Pergamon

Tetrahedron Letters 43 (2002) 8543–8546

TETRAHEDRON LETTERS

A convenient stereoselective route to novel tetrahydroxyindolizidines

Ana T. Carmona, José Fuentes and Inmaculada Robina*

Departamento de Química Orgánica, Facultad de Química, Universidad de Sevilla, Apartado 553, E-41071 Sevilla, Spain

Received 29 July 2002; accepted 19 September 2002

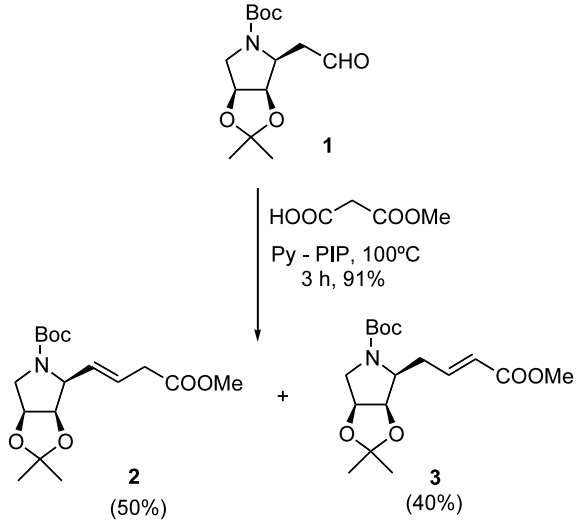
Abstract—A convenient stereoselective route, for the preparation of novel tetrahydroxyindolizidines, based on *syn*-hydroxylation reactions of alkenyl pyrrolidines followed by cyclization, is reported. Derivatives of (+)-swainsonine are prepared.

Polyhydroxylated indolizidines belong to an important class of alkaloids that possess a wide range of biological applications, mainly as glycosidase inhibitors,[1] and can be used as antiviral, antitumor, and immunomodulating agents.[2] This fact, together with their attractive chemical structures have led to many synthetic approaches.[3] Since small modifications in their structure may induce significant changes in their biological activity, potency and/or specificity on glycosidase enzymes or receptors,[4] the preparation of unnatural epimers and other structural analogues of the natural indolizidines has received much attention,[5] and new methodologies to generate structural analogues are still needed. To the best of our knowledge, of the synthetic analogues of polyhydroxyindolizidines, indolizidinones **8** and **9** and indolizidines **17**, **19** have not been described. Of these, **8** is a precursor of a hydroxy analogue of (+)-swainsonine described by Fleet and co-workers[6] to be a good inhibitor of naringinase.

In this communication we report the preparation of novel optically pure tetrahydroxyindolizidines via the cyclization of chiral imino-*C*-polyols, the latter being formed by elongation of pyrrolidines-carbaldehydes through Knoevenagel reaction followed by Sharpless asymmetric dihydroxylations, an approach that, as far as we are aware, has not been applied to that field.

Starting from 3,6-(*tert*-butoxycarbonyl)imino-2,3,6-trideoxy-4,5-*O*-isopropylidene-L-*arabino*-hexose[7] (**1**) Knoevenagel–Doebner reaction[8] with hydrogen methyl malonate gave, after 3 h, a mixture of the two *trans*-regioisomers **2** and **3** in 50 and 40% yield, respectively (Scheme 1).

