Pergamon

Tetrahedron Letters 42 (2001) 2767–2769

TETRAHEDRON LETTERS

Synthesis and theoretical study of azido and amino inositol derivatives from L-quebrachitol

Mauro V. De Almeida,[a] Renata M. Figueiredo,[a] Hélio F. Dos Santos,[a] Adilson D. Da Silva[a] and Wagner B. De Almeida[b,*]

[a]*Departamento de Química, ICE, Universidade Federal de Juiz de Fora, Juiz de Fora, MG, Brazil*
[b]*Laboratório de Química Computacional e Modelagem Molecular, Departamento de Química, ICEx, Universidade Federal de Minas Gerais, Belo Horizonte, MG 31270-901, Brazil*

Received 7 December 2000; revised 6 February 2001; accepted 23 February 2001

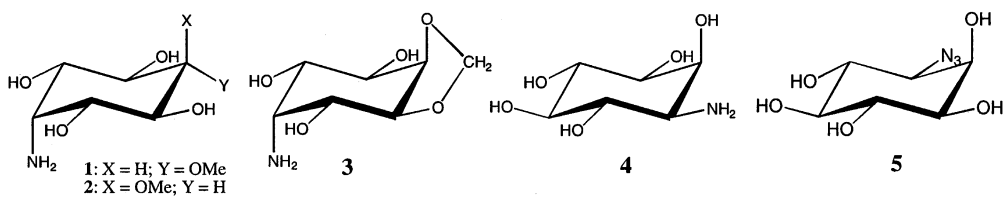
Abstract—Some azido and amino inositol derivatives were synthesised from L-quebrachitol. The reaction between the mesylated compound and sodium azide was studied experimentally. Ab initio quantum mechanical calculations were carried out for this process to better understand the reaction mechanism. © 2001 Elsevier Science Ltd. All rights reserved.

The chemotherapeutic success of the aminocyclitol antibiotics has stimulated research into the chemistry of their amino sugar components.[1,2] The structure 5-*O*-methyl-*myo*-inosamine **1** was first assigned to the cyclitol moiety of antibiotic KA-3093, related to hygromycin A, which contains an inosamine unit **3**.[3,4] Later, methoxyhygromycin was isolated[5] from the fermentation broth of *Streptomyces* sp. N° 207, and acid hydrolysis gave 5-*O*-methyl-*neo*-inosamine **2**. The antibiotic minosaminomycin, the product of *Streptomyces* N° MA 514-A1, contains 1-D-1-amino-1-deoxy-*myo*-inositol **4** as an aminocyclitol moiety.[6,7] Also, the aminosugars are components of several compounds of biological interest such as pancrastitatin.[8] Furthermore, Kozikowski and co-workers have found that azidoinositols such as the 3-azido-3-deoxy-*myo*-inositol **5** are selective inhibitors of the growth of v-*sis*-transformed NIH 3T3 cells.[9–11]

In this article we detail an expedient route to prepare 2,3-diazido-2,3-dideoxy-1-*O*-methyl-*scyllo*-inositol **14**, 1L-3-azido-3-deoxy-1-*O*-methyl-*chiro*-inositol **18** and 3-amino-3-deoxy-1-*O*-methyl-*chiro*-inositol **20**. The structures of all new compounds were unequivocally established by ^{1}H and ^{13}C NMR.[12] In the case of compounds **8**, **11**, **12**, **15**, **19** and **21**, COSY ^{1}H–^{1}H correlations were performed.

