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Total Synthesis of 10-Isothiocyanatoguaia-6-ene

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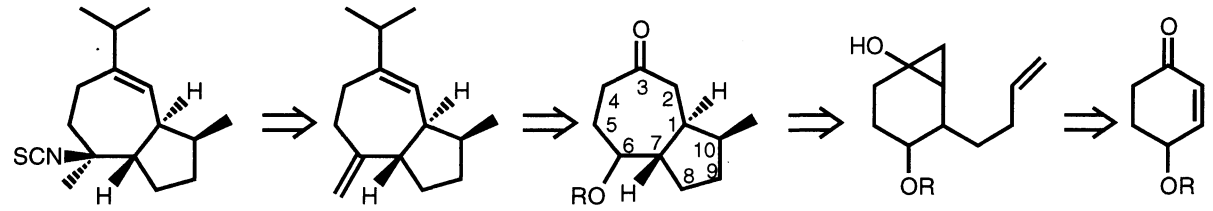
Total synthesis of a unique isothiocyano sesquiterpene, 10-isothiocyanatoguaia-6-ene, was achieved utilizing the oxidative radical cyclization reaction of a bicyclo[4.1.0]heptanol derivative with $Mn(pic)_3$ as the key step.

(1S*, 4S*, 5R*, 10S*)-10-Isothiocyanatoguaia-6-ene is a sesquiterpene recently isolated from the Palauan sponge *Trachyopsis aplysinoides* and belongs to a rather rare class of marine natural products which contain an isothiocyano group in the molecule.[1] This compound has a characteristic trans-fused bicyclo[5.3.0]decane skeleton with four chiral centers, and total synthesis of these isothiocyano sesquiterpenoids remains to be explored.[2]

In the previous paper, we reported that when 5-(3-butenyl)bicyclo[4.1.0]heptan-1-ol was oxidized with manganese(III) 2-pyridinecarboxylate($Mn(pic)_3$) in the presence of various radical trapping reagents, ring-expanded β-keto radical was generated and cyclized to give trans-fused bicyclo[5.3.0]decan-3-one derivatives in good yield with high stereoselectivity.[3] In particular, the reaction in the presence of tributyltin hydride as a radical trapping reagent gave the corresponding C-10 methylated product, which has both the basic skeleton and the correct relative stereochemistry of 10-isothiocyanatoguaia-6-ene.[4] In this paper is described the first total synthesis of this isothiocyano sesquiterpene based on the oxidative radical cyclization reaction according to the retrosynthetic plan as shown in Scheme 1.

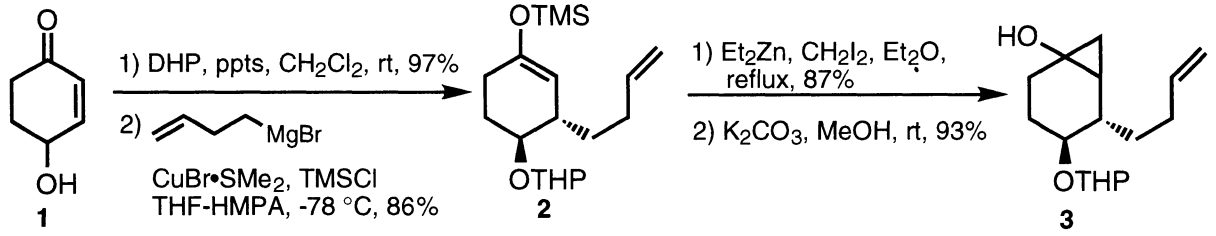


10-isothiocyanatoguaia-6-ene

Scheme 1.

The key intermediate **3** for the oxidative radical cyclization was prepared straightforwardly in good yield from 4-hydroxy-2-cyclohexen-1-one (**1**)[5] as shown in Scheme 2. Thus, hydroxyl group of **1** was protected as its tetrahydropyranyl(THP) ether by treatment with dihydropyran(DHP) and pyridinium *p*-toluenesulfonate(ppts) almost quantitatively, and then 3-butenyl group was introduced stereoselectively at C-3 position by 1,4-addition of 3-butenylmagnesium bromide in the presence of chlorotrimethylsilane and a catalytic amount of $CuBr{\bullet}SMe_2$ in THF-HMPA at -78 °C to give silyl enol ether **2** in 86% yield.[6] Cyclopropanation of this silyl enol ether **2** was

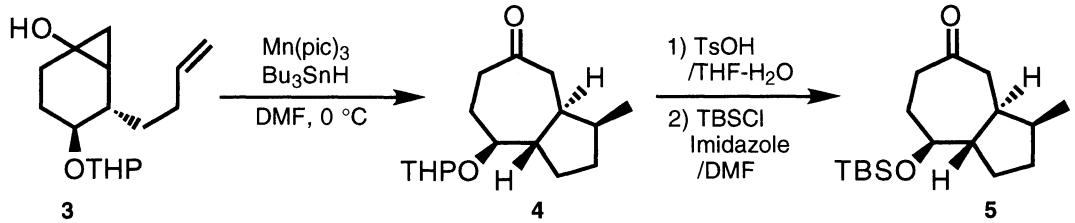
carried out by using diethylzinc and diiodomethane to afford a TMS-protected cyclopropanol as about 10:1 mixture of stereoisomers[7] in 87% yield. The cyclopropanol **3** was obtained by the deprotection of the TMS group in the presence of a catalytic amount of potassium carbonate in methanol in 93% yield.



1 **2** **3**

Scheme 2.

