



Indium-mediated coupling of 3-bromopropenyl acetate with (*S*)-Garner aldehyde: a route to 1,4-dideoxy-1,4-L-iminoribitol

Marco Lombardo,* Sebastiano Licciulli and Claudio Trombini*

Dipartimento di Chimica 'G. Ciamician', Università di Bologna, via Selmi 2, I-40126 Bologna, Italy

Received 16 September 2003; revised 29 September 2003; accepted 7 October 2003

Abstract—The indium organometallic complex generated by metallic indium and 3-bromopropenyl acetate in THF adds to the Garner aldehyde in excellent yield and with high diastereoselectivity; the usefulness of the corresponding *anti-anti* adduct was demonstrated by developing a short synthesis of the title compound, an azasugar known as a glycosidase inhibitor.
© 2003 Elsevier Ltd. All rights reserved.

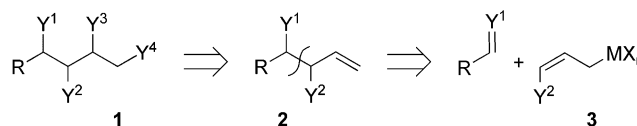
A challenge for synthetic chemists is offered by molecules containing sequences of contiguous hetero-substituted stereocenters, a structure motif which is widespread in natural products (monosaccharides, etc.) as well as in important families of natural and synthetic drugs. An example of a densely functionalised carbon chain is represented by structure **1**, where substituents Y^1 – Y^4 are oxygen or nitrogen groups. We focused our attention on the synthetic strategy depicted in Scheme 1.

An attractive precursor of **1** is provided by alkene **2**, thanks to the number of stereoselective functionalisation reactions of carbon–carbon double bonds available in the literature.^{1–5} In turn, **2** is accessible via stereocontrolled addition of a γ -heterofunctionalised allylic organometallic reagent **3** to a carbonyl compound or to an azomethine derivative.⁶

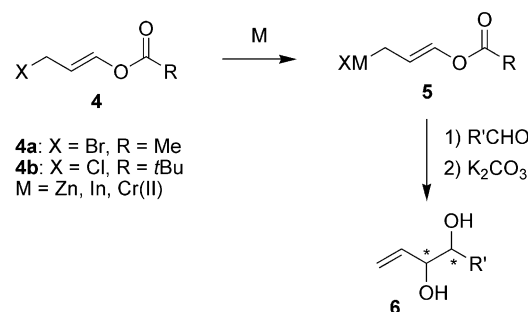
The usefulness of 3-halopropenyl esters **4** as precursors of heterofunctionalised allylic organometallic compounds **5** using zinc,^{7–9} indium^{9,10} and chromium,^{11,12} in water or aprotic solvents, has been recently disclosed (Scheme 2).

In conjunction with our efforts to develop new stereocontrolled routes to alk-1-ene-3,4-diols **6** from **4**,^{7–12} we now report the indium mediated¹³ asymmetric ace-

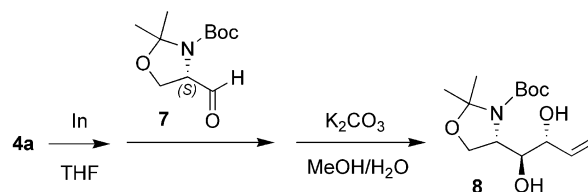
toxyallylation of (*S*)-*N*-Boc-serinal acetone **7** (Garner aldehyde)¹⁴ to give the *anti-anti* adduct **8** (Scheme 3).¹⁵



Scheme 1.



Scheme 2.



Scheme 3.

Keywords: 3-bromopropenyl acetate; Garner aldehyde; α -hydroxyallylation; 1,4-dideoxy-1,4-L-iminoribitol.

