A 'substrate-divergent' approach to chiral cyclopentanes and cyclohexanes from a common precursor based on levoglucosan

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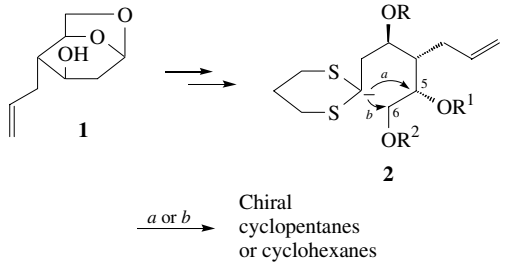
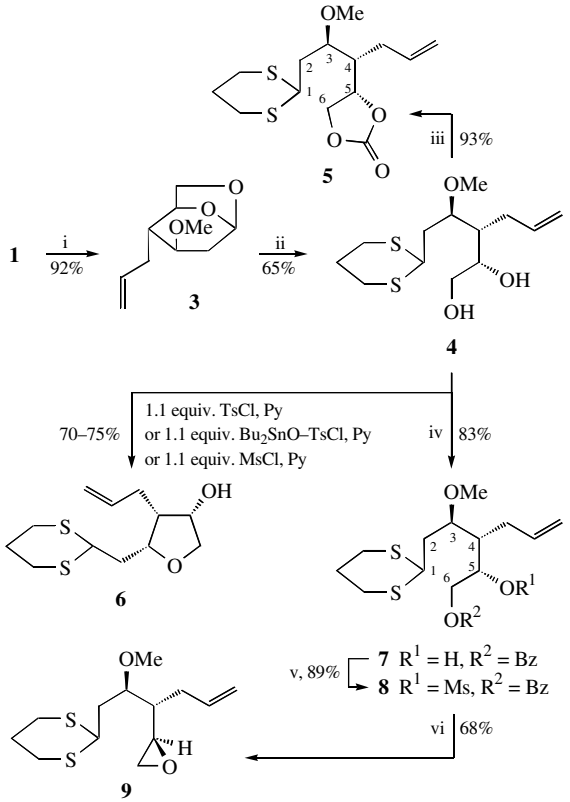
Acyclic 1,3-dithianes **8** and **9** were transformed to cyclopentane derivative **12** and cyclohexane derivative **10**, respectively, by treatment with BuLi.

The synthesis of chiral cyclopentane and cyclohexane derivatives by the recyclisation of monosaccharide derivatives (carbocyclisation) is a well-known and convenient pathway to enantiomerically pure block synthons with preset stereochemistry for a broad range of natural compounds.[1–10] In this work, we studied



Scheme 1

the potentialities of the 'substrate-divergent' recyclisation of levoglucosan derivative **1**[11] into the corresponding chiral cyclopentane or cyclohexane. On this route, acyclic 1,3-dithiane derivatives **2**, which are flexible in terms of 'varying' (functionalisation) in the C^5–C^6 diol fragment, were selected as key compounds in the study of intramolecular carbanionic C^1–C^5 and C^1–C^6 cyclisations.



Scheme 2 *Reagents and conditions:* i, NaOH–DMSO, MeI, 20 °C; ii, $CH_2(CH_2SH)_2$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 20 °C; iii, Im_2CO, THF, 60 °C; iv, 1.1 equiv. of Bu_2SnO–BzCl, Py; v, MsCl, Et_3N, CH_2Cl_2; vi, MeONa, MeOH.

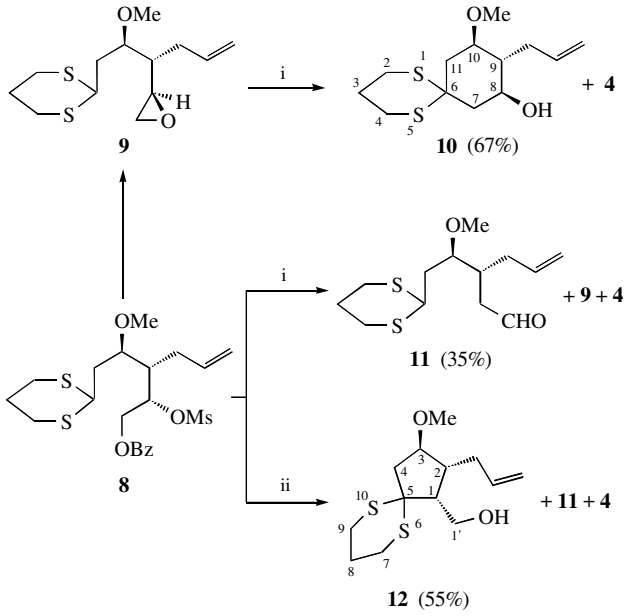
To prepare compounds **2** and their 5,6-epoxy equivalents, methoxy derivative **3** was used instead of compound **1**; the former is less prone to side transformations under mercaptolysis conditions. As a result, *trans*-dithioacetalisation of compound **3** with 1,3-propanedithiol in the presence of $BF_3{\cdot}Et_2O$ in CH_2Cl_2 gave acyclic diol **4** (characterised as carbonate **5**†) in 65% yield. Since attempts at the selective 6-O-tosylation (mesylation) of diol **4** failed (only the formation of compound **6** in > 70% yields was observed), we synthesised benzoate **7** and then its mesyl derivative **8**.‡ The latter was converted into epoxide **9** by treatment with MeONa in anhydrous MeOH; however, this was