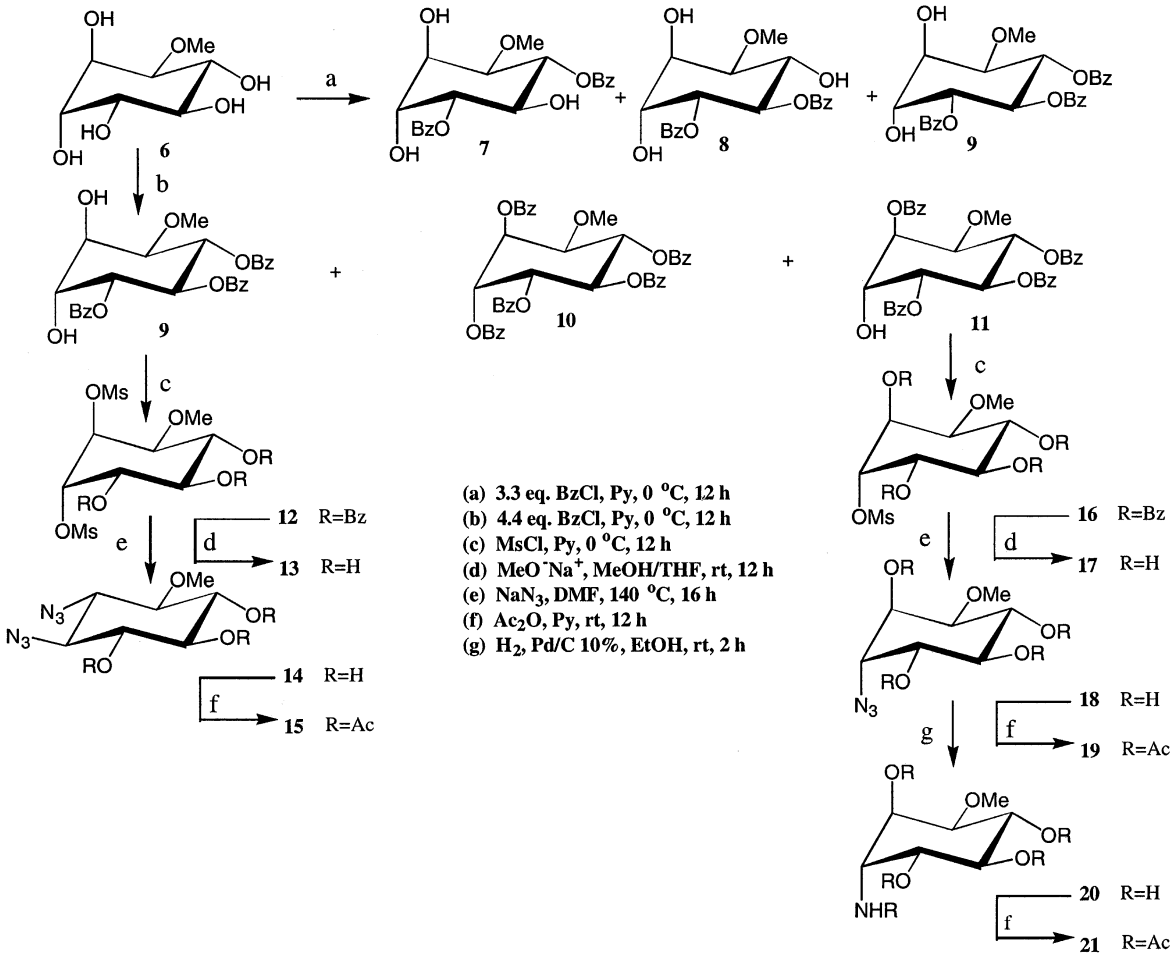
As starting material we have used quebrachitol **6** (1-*O*-methyl-*chiro*-inositol; Scheme 1) isolated from waste rubber solids by extraction with EtOH. Compound **6** was converted to a mixture of **7**, **8** and **9** in a 2/2/5 ratio (90% yield) using 3.3 equiv. of benzoyl chloride in pyridine at 0°C.[13] The reaction of **6** using 4.4 equiv. of benzoyl chloride in pyridine, at 0°C, furnished **9**, **10** and **11** in a 2/2/4 ratio (80% yield).[14]

Treatment of the diol **9** and alcohol **11** with methanesulfonyl chloride in pyridine gave 2,3-di-*O*-methanesulfonyl **12** and 3-*O*-methanesulfonyl **16** in 90 and 95% yield, respectively. Cleavage of the benzoyl groups of compounds **12** and **16** with sodium metoxide in methanol/THF afforded the triol **13** and the tetrol **17** in 85 and 88% yield, respectively. Reaction of compounds **13** and **17** with sodium azide in DMF followed by acetylation gave the diazide **15** and the azide **19**, respectively, in 25 and 70% overall yield. In the azidation reaction of **13** we observed the formation of three others azido compounds that were not isolated. Finally,



