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Stereoselective synthesis of 2,3,4-trisubstituted tetrahydrothiophenes

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ABSTRACT

We describe an efficient new approach for the synthesis of highly substituted chiral tetrahydrothiophenes, based on the oxidation of a chiral furan substrate with singlet oxygen, followed by intramolecular hetero Michael addition.

Substituted tetrahydrothiophenes, some of which are shown in Figure 1, have received considerable attention because of their wide spectrum of biological activities. The natural products salacinol (**1**) and kotalanol (**2**), isolated from *Salacia reticulata*, *Salacia oblonga,* and *Salacia chinesis*, are potent α-glucosidase inhibitors.[1] Significant efforts to prepare these cyclic sulfonium salts and synthetic analogues, such as **3** and **4**, have been made in the past few years.[2] Recently, the related compounds salaprinol (**5**) and ponkoranol (**6**) were also isolated from the same plant species.[3] Biotin (**7**) is involved in important biological functions.[4] The adenosine analogues LJ-568 (**8**) and LJ-1251 (**9**) are potent and selective A_3 agonist and antagonist, respectively.[5] The chiral dihydrothiophene **10** inhibits copper amine oxidases.[6] Furthermore, tetrahydrothiophenes have been used as templates to facilitate and control various chemical transformations, as in asymmetric metal catalysis hydrogenation, catalytic asymmetric epoxidation, and catalytic intramolecular cyclopropanation.[7] In nanochemistry, the study of adsorption and properties of thiophenes, tetrahydrothiophenes, and chiral sulfur compounds, as cysteine, on gold surfaces have acquired importance lately.[8] The substituted thiophene **11** has also been used for size control synthesis of gold nanoparticles.[9]

For these reasons, the development of new synthetic approaches to tetrahydrothiophenes is of interest for organic chemists. Previously, we have described a new methodology for the synthesis of oxacyclic compounds from methoxyallene or furan.[10] We have prepared chiral butenolides, natural oxacyclic products, polyoxepanes, and polytetrahydropyrans.[11] This methodology has also been extended to the synthesis of carbocyclic and azacyclic compounds.[12] In order to enlarge the scope of our methodology, we have focused our attention on the synthesis of thiacyclic compounds. Recently, we have reported the preparation of six-membered thiacyclic compounds.[13] The challenge to obtain the more constrained five-membered ring and the chemical and biological importance of tetrahydrothiophenes prompted us to extend our methodology to the synthesis of this class of compounds. Herein, we report the stereoselective synthesis of chiral 2,3,4-trisubstituted tetrahydrothiophenes **21**.

The chiral furan **16** is the key intermediate in our synthesis and it was prepared as shown in Scheme 1. Diol **13** was obtained from the commercially available tri-*O*-acetyl-D-glucal as previously reported.[11a] Selective protection of the primary alcohol of compound **13** by treatment with tosyl chloride in the presence of dibutyltin oxide[14] followed by protection of the secondary hydroxyl group of the rather unstable tosylate **14** provided compounds **15**[15] in good yield. We have used TBDPS and the less bulky TBS as protecting groups in order to study the influence of the steric hindrance in the process. Treatment of **15a** and **15b** with potassium thioacetate in DMF[16] gave the chiral furans **16a** (94%) and **16b** (92%).[15]

Oxidation of **16a** with singlet oxygen in MeOH–CH_2Cl_2 1:1 in the presence of diisopropylethylamine afforded the 4-hydroxybutenolide **17a**[15] as a 1.6:1 diastereomeric mixture in 71% yield (Scheme 2). Reduction of compound **17a** with sodium borohydride under Luche's conditions followed by in situ acid-catalyzed lactonization gave enantiomerically pure butenolide **18a**[15] in very good yield (84%). At this stage the stereochemistry at C4 was unknown; however, the influence of the vicinal O-silylprotected group observed previously for related compounds[11a] allowed us to anticipate that the absolute configuration would be 4*S*. This result will be unambiguously confirmed later. Treatment of **18a** with

