Pergamon

Tetrahedron Letters 40 (1999) 3629–3632

TETRAHEDRON LETTERS

Dioxolane Acetal Ring Expansion during a Sugar Triflate Displacement. Synthesis and Assignment of Diastereoisomer Configuration of Novel 9-Crown-3 Ether Derivatives

Velimir Popsavin *, Ostoja Berić, Mirjana Popsavin, János Csanádi, Djura Vujić and Richard Hrabal [a]

University of Novi Sad, Faculty of Sciences, Institute of Chemistry, Trg D. Obradovića 3, 21000 Novi Sad, Yugoslavia

[a] *Institute of Chemical Technology, NMR Laboratory, Technicka 5, CZ 166 28 Prague 6, Czech Republic*

Received 22 January 1999; accepted 2 March 1999

Abstract: Treatment of 2,5:3,6-dianhydro-6-thio-4-*O*-trifluoromethanesulfonyl-L-talose ethylene acetal (**5**) with lithium benzoate in boiling DMF unexpectedly gave the 9-crown-3 ether derivatives **7** and **8** instead of the substitution product **6**. The mechanism of the process presumably involved neighbouring group participation of the dioxolane acetal function. ^{1}H NMR and molecular mechanics calculations (MM3) provided the assignment of stereoisomer configuration since the results of semi-empirical PM3 calculations on postulated oxonium-ion intermediates reasonably explained the high stereoselectivity of the process.

The nucleophilic displacement of sugar triflates by oxygen nucleophiles represents an efficient route towards substituted products with inverted configuration at the electrophilic centers.[1] Accordingly, we assumed that solvolysis of the L-*talo*-derivative **5**, in the presence of benzoate anion as the nucleophile, might be used for the preparation of the L-*manno*-isomer **6** (Scheme 1), a possible intermediate in synthesis of (–)-*allo*-muscarine from D-glucose.[2] The triflic ester **5** was thus prepared starting from the known[3] 2,5-anhydro-L-idose derivative **1**.

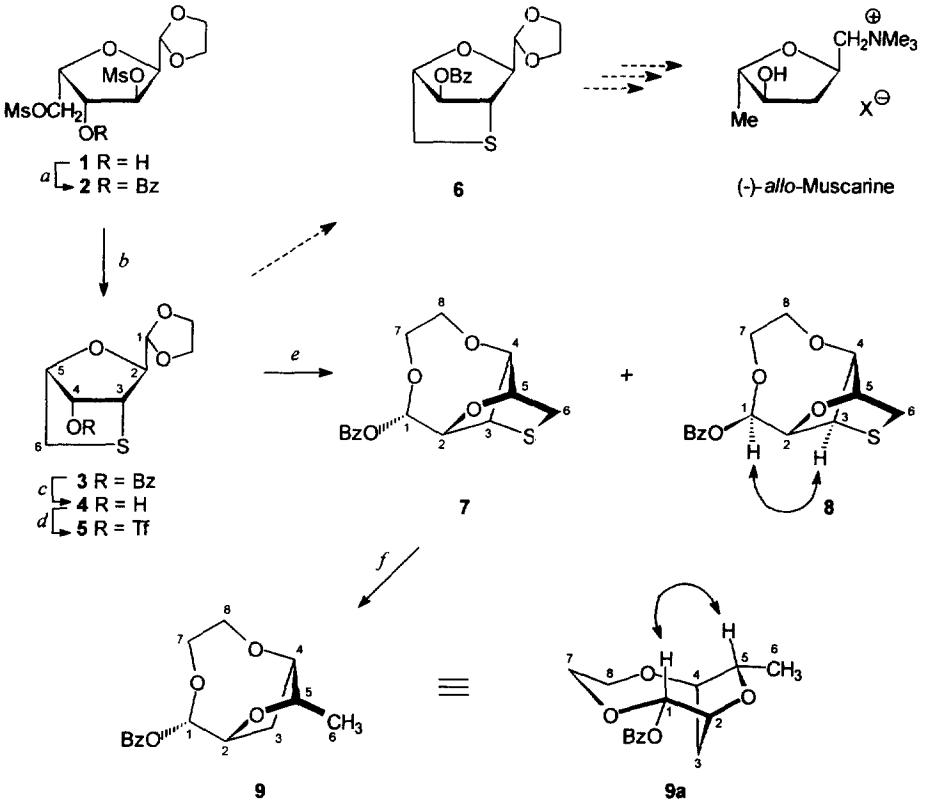
Reaction of **1** with benzoyl chloride in dry pyridine gave the expected 4-*O*-benzoyl derivative **2** which was further treated with sodium hydrogen sulfide in *N,N*-dimethylformamide to give the oxathiane derivative **3**. *O*-Debenzoylation of **3** with sodium hydroxide in dry methanol afforded the unstable alcohol **4** which was subsequently treated with triflic anhydride in a mixture of dichloromethane and pyridine to afford the triflate ester **5**. The four-step sequence **1** → **5** was carried out without purification of intermediates **2** – **4**, whereby the desired product **5** was isolated by flash column chromatography in an overall yield of 53% with respect to starting compound **1**.