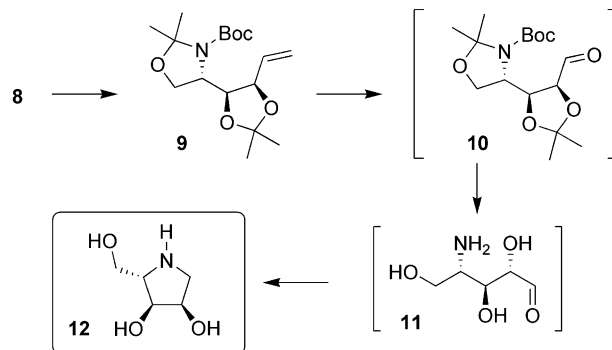
* Corresponding author. Tel.: +39-051-2099513; fax: +39-051-2099456; e-mail: marlom@ciam.unibo.it; trombini@ciam.unibo.it

A typical Grignard protocol was adopted for the formation of **5** ($R = \text{Me}$); 3-bromopropenyl acetate (0.67 g, 3.75 mmol) was added at 0°C to a suspension of indium (0.67 g, 3.75 mmol) in anhydrous THF (5 mL). The heterogeneous mixture was stirred for 30 min at 0°C, then stirring was continued for 3.5 h at rt. Garner aldehyde **7** (0.57 g, 2.5 mmol) was added at 0°C and the reaction mixture was stirred for 4 h at rt. After quenching with aq. NaHCO_3 , an alkaline hydrolysis ($\text{K}_2\text{CO}_3/\text{MeOH}/\text{H}_2\text{O}$) was performed on the crude extract;¹⁶ flash-chromatography on silica-gel (cyclohexane/ethyl acetate/triethylamine 85:14:1) first provided a fraction containing a mixture of isomers of **8** in 15% overall yield, then diol **8** was isolated in 80% yield as a pure isomer.¹⁷ The relative *anti-anti* configuration of the major isomer **8**, established by chemical correlation with the known title compound, was the consequence of an excellent control of both diastereo- and diastereofacial selectivity. Diastereoselectivity was *anti*, in agreement with the general observed trend in previous studies; indeed, *Z*-configured indium and zinc complexes derived from oxidative addition of $\text{Zn}(0)$ and $\text{In}(0)$ to the carbon–bromine bond of **4** displayed an interesting behaviour in the addition to prochiral aldehydes. When aromatic or α,β -unsaturated aldehydes are used the addition is *syn*-stereoselective, but in the case of saturated aldehydes the opposite *anti* adducts are preferentially formed. A rationale for the latter stereochemical outcome was proposed,⁹ assuming bicyclo[3.2.2]nonane-type TS structure **A** is the favoured one on the basis of steric grounds (Fig. 1).

With regard to π -facial discrimination, the preferential attack to the *re* or *si* face of the (*S*)-Garner aldehyde strongly depends on the carbon nucleophile and on the metal counterion;^{14,15} furthermore, stereoselectivity is known to be modified by the addition of chelating additives or by using different solvents.¹⁸

Both to confirm stereoassignments and to demonstrate the synthetic utility of adduct **8**, we converted it into 1,4-dideoxy-1,4-L-iminoribitol **12**, as shown in Scheme 4. Both **12** and its enantiomer are known to display remarkable bioactivity as inhibitors of mammalian glycosidases,^{19,20} of eukaryotic DNA polymerases²¹ and of HIV replication.²²

The reaction sequence required ozonisation of **8** which, unfortunately, produced the expected aldehyde in unsatisfactory yield. This drawback was easily overcome by protecting the diol moiety as acetonide **9**



Scheme 4.

(2,2-dimethoxypropane, Amberlyst® 15H, CH_2Cl_2 , 24 h, 70%);²³ the subsequent reaction sequence was carried out without isolation of intermediates. This involved ozonisation of **9** (O_3 , CH_2Cl_2 , -78°C , 30 min then Me_2S , 12 h), exhaustive acidic deprotection of **10** ($\text{TFA}/\text{H}_2\text{O}$ 20:1, 30 min, 0°C , then evaporation of excess TFA under vacuum), neutralisation to free amino aldehyde **11** (Amberlyst® A26, OH^-), and finally, reductive cyclisation to the target molecule **12** (H_2/Pd , MeOH , 12 h, 45 psi).

The overall sequence starting from **9** took place in 30% yield. Purification of 1,4-dideoxy-1,4-L-iminoribitol **12** was carried out by elution through a small pad of silica eluting with $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{EtOH}/\text{NH}_4\text{OH}$ 50:20:20:10;^{24,25} optical and NMR data of the derived hydrochloride (**12**·HCl)²⁶ corresponded to literature data.^{27–29}

In conclusion, the usefulness of 3-halopropenyl esters as precursors of the formal 1-hydroxyallyl anion was confirmed by the asymmetric hydroxyallylation of Garner aldehyde, which opens a route to 1,4-dideoxy-1,4-L-iminoribitol **12** and to *ent*-**12**, both enantiomers of which are enzymatic inhibitors.^{18–21}

Acknowledgements

This work was supported by MIUR-Rome (FIRB Funds to C.T., 2002).

