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Tetrahedron: *Asymmetry* 18 (2007) 1986–1989

Preparation of chiral cyclopropanes with a carbohydrate fragment from levoglucosenone

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Received 25 July 2007; accepted 13 August 2007

Abstract—Levoglucosenone (a chiral α,β-unsaturated ketone derivative of cellulose) underwent stereoselective cyclopropanation with sulfonium ylides to form chiral trisubstituted cyclopropanes annulated with the carbohydrate moiety in high yields.

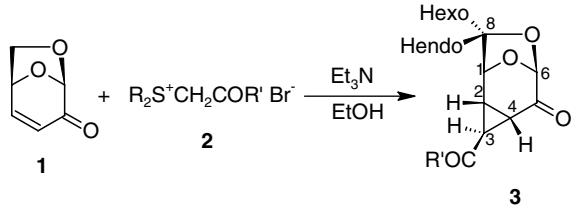
1. Introduction

Functionalized chiral cyclopropanes are of major interest both as key fragments of several biologically active natural and synthetic products[1,2] and as intermediates in organic synthesis.[3] They are usually prepared either by asymmetric cyclopropanation of achiral olefins in the presence of chiral catalysts,[4] or by direct cyclopropanation of chiral olefins.[1,5]

Levoglucosenone **1** [(1*S*,5*R*)-6,8-dioxabicyclo[3.2.1]oct-2-ene-4-one], an unsaturated ketone prepared by acid-catalyzed pyrolysis of cellulose, was previously used as a substrate in the stereoselective Michael addition of nucleophiles and cycloaddition to the C=C bond on the side opposite to the 1,6-anhydro bridge.[6–9] Therefore, we envisaged that **1** could be a suitable template for the preparation of chiral cyclopropanes using such well-recognized cyclopropanation agents as sulfur ylides.[10,11]

2. Results and discussion

We discovered that sulfonium ylides (generated in situ from the corresponding salts **2** and Et_3N) react stereoselectively with the double bond of levoglucosenone to afford cyclopropanes **3** in good yields[11,12] (Scheme 1, Table 1).



1 **2** **3**

Scheme 1.

Table 1. Preparation of compounds **3a–i**

Sulfonium salt **2**	R_2S	R′	Product **3**	Yield
2a	Me_2S	Ph	**3a**	80
2b	$(CH_2)_4S$	4-ClC_6H_4	**3b**	82
2c	Me_2S	4-BrC_6H_4	**3c**	84
2d	$(CH_2)_4S$	4-$MeOC_6H_4$	**3d**	92
2e	Me_2S		**3e**	71
2f	Me_2S		**3f**	69
2g	Me_2S	Cyclopropyl	**3g**	74
2h	$(CH_2)_4S$	1-Adamantyl	**3h**	95
2i	Me_2S	OEt	**3i**	79
2j	$(CH_2)_4S$	OEt	**3i**	78

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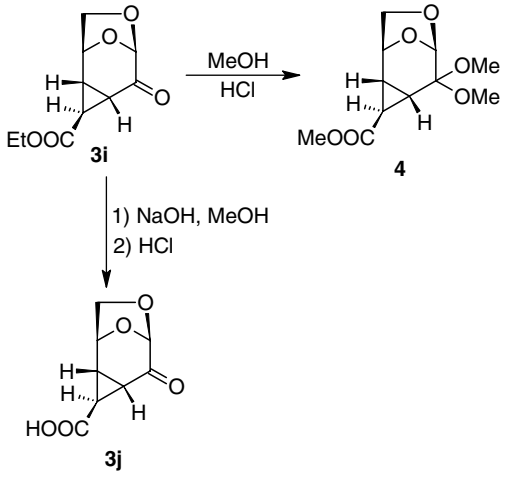
doi:10.1016/j.tetasy.2007.08.013

