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

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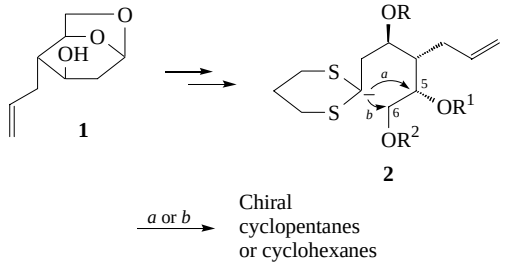
Acyclic 1,3-dithianes 8 and 9 were transformed to cyclopentane derivative 12 and cyclohexane derivative 10, respectively, by treatment with BuLi.

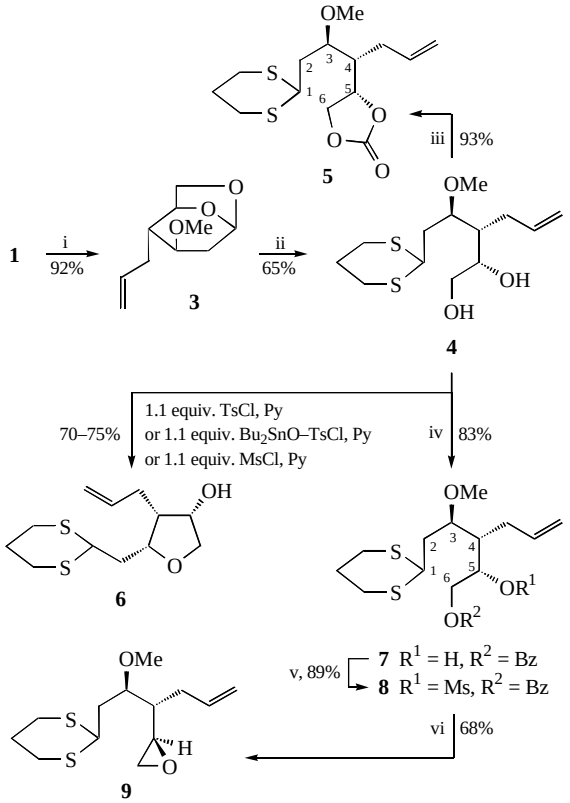
The synthesis of chiral cyclopentane and cyclohexane derivatives by the recyclisation of monosaccharide derivatives (carbocyclisation) is a well-known and convenient pathway to enantiomerically pure block synthons with preset stereochemistry for a broad range of natural compounds.[1–10] In this work,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



1 **2**

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.



1 **3** **4** **5** **6** **9**

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.

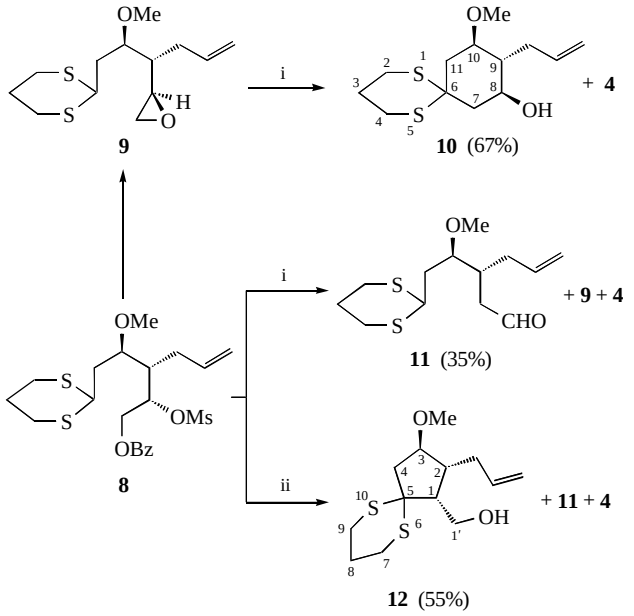
To prepare compounds **2** and their 5,6-epoxy equivalents, methoxy derivative **3** was used instead of compound **1**; the former is less prone to side transformations under mercaptolysis conditions. As a result, *trans*-dithioacetalisation of compound **3** with 1,3-propanedithiol in the presence 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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