* Corresponding author. E-mail: wagner@netuno.qui.ufmg.br

0040-4039/01/$ - see front matter © 2001 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(01)00326-4



Scheme 1.

hydrogenation in the presence of palladium allowed the reduction of the azido compound **18** into the corresponding amine derivative **20**, additionally purified as its penta-acetate **21** (90% overall yield from **18**). The reaction between the mesylated compound **17** and sodium azide in DMF at 140°C for 16 h (70% yield; Scheme 1) rests upon surprising total retention of the configuration, and the only product **18** was assigned by analysis of NMR spectra.

Theoretical investigation of this process was carried out to better understand the reaction mechanism. The calculations were performed at the Hartree–Fock (HF) level of theory using the split valence 6-31+G* basis-set for the energy calculations considering the HF/3-21+G* fully optimised geometries (HF/6-31+G*//3-21+G*). Three distinct mechanisms involving a carbocation, an epoxide intermediates and a transition state (TS) structure for a direct attack of the N_3^- species were investigated. The solvent (DMF, $\varepsilon=36.7$) effect was assessed at the HF level using the PCM (polarisable continuum model) approach.[15] The reaction Gibbs free energy in solution (ΔG^{DMF}) was evaluated using the well-known thermodynamical cycle according to the equation $\Delta G^{DMF}=\Delta G_g+(\Delta G_P{}^{solv}-\Delta G_R{}^{solv})$,[16] where ΔG_g is the gas phase reaction Gibbs free energy and $\Delta G_P{}^{solv}$ and $\Delta G_R{}^{solv}$ are the solvation free energies of products and reagents, respectively.

The experimentally observed axial product can be justified based on the thermodynamic aspects of the process. On the basis of the theoretical results the axial product **18** was found to be present in DMF in a relative concentration of 86%. However, aiming at a complete description of the process investigated, a systematic analysis was developed with regard to the reaction mechanism. The axial product can be obtained either via the carbocation formation or from the epoxide. The synchronised mechanism (S_N2) involving the direct attack leads exclusively to the formation of the equatorial product. Considering the carbocation formation, both products can be obtained depending on the attack position of the reagent N_3^-. This mechanism might be used to understand the experimental finding considering that the axial product is thermodynamically more favourable. However, comparing the relative stability of the carbocation and epoxide intermediates, it was observed that the reaction pathway involving the epoxide is favoured. From the theoretical calculations including solvent effects it was found that the epoxide intermediate was 30 kcal/mol more stable than the carbocation one. The calculated activation free energy ($TS_{epoxide}$) for the epoxide opening was found to be 47.1 kcal/mol in DMF solution at 140°C. Therefore, the reaction pathway can be traced considering the process through two stages. Firstly, the reaction passes through

the epoxide intermediate and then ring epoxide opening takes place leading to the formation of the axial product.

Acknowledgements

This work was partially supported by CNPq. W.B.D.A. would like to thank the members of the Departamento de Química, Universidade Federal de Juiz de Fora (UFJF) for the very pleasant stay during the time that this work was carried out, and the Pró-Reitoria de Pós-Graduação e Pesquisa (PROPP–UFJF) for a Visiting Professor Fellowship. The authors also thank the CENAPAD-MG/CO-NAR-UFJF for providing computational facilities.