The reaction proceeds with the stereospecific formation of three new asymmetric centers, two of which originate from the levoglucosenone molecule (C-2 and C-4) and another one from the sulfonium ylide (C-3). The configurations of the C-2 and C-4 atoms are assigned assuming that the cyclopropanation of **1** (analogously to the other similar reactions previously described in the literature[6–9]) occurs on the less sterically hindered side, that is on the side opposite to the 1,6-anhydro bridge. This assumption is confirmed by the values of the coupling constants $J_{1,2} = 1.3–1.5$ Hz in the ^{1}H NMR spectrum of **3** (products of the addition to the more sterically hindered side are rare and have substantially larger J values[7,9]). The other coupling constants values $J_{2,3} \sim J_{3,4} = 4.0–4.3$ Hz, $J_{2,4} = 7.7–7.8$ Hz imply that the H-3 atom is in the *trans*-position to H-2 and H-4, considering that *cis*-constants in cyclopropanes are larger than *trans*. The assigned C-3 configuration is in a good agreement with the fact that the reactions of carbonyl-stabilized sulfonium ylides with α,β-unsaturated carbonyl compounds tend to yield cyclopropanes with *trans*-located carbonyl substituents.[13] Additional evidence for the stereochemistry of **3a–i** comes from X-ray diffraction analysis of derivative **4** (see below).

In all cases, cyclopropanes **3** are isolated as single isomers, and no signals of other stereoisomers are found in NMR spectra of the reaction mixtures. The crystalline products **3a–i** do not require any further purification, which is in contrast to the previously studied reactions of the sulfonium ylides with other unsaturated 6-membered cyclic ketones.[13–15] Most likely, the rigid bicyclic structure of **1** causes a significant energy difference between the corresponding transition states, thus limiting the possible diastereomeric products to only one isomer. Interestingly, very high stereoselectivity was previously observed for the cyclopropanation of some chiral bicyclic cyclopent-2-enones as well.[16,17] It is noteworthy that the yields and selectivities of the reactions are little affected by the nature of the R_2S substituents in the sulfonium ylides (cf. preparation of **3i** from the salt of dimethylsulfide **2i** and the salt of tetrahydrothiophene **2j**, Table 1).



Scheme 2.

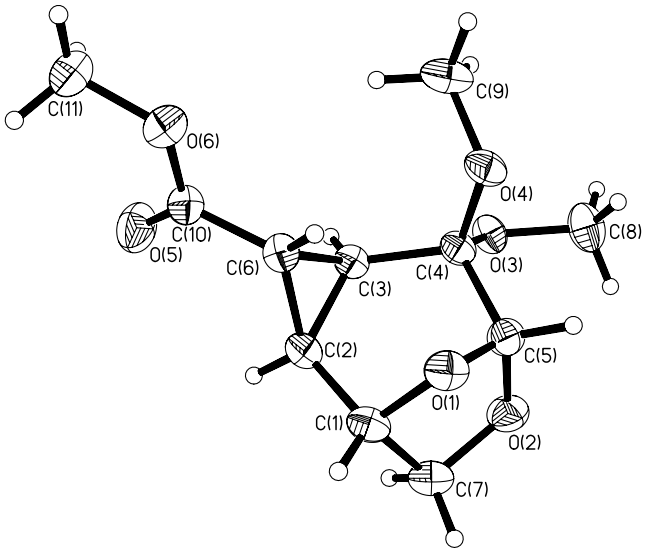


Figure 1. X-ray structure of **4**.

The keto-ester **3i** can undergo further transformations. Thus, heating it in methanolic NaOH affords the acid **3j**, while refluxing **3i** in methanolic HCl affects both the ester- and the keto-groups and results in the formation of ketal **4** (Scheme 2). Similar ketals were formed by the addition of MeOH to levoglucosenone **1**.[18]

The structure of compound **4** was supported by X-ray diffraction analysis (Fig. 1), thus providing additional proof for the assignment of the stereocenters in keto-ester **3i** and its analogues **3a–h,j**.

Taking into account the lability of the carbohydrate moiety,[19,20] compounds **3** can serve as starting reagents for the preparation of the highly derivatized chiral cyclopropanes. Such an investigation is currently underway.

3. Experimental

3.1. General

NMR spectra were recorded on a Bruker-DRX500 spectrometer (500.13 MHz for ^{1}H, 125.75 MHz for ^{13}C). Optical rotations were measured on a Jasco-340 polarimeter. X-ray diffraction study was performed by Professor V. S. Sergienko at the N. S. Kurnakov Institute of General and Inorganic Chemistry (Moscow). Crystallographic data for the structure in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 653502. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

3.2. Synthetic procedures

3.2.1. Sulfonium salts 2a–j (general procedure). A mixture of the corresponding bromide[21] (10 mmol) and Me_2S or

tetrahydrothiophene (12 mmol) in acetone (5 ml) was kept at 0 °C for 24 h, after which the resulting precipitate was filtered off and washed with acetone (2 ml). The product was used without further purification. Yields: 85–95%.

