Pergamon

Tetrahedron Letters 41 (2000) 1997–2000

TETRAHEDRON LETTERS

Radical mediated stereoselective synthesis of chiral spiroacetals from enol-esters†

G. V. M. Sharma,[a,*] A. Subash Chander,[a] V. Goverdhan Reddy,[a] K. Krishnudu,[a] M. H. V. Ramana Rao [b] and A. C. Kunwar [b]

[a]*Discovery Laboratory, Organic Chemistry Division III, Indian Institute of Chemical Technology, Hyderabad-500 007, India*
[b]*NMR Group, Indian Institute of Chemical Technology, Hyderabad-500 007, India*

Received 22 November 1999; accepted 11 January 2000

Abstract

Stereoselective synthesis of chiral spiroacetals starting from enol-ester **1**, derived from D-manno lactone, is described. The strategy involves 1,4-addition of a variety of alcohols to **1** in the presence of NBS to give α-bromo acetals, which undergo a regio- and stereoselective radical cyclisation to give highly functionalised chiral spiroacetals.

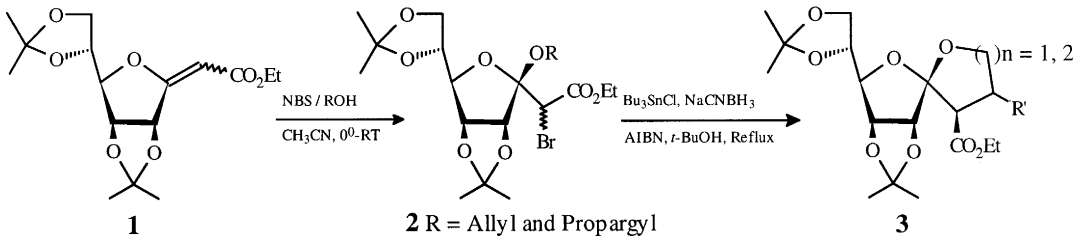
Keywords: spiroacetals; radical cyclisation; enol-ester; α-bromo acetals.

Spiroacetals such as 1,6-dioxaspiro[4,4]nonane, 1,6-dioxaspiro[4,5]decane and 1,7-dioxaspiro[5,5]undecane are part structures of several natural products of biological importance (for example: sex pheromones, polyether antibiotics etc.). These metabolites are produced from sources that include insects, microbes, plants, fungi and marine organisms.[1] Papulachandrins A–D,[2,3] having antibiotic activity, represent a pyranoside based spiroacetal class of natural products. The interesting pharmacological importance of natural products containing spiroacetals has triggered immense interest for the development of synthetic methods for spiroacetals[4,5] and enantiomerically enriched spiroacetals from carbohydrates.[6–8] Herein, we report a protocol, utilising an intramolecular radical cyclisation of α-halo acetals of chiral templates derived from mannofuranoside enol-ester **1**, for the synthesis of functionalised enantiomerically enriched spiroacetals.

The formation of a C–C bond at the anomeric centre of sugars can lead to stereoselective *C*-glycoside formation.[9–11] In the present study, intramolecular regio- and stereoselective radical cyclisation[12] was envisaged as the appropriate route for C–C bond formation on chiral α-halo acetals[13,14] (Scheme 1) derived from the enol-ester **1**[15] prepared from D-mannose. Radical reactions on enol-esters[16] have been rarely exploited in organic synthesis.

* Corresponding author.
† IICT Communication No. 4456.

0040-4039/00/$ - see front matter
PII: S0040-4039(00)00083-6



Scheme 1.

The enol-ester **1**, derived from D-manno lactone on reaction with NBS in the presence of propargyl alcohol gave α-bromo acetal **4**[17–21] through a 1,4-addition reaction. The epimers were separated by chromatography and independently subjected to regio- and stereoselective radical cyclisation[22] of the 5-hexynyl system using *n*-Bu_3SnCl[23,24]–$NaCNBH_3$[25] in presence of AIBN in *t*-BuOH at reflux to afford the functionalised spiroacetal **5**.‡ The stereochemistry at the spirocentre was defined by extensive ^1H NMR studies (DQFCOSY, NOESY, difference NOE and indirect couplings). Of special significance is the characteristic cross peak in the NOESY spectrum between H-3 and H-5.

Having utilised successfully enol-ester **1** for the synthesis of functionalised spiroacetals, the methodology was extended to the synthesis of a variety of spiroacetals. Accordingly, **1** was subjected to addition with propargylic alcohols such as butyne-1,4-diol and 4-butynol to give acetals **6** and **7** (Table 1), respectively. Similarly reaction of **1** with allyl alcohol and *cis*-butene-1,4-diol furnished **10** and **11**, respectively.