References

1. Da Silva, E. T.; Le Hyaric, M.; Machado, A. S.; De Almeida, M. V. *Tetrahedron Lett*. **1998**, *39*, 6659.
2. (a) Ogawa, S.; Isaka, A. *Carbohydr. Res*. **1991**, *210*, 105; (b) Arjona, O.; De Rios, A.; Plumet, J.; Saez, B. *Tetrahedron Lett*. **1995**, *8*, 6659.
3. Pittenger, R. C.; Wolfe, R. N.; Hochn, M. M.; Marks, P. N.; Daily, W. A.; McGuire, J. M. *Antibiot. Chemother*. **1953**, *3*, 6659.
4. Mann, R. L.; Gale, R. M.; Van Abeele, F. R. *Antibiot. Chemother*. **1953**, *3*, 1279.
5. Chida, N.; Nakazawa, K.; Ohtsuka, M.; Suzuki, M.; Ogawa, S. *Chem. Lett*. **1990**, 423.
6. Olesker, A.; Mercier, D.; Gero, S. D.; Pearce, C. J.; Barnett, J. E. G. *J. Antibiot*. **1975**, *28*, 491.
7. Hamada, M.; Kondo, S.; Yokoyama, T.; Miura, K.; Iimura, K.; Yamamoto, H.; Maeda, K.; Takeuchi, T.; Umezawa, H. *J. Antibiot*. **1974**, *27*, 81.
8. (a) Aceña, J. L.; Arjona, O.; Iradier, F.; Plumet, J. *Tetrahedron Lett*. **1996**, *37*, 105; (b) Pettit, G. R.; Gaddamidi, V.; Gragg, G. M.; Herald, D. L.; Sagawa, Y. *J. Chem. Soc., Chem. Commun*. **1984**, 1693.
9. Kozikowski, A. P.; Fauq, A. H.; Powis, G.; Kurian, P.; Crews, F. T. *J. Chem. Soc., Chem. Commun*. **1992**, 362.
10. Kozikowski, A. P.; Fauq, A. H.; Powis, G.; Melder, D. C. *J. Am. Chem. Soc*. **1990**, *112*, 4528.
11. Brunn, G.; Fauq, A. H.; Chow, S.; Kozikowski, A. P.; Gallegos, A.; Powis, G. *Cancer Chemother. Pharmacol*. **1994**, *35*, 71.
12. **7**: mp 170–172°C; ^{1}H NMR (400 MHz, acetone-d_6) δ: 5.67 (t, 1H, H6, $J_{6-1}=J_{6-5}=9.8$), 5.49 (dd, 1H, H4, $J_{4-3}=3$; $J_{4-5}=10$), 4.85 (d, 1H, OH, $J=4.3$), 4.60 (d, 1H, OH, $J=5.6$), 4.38 (m, 4H, H2, H3, H5, OH), 3.80 (dd, 1H, H1, $J_{1-2}=2.8$); **8**: mp 171–173°C; ^{1}H NMR (400 MHz, acetone-d_6) δ: 5.87 (t, 1H, H5, $J_{5-4}=J_{5-6}=10$), 5.58 (dd, 1H, H4, $J_{4-5}=10$), 4.40 (t, 1H, H3, $J_{3-4}=J_{3-2}=3$), 4.32 (t, 1H, H2, $J_{2-1}=3$), 4.15 (t, 1H, H6, $J_{6-1}=10$), 3.60 (dd, 1H, H1); ^{13}C NMR (100 MHz, acetone-d_6) δ: 57.8 (OCH_3), 68.2, 68.9, 70.1, 71.0, 73.6, 73.9, 81.8 (C1, C2, C3, C4, C5, C6); (found: C, 62.93; H, 5.46. $C_{21}H_{22}O_8$ requires C, 62.68; H, 5.51%); **9**: oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.09 (t, 1H, H5, $J_{5-4}=J_{5-6}=10$), 5.90 (dd, 1H, H6, $J_{6-1}=9.6$), 5.76 (dd, 1H, H4, $J_{4-3}=3$), 4.58 (t, 1H, H3, $J_{3-2}=3$), 4.42 (t, 1H, H2, $J_{2-1}=3$), 3.94 (dd, 1H, H1); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 58.8 (OCH_3), 68.7, 69.5, 70.2, 71.9, 72.8, 79.5 (C1, C2, C3, C4, C5, C6); **11**: mp 162–164°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.20 (t, 1H, H6, $J_{6-5}=J_{6-1}=10$), 5.99 (t, 1H, H5, $J_{5-4}=10$), 5.94 (dd, 1H, H2, $J_{2-3}=J_{2-1}=4$), 5.72 (dd, 1H, H4, $J_{4-3}=4$), 4.60 (q, 1H, H3, $J_{3-OH}=4$), 4.15 (dd, 1H, H1); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 