Although most sugar triflates have been shown to be rather reactive towards a variety of nucleophiles[1,4] the triflic ester **5** remained unchanged even after prolonged treatment with an excess of potassium benzoate in *N,N*-dimethylformamide at 140°C. This implied that the approach of an external nucleophile to the electrophilic center was sterically hindered by the β-orientated dioxolane acetal ring. Therefore, the reaction was carried out in boiling *N,N*-dimethylformamide, whereupon the conversion of starting compound was completed after 48 h. However, this reaction did not afford the substitution product **6**, but resulted in the formation of the 9-crown-3

* Corresponding author. *Fax*: +38 121 54 065; *E-mail*: vpops@eunet.yu

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00492-X

ether derivative **7**, isolated by flash column chromatography in 26% yield.[5] A somewhat different result was obtained by using lithium benzoate as the nucleophilic agent. Treatment of compound **5** with an excess of lithium benzoate in boiling *N,N*-dimethylformamide for 24 hours gave an approximately 12:1 mixture of stereoisomers **7** and **8** in a 42% combined yield. The products **7** and **8** were easily separated by flash column chromatography and characterized by ^{1}H and ^{13}C NMR spectral data.[6]



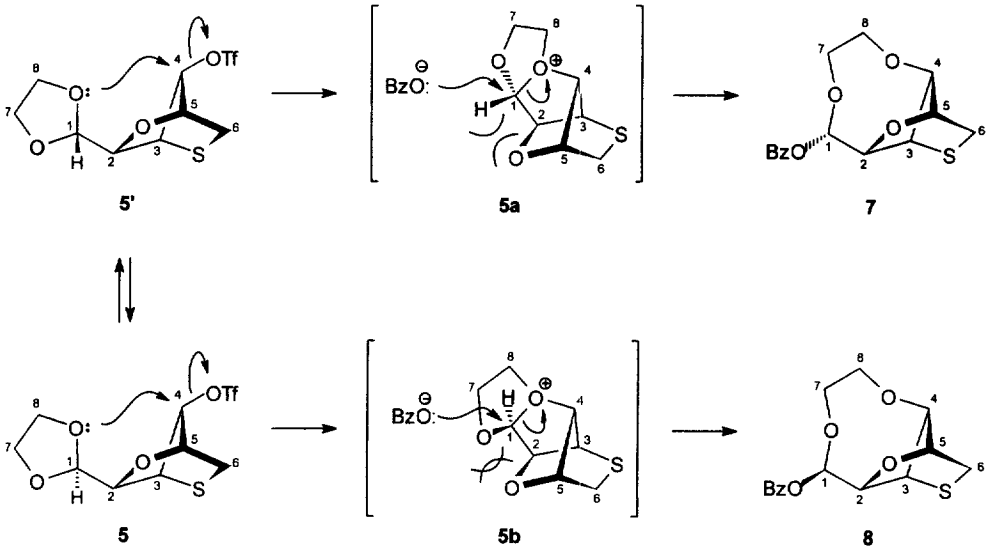
a) BzCl, py, RT, 24 h; b) NaSH, DMF, N_2, 80 °C, 40 h; c) NaOH, MeOH, 80 °C, 40 min; d) Tf_2O, py, CH_2Cl_2, 0 °C → RT, 30 min; e) LiOBz, DMF↑↓, 24 h; f) H_2/RaNi, EtOH, 80 °C, 1 h.

