Pergamon

Tetrahedron Letters, Vol. 37, No. 13, pp. 2303-2306, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00249-3

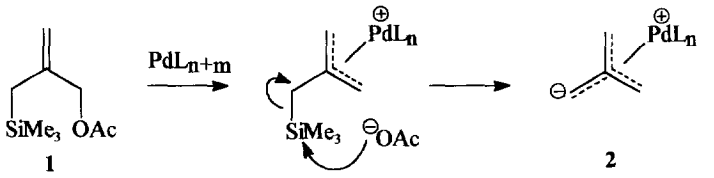
Palladium-catalysed [3 + 2]-Cycloaddition Reactions Employing Sulphonyl-activated Unsaturated Carbohydrate Derivatives.

Cedric W. Holzapfel* and Thilo L. van der Merwe

Department of Chemistry and Biochemistry, Rand Afrikaans University, P.O. Box 524, Auckland Park, 2006, South Africa.

Abstract: The Pd(0)-catalysed [3 + 2]-cycloaddition reactions of phenylsulphonyl-activated unsaturated carbohydrate derivatives afforded a variety of chiral 5,6-bicyclic systems possessing useful exocyclic unsaturation. This procedure was used to prepare a synthon for ajmalicine **3** and tetrahydroalstonine **4**.

Although 1,3-dipolar cycloaddition reactions have been successfully employed in the synthesis of heterocyclic five-membered rings for some time,[1] the application of cycloaddition reactions to the construction of carbocyclic equivalents has only recently received attention.[2] The use of a 1,3-dipole, such as the trimethylmethylene zwitterion **2** (TMM), to effect [3 + 2]-cycloadditions to suitable olefinic acceptors has unlocked a powerful means of rapidly generating five-membered carbocycles.

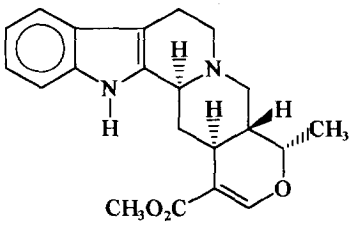


1 **2**

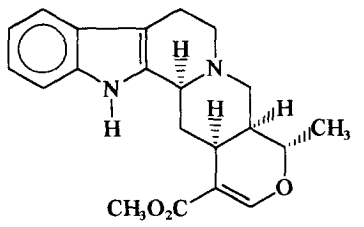
Scheme 1

Various TMM precursors **1**[3] readily form TMM complex **2** in the presence of a suitable Pd(0) catalyst. Appropriate double bond activators include ester-, cyano- and sulphone groups.[4] We report here our results making use of the sulphonyl group as a double bond activator in various unsaturated carbohydrate derivatives.

The potential for preparing precursors of several natural products (*e.g.* brevaldin A, loganin, ajmalicine **3** and tetrahydroalstonine **4**) from carbohydrate derivatives, making use of [3 + 2]-cycloaddition reactions, drew our attention to this particular problem. The unsaturated sulphonyl carbohydrate derivatives were prepared from the corresponding unsaturated compounds, by a sequence involving addition of PhSCl to the double bond, oxidation of the ensuing sulphide to a sulphone, and base-mediated elimination of HCl.[5]