3.2.2. Reaction of levoglucosenone with sulfonium ylides (general procedure). To a suspension of levoglucosenone **1** (0.50 g, 4 mmol) and sulfonium salt **2** (4 mmol) in EtOH (5 ml), Et_3N (0.44 g, 4.4 mmol, 10% molar excess) was added, and the resulting solution kept at 35–40 °C for 3 h. Then the reaction mixture was concentrated to ca. 1/2 of the initial volume, diluted with water (10 ml), and extracted with $CHCl_3$ (3 × 5 ml). The organic solvent was evaporated to dryness, the residue triturated with 3 ml MeOH (ether is used for **3g**), and the resulting crystalline product filtered off and dried. For the preparation of **3f**, 25% molar excess of Et_3N was used, and the reaction mixture kept at 50–60 °C for 5 h.

3.2.3. (1*S*,2*S*,3*S*,4*S*,6*R*)-3-Benzoyl-7,9-dioxatricyclo-[4.2.1.0^{2,4}]-nonane-5-one 3a. Mp 119–120 °C (EtOH). $[\alpha]_D^{22} = -55.1$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (acetone-d_6): 2.27 (ddd, $J = 7.8$, 4.1, 1.5 Hz, 1H, H-2); 2.36 (dd, $J = 7.8$, 4.1 Hz, 1H, H-4); 3.63 (t, $J = 4.1$ Hz, 1H, H-3); 3.88 (dd, $J = 7.1$, 4.7 Hz, 1H, H-8*exo*); 4.17 (d, $J = 7.1$ Hz, 1H, H-8*endo*); 4.98 (s, 1H, H-6); 5.11 (br d, $J = 4.7$ Hz, 1H, H-1); 7.56 (t, $J = 8.1$ Hz, 2H); 7.67 (t, $J = 8.1$ Hz, 1H); 8.10 (d, $J = 8.1$ Hz, 2H). ^{13}C NMR (DMSO-d_6): 25.4, 27.2, 30.1, 69.1, 71.7, 100.1, 129.2, 129.8, 134.7, 137.4, 195.6, 196.0. Anal. Calcd for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95. Found: C, 69.06; H, 4.83.

3.2.4. (1*S*,2*S*,3*S*,4*S*,6*R*)-3-(4-Chlorobenzoyl)-7,9-dioxatricyclo[4.2.1.0^{2,4}]-nonane-5-one 3b. Mp 110–111 °C (EtOH). $[\alpha]_D^{22} = -69.8$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (DMSO-d_6): 2.27 (m, 2H, H-2, H-4); 3.65 (t, $J = 4.3$ Hz, 1H, H-3); 3.79 (dd, $J = 7.4$, 4.9 Hz, 1H, H-8*exo*); 4.09 (d, $J = 7.4$ Hz, 1H, H-8*endo*); 5.11 (m, 2H, H-1, H-6); 7.64 (d, $J = 8.6$ Hz, 2H); 8.04 (d, $J = 8.6$ Hz, 2H). Anal. Calcd for $C_{14}H_{11}ClO_4$: C, 60.34; H, 3.98. Found: C, 60.08; H, 4.13.

3.2.5. (1*S*,2*S*,3*S*,4*S*,6*R*)-3-(4-Bromobenzoyl)-7,9-dioxatricyclo[4.2.1.0^{2,4}]-nonane-5-one 3c. Mp 152–153 °C (EtOH). $[\alpha]_D^{23} = -58.6$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (acetone-d_6): 2.27 (ddd, $J = 7.7$, 4.1, 1.5 Hz, 1H, H-2); 2.33 (dd, $J = 7.7$, 4.1 Hz, 1H, H-4); 3.62 (t, $J = 4.1$ Hz, 1H, H-3); 3.87 (dd, $J = 7.1$, 4.9 Hz, 1H, H-8*exo*); 4.15 (d, $J = 7.1$ Hz, 1H, H-8*endo*); 4.98 (s, 1H, H-6); 5.11 (br d, $J = 4.9$ Hz, 1H, H-1); 7.75 (d, $J = 8.1$ Hz, 2H); 8.04 (d, $J = 8.1$ Hz, 2H). Anal. Calcd for $C_{14}H_{11}BrO_4$: C, 52.04; H, 3.43; Br, 24.73. Found: C, 51.77; H, 3.32; Br, 24.95.

