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

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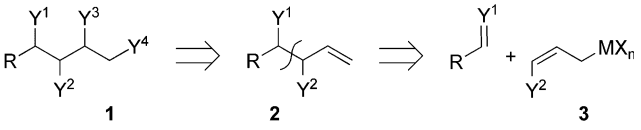
Abstract—The indium organometallic complex generated by metallic indium and 3-bromopropenyl acetate in THF adds to the Garner aldehyde in excellent yield and with high diastereoselectivity; the usefulness of the corresponding *anti–anti* adduct was demonstrated by developing a short synthesis of the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

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.

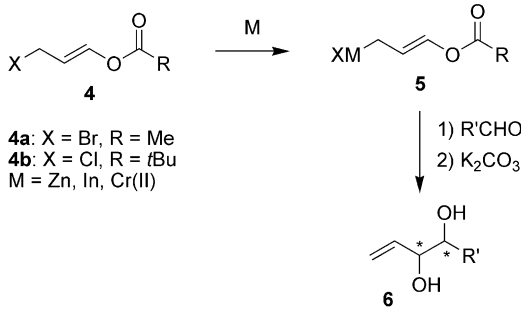
An attractive precursor of **1** is provided by alkene **2**, thanks to the number of stereoselective functionalisation reactions of carbon–carbon double bonds available in the literature.[1–5] In turn, **2** is accessible via stereocontrolled addition of a γ-heterofunctionalised allylic organometallic 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).

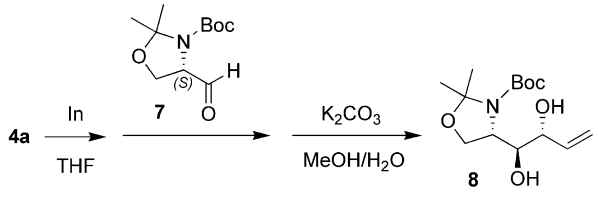
In conjunction with our efforts to develop new stereocontrolled routes to alk-1-ene-3,4-diols **6** from **4**,[7–12] we now report the indium mediated[13] asymmetric acetoxyallylation of (*S*)-*N*-Boc-serinal acetonide **7** (Garner aldehyde)[14] to give the *anti–anti* adduct **8** (Scheme 3).[15]



Scheme 1.



Scheme 2.



Scheme 3.

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

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A typical Grignard protocol was adopted for the formation of **5** (R = 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 (K_2CO_3/MeOH/H_2O) 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 Zn(0) and 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 polymerases[21] 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**

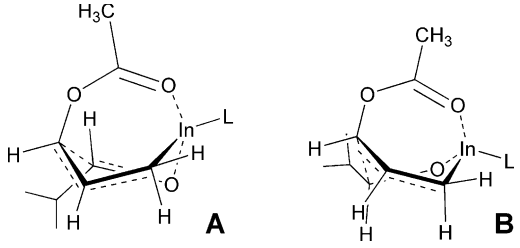
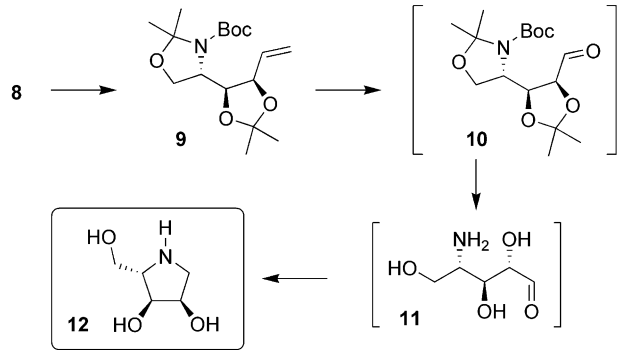


Figure 1.



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** (TFA/H_2O 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 CH_2Cl_2/MeOH/EtOH/NH_4OH 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

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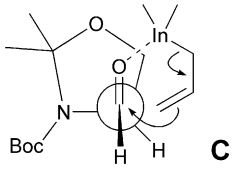

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16. HPLC–MS analysis of the crude reaction mixture (column: Zorbax C-8, elution: 5 min isocratic H_2O/CH_3CN 70:30 v/v, gradient ramp up to H_2O/CH_3CN = 20:80 v/v in 10 min, flow: 0.5 ml/min) revealed the presence of three peaks in an 85:7:8 relative ratio, corresponding to **8** and two isomeric products on the basis of mass analysis. MS *m*/*z*: 597.4 $[2M+Na]^+$, 326.2 $[M+K]^+$, 310.2 $[M+Na]^+$.
17. **8**: $[\alpha]_{20}^{D}$ = +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, $[M^+-15]$), 216 (4), 174 (14), 155 (6), 143 (12), 116 (47), 87 (10), 57 (100).
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23. **9**: $[\alpha]_{20}^{D}$ = −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, $[M^+-15]$), 256 (6), 213 (5), 200 (10), 144 (12), 100 (41), 84 (13), 69 (16), 57 (100).
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26. **12·HCl**: $[\alpha]_{20}^{D}$ = −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, C*H*$_2$OH), 3.94 (dd, *J* = 3.3/12.6 Hz, 1H, C*H*$_2$OH), 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 (*C*H$_2$OH), 70.4 (C-4), 72.1 (C-3).
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