

A Rapid Access to the Spiroaminoketal Framework

Ahmatjan Tursun, Bettina Aboab, Anne-Sophie Martin, Marie-Eve Sinibaldi,* Isabelle Canet*

Laboratoire de Synthèse Et Etude de Systèmes à Intérêt Biologique (SEESIB), UMR 6504, Université Blaise Pascal, 63177 Aubière Cedex, France

Fax +33(4)73407717; E-mail: icanet@chimie.univ-bpclermont.fr; E-mail: sinibald@chimie.univ-bpclermont.fr

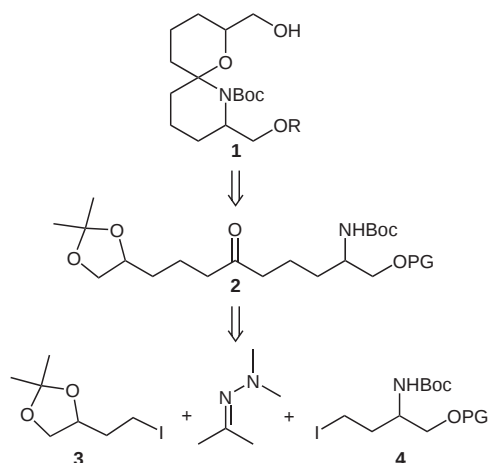
Received 16 June 2005

Abstract: A convergent and stereoselective synthesis of 1-oxa-7-azaspiro[5.5]undecane is described. This functional new spiroheterocycle is readily available from acetone *N,N*-dimethylhydrazone via a double alkylation and subsequent spiroannulation process.

Key words: spiro compounds, alkylations, hydrazones, synthesis, amino acid

Molecules possessing heterocycles fused by a spirocarbon atom are ubiquitous in nature, with many of them displaying interesting biological properties. 1,7-Dioxaspiro[5.5]undecane (6,6-spiroketal) moieties have received particular attention as they are found in a wide and diverse series of natural products such as polyether ionophores, marine alkaloids, or insect pheromones. Approaches for the elaboration of this ring system have been extensively reported in the literature.¹

On the contrary, synthesis of spiroaminoketals, key intermediates in the preparation of biologically active compounds such as hydantocidin,² spironucleosides,³ azaspiracid,⁴ sanglifehrin,⁵ or solanum alkaloids,⁶ have been less explored.⁷ As part of our continued interest in the synthesis of homochiral spiroheterocycles of biological interest, we wish to report herein an efficient approach to spiroaminoketal **1** using the spiroannulation methodology we have previously reported for the preparation of spiroketals^{8a} (Scheme 1).

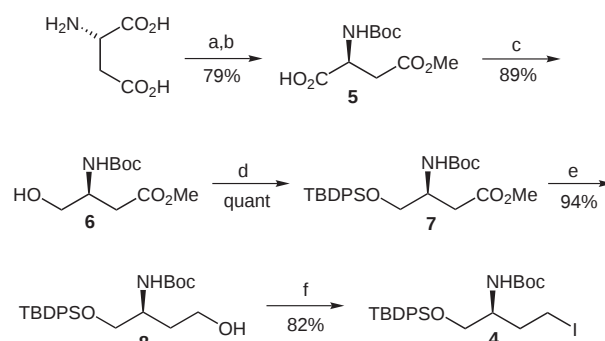


Scheme 1

Our synthetic strategy lies in the use of iodides **3** and **4** as key precursors for the iterative alkylation of acetone *N,N*-dimethylhydrazone.^{8b,c,d} Upon synthesis of the dissymmetric ketone **2**, cyclization should provide an efficient access to the [5.5]azaaxaspiranic core.