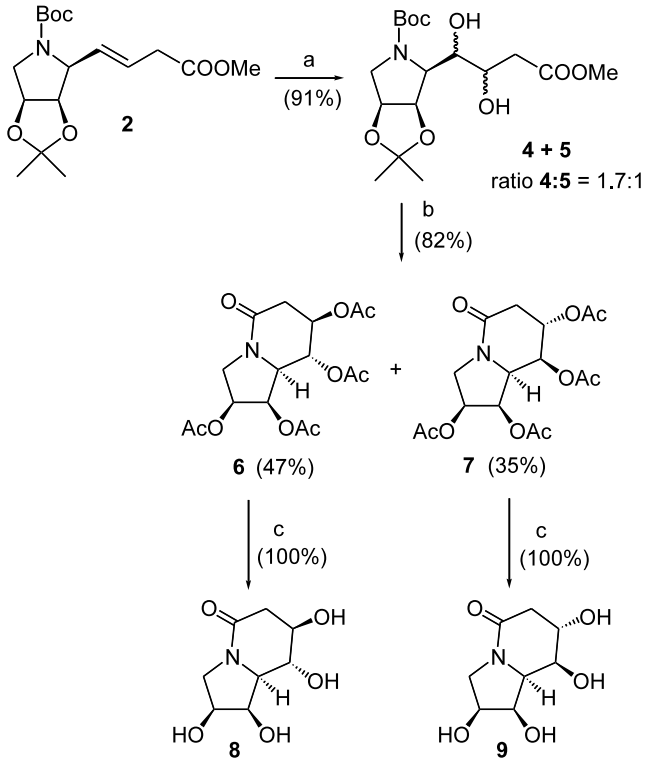
In the case of compound **2**, dihydroxylation reaction with a catalytic amount of osmium tetraoxide[9] gave a mixture of diols **4** and **5** in 91% yield and a low stereoselectivity of 1.7:1[10] (Scheme 2), which indicates that the sugar moiety exerts a weak control into the stereoselectivity. Reaction of the mixture **4** and **5** with trifluoroacetic acid followed by heating with NaOMe in MeOH under reflux afforded a mixture of indolizidinones that were separated by chromatography, after acetylation, giving compounds **6** and **7** in 47 and 35% yield, respectively. Compound **6** is the major one indi-



Scheme 1.

* Corresponding authors. Fax: +34-95-462-4960; e-mail: robina@us.es

0040-4039/02/$ - see front matter
PII: S0040-4039(02)02084-1

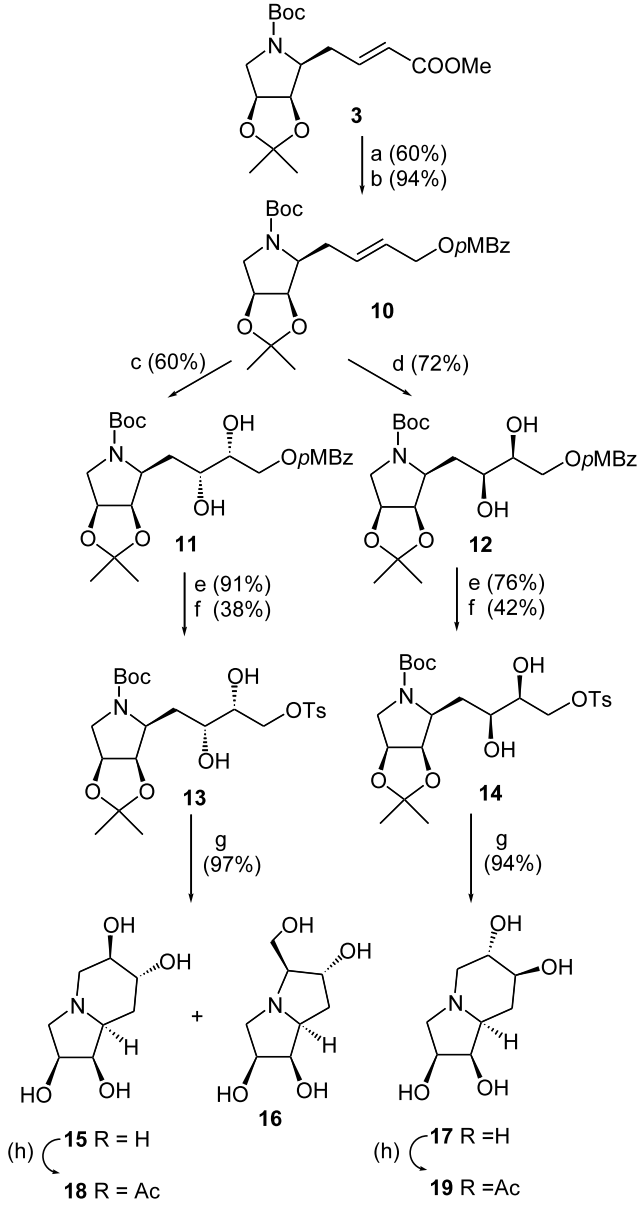


Scheme 2. *Reaction conditions*: (a) OsO_4 (cat.), NMO, acetone–H_2O 4:1, rt, 4 days; (b) 1. TFA aq., 2 h, 2. NaOMe, MeOH reflux, 16 h; 3. Ac_2O, Py, DMAP, rt, 16 h; (c) NaOMe, MeOH, rt, 2 h.

cating that the OsO_4 attack has taken place with preference for the top face. In order to improve the selectivity of the reaction, double asymmetric reactions[11] with the commercial reagents AD-mixα and AD-mixβ were carried out, although the reaction failed probably due to the high steric hindrance between the catalyst and the bulky protecting group. Treatment of **6** and **7** separately with NaOMe in MeOH rendered compounds **8** and **9** in quantitative yield. The spectral data of **6** and **7**[12] were consistent with the configuration assigned. Compound **6** shows large coupling constants $J_{7,8} = J_{8,8a} = 8.9$ Hz and NOEs between pairs of protons H7/H8a. On the other hand, compound **7**, presents a *gauche* relationship between H7, H8 and H8a ($J_{7,8} = J_{8,8a} = 4.6$ Hz) and NOEs between pairs of protons H8/H8a.