References

- Bonini, C.; Righi, G. *Tetrahedron* **2002**, *58*, 4981–5021.
- Katsuki, T. In *Asymmetric Oxidation Reactions*; Ito, Y. N.; Katsuki, T., Eds.; Oxford University Press: Oxford, 2001; pp. 19–37.
- Frohn, M.; Shi, Y. *Synthesis* **2000**, 1979–2000.
- Flessner, T.; Doye, S. *J. Prakt. Chem.* **1999**, *341*, 436–444.
- Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2024–2032.
- Katritzky, A. R.; Piffl, M.; Lang, H.; Anders, E. *Chem. Rev.* **1999**, *99*, 665–722.

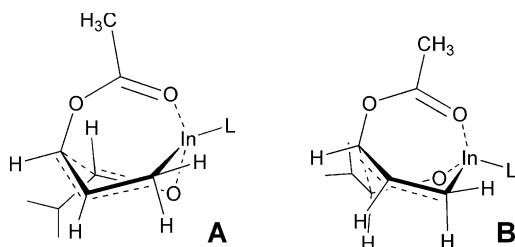
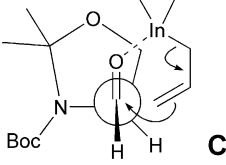


Figure 1.

7. Lombardo, M.; Girotti, R.; Morganti, S.; Trombini, C. *Chem. Comm.* **2001**, 2310–2311.
 8. Lombardo, M.; Morganti, S.; d'Ambrosio, F.; Trombini, C. *Tetrahedron Lett.* **2003**, *44*, 2823–2826.
 9. Lombardo, M.; Morganti, S.; Trombini, C. *J. Org. Chem.* **2003**, *68*, 997–1006.
 10. Lombardo, M.; Girotti, R.; Morganti, S.; Trombini, C. *Org. Lett.* **2001**, *3*, 2981–2983.
 11. Lombardo, M.; Morganti, S.; Licciulli, S.; Trombini, C. *Synlett* **2003**, 43–46.
 12. Lombardo, M.; Licciulli, S.; Morganti, S.; Trombini, C. *Chem. Commun.* **2003**, 1762–1763.
 13. (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207–2293; (b) Li, C.-J.; Chan, T.-H. *Tetrahedron* **1999**, *55*, 11149–11176; (c) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763–2793.
 14. Liang, X.; Andersch, J.; Bols, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2136–2157.
 15. The simple indium-mediated allylation of Garner aldehyde was reported by Paquette to give *anti* adducts both in THF and in aq. solvents, consistent with the adoption of the Felkin–Ahn TS **C**; the *anti/syn* ratio ranged from 2.2 in THF to 3.5 in 0.5 M NH_4Cl . See: Paquette, L. A.; Mitzel, T. M.; Isaac, M. B.; Crasto, C. F.; Shomer, W. *J. Org. Chem.* **1997**, *62*, 4293–4301.
- 
16. HPLC–MS analysis of the crude reaction mixture (column: Zorbax C-8, elution: 5 min isocratic $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ 70:30 v/v, gradient ramp up to $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ = 20:80 v/v in 10 min, flow: 0.5 ml/min) revealed the presence of three peaks in an 85:7:8 relative ratio, corresponding to **8** and two isomeric products on the basis of mass analysis. MS m/z : 597.4 $[2\text{M}+\text{Na}]^+$, 326.2 $[\text{M}+\text{K}]^+$, 310.2 $[\text{M}+\text{Na}]^+$.