Synthesis of (*S*)-**3** has been previously reported.^{8a} Preparation of (*S*)-**4** was accomplished from L-aspartic acid (Scheme 2). L-Aspartic acid was transformed by classical procedures into its *N*-Boc methylester **5** in two steps and 79% yield. The reduction of the carboxylic function of **5**, via its activated ester, led efficiently to **6**⁹ (89% yield). Protection of the resulting alcohol using TBDPSCl in the presence of imidazole in CH₂Cl₂ gave, nearly quantitatively, the *tert*-butyldiphenylsilyl ether **7**. The ester function was then reduced by treatment with a 2 M solution of LiBH₄ in THF, resulting in the formation of alcohol **8** in 94% yield. Finally, conversion of **8** into the required iodide **4**¹⁰ was cleanly realized by treatment with iodine and triphenylphosphine/imidazole in toluene at room temperature in 82% yield. Thus (*S*)-**4** was obtained in six steps and 54% overall yield from L-aspartic acid.

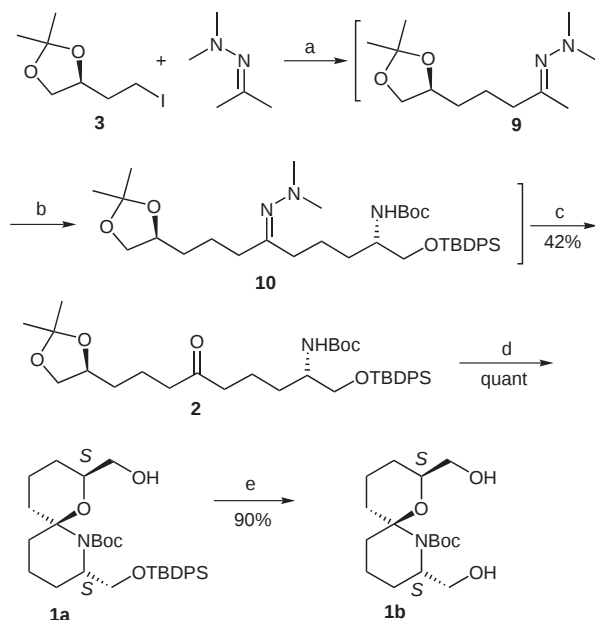
With synthons **3** and **4** in hand, we then began the alkylation process (Scheme 3). We first used the experimental protocol developed for the synthesis of spiroketals,^{8a} namely: initial alkylation of acetone *N,N*-dimethylhydrazone using LDA as base and iodide (*S*)-**3** followed by the second using BuLi as base and (*S*)-**4**. The first step resulted in quantitative formation of compound **9**, however, and



Scheme 2 Synthesis of iodide **4**. *Reagents and conditions:* a) SOCl₂, MeOH, −10 °C then r.t., 25 min; b) (*t*-BuOCO)₂O, Na₂CO₃, dioxane–H₂O, r.t., 12 h; c) *N*-hydroxysuccinimide (1.2 equiv), DCC (1.2 equiv), CH₂Cl₂, r.t., 3 h, NaBH₄ (1.0 equiv), THF–EtOH (3–1), 0 °C, 15 min; d) TBDPSCl (1.2 equiv), imidazole (1.5 equiv), CH₂Cl₂, 0 °C (10 min), r.t. (3 h); e) 2 M LiBH₄ (1.5 equiv, THF), 0 °C (10 min), r.t. (12 h); f) I₂ (3.1 equiv), imidazole (2.9 equiv), PPh₃ (3.0 equiv), toluene, r.t., 48 h.

in spite of numerous attempts, the second alkylation step led to complex mixtures in which the dialkylated product was obtained in very poor yield. This result was certainly disappointing but in agreement with those reported by others authors.^{8b,c,d} Indeed, in the literature, alkylation of monosubstituted *N,N*-dimethylhydrazones was achieved using various experimental conditions depending on the nature of the coupled iodide and an extensive work was often required. We therefore began a systematic study of the experimental conditions for this second step, varying the nature and amount of base, the temperature for the anion formation, and the use, in various quantities, of additives such as DMPU, HMPA, DABCO, or 18-crown-6.