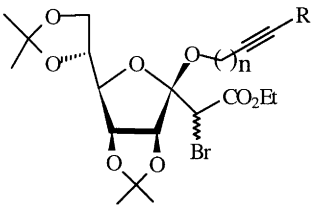
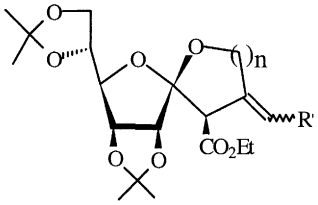
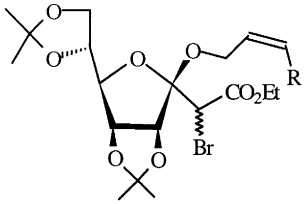
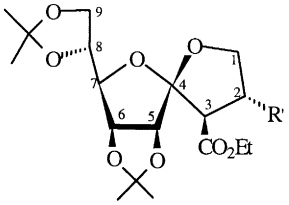
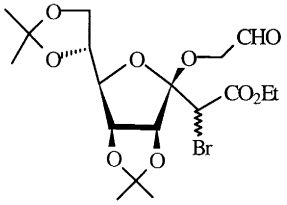
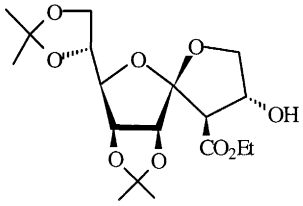
The alcohol **6** underwent radical cyclisation to afford **8** as a mixture of geometrical isomers, while acetal **7** gave the 1,7-dioxaspiro[5,4]decane system **9**.‡ Characteristic indirect couplings (^3J) in the six-membered ring, as well as the cross peak in the NOESY spectrum between protons H-4 and H-6 were utilised to fix the structure and stereochemistry of **9**. Similarly the acetals **10** and **11** were reacted with *n*-Bu_3SnCl–$NaCNBH_3$ to afford the spiroacetals **12** and **13**, respectively. The indirect couplings $J_{1,2}$, $J_{1',2}$ and $J_{2,3}$ of 7.8, 7.8 and 4.7 Hz are consistent with the expected stereochemistry at C-2 in **12**.

Spiroacetals containing hydroxyl groups have been the subject of recent interest. After successful radical cyclisation of 5-hexenyl, 5- and 6-hexynyl systems, the study was extended to the 5-oxo[26] radical system to furnish spiroacetals bearing hydroxyl groups. Accordingly, **10** was subjected to ozonolysis to afford aldehyde **14**, which successfully underwent regio and stereoselective cyclisation onto the carbonyl to afford the spiroacetal **15** in 84% yield, $[\alpha]_D$ +31.2 (*c* 1.0, $CHCl_3$).

Thus, in the present radical cyclisation protocol: (a) less well studied enol-ester radical reactions are utilised; (b) enol-ester **1** prepared from D-manno lactone by olefination was exploited for the first time; and (c) 5-hexenyl, 5- and 6-hexynyl and 5-oxo systems have been efficiently used to provide

‡ Spectral data of selected compounds. Compound **5**: $[\alpha]_D$ +78.7 (*c* 1.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.26 (t, 3H, *J*7.1 Hz, -OCH_2CH_3), 1.30, 1.37, 1.43, 1.44 (4s, 12H), 3.58 (s, 1H, H-3), 3.87 (dd, 1H, $J_{8,9'}$4.1, $J_{9,9'}$8.7 Hz, H-9′), 3.97 (dd, 1H, $J_{6,7}$2.8, $J_{7,8}$8.2 Hz, H-7), 4.07 (dd, 1H, $J_{8,9}$6.2 Hz, H-9), 4.19 (m, 2H, -OCH_2CH_3), 4.36 (ddd, 1H, H-8), 4.44 (br.d, 1H, $J_{1',1}$12.8 Hz, H-1′), 4.57 (ddd, 1H, H-1), 4.82 (dd, 1H, $J_{5,6}$6.0 Hz, H-6), 4.83 (d, 1H, H-5), 5.0 7 (br.s, 1H, *J*4.35 Hz, C=CH_2), 5.26 (dd,1H, C=CH_2); FABMS: 369 (M-15). Compound **9**: $[\alpha]_D$ −19.4 (*c* 1.15, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.24 (t, 3H, *J*7.03 Hz, -OCH_2CH_3), 1.29, 1.37, 1.43, 1.45 (4s, 12H), 2.09 (br.d, 1H, $J_{1,2'}$2.6, $J_{2,2'}$14.0 Hz, H-2′), 2.51 (ddd, 1H, $J_{1,2}$12.5, $J_{1',2}$5.8 Hz, H-2), 3.36 (s, 1H, H-4), 3.68 (ddd, 1H, $J_{1,1'}$10.8 Hz, H-1), 3.78 (br. dd, 1H, H-1′), 3.79 (m, 1H, $J_{7,8}$3.4, $J_{8,9}$8.1 Hz, H-8), 3.96 (dd, 1H, $J_{9,10}$4.3, $J_{10,10'}$8.9 Hz, H-10), 4.09 (dd, 1H, $J_{9,10'}$6.3 Hz, H-10′), 4.10–4.25 (m, 2H, -OCH_2CH_3), 4.37 (ddd, 1H, H-9), 4.67 (d, 1H, $J_{6,7}$5.9 Hz, H-6), 4.78 (dd, 1H, H-7), 4.97 (t, 1H, *J*1.7 Hz, C=CH_2), 5.03 (t, 1H, C=CH_2); FABMS: 399 (M+1), 398 (M^+), 383 (M−15).

