4871 (1969).

7. C.R. Johnson and G.A. Dutra, J.Am.Chem.Soc., 95, 7777 (1973).

8. For a review : G.H. Posner, Org.Reactions, 22, 253 (1975).

9. a, S. Raucher, Tetrahedron Lett., 1161 (1976); b, H.H. Meyer, Liebigs Ann.Chem., 732 (1977); c, U. Ravid, R.M. Silverstein and L.R. Smith, Tetrahedron, 34, 1449 (1978);d,J.R. Pougny and P. Sinaÿ, Tetrahedron Lett., 3301 (1978); e, K. Mori, T. Takigawa and M. Matsui, Tetrahedron, 35, 883 (1979).

10. M.Mori, T.Chuman, M. Kohno, K. Kato and M. Noguchi, Tetrahedron Lett., 667 (1982).The yield of the coupling reaction was not given.

11. All new compounds exhibited satifactory microanalytical and/or spectroscopic properties.

12. N. Sueda, H. Ohrui and H. Kuzuhara, Tetrahedron Lett., 2039 (1979).

13. M. Pietraszkiewicz and P. Sinaÿ, Tetrahedron Lett., 4741 (1979).

14. Condensation of commercially available crotyl chloride with propargylic alcohol and subsequent reduction of the triple bond with lithium aluminium hydride in THF yielded the 2E,5E-heptadienol (63%) which was chlorinated [DMF, $(Ipr)_2$ NEt, LiCl, MsCl] (91%). Purification by distillation at each step allowed to isolate the 2E,5E-heptadienyl chloride contaminated by less than 1% of its 2Z,5E isomer (determined by v.p.c.).

15. U. Gräfe and I. Eritt, J. Antibiotics, 36, 1592 (1983).

16. L. Stamatatos, P. Sinaÿ and J.R. Pougny, Tetrahedron, accepted for publication.

17. A. Canas-Rodriguez and C. Martinez Tobed, A. Gomez Sanchez and C.Martin Madero, Carbohydr. Res., 56, 289 (1977).

18. N.Pravdic and H.G. Fletcher, Jr., Carbohydr.Res., 19, 339 (1971).

**(Received in France 27 March 1984)**