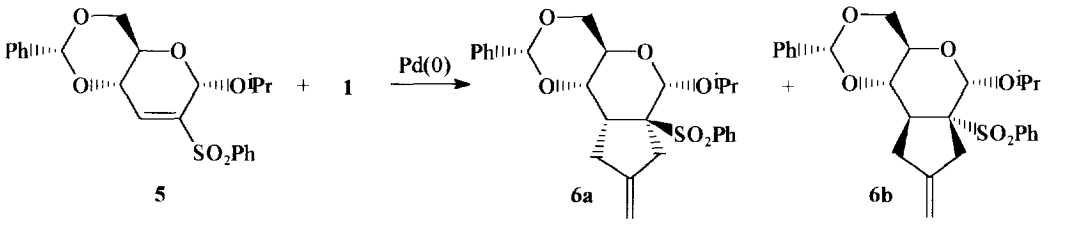


3

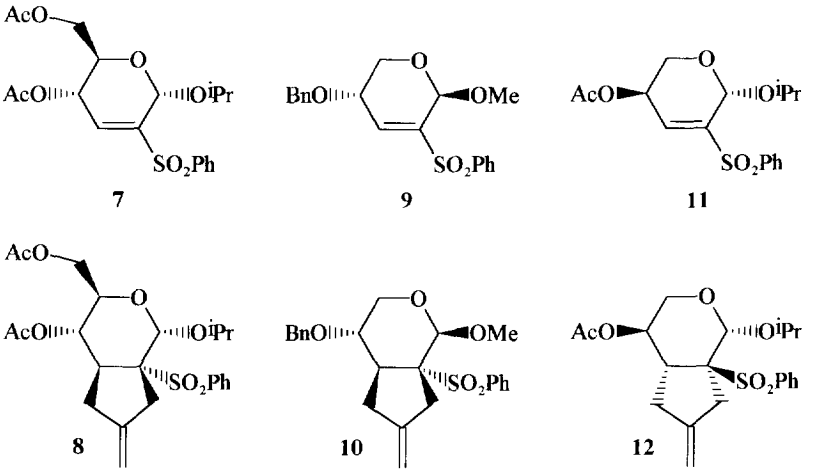


4

Reaction of sulphonyl **5** with TMM precursor **1** in the presence of an *in situ*-generated Pd(0) catalyst[6] in toluene under reflux[7] afforded the two isomers **6a** and **6b** as an inseparable 2.5:1 (by NMR)[8] mixture (Scheme 2). Similarly, compounds **7**, **9** and **11** were treated with acetate **1**, affording the corresponding 5,6-bicycles **8**, **10** and **12**, as single isomers (Scheme 3). The reaction is thought to follow a two-step sequence,[9] involving an initial Michael-type addition to the electron deficient double bond, followed by an attack of the resultant stabilised anion on the η^3-palladium complex. The present set of reactions (Scheme 3) affords single isomers due to exclusive attack of the TMM complex on the least hindered face of the preferred conformation of the sulphone. In the case of products **10** and **12**, the transition state is chair-like, while for **8** the transition state is boat-like.

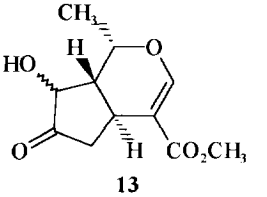


Scheme 2



Scheme 3

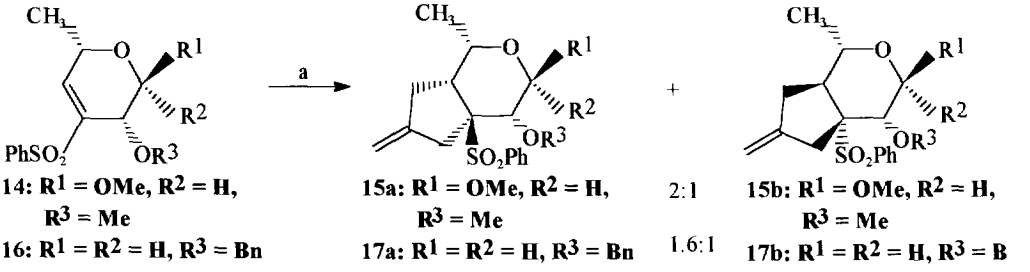
These results led us to investigate the possibility of using this cycloaddition approach in preparing antecedent molecules for ajmalicine **3**. To this end, hydroxyketone **13** has been identified as a synthon for ajmalicine **3**. Our procedure provided a compound **22** that can be converted[5] into **13**.



13

The 3,4-unsaturated sulphonyl derivatives **14**, **16** and **18** were prepared from L-rhamnose,[5] and were treated with acetate **1** as previously described (Scheme 4). The major products in the reactions of **14** and **16**

were those of β-attack (products a) on the more hindered face of the sulphones, proceeding through a chair-like transition state, as opposed to α-attack on the less hindered face, proceeding though a boat-like transition state. This latter scenario was, however, the case in the reaction of **18** with **1**. In order to advantage α-attack, it was desirable to effect such attack *via* a chair-like transition state. This was accomplished by synthesising an unsaturated carbohydrate **20** from L-rhamnose[5] possessing a phenyl-sulphonyl group at C-4. The stereocontrol of the reaction of carbohydrate **20** with acetate **1** was found to be absolute: the product **21** of α-attack only was isolated (Scheme 5). Reductive desulphonylation[10] of bicycle **21** afforded bicycles **22** and **23**, providing precursors for ajmalicine **3** and tetrahydroalstonine **4**, respectively. Similar isomerisations during reductive removal of tertiary sulphones of bicyclic systems have been observed.[11]