Table 1

α-Bromo acetal	Spiroacetal	Yield (%)
		
4 n = 1, R = H **6** n = 1, R = CH_2OH **7** n = 2, R = H	**5** n = 1, R' = H **8** n = 1, R' = CH_2OH **9** n = 2, R' = H	62 79 78
		
10 R = H **11** R = CH_2OH	**12** R' = CH_3 **13** R' = CH_2CH_2OH	85 67
		84
14	**15**	

highly functionalised spiroacetals with a variety of functional groups that could be used for further functionalisation.

Acknowledgements

A. Subash Chander is grateful to the UGC, New Delhi and V. Goverdhan Reddy is thankful to CSIR, New Delhi, for financial assistance.

References

1. For reviews, see: Vaillancourt, V.; Praft, N. E.; Perron, F.; Albizati, K. F. *In the Total Synthesis of Natural Products*; Apsimon, J., Ed.; Wiley: New York, 1992; Vol. 8, pp. 533–691. Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309–3364.
2. Traxler, P.; Tosch, W.; Zak, O. *J. Antibiotics* **1987**, *40*, 1146–1164; references cited therein.
3. Traxler, P.; Fritz, H.; Fuhrer, H.; Richter, W. J. *J. Antibiotics* **1980**, *33*, 967–978.
4. Perron, F.; Albizati, K. F. *Chem. Rev*. **1989**, *89*, 1617–1661.

5. Kluge, A. F. *Heterocycles* **1986**, *24*, 1699–1740.
6. Cubero, I. I.; Lopez Espinosa, M. T. P.; Kari, N. *Carbohydr. Res*. **1995**, *268*, 187–200.
7. Van Hooft, P. A. V.; Leeuwenburgh, M. A.; Overkleeft, H. S.; Van der Marel, G. A.; Van Boeckel, C. A. A.; Van Boom, J. H. *Tetrahedron Lett.* **1998**, *39*, 6061–6064.
8. Martin, A.; Salazar, J. A.; Suarez, E. *J. Org. Chem*. **1996**, *61*, 3999–4006.
9. For reviews, see: Postema, M. H. D. *Tetrahedron* **1992**, *48*, 8545–8599; *Recent Developments in* C-*glycosides Synthesis*; Herscoviei, J.; Antonkis, K. In Studies in Natural Products Chemistry, Atta-ur-Rahman, Ed.; Elsevier, Oxford; 1992.
10. Sharma, G. V. M.; Chander, A. S.; Krishnudu, K.; Krishna, P. R. *Tetrahedron Lett*. **1997**, *38*, 9051–9054.
11. Sharma, G. V. M.; Chander, A. S.; Krishnudu, K.; Krishna, P. R. *Tetrahedron Lett*. **1998**, *39*, 6957–6960.
12. Giese, B.; Kopping, B.; Gobel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Tarach, F. Radical Cyclisation Reactions. In *Organic Reactions*; Paquet, L. A. et al. 1996, John Wiley & Sons: New York, Vol. 48, p. 301.
13. Sharma, G. V. M.; Krishnudu, K. *Carbohydr. Res*. **1995**, *268*, 287–293.
14. Sharma, G. V. M.; Rao, V. S. *Carbohydr. Res*. **1992**, *226*, 185–188.
15. Lakhrissi, M.; Chapleur, Y. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 750–752.
16. Lubbers, T.; Schafer, H. J. *Synlett* **1991**, 861.
17. Stork, G.; Mook Jr., R. *J. Am. Chem. Soc*. **1983**, *105*, 3720–3722; idem *ibid* **1987**, *109*, 2829–2831.
18. Morikawa, T.; Nishiwaki, T.; Iitaka, Y.; Kobayashi, Y. *Tetrahedron Lett*. **1987**, *28*, 671–674.
19. Ueno, Y.; Chino, K. *J. Am. Chem. Soc.* **1982**, *104*, 5564–5566.
20. De Mesmaeker, A.; Hoffmann, P.; Winkler, T.; Waldner, A. *Synlett* **1990**, 201–204.
21. Audim, C.; Lancelin, J. M.; Beau, J. M. *Tetrahedron Lett*. **1988**, *29*, 3691–3694.
22. Giese, B. *Radicals in Organic Synthesis: Formation of Carbon Bonds*; Pergamon, Oxford, 1986.
23. Stork, G.; Sher, P. M. *J. Am. Chem. Soc*. **1986**, *108*, 303–304.
24. Neumann, W. P. *Synthesis* **1987**, 665–683.
25. Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1975**, *40*, 2554–2557.
26. Tsang, R.; Dickson Jr., J. K.; Pak, H.; Walton, R.; Fraser-Reid, B. *J. Am. Chem. Soc*. **1987**, *109*, 3484–3486.