3.2.6. (1*S*,2*S*,3*S*,4*S*,6*R*)-3-(4-Methoxybenzoyl)-7,9-dioxatricyclo[4.2.1.0^{2,4}]-nonane-5-one 3d. Mp 140–141 °C (EtOH). ^{1}H NMR (DMSO-d_6): 2.25 (m, 2H, H-2, H-4); 3.60 (t, $J = 4.3$ Hz, 1H, H-3); 3.78 (dd, $J = 7.8$, 4.2 Hz, 1H, H-8*exo*); 3.88 (s, 3H, CH_3); 4.09 (d, $J = 7.8$ Hz, 1H, H-8*endo*); 5.09 (m, 2H, H-1, H-6); 7.11 (d, $J = 9.1$ Hz, 2H); 8.07 (d, $J = 9.1$ Hz, 2H). Anal. Calcd for $C_{15}H_{14}O_5$: C, 65.69; H, 5.14. Found: C, 65.48; H, 5.31.

3.2.7. (1*S*,2*R*,3*S*,4*S*,6*R*)-3-(2-Thienoyl)-7,9-dioxatricyclo-[4.2.1.0^{2,4}]-nonane-5-one 3e. Mp 146–147 °C (EtOH). ^{1}H NMR (acetone-d_6): 2.25–2.35 (m, 2H, H-2 and H-4); 3.57 (t, $J = 4.1$ Hz, 1H, H-3); 3.87 (dd, $J = 7.2$, 4.8 Hz, 1H, H-8*exo*); 4.16 (d, $J = 7.2$ Hz, 1H, H-8*endo*); 4.99 (s, 1H, H-6); 5.10 (br d, $J = 4.8$ Hz, 1H, H-1); 7.30 (dd, $J = 5.0$, 3.8 Hz, 1H); 8.00 (d, $J = 5.0$ Hz, 1H); 8.20 (d, $J = 3.8$ Hz, 1H). ^{13}C NMR (DMSO-d_6): 24.2, 26.5, 29.2, 68.1, 70.6, 99.0, 129.2, 134.7, 136.2, 143.3, 187.9, 194.7. Anal. Calcd for $C_{12}H_{10}O_4S$: C, 57.59; H, 4.03; S, 12.81. Found: C, 57.67; H, 3.80; S, 13.00.

3.2.8. (1*S*,2*S*,3*S*,4*S*,6*R*)-3-(5-Methylfurazane-4-yl)carbonyl-7,9-dioxatricyclo[4.2.1.0^{2,4}]nonane-5-one 3f. Mp 152–154 °C (MeOH). $[\alpha]_D^{24} = -4.8$ (*c* 1.0, DMSO). ^{1}H NMR (DMSO-d_6): 2.42 (m, 2H, H-2 and H-4); 2.52 (s, 3H); 3.60 (t, $J = 4.0$ Hz, 1H, H-3); 3.80 (dd, $J = 7.2$, 4.7 Hz, 1H, H-8*exo*); 4.12 (d, $J = 7.2$ Hz, 1H, H-8*endo*); 5.07 (br d, $J = 4.7$ Hz, 1H, H-1); 5.14 (s, 1H, H-6). Anal. Calcd for $C_{11}H_{10}N_2O_5$: C, 52.80; H, 4.03; N, 11.20. Found: C, 53.18; H, 3.84; N, 11.36.

3.2.9. (1*S*,2*S*,3*S*,4*S*,6*R*)-3-(Cyclopropyl)carbonyl-7,9-dioxatricyclo[4.2.1.0^{2,4}]nonane-5-one 3g. Mp 85–86 °C (Et_2O). $[\alpha]_D^{23} = +37.3$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (DMSO-d_6): 0.9-1.0 (m, 4H); 2.09 (m, 2H, H-2 and H-4); 2.34 (m, 1H); 3.04 (t, $J = 4.1$ Hz, 1H, H-3); 3.75 (dd, $J = 7.1$, 4.7 Hz, 1H, H-8*exo*); 4.03 (d, $J = 7.1$ Hz, 1H, H-8*endo*); 5.03 (br d, $J = 4.7$ Hz, 1H, H-1); 5.06 (s, 1H, H-6). Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.23; H, 5.99.