 17. **8**: $[\alpha]_{20}^{\text{D}} = +0.9$ (*c* 2.6, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ : 1.43 (s, 3H), 1.48 (s, 9H), 1.50 (s, 3H), 3.40–3.58 (m, 1H), 3.62–3.76 (m, 1H), 3.80–4.08 (m, 2H), 4.12–4.30 (m, 1H), 5.10–5.42 (m, 2H), 5.95 (ddd, $J = 4.5/10.8/16.8$ Hz, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ : 24.2, 26.9, 28.3, 58.6, 65.1, 74.4, 74.6, 81.2, 93.9, 114.8, 136.8, 153.7. GC–MS (70 eV) m/z (%): 272 (0.5, $[\text{M}^+-15]$), 216 (4), 174 (14), 155 (6), 143 (12), 116 (47), 87 (10), 57 (100).
 18. Herold, P. *Helv. Chim. Acta* **1988**, *71*, 354–362.
 19. Popowycz, F.; Gerber-Lemaire, S.; Demange, R.; Rodriguez-Garcia, E.; Asenjo, A. T. C.; Robina, I.; Vogel, P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2489–2493.
 20. Asano, N.; Oseki, K.; Kizu, H.; Matsui, K. *J. Med. Chem.* **1994**, *37*, 3701–3706.
 21. Mizushima, Y.; Xu, X.; Asano, N.; Kasai, N.; Kato, A.; Takemura, M.; Asahara, H.; Linn, S.; Sugawara, F.; Yoshida, H.; Sakaguchi, K. *Biochem. Biophys. Res. Commun.* **2003**, *304*, 78–85.
 22. Fleet, G. W. J.; Karpas, A.; Dwek, R. A.; Fellows, L. E.; Tynms, A. S.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Smith, P. W. *FEBS Lett.* **1988**, *237*, 128–132.
 23. **9**: $[\alpha]_{20}^{\text{D}} = -38$ (*c* 1.9, CHCl_3). ^1H NMR (300 MHz, CDCl_3) δ : 1.38 (s, 6H), 1.49 (s, 9H), 1.54 (s, 6H), 3.86 (dd, $J = 6.9/9.3$ Hz, 1H), 3.92–4.05 (m, 1H), 4.11 (dd, $J = 2.7/9.3$ Hz, 1H), 4.60–4.85 (m, 2H), 5.26 (broad d, $J = 10.8$ Hz), 5.40 (broad d, $J = 18.0$ Hz), 5.65–5.80 (m, 1H). ^{13}C NMR (75 MHz, CDCl_3) δ : 24.9, 26.5, 28.4, 57.9, 63.5, 76.5, 78.0, 80.2, 93.6, 105.5, 118.2, 133.6, 152.4. GC–MS (70 eV) m/z (%): 312 (1, $[\text{M}^+-15]$), 256 (6), 213 (5), 200 (10), 144 (12), 100 (41), 84 (13), 69 (16), 57 (100).
 24. Lombardo, M.; Fabbri, S.; Trombini, C. *J. Org. Chem.* **2001**, *66*, 1264–1268.
 25. Huang, Y.; Dalton, D. R.; Carroll, P. J. *J. Org. Chem.* **1997**, *62*, 372–376.
 26. **12·HCl**: $[\alpha]_{20}^{\text{D}} = -57$ (*c* 0.8, H_2O). ^1H NMR (300 MHz, D_2O) δ : 3.33 (dd, $J = 1.5/12.9$ Hz, 1H, H-5), 3.46 (dd, $J = 3.9/12.9$ Hz, 1H, H-5), 3.57 (ddd, $J = 3.3/5.7/8.7$ Hz, 1H, H-2), 3.79 (dd, $J = 5.7/12.6$ Hz, 1H, CH_2OH), 3.94 (dd, $J = 3.3/12.6$ Hz, 1H, CH_2OH), 4.17 (dd, $J = 4.2/8.7$ Hz, 1H, H-3), 4.34 (broad ddd, $J = 1.5/3.9/4.2$ Hz, 1H, H-4). ^{13}C NMR (75 MHz, D_2O) δ : 50.6 (C-5), 58.9 (C-2), 62.8 (CH_2OH), 70.4 (C-4), 72.1 (C-3).
 27. Fleet, G. W. J.; Son, J. C. *Tetrahedron* **1988**, *44*, 2637–2647.
 28. Takano, S.; Moriya, M.; Ogasawara, K. *Tetrahedron: Asymmetry* **1992**, *6*, 681–684.
 29. Defoin, A.; Sifferlen, T.; Streith, J. *Synlett* **1997**, 1294–1296.