Pergamon

Tetrahedron Letters, Vol. 38, No. 49, pp. 8585-8586, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10288-X

Palladium-Catalysed Cascade Reactions of Unsaturated Carbohydrate Derivatives. Synthesis of Enantiopure Tricyclic Compounds

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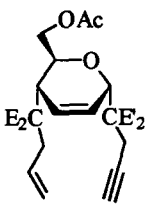
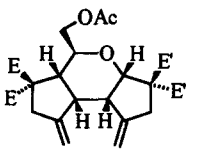
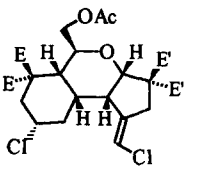
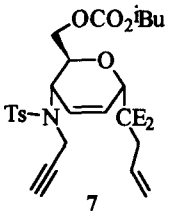
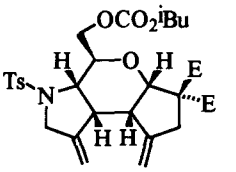
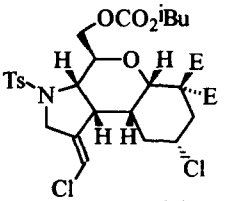
Abstract: The palladium-catalysed cascade cyclisation reactions of carbohydrate derived dienynes for the synthesis of enantiopure tricyclic compounds is described. Carbocyclisation under Wacker conditions in the presence of LiCl gave rise to a remarkable stereocontrolled ring expansion process and formation of two C-Cl bonds. © 1997 Elsevier Science Ltd.

The palladium-catalysed cyclisation and functionalisation reactions[1] of unsaturated carbohydrate derivatives have recently attracted much attention for the stereocontrolled preparation of versatile synthetic intermediates for natural product synthesis. We herein report the palladium-catalysed cascade cyclisation of 1,4-disubstituted unsaturated carbohydrate derivatives for the formation of multifunctional tricyclic compounds.

Table 1

Entry	Starting material	Product A[a] (isolated yield)	Product B[b] (isolated yield)
			
1	**1** E = CO_2Et; E' = CO_2CH_3	**2** (50%)	**3** (53%)
2	**4** E = SO_2Ph; E' = CO_2CH_3	**5** (53%)	**6** (55%)
3	 **7** E = CO_2Et	 **8**[c] (15%)	 **9** (50%)

[a] A solution of the substrate, $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol%) and tri-o-tolylphosphine (10 mol%) was stirred in acetic acid/benzene at rt for 12 h. [b] A solution of the substrate, $PdCl_2(CH_3CN)_2$ (10 mol%), $CuCl_2$ (5 mol equiv) and LiCl (20 mol equiv) was stirred in acetic acid/MeCN at rt for 12 h. [c] A solution of the substrate, $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol%) and acetic acid (5 mol%) was stirred in dichloroethane at rt for 4 h.

The starting materials for this investigation were prepared by the consecutive introduction of unsaturated

side chains at positions C-4[1a,2] and C-1,[3] respectively, of a suitable 2-enopyranoside (pseudoglycal) by palladium(0)-catalysed nucleophilic allylic substitution.[4] Acetolysis of the anomeric glycoside bond of a 4-substituted 2-enopyranoside furnished the corresponding acetoxy compound which, when subjected to a second palladium catalysed substitution reaction, afforded the disubstituted product, generally in very good overall yields.

Atom economical cycloisomerisation[5] of the dienyne substrates into the corresponding tricyclic products was effected by exposure of **1** and **4** (Table 1) to $Pd_2(dba)_3$•$CHCl_3$/tri-*o*-tolylphosphine in acetic acid/benzene at room temperature. Subjecting the amide **7** to similar reaction conditions gave none of the desired cyclisation product **8**. However, 'ligandless'[6] $Pd_2(dba)_3$•$CHCl_3$ in acetic acid (5 mol%) and dichloroethane emerged as a more effective catalyst system for the synthesis of **8** (15% isolated yield). The reaction was not, however, further optimised.

When the branched-chain carbohydrate derivatives **1**, **4** and **7** were treated with a catalytic amount of $PdCl_2(CH_3CN)_2$ in the presence of the oxidant $CuCl_2$ and LiCl in acetic acid/acetonitrile at room temperature the tricyclic compounds **3**, **6** and **9**, respectively, were obtained in reasonable yields and as single stereoisomers (Table 1). A probable reaction mechanism[7] involves coordination of the substrate with Pd and/or Cu to form a metal-alkyne complex,[8] subsequent stereoselective *cis*-chloropalladation in the presence of $CuCl_2$, followed by intramolecular carbopalladation. Instead of undergoing a final β-elimination step, the reaction is terminated by a copper-mediated oxidative C-Pd bond cleavage,[9] stereocontrolled rearrangement of the carbon skeleton and chloride anion capture.

Palladium(0)- and Pd(II)-catalysed reactions with pseudoglycals containing oxygen atoms on C-1 and/or C-4 only led to extensive decomposition, in agreement with literature findings.[10]

Acknowledgements We are grateful to AECI (Ltd) and the Rand Afrikaans University for financial support.

References and Notes

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(*Received in UK* 26 *August* 1997; *accepted* 2 *October* 1997)