3.2.10. (1*S*,2*S*,3*S*,4*S*,6*R*)-3-(1-Adamantoyl)-7,9-dioxatricyclo[4.2.1.0^{2,4}]-nonane-5-one 3h. Mp 124–125 °C (EtOH). $[\alpha]_D^{23} = -13.3$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (DMSO-d_6): 1.71, 1.83, 2.01 (m, 17H, CH-adamantyl, H-2, H-4); 3.09 (t, $J = 4.3$ Hz, 1H, H-3); 3.76 (dd, $J = 7.4$, 4.9 Hz, 1H, H-8*exo*); 4.03 (d, $J = 7.4$ Hz, 1H, H-8*endo*); 4.99 (br d, $J = 4.9$ Hz, 1H, H-1); 5.04 (s, 1H, H-6). Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.29; H, 7.56.

3.2.11. Ethyl (1*S*,2*R*,3*S*,4*S*,6*R*)-5-oxo-7,9-dioxatricyclo-[4.2.1.0^{2,4}]nonane-3-carboxylate 3i. Mp 135–136 °C (EtOH). $[\alpha]_D^{23} = -24.2$ (*c* 1.0, $CHCl_3$). ^{1}H NMR (DMSO-d_6): 1.21 (t, $J = 7.1$ Hz, 3H); 2.11 (dd, $J = 7.9$, 4.1 Hz, 1H, H-4); 2.19 (ddd, $J = 7.9$, 4.1, 1.3 Hz, 1H, H-2); 2.43 (t, $J = 4.1$ Hz, 1H, H-3); 3.75 (dd, $J = 7.1$, 4.8 Hz, 1H, H-8*exo*); 4.07 (d, $J = 7.1$ Hz, 1H, H-8*endo*); 4.12 (q, $J = 7.1$, 2H); 5.02 (br d, $J = 4.8$ Hz, 1H, H-1); 5.03 (s, 1H, H-6). Anal. Calcd for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70. Found: C, 56.65; H, 5.84.

3.2.12. (1*S*,2*R*,3*S*,4*S*,6*R*)-5-Oxo-7,9-dioxatricyclo- [4.2.1.0^{2,4}]-nonane-3-carboxylic acid 3j. A solution of **3i** (212 mg, 1 mmol) and NaOH (0.10 g, 2.5 mmol) in MeOH (2 ml) was refluxed for 2 h, neutralized with HCl and evaporated to dryness. To the residue, water (2 ml) was added, and the resulting suspension extracted with EtOAc (3 × 3 ml), and the solvent evaporated to dryness to yield essentially pure **3j**. Yield 147 mg (80%), mp 150–151 °C (EtOH). $[\alpha]_D^{24} = -30.1$ (*c* 1.0, DMSO). ^{1}H NMR (DMSO-d_6): 2.07 (dd, $J = 7.9$, 4.0 Hz, 1H, H-4); 2.13 (ddd, $J = 7.9$, 4.0, 1.4 Hz, 1H, H-2); 2.31 (t, $J = 4.0$ Hz, 1H, H-3); 3.75 (dd,

$J = 7.1$, 4.7 Hz, 1H, H-8*exo*); 4.06 (d, $J = 7.1$ Hz, 1H, H-8*endo*); 5.01 (m, 2H, H-1 and H-6); 12.84 (br s, 1H, COOH). Anal. Calcd for $C_8H_8O_5$: C, 52.18; H, 4.38. Found: C, 51.95; H, 4.44.

3.2.13. Methyl (1*S*,2*R*,3*S*,4*S*,6*R*)-5,5-dimethoxy-7,9-dioxatricyclo[4.2.1.0^{2,4}]nonane-3-carboxylate 4. To a solution of **3i** (212 mg, 1 mmol) in MeOH (2 ml), three drops of concd HCl was added, and the solution was refluxed for 4 h and kept overnight. The resulting crystals of **4** are filtered off and dried. Yield 124 mg (51%), mp 99–100 °C (EtOH). ^{1}H NMR (DMSO-d_6): 1.40 (br dd, $J = 9.0$, 4.5 Hz, 1H, H-2); 1.71 (t, $J = 4.5$ Hz, 1H, H-3); 1.77 (dd, $J = 9.0$, 4.5 Hz, 1H, H-4); 3.17 (s, 3H, OMe); 3.20 (s, 3H, OMe); 3.63 (m, 4H, COOMe and H-8*exo*); 3.94 (d, $J = 7.0$ Hz, 1H, H-8*endo*); 4.71 (d, $J = 4.3$ Hz, 1H, H-1); 5.05 (s, 1H, H-6). Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 54.29; H, 6.51.

Acknowledgment

This research was supported by grant from Chemical Block Ltd. (www.chemblock.com).

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