The best results were obtained using BuLi (2.0 equiv), a reaction temperature of -10°C , and a reaction time of 1.5 hours; followed by the addition of a mixture of **4** (0.95 equiv) and freshly distilled DMPU (10.0 equiv). In these conditions, hydrazone **10** was obtained and used without purification in the hydrolysis step. $\text{SiO}_2/\text{H}_2\text{O}$ induced cleavage of **10** furnished ketone **2**,¹¹ which was easily purified and isolated in 42% overall yield from acetone *N,N*-dimethylhydrazone (Scheme 3).



Scheme 3 Synthesis of spiroaminoketal **1**. *Reagents and conditions:* a) LDA (1.1 equiv), THF, 1 h, -25°C , (*S*)-**3** (1.0 equiv), 10 min; b) *n*-BuLi (2.0 equiv), THF, 1.5 h, -10°C ; (*S*)-**4** (0.95 equiv), DMPU (10.0 equiv), r.t., overnight; c) $\text{SiO}_2/\text{H}_2\text{O}$, CH_2Cl_2 , r.t., 48 h; d) *p*-TsOH (0.02 equiv), MeOH, 40°C (2 h), r.t. (12 h); e) TBAF, THF, r.t., 3 h.

Finally, acetonide deprotection with concomitant ring closure was performed by treatment of **2** with a catalytic amount of *p*-TsOH in MeOH to afford spiroaminoketal **1a** as the sole product in quantitative yield.¹² Treatment of **1a** with TBAF in anhydrous THF for three hours led to the expected diol **1b**¹³ in 90% yield.

The stereochemical course of the acid-catalyzed ring closure of **2** has been investigated by NMR and through molecular modeling of **1a**. Conformational analysis¹⁴ showed that the (2*S*,6*S*,8*S*)-**1a** ($\Delta H_f = -240.09 \text{ Kcal mol}^{-1}$) is more stable than its (2*S*,6*R*,8*S*) isomer by 1.4 Kcal mol^{-1} (Figure 1). This results in a 95:5 theoretical ratio between the isomers, which was consistent with the experimental observation of only one product. Thus, compound **1a** exhibited a structure stabilized by a double anomeric effect and a weak hydrogen bond between OH and O-1 (calculated distance $d = 2.43 \text{ \AA}$, valence angle: 105°). NOESY experiments (Figure 2) confirmed the proposed spirocenter stereochemistry as 6*S*.

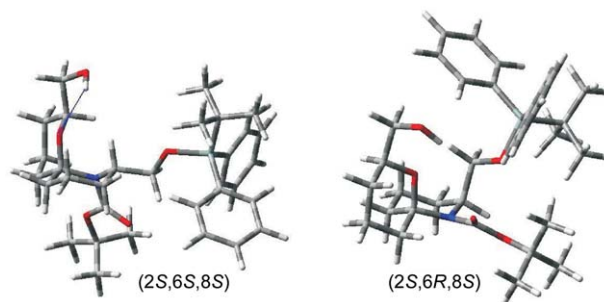


Figure 1 Calculated structures for (2*S*,6*S*,8*S*)-**1a** and its isomer (2*S*,6*R*,8*S*). Hydrogen bond is represented by a blue line.

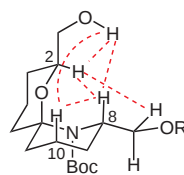


Figure 2 Selected NOE (red dashed lines) for (2*S*,6*S*,8*S*)-**1a**.

In summary, we have shown that our double alkylation–spiroannulation sequence allowed a rapid and stereoselective access to the spiroaminoketal framework. Functionalized 1-oxa-7-azaspiro[5.5]undecanes **1** could be efficiently assembled in only five steps and 37% overall yield, starting from acetone *N,N*-dimethylhydrazone and chiral iodides **3** and **4**.