Scheme 1.

A comparison of the ^{1}H NMR data of **5** and **7** showed a distinctive downfield shift of H-1, as well as an upfield shift of the H-4 signal of **7** (0.95 and 0.43 ppm, respectively). This confirmed the presence of a benzoyloxy group at C-1 rather than at C-4. However, the assignment of configuration at C-1 from ^{1}H NMR coupling constants, as well as from an *NOE* experiment performed on the main reaction product **7** seemed to be uncertain. Upon irradiation of the H-1 doublet (δ 5.76) an enhancement of the H-2, H-7 and/or H-8 proton signals was observed; however these results are not relevant for the stereochemistry at C-1. The assignment of diastereoisomer configuration was achieved after the Raney nickel desulfurization of **7** carried out in ethanol for 1 h at 80 °C, whereupon the corresponding 3,6-dideoxy derivative[7] **9** was obtained in 50% yield. A significant *NOE* was observed upon irradiation of both the H-1 and H-5 signals, indicating a spatial vicinity of

these protons and consequently, the 1*S*-absolute configuration of **9**. Molecular mechanics calculations[8] (MM3) gave the lowest energy conformation of **9a** as having *chair-boat* geometry of the nine-membered ring and an E^3-geometry of the tetrahydrofuran ring. The calculated distance between H-1 and H-5 (2.90 Å) was consistent with *NOE* results and definitely proved the stereochemistry of **9** and, accordingly, the structure of its synthetic precursor **7**. Moreover, the 1*R*-configuration of minor product **8** was unambiguously established by a significant *NOE* signal enhancement of H-3 (δ 3.51) when irradiating the H-1 doublet (δ 6.08).

A possible mechanism of the solvolytic reaction may involve dioxolane neighboring group participation in the first step. As outlined in Scheme 2, both stereochemically distinct intermediates **5a** and **5b** might be formed from **5**. Further reaction of the *exo*-oxonium ion **5a** with benzoate anion would give the major product **7** having the *S*-configuration at C-1. Similar reaction of the *endo*-oxonium ion **5b** would lead to the 1*R*-stereoisomer **8** isolated as a minor product from the reaction mixture. Presumably this is because the *endo*-oxonium ion **5b** is too strained to form readily. In fact, semiempirical PM3 calculations[8] performed on both **5a** and **5b** confirmed a lower stability of **5b** (ΔE = 10.16 kJ/mol in favour of **5a**). This is mainly due to the repulsive van der Waals interactions between the *syn*-orientated O-1 and O-2(5) atoms. The calculated distance between these atoms in an optimized structure **5b** amounts to 2.68 Å, that is less then the sum of the corresponding van der Waals radii (2.80 Å).[9] On the other hand, the intermediate **5a** is less strained since the distance between H-1 and O-2(5) atom (2.59 Å) is similar to the sum of their van der Waals radii (2.60 Å), as calculated from the optimized structure **5a**. Consequently, the *exo*-ion is preferentially formed, leading to the stereoisomer **7** as the major reaction product. Alternatively, the second step of the rearrangement (**5a** → **7**), may well be an S_N1 type of process with oxonium ion capture preferentially from the less hindered face.



Scheme 2.

In conclusion, a synthesis of tricyclic 9-crown-3 ether derivatives **7** and **8** bearing a chiral oxathiane ring was achieved by utilizing nucleophilic displacement of a triflic ester leaving group assisted by neighboring

group participation of the dioxolane acetal function. This reaction is potentially useful for preparation of thia analogs of **7** and **8**. In addition, the main reaction product **7** represents a possible intermediate for preparation of higher homologues, which are potential chiral cation receptors.

Acknowledgement. This work was supported by a research grant from the Ministry of Science and Technology of the Republic of Serbia.

