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Communication

First Total Synthesis of 4-Methylthio-3-butenyl Glucosinolate

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The first total synthesis of 4-methylthio-3-butenyl glucosinolate (MTBG), a natural bioactive compound and a precursor of radish phototropism-regulating substances, was achieved from commercially available 1,4-butanediol. The glucosinolate framework was prepared by coupling of an oximyl chloride derivative and tetraacetyl thioglucose. A methylthio group was introduced to the framework by a Wittig reaction between triphenylphosphonium thiomethylmethylide and an aldehyde intermediate of glucosinolate. The synthetic route should facilitate preparation of various derivatives needed for probe synthesis based on MTBG.

Key words: 4-methylthio-3-butenyl glucosinolate; phototropism; radish; synthesis; natural product

4-Methylthio-3-butenylisothiocyanate (MTBI) was isolated and identified from light-grown radish seedlings as candidates for growth inhibitors involved in the phototropism of radish (*Raphanus sativus*) hypocotyls.[1,2)] More recently, MTBI and its bioprecursor, 4-methylthio-3-butenyl glucosinolate (MTBG, **1**), have been found to possess unique antioxidant and cytotoxic activities, boosting intense research interest in them.[3)]

Kosemura *et al.* (1993) suggested that MTBI is released from MTBG *via* myrosinase (thioglucosidase) action (Fig. 1).[4)] However, no work has been done on receptors or direct binding molecules of these substances so far, while the identification of interacting targets is essential to figure out the mechanism underlying several bioactivities including plant-growth inhibition and selective cytotoxicity. Labeling of MTBI and MTBG (**1**) such as biotinylation or fluorescence-probing is presumably a powerful means to identify its receptors. The problem with the probe synthesis based on MTBI and MTBG (**1**) is the difficulty in directly labeling them with important sites retaining their bioactivities. Hence, we carried out the synthetic study of MTBG (**1**) to obtain intermediates which can be converted to various derivatives needed to design probes of both MTBG (**1**) and MTBI. Since the total synthesis of MTBG (**1**) have not reported yet, in this communication we report the first total synthesis of MTBG (**1**).

As the synthetic route of MTBG (**1**), we envisaged the introduction of a thioalkyl side chain into a glucosinolate framework, since the use of alkylation reagents with different structures enables us to obtain new derivatives bearing various lengths and structures of the thioalkyl side chain keeping the fundamental framework of MTBG (**1**) and MTBI. The glucosinolate framework for MTBG (**1**) was prepared with the most convenient synthetic route to glucosinolates, which involves the coupling of an oximyl chloride derivative and a commercially available tetraacetyl thioglucose.[5)] Synthesis of the desired aldehyde (**2**) commenced from 1,4-butanediol (**3**) (Scheme 1). Compound **3** was monosilylated to known 4-[(*t*-butyldimethylsilyl)oxyl]-butan-1-ol (**4**),[6)] followed by an oxidation reaction using PCC[7)] to afford the silyl ether of 4-hydroxybutanal **5**. Aldehyde **5** was treated with hydroxylamine hydrochloride in the presence of sodium carbonate at room temperature for 1 h to yield a mixture of *syn*- and *anti*-oximes **6** (89%), which was treated in turn with *N*-chlorosuccinimide (NCS) at room temperature overnight to give the corresponding oximyl chloride **7** with a yield of 85%. The coupling between **7** and tetraacetylthioglucose was carried out in dry THF in the presence of TEA at room temperature for 3.5 h to give **8**. The thiohydroximate **8** was found to be unstable and hence was used without purification in the next reaction. Compound **8** was acetylated in dry pyridine with Ac_2O at room temperature overnight to obtain pentaacetate **9**, which was then desilylated without purification to give **10** with an overall yield of 55% from **7**. The terminal hydroxyl of **10** was oxidized with Dess-Martin periodinane at room temperature for 3.5 h to give the aldehyde **2** in 84% yield.

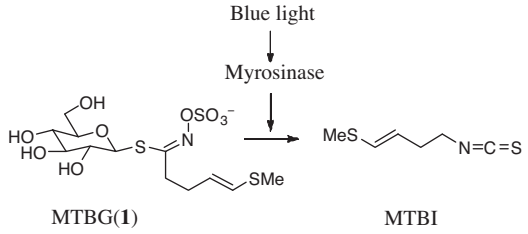

Fig. 1. Formation of MTBI, a Radish Phototropism-Regulating Substance, from MTBG (**1**).