Similar results were obtained for compound **3**. Dihydroxylation reaction with a catalytic amount of OsO_4 and *N*-methylmorpholine at rt for 24 h, gave a mixture of the two diastereoisomeric diols in quantitative yield and a 1.4:1 ratio. With the idea of having a better diastereoselectivity in the hydroxylation reaction, we envisaged carrying out asymmetric Sharpless dihydroxylation in the *p*-methoxybenzoyl ester **10** (Scheme 3) obtained from **3** after reduction of the ester group with DIBALH (60%) and reaction with *p*-methoxybenzoyl chloride in the presence of triethylamine and dimethylaminopyridine (94%). Compound **10** is a good substrate for asymmetric dihydroxylation, because it is known[13] that aromatic moieties attached to allylic alcohols produce an excellent control in the diastereoselectivity when using the pseudoenantiomeric Cinchona alkaloid ligands for Sharpless reagents. Thus, hydroxylation of compound **10** with AD-mixβ[14] gave **11** as major compound (60% yield, d.e. = 91%). On the other hand, reaction of **10** with AD-mixα gave **12** as major compound (72% yield, d.e. = 97%).

Treatment of **11** and **12** separately with NaOMe/MeOH followed by regioselective tosylation of the primary alcohol afforded compounds **13** and **14** in moderate-to-good yield. Boc-deprotection of **13** (TFA aq.) followed by NH_4OH neutralization afforded tetrahydroxyindolizidine **15** (69%) and pyrrolizidine **16** (28%), via ring opening of the terminal epoxide formed from **13**. When the same conditions were applied to **14**,



Scheme 3. *Reaction conditions*: (a) DIBALH, DCM, −15°C; (b) 4-MeOBzCl, TEA, DMAP; (c) AD-mixβ, 0°C, 48 h; (d) AD-mixα, 0°C, 24 h; (e) NaOMe/MeOH, rt, 3 h; (f) TsCl, Py, −15°C, 2 h; (g) 1. TFA aq., 2. NH_4OH; (h) Ac_2O, Py.

Table 1.

Comp.	H-1	H-2	H-6	H-7
15	4.06	4.42	3.76	3.94
18	5.42	5.33	4.89	5.05
17	3.99	4.31	3.50	3.40
19	5.33	5.29	5.08	4.28

only indolizidine **17** was obtained in 94% yield. The spectroscopic data of **15**, **16** and **17** confirmed the proposed structures.[15] The absolute configuration of compounds **15** and **17** were based upon NOEs between pair of protons H7/H8-β for compound **15** and NOEs between H7/H8a, H7/H8-α and H6/H8-β for compound **17**. The indolizidine character of compounds **15** and **17** was demonstrated with the ^{1}H NMR spectra of their corresponding peracetates derivatives **18** and **19** (Table 1). A deshielding of the resonances for H1, H2, H6 and H7, was observed confirming the proposed structures. In the case of compound **16**, the pyrrolizidine structure and absolute configuration was based on its MSCI spectrum, where a loss of a hydroxymethyl group were observed and on its ^{1}H NMR spectrum where NOEs between pair of protons H7a/H7-α, H5/H7-α, H6/H7-β and H3-β/H-8 were observed.

This work presents a new synthetic approach for the construction of polyhydroxyindolizidines based on *syn*-hydroxylation of alkenyl pyrrolidines followed by cyclization. High stereoselectivity is obtained when using double asymmetric reactions. The present paper discloses for the first time the preparation of tetrahydroxyderivatives **8**, **9**, **15**, **17**.

Biological evaluation of the new molecules will be carried out and be reported in a forthcoming paper.