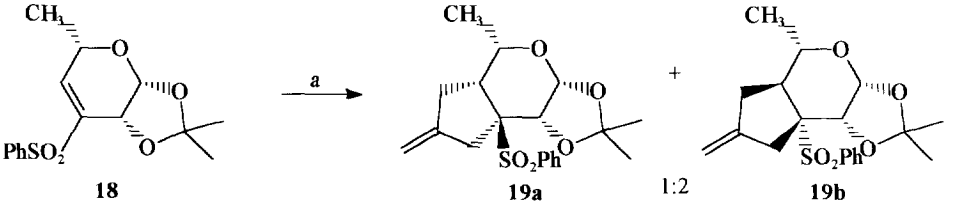


14: R¹ = OMe, R² = H, R³ = Me
16: R¹ = R² = H, R³ = Bn

15a: R¹ = OMe, R² = H, R³ = Me
17a: R¹ = R² = H, R³ = Bn

2:1
1.6:1

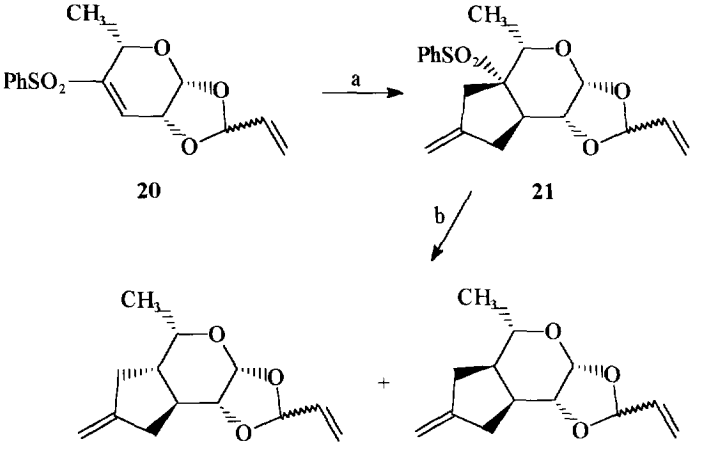
15b: R¹ = OMe, R² = H, R³ = Me
17b: R¹ = R² = H, R³ = B



18 **19a** 1:2 **19b**

a) **1**, Pd(0)

Scheme 4



20 **21**

22 2.5:1 **23**

a) **1**, Pd(0); b) Na(Hg), NaH_2PO_4 buffer

Scheme 5

In conclusion, we have shown the effect of various combinations of stereochemistry on the outcome of Pd(0)-catalysed [3 + 2]-cycloaddition reactions: the judicious selection of substituents and stereochemistry may enable absolute stereocontrol in such reactions. This powerful technology has been put to use in the synthesis of predecessors of the alkaloids ajmalicine **3** and tetrahydroalstonine **4**.

Acknowledgements: we thank the FRD (South Africa), AECI and SASOL for funding.

REFERENCES AND NOTES

1) For some review articles see: Oppolzer, W. *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 10; Kozikowski, A.P. Acc. *Chem. Res.* **1984**, *17*, 410.

2) Trost, B.M. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 1; Trost, B.M. *Pure Appl. Chem.* **1988**, *60*, 1615.

3) Shimizu, I.; Ohashi, Y.; Tsuji, J. *Tetrahedron Lett.* **1984**, *25*, 5183; Trost, B.M.; Chan, D.M.T.; Nanninga, T.N. *Org. Synth.* **1984**, *62*, 58.

4) Trost, B.M.; Chan, D.M.T. *J. Am. Chem. Soc.* **1983**, *105*, 2315.

5) Van der Merwe, T.L. Ph. D. thesis, Rand Afrikaans University 1994.

6) The catalyst was prepared by treatment of $Pd(OAc)_2$ (3 mg, 0.013 mmol) with tri-isopropylphosphite (20 µl, 0.077 mmol), followed by stirring at ambient temperature for 30 min.

7) General procedure for cycloaddition reactions (*e.g.* reaction of **20** with **1**): to 0.049 mmol Pd(0) catalyst[6] was added sulphone **20** [150 mg, 0.487 mmol in toluene (2 ml)] and 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate (124 µl, 1.2 eq.). The reaction mixture was placed in a preheated (150°C) oil bath, and was heated under reflux for two hours. The solvent was removed *in vacuo*, and the residue was subjected to flash chromatography (EtOAc/hexane: 1/3) to afford bicycle **21**.

8) All product provided satisfactory analytical data. For example, for product **21**: 75%; mp.: 81-82°C; IR: ν_{max} 1141 and 1304 cm^{-1} (S=O); NMR (performed in $CDCl_3$ on a Varian VXR 200 spectrometer): ^1H δ 1.74 (3H, d, J = 6.8 Hz), 2.26 (1H, m), 2.58 (1H, d, J = 17.3 Hz), 2.72 (1H, dd, J = 10.0 and J = 16.5 Hz), 3.08 (1H, dt, J = 1.3 and J = 10.0 Hz), 3.16 (1H, m), 3.75 (1H, q), 4.87 and 4.94 (2×H, 2×m), 5.05 (1H, d, J = 6.3 Hz), 5.25-5.43 (3H, m), 5.75 (1H, ddd, J = 10.1 and J = 16.4 Hz), 7.54 (3H, m), 8.03 (2H, m); ^{13}C δ 16.9, 36.3, 40.3, 42.0, 70.5, 70.6, 75.1, 96.3, 104.4, 109.2, 120.3, 128.4, 131.3, 133.4, 134.1, 138.3, 142.6; m/z: 165 (M^+-SO_2Ph and $OCH_2CH{=}CH_2$, 58%), 147 (165-H_2O, 37%).

9) Trost, B.M.; Miller, M.L. *J. Am. Chem. Soc.* **1988**, *110*, 3687.

10) Trost, B.M.; Arndt, H.C.; Strege, P.E.; Verhoeven, T.R. *Tetrahedron Lett.* **1976**, 3477.

11) Trost, B.M.; Sleoane, P.; Mignanin, S.; Acemoglu, M. *J. Am. Chem. Soc.* **1989**, *111*, 7487.

(*Received in UK* 23 *January* 1996; *accepted* 9 *February* 1996)