Following introduction of a methylthio group, we utilized a Wittig reaction between triphenylphosphonium thiomethylmethylide and the prepared aldehyde **2** (Scheme ★★). This type of reaction is not generally stereospecific, and Wittig thiomethylenation of **2** afforded a 100:77 mixture of the *E* and *Z* vinyl sulfides **11** (72%).[8)] At this point, the products included *anti*/*syn*

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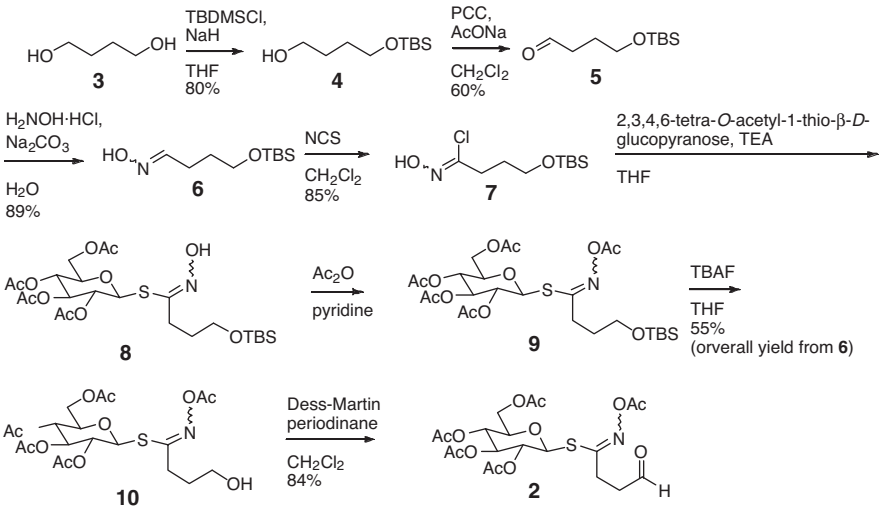
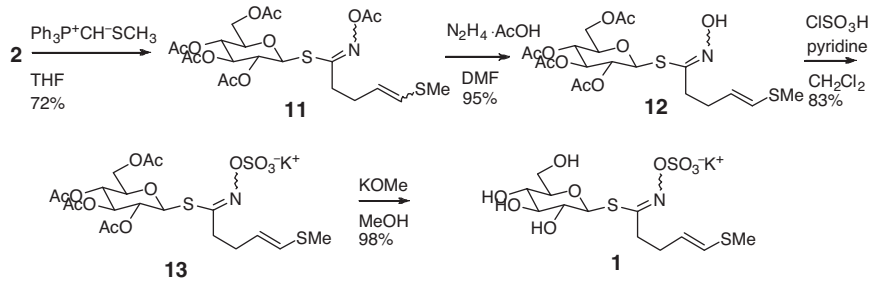


Scheme 1. Synthesis of **2**.



oxmic and *E*/*Z* vinyl isomers, which were separated by C_{18} reversed-phase HPLC to yield four isomeric pure sulfides. Among them, one isomer **11a** (21%) showed oximic and vinyl proton signals in the ^{1}H NMR spectrum, in agreement with the values given in those of the desulfated and acetylated derivatives of natural MTBG. While the *E*-configuration of the vinyl sulfide in **11a** was proved by the coupling constant ($J = 15.1$ Hz) of the vinyl protons, it was not possible to determine the streochemistry of the oxime moiety. Selective deacetylation of the acetoxime group by treatment of **11a** with hydrazine acetate in DMF at room temperature for 30 min afforded the tetraacetate **12** in 95% yield. Sulfation of the oxime was performed with chlorosulfonic acid in pyridine at room temperature for 30 min, resulting in the sulfated product **13** in 83% yield. Finally, **13** was treated with potassium methoxide in methanol at room temperature overnight, and the product was purified by C_{18} reversed-phase column chromatography to afford MTBG (**1**, 98%), whose ^{1}H and ^{13}C NMR, IR, MS, optical rotaion data, and HPLC retention time were identical with those of the natural compound.[9),*]

In summary, the first total synthesis of MTBG (**1**) was accomplished starting from 1,4-butanediol (**3**). The disclosed synthetic route in this study may be amenable to the synthesis of new analogs of MTBG (**1**), which are required for preparing probes of putative bioactive substances relating to phototropism and also may be useful to clarify the structural requirements for its various bioactivities.

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* Spectral data of **1** (*E*-isomer):$[\alpha]^{24}_D$ −23° (*c* 0.2, H_2O) ; ν_{max} (KBr) 3427, 1604, 1398, 1333, 1268, 1138, 1072 cm^{-1}; ^{1}H NMR (D_2O, 500 Hz): δ 6.10 (1H, d, $J = 15.1$ Hz), 5.44 (1H, dt, $J = 15.1$, 7.6 Hz), 4.92 (1H, d, $J = 9.8$ Hz), 3.79 (1H, dd, $J = 12.6$, 2.3 Hz), 3.54 (1H, dd, $J = 12.6$, 4.3 Hz), 3.33–3.46 (4H, m), 2.70 (2H, t, $J = 7.6$ Hz), 2.43 (2H, q, $J = 7.6$ Hz), 2.14 (3H, s); ^{13}C NMR (D_2O, 125 Hz): δ 163.91, 125.51, 124.99, 82.15, 80.42, 77.38, 72.26, 69.46, 60.93, 32.39, 30.41, 14.03; HRESIMS calcd for $C_{12}H_{20}NO_9S_3$ $[M - K]^-$ 418.03131; found: 418.03002.

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