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The furan approach to thiacyclic compounds. Stereoselective synthesis of 2,3-disubstituted tetrahydrothiopyrans

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Abstract

We describe an efficient new approach to the synthesis of thiacyclic compounds that extends the methodology we previously developed for oxacycles: oxidation of a furan ring with singlet oxygen, followed by intramolecular hetero Michael addition. The new approach provides a new entry to nucleoside analogues and α-glucosidase inhibitors.
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Cyclic sulfides have been widely used as templates to facilitate and control various chemical transformations,[1] one of their advantages for this purpose being the relative ease with which the sulfur atom can be removed from the final product. In particular, scaffolds derived from thiopyran have been exploited in the construction of a huge number of synthetic targets.[2] A decade ago, interest in cyclic sulfides chemistry received new impetus from the finding that the natural products salacinol (**4**) and kotalanol (**5**), shown in Figure 1, are potent α-glucosidase inhibitors.[3] The synthesis of these cyclic sulfonium salts and their synthetic analogues such as **6** and **7** has attracted considerable attention in the past few years.[4]

In view of the challenging opportunities noted above, we investigated whether the synthesis of thiacyclic compounds might profitably be approached by adopting the methods we have developed for the synthesis of oxacyclic compounds from methoxyallene or furan.[5] This methodology has given access to chiral butenolides,[6a] natural oxacyclic products,[6b] polyoxepanes[6c] and polytetrahydropyrans,[6d] and has also been extended to the synthesis of carbocyclic systems.[7] Here we report its extension to the stereoselective synthesis of the cis and trans 2,3-disubstituted tetrahydrothiopyrans **2** and **3** (Scheme 1).

We envisaged that compounds **2** and **3** could be prepared as shown in Scheme 1 from furan **6**, which is easily

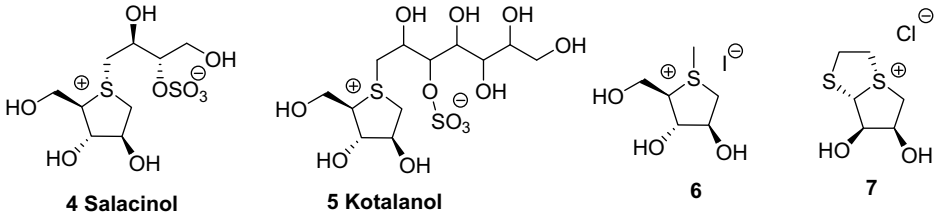

Fig. 1. Structures of some natural (**4**, **5**) and synthetic (**6**, **7**) glucosidase inhibitors.

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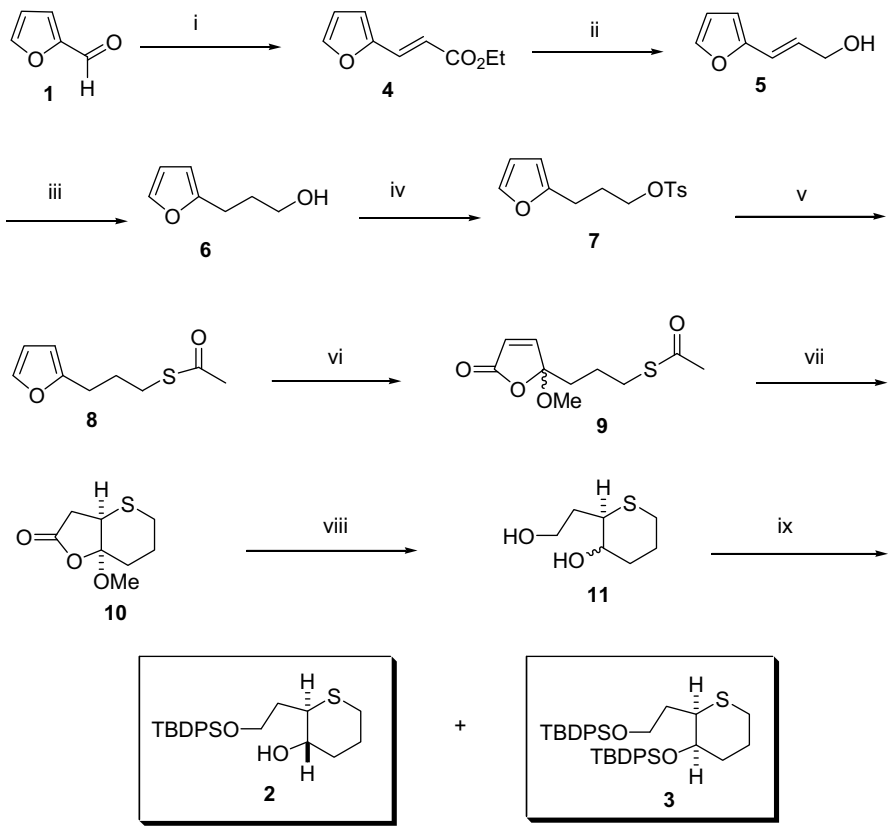