Extension of this procedure to spiroaminoketals in the [4.5]decane and [4.4]nonane series, is in progress in our laboratory and will be published with full experimental details in due course.

References

- (1) For reviews, see (a) Mead, K. T.; Brewer, B. N. *Curr. Org. Chem.* **2003**, 7, 227. (b) Vaillancourt, V.; Pratt, N. E.; Perron, F.; Albizati, K. F. In *The Total Synthesis of Natural Products*, Vol. 8; John Wiley & Sons: New York, **1992**, 533. (c) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, 89, 1617.
- (2) Shiozaki, M. *Carbohydr. Res.* **2002**, 337, 2077; and references cited therein.

- (3) (a) Gasch, C.; Pradera, M. A.; Salameh, B. A. B.; Molina, J. L.; Fuentes, J. *Tetrahedron: Asymmetry* **2001**, *12*, 1267. (b) Chatgililoglu, C.; Gimisis, T.; Spada, G. P. *Chem.-Eur. J.* **1999**, *5*, 2866. (c) Kittaka, A.; Asakura, T.; Kuse, T.; Tanaka, H.; Yamada, N.; Nakamura, K. T.; Miyasaka, T. *J. Org. Chem.* **1999**, *64*, 7081. (d) Kittaka, A.; Tanaka, H.; Odanaka, Y.; Ohnuki, K.; Yamaguchi, K.; Miyasaka, T. *J. Org. Chem.* **1994**, *59*, 3636.
- (4) (a) Nicolaou, K. C.; Li, Y.; Uesaka, N.; Koftis, T. V.; Vyskocil, S.; Ling, T.; Govindasamy, M.; Qian, W.; Bernal, F.; Chen, D. Y.-K. *Angew. Chem. Int. Ed.* **2003**, *42*, 3643. (b) Sasaki, M.; Iwamuro, Y.; Nemoto, J.; Oikawa, M. *Tetrahedron Lett.* **2003**, *44*, 6199. (c) Nicolaou, K. C.; Pihko, P. N.; Diedrichs, N.; Zou, N.; Bernal, F. *Angew. Chem. Int. Ed.* **2001**, *40*, 1262. (d) Ofuji, K.; Satake, M.; McMahon, T.; James, K. J.; Naoki, H.; Oshima, Y.; Yasumoto, T. *Biosci., Biotechnol., Biochem.* **2001**, *65*, 740. (e) Forsyth, C. J.; Hao, J.; Aiguade, J. *Angew. Chem. Int. Ed.* **2001**, *40*, 3663. (f) Aiguade, J.; Hao, J.; Forsyth, C. J. *Tetrahedron Lett.* **2001**, *42*, 817. (g) Satake, M.; Ofuji, K.; Naoki, H.; James, K. L.; Furey, A.; McMahon, T.; Silke, J.; Yasumoto, T. *J. Am. Chem. Soc.* **1998**, *120*, 9967.
- (5) (a) Lindel, T. *Organic Synthesis Highlights V*; Schmalz, H. G.; Wirth, T., Eds.; Wiley: New York, **2003**, 350. (b) Paquette, L. A.; Duan, M.; Konetzki, I.; Kempmann, C. *J. Am. Chem. Soc.* **2002**, *124*, 4257. (c) Duan, M.; Paquette, L. A. *Angew. Chem. Int. Ed.* **2001**, *40*, 3632. (d) Nicolaou, K. C.; Murphy, F.; Barluenga, S.; Ohshima, T.; Wei, H.-X.; Xu, J.; Gray, D. L. F.; Baudoin, O. *J. Am. Chem. Soc.* **2000**, *122*, 3830. (e) Nicolaou, K. C.; Xu, J.; Murphy, F.; Barluenga, S.; Baudoin, O.; Wei, H.-X.; Gray, D. L. F.; Ohshima, T. *Angew. Chem. Int. Ed.* **1999**, *38*, 2447. (f) Fehr, T.; Kallen, J.; Oberer, L.; Sanglier, J. J.; Schilling, W. *J. Antibiot.* **1999**, *52*, 474.