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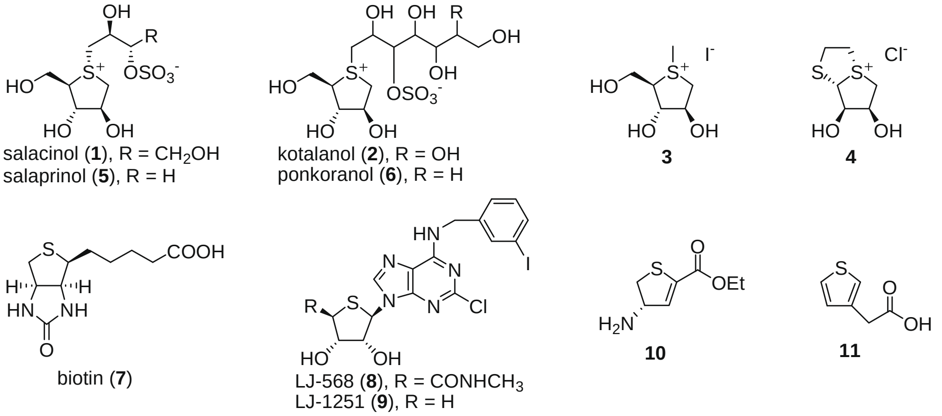
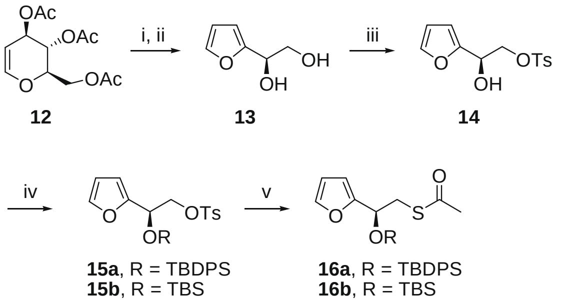
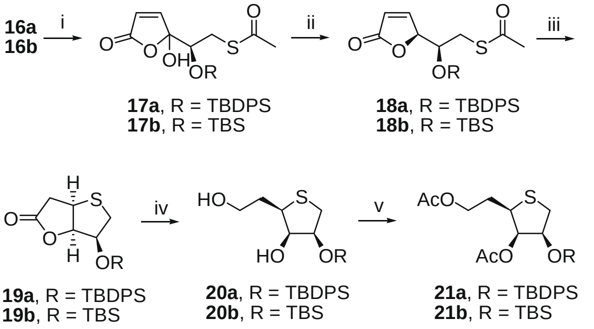


Figure 1. Substituted tetrahydrothiophenes with important biological and chemical applications.



Scheme 1. Reagents and conditions: (i) K_2CO_3, MeOH, rt; (ii) $InCl_3\cdot 4H_2O$, CH_3CN, rt, 77% from **12**; (iii) *p*-TsCl, Bu_2SnO, Et_3N, CH_2Cl_2, rt; (iv) TBDPSCl or TBSCl, Im, DMAP, DMF, rt, 69% (**15a** from **13**), 61% (**15b** from **13**); and (v) $KSCOCH_3$, DMF, 70 °C, 94% (**16a**), 92% (**16b**).



Scheme 2. Reagents and conditions: (i) (a) $^1O_2$, *hv*, rose bengal, MeOH, CH_2Cl_2, DIPEA, −78 °C; (b) $H_2C_2O_4$ 0.12 M, CH_2Cl_2, rt, 71% (**17a**), 69% (**17b**); (ii) (a) $CeCl_3\cdot 7H_2O$, $NaBH_4$, MeOH, 0 °C; (b) MeOH, HCl, rt, 84% (**18a**), 73% (**18b**); (iii) K_2CO_3, MeOH, 0 °C, 53% (**19a**), 68% (**19b**) (iv) $BF_3\cdot OEt_2$, $LiAlH_4$, Et_2O, rt; and (v) Ac_2O, DMAP, Py, rt, 84% (**21a** from **19a**), 88% (**21b** from **19b**).

potassium carbonate in methanol at 0 °C gave a 53% yield of the bicyclic lactone **19a**[15] through an intramolecular Michael reaction. The lactone ring of **19a** was then opened with lithium aluminium hydride to afford diol **20a**[15] which was acetylated without further purification to give tetrahydrothiophene **21a**[17a] (84%, two steps).