Scheme 1. Reagents and conditions: (i) Ph_3P, $BrCH_2CO_2Et$, LiOH, LiCl, H_2O, reflux (99%); (ii) $LiAlH_4$, Et_2O (95%); (iii) H_2, Pd/C, MeOH (98%); (iv) *p*TsCl, pyr (97%); (v) MeCOSK, DMF (70%); (vi) (a) $^1O_2$, MeOH, rose Bengal, *hv*; (b) Ac_2O, py, DMAP (>99%, 2 steps); (vii) K_2CO_3, MeOH, 0 °C (77%); (viii) LAH, $BF_3{\cdot}OEt_2$ (99%); (ix) TBDPSCl, Im, DMF, DMAP [45% (**2**); 52% (**3**)].

obtained in 92% yield from the inexpensive furaldehyde **1** by a one-pot Wittig reaction [8] followed by LAH reduction and catalytic hydrogenation (for the synthesis of large quantities of alcohol **6**, this three-step route is much cheaper than LAH reduction of commercial ethyl 3-(furan-2-yl)propanoate[5d]). Alcohol **6** was easily converted in 97% yield into tosylate **7**,[9] which upon reaction with potassium thioacetate in DMF [10] gave furan **8** (70%).[9] Oxidation of **8** with singlet oxygen, followed by treatment with acetic anhydride in pyridine, then afforded butenolide **9**[9] (99%, two steps); and treatment of **9** with potassium carbonate in methanol at 0 °C gave a 77% yield of the bicyclic lactone **10** [9] through an intramolecular Michael reaction. The lactone ring of **10** was then opened with LAH, affording a mixture of the diastereoisomeric *cis* and *trans* 2,3-tetrahydrothiopyran diols **11**.[9] Unlike related tetrahydropyrans,[5d] these isomers could not be separated by column chromatography. However, the reaction of **11** with TBDPSCl for 1 h afforded the monoprotected tetrahydrothiopyran **2**[11a] (45%) and the diprotected tetrahydrothiopyran **3**[11b] (52%), which were easily separated. A likely explanation of the selective protection of the cis-diastereoisomer of compound **11** could be that because of steric hindrance one diastereoisomer reacts more rapidly than the other. The control of reaction time is crucial. The relative stereochemistry of **3** was confirmed by NOE experiments (Fig. 2).

In conclusion, we have shown that the furan approach to oxacycles that we developed some years ago can be extended to the synthesis of thiacyclic systems. Work is now in progress on the use of this methodology to build templates for important synthetic targets and to explore the fascinating world of thiosugars.

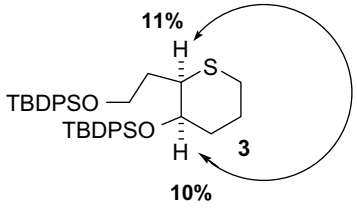

Fig. 2. NOE correlations in **3**.

Acknowledgements

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11. (a) Selected data for compound **2**: colourless oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.69 (m, 4H), 7.40 (m, 6H), 3.82 (m, 1H), 3.78 (m, 2H), 3.18 (m, 1H), 2.73 (m, 1H), 2.56 (m, 1H), 2.45 (m, 1H), 1.88 (m, 3H), 1.71 (m, 2H), 1.50 (m, 1H), 1.06 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 135.5, 134.8, 133.6, 129.7, 127.6, 66.5, 61.0, 44.9, 34.7, 32.8, 28.5, 26.8, 21.9, 19.1; LRMS: (FB+) [*m*/*z*, %]: 401.11 ($M+1^{+}$, 15%), 383.10 (94%), 265.01 (100%), 199.09 (77%); (b) Selected data for compound **3**: colourless oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.67 (m, 8H), 7.37 (m, 12H), 4.10 (m, 1H), 3.85 (m, 2H), 2.85 (m, 1H), 2.41 (m, 2H), 2.12 (m, 1H), 1.65 (m, 1H), 1.53 (m, 1H), 1.52 (m, 1H), 1.44 (m, 1H), 1.47 (m, 1H), 1.09 (s, 9H), 1.04 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 135.9, 135.8, 135.7, 135.6, 135.5, 134.8, 134.5, 134.1, 134.0, 133.9, 129.7, 129.6, 129.5, 127.8, 127.6, 127.5, 127.4, 72.4, 61.9, 41.1, 30.4, 29.7, 28.9, 23.2, 19.3; LRMS: (FB+) [*m*/*z*, %]: 581.23 ($M-{}^{t}Bu^{+}$, 46%), 383.10 (17%), 259.06 (14%), 197.14 (100%).