- (6) (a) Driedger, D. R.; Sporns, P. *Food Agric. Immunol.* **2001**, *13*, 33. (b) Weissenberg, M. *Phytochemistry* **2001**, *58*, 501. (c) Laurila, J.; Laakso, I.; Väänänen, T.; Kuronen, P.; Huopalahti, R.; Pehu, E. *J. Agric. Food Chem.* **1999**, *47*, 2738. (d) Ripperger, H.; Schreiber, K. In *The Alkaloids*, Vol. XIX; Rodrigo, R. G. A., Ed.; Academic Press: New York, **1981**.
- (7) For syntheses of other spiroaminoketals, see: (a) Freire, R.; Martin, A.; Perez-Martin, I.; Suarez, E. *Tetrahedron Lett.* **2002**, *43*, 5113. (b) Izquierdo, I.; Plaza, M. T.; Robles, R.; Rodriguez, C.; Ramirez, A.; Mota, A. J. *Eur. J. Org. Chem.* **1999**, 1269. (c) Aamlid, K. H.; Hough, L.; Richardson, A. C. *Carbohydr. Res.* **1990**, *202*, 117. (d) Alanine, A. I. D.; Fishwick, C. W. G.; Szantay, C. J. *Tetrahedron Lett.* **1989**, *30*, 6573.
- (8) (a) Tursun, A.; Canet, I.; Aboab, B.; Sinibaldi, M.-E. *Tetrahedron Lett.* **2005**, *46*, 2291. For the synthesis of others spiroacetals using alkylation of hydrazones, see: (b) Dias, L. C.; de Oliveira, L. G. *Org. Lett.* **2004**, *6*, 2587. (c) Crimmins, M. T.; Rafferty, S. W. *Tetrahedron Lett.* **1996**, *37*, 5649. (d) Schreiber, S. L.; Wang, Z. *J. Am. Chem. Soc.* **1985**, *107*, 5303.
- (9) (a) Markidis, T.; Kokotos, G. *J. Org. Chem.* **2001**, *66*, 1919. (b) Kadota, I.; Saya, S.; Yamamoto, Y. *Heterocycles* **1997**, *46*, 335.
- (10) Selected data for (S)-**4**: yellow solid; mp 57 °C; $[\alpha]_{\text{D}}^{25}$ -17.3 (c 0.15, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ = 1.07 (s, 9 H), 1.44 (s, 9 H), 2.10 (m, 2 H), 3.13 (m, 2 H), 3.60 (dd, J = 10.0, 2.0 Hz, 1 H), 3.69 (dd, J = 10.0, 3.0 Hz, 1 H), 3.75 (m, 1 H), 4.70 (d, J = 8.0 Hz, 1 H), 7.41 (m, 6 H), 7.62 (m, 4 H). ¹³C NMR (100 MHz, CDCl₃): δ = 1.0, 18.9, 26.6, 28.0, 36.4, 52.5, 64.9, 79.0, 127.5, 129.5, 132.6, 135.1, 155.1. HRMS: m/z calcd for C₂₅H₃₆INO₃Si [M + Na⁺]: 576.1407. Found: 576.1421.