† *4-C-Allyl-2,4-dideoxy-3-*O*-methyl-D-arabinohexose propane-1,3-diyldithioacetal 5,6-carbonate* **5**: yield 93%, $[\alpha]_D^{20}$ –7° (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.82 (m, 2H, C^2H^a, C^4H), 1.95 (dt, 1H, C^2H^b, ^2J –13.9 Hz and ^3J 7.0 Hz), 2.18 (m, 3H, CH_2-allyl, SCH_2CH_2), 2.25 (m, 1H, CH_2-allyl), 2.85 (m, 4H, $2SCH_2$), 3.38 (s, 3H, OMe), 3.80 (td, 1H, C^3H, *J* 7.4, 7.4 and 2.0 Hz), 4.06 (dd, 1H, C^1H, *J* 6.7 and 7.6 Hz), 4.22 (t, 1H, C^6H^a, ^3J 8.1 Hz), 4.49 (t, 1H, C^6H^b, ^3J 8.1 Hz), 4.80 (q, 1H, C^5H, *J* 8.1 Hz), 5.09 (m, 2H, CH_2=), 5.70–5.81 (m, 1H, CH=). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 25.29 (SCH_2CH_2), 28.42 and 29.74 ($2SCH_2$), 29.92 (CH_2-allyl), 36.53 (C^2), 43.43 (C^4), 44.68 (C^1), 57.74 (OMe), 67.55 (C^6), 76.15 and 77.24 (C^3, C^5), 117.15 (CH_2=), 135.17 (CH=), 154.15 (C=O).

‡ *4-C-Allyl-6-*O*-benzoyl-2,4-dideoxy-5-*O*-mesyl-3-*O*-methyl-D-arabinohexose propane-1,3-diyldithioacetal* **8**: yield 89%, $[\alpha]_D^{20}$ +32° (*c* 2.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.78–2.00 (m, 3H, C^2H_2, C^4H), 2.02–2.20 (m, 2H, SCH_2CH_2), 2.30 (m, 2H, CH_2-allyl), 2.80 (m, 4H, $2SCH_2$), 3.05 (s, 3H, SO_2Me), 3.41 (s, 3H, OMe), 3.72 (m, 1H, C^3H), 4.12 (dd, 1H, C^1H, *J* 9.4 and 4.8 Hz), 4.55 (dd, 1H, C^6H^a, ^2J –12.5 Hz and ^3J 6.8 Hz), 4.65 (d, 1H, C^6H^b, ^2J –12.5 Hz and ^3J 2.0 Hz), 5.15 (m, 3H, C^5H, CH_2=), 5.85 (m, 1H, CH=), 7.45 (m, 2H, Ph), 7.56 (m, 1H, Ph), 8.05 (d, 1H, Ph). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 25.92 (SCH_2CH_2), 30.05 and 30.37 ($2SCH_2$), 30.78 (CH_2-allyl), 37.32 (C^2), 38.98 (SO^2Me), 42.52 (C^1), 44.31 (C^4), 57.68 (OMe), 65.04 (C^6), 77.52 (C^5), 81.34 (C^3), 117.69 (CH_2=), 128.52, 129.56, 129.70 and 133.31 (Ph), 135.82 (CH=), 166.37 (CO_2).