REFERENCES AND NOTES:

1. Binkley, R. W.; Ambrose, M. G. *J. Carbohydr. Chem.* **1984**, *3*, 1-49.
2. An alternative route to the intermediate **6**, as well as its conversion to (−)-*allo*-muscarine was reported recently: Popsavin, V.; Berić, O.; Popsavin, M.; Csanádi, J.; Lajšić, S.; Miljković, D. *Collect. Czech. Chem. Commun.* **1997**, *62*, 809-815; Popsavin, V.; Berić, O.; Popsavin, M.; Csanádi, J.; Miljković, D. *Carbohydr. Res.* **1996**, *288*, 241-247.
3. Popsavin, V.; Berić, O.; Popsavin, M.; Csanádi, J.; Miljković, D. *Carbohydr. Res.* **1995**, *269*, 343-347.
4. Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis*, **1982**, 85-126.
5. Apart from the isolated product **7**, a TLC of the reaction mixture showed the presence of several additional components of higher polarity with one of them presumably being the stereoisomer **8**. However, none of these by-products could be obtained in pure form due to their similar chromatographic properties.
6. *Compound* **7**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.86 (dd, 1 H, $J_{6a,6b}$ 10.5, $J_{5,6a}$ 1.3 Hz, H-6a), 2.91 (dd, 1 H, $J_{5,6b}$ 1.9 Hz, H-6b), 3.60 (m, 1 H, H-8a), 3.77 (d, 1 H, $J_{3,4}$ 1.8 Hz, H-3), 3.87-4.02 (m, 3 H, 2 H-7 and H-8b), 4.38 (d, 1 H, H-4), 4.47 (bs, 1 H, H-5), 4.80 (d, 1 H, $J_{1,2}$ 3 Hz, H-2), 5.75 (d, 1 H, H-1), 7.40-8.10 (m, 5 H, ArH). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 32.39 (C-6), 44.66 (C-3), 69.48 and 69.82 (C-7 and C-8), 79.05 (C-5), 84.68 (C-4), 90.46 (C-2), 104.41 (C-1), 128.31, 129.58, 129.77 and 133.25 (ArC), 165.54 (C=O).

   Compound **8**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.96 (d, 2 H, $J_{5,6}$ 1.6 Hz, 2 H-6), 3.51 (d, 1 H, $J_{3,4}$ 1.6 Hz, H-3), 3.70-4.12 (m, 4 H, 2 H-7 and 2 H-8), 4.59 (d, 1 H, H-4), 4.73 (m, 2 H, H-2 and H-5), 6.08 (d, 1 H, $J_{1,2}$ 3.2 Hz, H-1), 7.40-8.20 (m, 5 H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.4 (C-6), 47.99 (C-3), 68.15 and 68.40 (C-7 and C-8), 78.94 (C-5), 85.50 (C-4), 88.51 (C-2), 96.83 (C-1), 129.12, 130.16, 130.69 and 134.13 (ArC), 165.81 (C=O).
7. *Compound* **9**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.14 (d, 3 H, $J_{5,6}$ 6.7 Hz, 3 H-6), 1.88 (ddd, 1 H, $J_{3a,3b}$ 14.1, $J_{2,3a}$ 7.3, $J_{3a,4}$ 3 Hz, H-3a), 2.72 (d, 1 H, H-3b), 3.63-3.98 (m, 4 H, 2 H-7 and 2 H-8), 4.03 (bd, 1 H, $J_{4,5} \approx 1$ Hz, H-4), 4.26 (bq, 1 H, H-5), 4.59 (dd, 1 H, $J_{1,2}$ 4.4 Hz, H-2), 5.76 (d, 1 H, H-1), 7.45-8.15 (m, 5 H, ArH). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 19.82 (C-6), 30.20 (C-3), 66.28 and 70.34 (C-7 and C-8), 80.88 (C-2), 81.58 (C-4), 82.14 (C-5), 103.41 (C-1), 128.28, 129.61, 129.81 and 133.15 (ArC), 165.98 (C=O).
8. 3D-Molecular Modeling Software Alchemy 2000, Tripos Associates, Inc. 1996.
9. Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis;* John Wiley & Sons: New York, 1967; pp. 452-453.