- (11) Selected data for **2**: pale yellow oil; $[\alpha]_{\text{D}}^{25}$ -9.3 (c 0.80, CHCl₃). ¹H NMR (400 MHz, CDCl₃): δ = 1.05 (s, 9 H), 1.33 (s, 3 H), 1.39 (s, 3 H), 1.43 (s, 9 H), 1.40–1.72 (m, 8 H), 2.39 (m, 2 H), 2.42 (t, J = 6.5 Hz, 2 H), 3.49 (t, J = 7.0 Hz, 1 H), 3.57 (dd, J = 9.0, 3.0 Hz, 1 H), 3.65 (m, 2 H), 4.02 (t, J = 7.0 Hz, 1 H), 4.04 (m, 1 H), 4.65 (d, J = 8.5 Hz, 1 H), 7.39 (m, 6 H), 7.62 (m, 4 H). ¹³C NMR (100 MHz, CDCl₃): δ = 19.3, 19.9, 20.0, 25.7, 26.8, 26.9, 28.4, 31.2, 32.9, 42.3, 51.4, 65.6, 69.3, 75.7, 79.0, 108.7, 127.7, 129.7, 133.2, 135.5, 155.6, 210.3. HRMS: m/z calcd for C₃₅H₅₃NO₆Si [M + Na⁺]: 634.3540. Found: 634.3549.
- (12) Selected data for **1a**: foam; $[\alpha]_{\text{D}}^{25}$ -29.2 (c 0.88, CHCl₃). ¹H NMR (400 MHz, C₆D₆): δ = 0.98 (m, 1 H), 1.12 (s, 9 H), 1.33 (m, 2 H), 1.46 (s, 9 H), 1.46 (m, 1 H), 1.49 (m, 2 H), 1.58 (m, 3 H), 1.74 (m, 3 H), 3.48 (dd, J = 10.0, 4.0 Hz, 1 H), 3.55 (t, J = 6.5 Hz, 1 H), 3.59 (m, 2 H), 3.87 (m, 1 H), 4.08 (m, 1 H), 4.47 (d, J = 9.0 Hz, 1 H, OH), 7.23 (m, 6 H), 7.73 (m, 4 H). ¹³C NMR (100 MHz, C₆D₆): δ = 17.3, 19.5, 20.1, 27.1, 28.6, 28.7, 32.3, 34.4, 38.0, 52.3, 66.3, 69.0, 74.7, 78.4, 108.8, 128.1, 130.0, 133.9, 136.0, 155.6. HRMS: m/z calcd for C₃₂H₄₇NO₅Si [M + Na⁺]: 576.3121. Found: 576.3134.
- (13) Selected data for **1b**: white solid; mp 86 °C. $[\alpha]_{\text{D}}^{25}$ -41.8 (c 1.00, CHCl₃). ¹H NMR (400 MHz, C₆D₆): δ = 0.97 (m, 1 H), 1.21 (m, 1 H), 1.35 (m, 2 H), 1.43 (s, 9 H), 1.49 (m, 2 H), 1.56 (m, 3 H), 1.69 (m, 3 H), 2.55 (br s, 1 H, OH), 3.34 (m, 1 H), 3.44 (m, 1 H), 3.56 (m, 2 H), 3.68 (m, 1 H), 4.08 (m, 1 H), 4.60 (d, J = 7.5 Hz, 1 H, OH). ¹³C NMR (100 MHz, C₆D₆): δ = 17.3, 20.1, 28.5, 28.6, 31.8, 34.3, 37.8, 53.1, 65.7, 69.0, 74.7, 78.8, 108.8, 156.5. HRMS: m/z calcd for C₁₆H₂₉NO₅ [M + Na⁺]: 338.1943. Found: 338.1938.
- (14) Conformational analysis was performed using the Monte-Carlo Multiple Minimum Method with MM3: (a) Chang, G.; Wayne, C.; Guida, W.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379. (b) Allinger, N. L.; Yuh, Y. H.; Lii, J. H. *J. Am. Chem. Soc.* **1989**, *111*, 8551. (c) Force field Macromodel 7.0 program was used: *Macromodel 7.0*; Schroedinger Inc.: Portland, OR, **2001**. (d) Quantum semi-empirical calculations AM1, were carried out: Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902. (e) Geometries of global minima of both 6-S and 6-R **1a** isomers were carried out using AMPAC 7.0: *Ampac 7.0*; Semichem: USA, **2000**.