58.8 (OCH_3), 68.3, 68.9, 70.2, 71.8, 72.9, 77.6 (C1, C2, C3, C4, C5, C6); (found: C, 68.68; H, 4.66. $C_{35}H_{30}O_{10}$ requires C, 68.85; H, 4.95%); **12**: mp 167–170°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.97 (t, 1H, H5, $J_{5-6}=J_{5-4}=10$), 5.85 (t, 1H, H6, $J_{6-1}=10$), 5.78 (dd, 1H, H4, $J_{4-5}=10$, $J_{4-3}=3.8$), 5.47 (dd, 1H, H3, $J_{3-2}=3.5$), 5.42 (dd, 1H, H2 $J_{2-1}=4$), 4.05 (dd, 1H, H1); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 38.5, 39.1 (CH_3S), 59.5 (OCH_3), 69.3, 69.4, 70.5, 74.3, 74.9 (C1, C2, C3, C4, C5, C6); (found: C, 54.41; H, 4.83. $C_{30}H_{30}O_{13}S_2$ requires C, 54.37; H, 4.56%); **15**: oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.11–4.97 (3t, 3H, H6, H5, H4,), 2.70–2.58 (3t, 3H, H1, H2, H3); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 60.4 (OCH_3), 62.6, 63.6, 71.1, 71.2, 72.2, 81.4 (C1, C2, C3, C4, C5, C6); **19**: mp 69–72°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.43 (dd, 1H, H2, $J_{2-1}=3.2$, $J_{2-3}=4$), 5.41 (t, 1H, H5, $J_{5-4}=J_{5-6}=10$), 5.30 (dd, 1H, H4, $J_{4-3}=4$, $J_{4-5}=10$), 5.25 (t, 1H, H6, $J_{1-6}=10$), 4.12 (t, 1H, H3), 3.55 (dd, 1H, H1); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 58.5 (OCH_3), 59.5, 66.8, 69.9, 70.9, 71.2, 76.3 (C1, C2, C3, C4, C5, C6); **21**: oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.65 (dd, 1H, H2, $J_{2-1}=4.8$, $J_{2-3}=3$), 5.41–5.22 (m, 3H, H4, H5, H6), 4.60 (dd, 1H, H3, $J_{3-4}=4$, $J_{3-2}=3$), 3.58 (dd, 1H, H1, $J_{1-6}=8$, $J_{1-2}=4.8$); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 48.3 (C3), 58.3 (OCH_3), 66.7, 69.0, 69.8, 70.8, 77.0 (C1, C2, C4, C5, C6).
13. To a solution of powered quebrachitol (3.88 g; 20 mmol) in dry pyridine (100 mL) benzoyl chloride (7.7 mL; 66 mmol) was slowly added over 10 h at 0°C. After the addition, the solution was stirred for 6 h at 0–10°C and for 6 h at room temperature. The mixture was extracted with CH_2Cl_2, the organic layer was dried in $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel 70–230 mesh (AcOEt/hexane) to give compounds **7** (1.6 g; 20%), **8** (1.6 g; 20%) and **9** (5.0 g; 50%).
14. Compounds **9**, **10** and **11** were obtained by the same experimental procedure described above for the preparation of **7**, **8** and **9** from quebrachitol (3.88 g; 20 mmol) using 10.3 mL (88 mmol) of benzoyl chloride. Purification by chromatography on silica gel 70–230 mesh (CH_2Cl_2; then AcOEt/hexane) afforded compounds **9** (2.0 g; 20%), **10** (2.8 g; 20%) and **11** (4.8 g; 40%).
15. (a) Cossi, M.; Barone, V.; Camimi, R.; Tomasi, J. *Chem. Phys. Lett*. **1996**, *255*, 327; (b) Barone, V.; Cossi, M.; Tomasi, J. *J. Chem. Phys*. **1997**, *107*, 3210.
16. De Almeida, W. B.; Dos Santos, H. F.; Zerner, M. C. *J. Pharm. Sci*. **1998**, *87*, 1101.