(8S,9R,10R)-9-Allyl-10-methoxy-1,5-dithiaspiro[5.5]undecan-8-ol **10**: yield 67%, $[\alpha]_D^{20}$ –32° (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.52 (m, 2H, $C^{11}H_2$), 1.55 (dd, 2H, C^7H^a, ^2J –10.5 Hz and ^3J 4.2 Hz), 1.70 (dd, 1H, C^7H^b, ^3J –13.3 Hz and ^2J 10.5 Hz), 2.00 (m, 2H, SCH_2CH_2), 2.35–2.55 (m, 2H, CH_2-allyl), 2.75 (m, 1H, C^9H), 2.85–2.97 (m, 4H, $2SCH_2$), 3.32 (td, 1H, $C^{10}H$, $J_{10,9}$ 10.5 Hz, $J_{10,11a}$ 10.5 Hz and $J_{10,11b}$ 4.2 Hz), 3.40 (s, 3H, OMe), 3.83 (td, 1H, C^8H, $J_{8,7a}$ 10.5 Hz, $J_{8,7b}$ 4.3 Hz and $J_{8,9}$ 10.5 Hz), 5.08–5.20 (m, 2H, CH_2=), 5.95 (m, 1H, CH=). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 25.59 (SCH_2CH_2), 25.94 and 26.43 ($2SCH_2$), 32.20 (CH_2-allyl), 40.99 (C^{11}), 44.78 (C^7), 46.76 (C^6), 50.66 (C^9), 56.99 (OMe), 66.74 (C^8), 76.16, (C^{10}), 117.00 (CH_2=), 136.62 (CH=).

(1R,2R,3R)-2-Allyl-1-hydroxymethyl-3-methoxy-6,10-dithiaspiro[4.5]-decane **12**: yield 55%, $[\alpha]_D^{20}$ –36° (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.01 (m, 2H, SCH_2CH_2), 2.22 (dd, 1H, C^4H^a, ^2J –14.6 Hz and ^3J 4.0 Hz), 2.25–2.40 (m, 2H, CH_2-allyl), 2.58 (m, 2H, C^1H, C^2H), 2.71 (dd, 1H, C^4H^b, ^2J –14.6 Hz and ^3J 6.5 Hz), 2.90 (m, 4H, $2SCH_2$), 3.28 (s, 3H, OMe), 3.70 (ddd, 1H, C^3H, *J* 7.9, 6.0 and 4.0 Hz), 3.83 (dd, 1H, $C^{1'}H^a$, ^2J –12.2 Hz and ^3J 5.0 Hz), 3.95 (dd, $C^{1'}H^b$, 1H, ^2J –12.2 Hz and ^3J 3.0 Hz), 5.10–5.18 (m, 2H, CH_2=), 5.80 (m, 1H, CH=). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ: 25.21 (SCH_2CH_2), 28.75 and 29.15 ($2SCH_2$), 34.21 (CH_2-allyl), 46.12 (C^2), 47.75 (C^4), 52.03 (C^1), 57.45 (OMe), 60.40 ($C^{1'}$), 63.01 (C^5), 85.25 (C^3), 115.82 (CH_2=), 137.46 (CH=).



Scheme 3 *Reagents and conditions*: i, 1.1 equiv. BuLi, THF, –50 °C, 3 h at 20 °C; ii, 1.1 equiv. BuLi, THF, –50 °C, 1 h at 20 °C, then 1.1 equiv. BuLi, –50 °C, 3 h at 20 °C.

accompanied by partial saponification of compound **8** with the recovery of original diol **4**.

At the next stage, resulting mesylate **8** and epoxide **9** were tested in intramolecular cyclisation reactions. The metallation of epoxydithiane **9** with 1.1 equiv. of BuLi in THF at –50 °C followed by keeping the reaction mixture at room temperature until the disappearance of the parent compound (TLC, 3 h) gave cyclohexane derivative **10** in 67% yield.‡ The direct treatment of the mesyl benzoate **8** with 1.1 equiv. of BuLi in THF at –50 °C followed by keeping the reaction mixture at room temperature for 3 h gives aldehyde **11** in a moderate yield; the reaction is complicated by the formation of a considerable amount (~20% overall) of diol **4** and epoxide **9**. Cyclopentane derivative **12**‡ is formed in > 50% upon the 'stepwise' treatment of compound **8** with 2.2 equiv. of BuLi in THF at –50 °C; this reaction gave aldehyde **11** (20%) and diol **4** (10%) as minor products.

In general, the methodology of the 'divergent' synthesis of chiral cyclopentanes and cyclohexanes developed in this work, particularly the 'unusual chemistry' in the steps where compounds **6** and **10**–**12** are formed, are of undoubted synthetic interest; *cis*-disubstituted hydroxycyclopentanone dithiane **12** may be used in the synthesis of isoprostanes[12] and neuroprostanes.[13]

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