The stereochemistry of compound **21a** was established unequivocally using nOe experiments (Fig. 2), these results also confirmed the stereochemistry for compound **18a** anticipated by us. Tetrahydrothiophene **21b**[17b] was obtained from furan **16b** following the same sequence of reactions (Scheme 2). The intramolecular Michael reaction for the less bulky compound **18b** provided 68% yield of the bicyclic lactone **19b**, which was uneventfully converted into target compound **21b**.

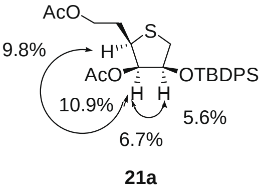


Figure 2. NOe correlations for **21a**.

In conclusion, a new and efficient method for the stereoselective synthesis of highly substituted chiral tetrahydrothiophenes from the commercially available tri-*O*-acetyl-D-glucal is described. The use of this methodology for the synthesis of natural products and synthetic analogues with pharmacological activity is now in progress in our laboratories.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.104.

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17. *Selected data for compound* **21a**: $[\alpha]_D$ −48.67 (c 0.35, CHCl$_3$); ^{1}H NMR (CDCl$_3$) δ 7.69 (4H, m, H-Ph), 7.44 (6H, m, H-Ph), 5.26 (1H, m, H3), 4.44 (1H, m, H4), 4.14 (2H, m, H2′), 3.93 (1H, m, H2), 2.93 (1H, dd, J = 11.3 and 4.2 Hz, 1H5), 2.69 (1H, dd, J = 11.3 and 1.6 Hz, 1H5), 2.07 (3H, s, COCH$_3$), 2.06 (1H, m, 1H1′), 2.01 (3H, s, COCH$_3$), 1.82 (1H, m, 1H1′), 1.11 (9H, s, C(CH$_3$)$_3$); ^{13}C NMR (CDCl$_3$) δ 170.9, 169.9, 135.7, 135.6, 133.3, 132.8, 130.0, 129.9, 127.8, 127.7, 80.3, 77.4, 63.2, 44.6, 36.3, 29.3, 26.8, 20.9, 20.8, 19.1; HRMS *m/z* calcd for $C_{26}H_{34}NaO_5SSi$ 509.17884, found 509.17874 (M+Na)$^+$; (b) *Selected data for compound* **21b**: $[\alpha]_D$ −63.51 (c 0.36, CHCl$_3$); ^{1}H NMR (CDCl$_3$) δ 5.09 (1H, m, H3), 4.39 (1H, m, H4), 4.12 (2H, m, H2′), 3.78 (1H, m, H2), 3.14 (1H, m, 1H5), 2.73 (1H, m, 1H5), 2.10 (3H, s, COCH$_3$), 2.07 (1H, m, 1H1′), 2.05 (3H, s, COCH$_3$), 1.86 (1H, m, 1H1′), 0.90 (9H, s, C(CH$_3$)$_3$), 0.12 (3H, s, SiCH$_3$), 0.11 (3H, s, SiCH$_3$); ^{13}C NMR (CDCl$_3$) δ 170.9, 170.1, 80.7, 76.6, 63.3, 44.4, 36.7, 29.2, 25.6, 20.9, 17.9, −4.9, −5.0; HRMS *m/z* calcd for $C_{16}H_{31}O_5SSi$ 363.16246, found 363.16594 (M+H)$^+$.