Acknowledgements

We thank Professor Pierre Vogel of the 'Institut des Sciences Moléculaires de l'Ecole Polytechnique Fédérale de Lausanne, Suisse' for discussions. This work was supported by the Ministerio de Educación y Cultura, (PB97/0730), the Junta de Andalucía, Spain (FQM 134). This work is part of the Action COST-D13-0001/99.

References

1. See e.g.: (a) Casiraghi, G.; Zanardi, F. *Chem. Rev*. **1995**, *95*, 1677–1716; (b) *Iminosugars as Glycosidase Inhibitors*; Stütz, A. E., Ed.; Wiley-VCH: Weinheim, 1999; (c) Zeng, Y.; Pan, Y. T.; Asano, N.; Nash, R. J.; Elbein, A. D. *Glycobiology* **1997**, *7*, 297; (d) Asano, N.; Nash, R. J.; Molyneux, R. J. Fleet, G. W. *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680; (e) Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols. M. *Chem. Rev*. **2002**, *102*, 515–553.
2. See e.g.: (a) Goss, P. E.; Baker, M. A.; Carver, J. P.; Dennis, J. W. *Clin. Cancer Res*. **1995**, *1*, 935; (b) Das, P. C.; Robert, J. D.; White, S. L.; Olden, K. *Oncol. Res*. **1995**, *7*, 425.
3. For reviews, see e.g.: (a) Cossy, J.; Vogel, P. *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1993; Vol. 12, pp. 275–363; (b) El Nemr, A. *Tetrahedron* **2000**, *56*, 8579–8629; (c) El Ashry, E. S. H.; Rahed, N.; Shobier, A. H. S. *Pharmazie* **2000**, *55*, 331–348.
4. See e.g.: lentiginosine and derivatives: (a) Brandi, A.; Cicchi, S.; Cordero, F. M.; Frignoli, R.; Goti, A.; Picasso, S.; Vogel, P. *J. Org. Chem*. **1995**, *60*, 6806–6812; (b) Cardona, F.; Goti, A.; Picasso, S.; Vogel, P.; Brandi, A. *J. Carbohydr. Chem*. **2000**, *19*, 585–601; (c) pentahydroxyindolizidines: Chen, Y.; Vogel, P. *J. Org. Chem*. **1994**, *59*, 2487–2496; Picasso, S.; Chen, Y.; Vogel, P. *Carbohydr. Lett*. **1993**, *1*, 1–8; (d) Izquierdo, I.; Plaza, M. J.; Robles, R.; Mota, A. J. *Tetrahedron: Asymmetry* **1998**, *9*, 1015–1027; 5-azacastanospermine: (e) Søndergard, K.; Liang, X.; Bols, M. *Chem. Eur. J*. **2001**, *7*, 2324–2331.
5. (a) Patil, N. T.; Tilekar, J. N.; Dhavale, D. D. *J. Org. Chem*. **2001**, *6*, 1065–1074; (b) Back, T. G.; Nakajima, K. *Org. Lett*. **1999**, *1*, 261–263; (c) Kawakami, T.; Ohtake, H.; Arakawa, H.; Okachi, T.; Imada, Y.; Murahashi, S.-I. *Org. Lett*. **1999**, *1*, 107–110; (d) Clark, R. B.; Pearson, W. H. *Org. Lett*. **1999**, *1*, 349–351.
6. Davis, B.; Bell, A. A.; Nash, R. J.; Watson, A. A.; Griffiths, R. C.; Jones, M. G.; Smith, C.; Fleet, G. W. J. *Tetrahedron Lett*. **1996**, *37*, 8565–8568.
7. Cardona, F.; Robina, I.; Vogel, P. *J. Carbohydr. Chem*. **2000**, *19*, 555–571.
8. López-Herrera, F. J.; Pino González, M. S. *Carbohydr. Res*. **1986**, *152*, 283–291 and references cited therein.
9. Donohoe, T. J.; Moore, P. R.; Beddoes, R. L. *J. Chem. Soc., Perkin Trans. 1* **1997**, 43–51.
10. Typical procedure for osmylation: Alkene **2** or **3** (1 mmol) was dissolved in acetone:H_2O 4:1 (3 mL), *N*-methylmorpholine (4 equiv.) and OsO_4/Bu^{t}OH (0.1 equiv.) was added and the reaction mixture stirred for 24 h at rt. An excess of Na_2SO_3 was added and the mixture stirred for 30 min at rt and then extracted with AcOEt. The combined extracts were washed with brine and water, dried and evaporated. Purification was achieved by column chromatography with DCM:acetone 25:1 as eluant.
11. Kolb, K. C.; van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev*. **1994**, 2483–2547.
12. Selected data for **6**: ^{1}H NMR (500 MHz, $CDCl_3$, δ ppm, *J* Hz) δ 5.27 (t, 1H, $J_{8,8a}=J_{8,7}=9.4$, H-8), 5.21 (ddd, 1H, $J_{7,6}=6.9$, $J_{7,6'}=8.8$, H-7), 3.80 (dd, 1H, $J_{1,8a}=2.8$, H-8a), 3.04 (dd, 1H, $^2J_{6,6'}=17.8$, H-6), 2.49 (dd, 1 H, H-6′). Selected data for **7**: ^{1}H NMR (300 MHz, $CDCl_3$, δ ppm, *J* Hz) δ 5.61 (t, 1H, $J_{8,8a}=J_{8,7}=4.6$, H-8), 5.36 (td, 1H, $J_{7,6}=7.2$, H-7), 4.21 (dd, 1H, $J_{1,8a}=3.2$, H-8a), 3.77 (d, 2H, H-6).
13. Guzmán Pérez, A.; Corey, E. J. *Tetrahedron Lett*. **1997**, *38*, 5941–5944.
14. Typical procedure for asymmetric dihydroxylation: To a solution of alkene **10** (0.1 mmol) in Bu^{t}OH:H_2O 1:1 (1.2 mL) at 0°C, AD-mixα or AD-mixβ (0.14 g) and $MeSO_2NH_2$ (0.1 equiv.) was added. The reaction mixture was stirred at 0°C for *x* days (AD-mixα, $x=1$; AD-mixβ, $x=2$). Work-up procedure is as described for osmylation.

15. Selected data for **15**: ^{1}H NMR (300 MHz, MeOD, δ ppm, J Hz) δ 3.94 (*c*, 1H, $J_{7,6}=J_{7,8\beta}=J_{7,8\alpha}=3.0$, H-7), 3.76 (m, 1H, H-6), 3.23–3.06 (m, 5H, H-3α, H-3β, H-5α, H-5β, H-8a), 2.30 (ddd, 1H, $J_{8\beta,8a}=12.5$, $^2J_{8\beta,8\alpha}=14.5$, H-8β), 1.79 (dt, 1H, $J_{8\alpha,8a}=2.7$, H-8α). Selected data for **16**: ^{1}H NMR (500 MHz, MeOD, δ ppm, J Hz) δ 4.43 (dt, 1H, $J_{7a,7\alpha}=9.9$, $J_{7a,7\beta}=J_{7a,1}=4.1$, H-7a), 4.33 (ddd, 1H, $J_{2,1}=4.0$, $J_{2,3\beta}=6.3$, $J_{2,3\alpha}=10.4$, H-2), 4.26 (ddd, 1H, H-6), 4.07 (t, 1H, H-1), 3.92 (dd, 1H, $J_{8,5}=3.6$, $^2J_{8,8'}=13.0$, H-8), 3.81 (dd, 1H, $J_{8',5}=9.1$, H-8′), 3.52 (td, 1H, $J_{5,6}=8.6$, H-5), 3.46 (dd, 1H, $^2J_{3\beta,3\alpha}=10.8$, H-3β), 3.27 (t, 1H, H-3α), 2.48 (ddd, 1H, $J_{7\beta,6}=6.2$, $^2J_{7\beta,7\alpha}=12.6$, H-7β), 1.92 (dd, 1H, $J_{7\alpha,6}=8.0$, H-7α). Selected data for **17**: ^{1}H NMR (300 MHz, MeOD, δ ppm, J Hz) δ 3.50 (ddd, 1H, $J_{6,5\alpha}=10.0$, $J_{6,7}=8.9$, $J_{6,5\beta}=4.8$, H-6), 3.40 (ddd, 1H, $J_{7,8\alpha}=4.9$, $J_{7,8\beta}=11.0$, H-7), 3.17 (dd, 1H, $^2J_{5\beta,5\alpha}=10.8$, H-5β), 2.28 (ddd, 1H, $J_{8a,1}=3.9$, $J_{8a,8\beta}=11.7$, H-8a), 2.04 (t, 1H, $J_{5\alpha,6}=10.5$, H-5α), 1.97 (ddd, 1H, $J_{8\alpha,8a}=2.6$, $^2J_{8\alpha,8\beta}=13.1$, H-8α), 1.68 (ddd, 1H, $J_{8\beta,8a}=1.2$, H-8β).