As the substrate with appropriate functionalities for the oxidative cyclization was now in hand, the oxidative intramolecular radical cyclization of cyclopropanol **3** was examined according to the reported procedure.[3] Thus, **3** was treated with 1.5 mole amount of $Mn(pic)_3$ in the presence of 1.3 mole amount of $Bu^n{}_3SnH$ in DMF. The reaction proceeded smoothly at 0 °C and the desired cyclized compound **4** was obtained in 76% yield in more than 90% purity. The 500 MHz ^1H NMR spectrum indicated that three minor, presumably isomeric products were present in less than 10%, but these products could not be separated at this stage.[8] For the purpose of simplifying the NMR spectrum and attaining higher stability of a hydroxyl protective group at C-6, tetrahydropyranyl group of **4** was removed by *p*-toluenesulfonic acid(TsOH) in THF-water, and then reprotected by TBSCl and imidazole in DMF to afford a TBS protected derivative **5**.[9]

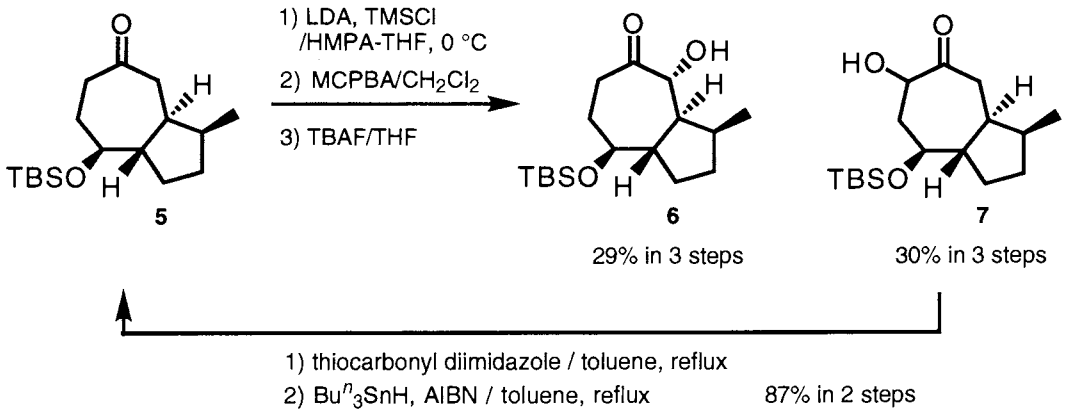


3 **4** **5**

76%, >90% selectivity 83% in 2 steps

Scheme 3.

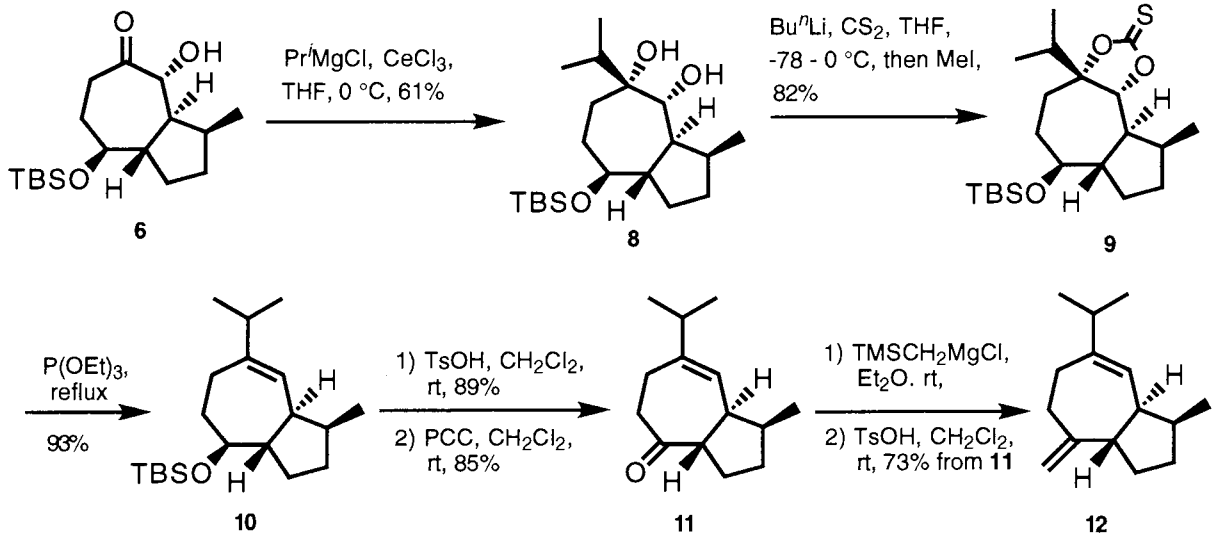
As the basic skeleton with three correct relative stereochemistries for the synthesis of 10-isothiocyanato-guaia-6-ene was obtained, we next examined the introduction of isopropyl group at C-3 position along with C-2-C-3 double bond. Model reactions with the substrate having no C-6 hydroxyl functionality revealed that regioselective dehydration of the tertiary alcohol obtained by the reaction with isopropylmagnesium chloride-cerium(III) chloride reagent[10] proved to be quite difficult. For example, the dehydration under acidic conditions gave a mixture of olefins in which exo olefin was obtained as a major product. Thus, we decided to examine an indirect method for the introduction of C-2-C-3 double bond. Treatment of the ketone **5** with lithium diisopropylamide(LDA) followed by the addition of TMSCl in THF gave a regioisomeric mixture of silyl enol ethers, which were, without purification, oxidized with *m*-chloroperbenzoic acid(MCPBA) in CH_2Cl_2 to give a 1:1 mixture of the corresponding α-trimethylsiloxyketones. Selective deprotection of TMS group with tetrabutylammonium fluoride in THF produced α-hydroxyketones **6** and **7** in 59% yield from the ketone **5**. The desired isomer **6** was obtained as a single diastereomer by silica-gel chromatography.[11] The other isomer **7** could be converted back to the ketone **5** by treatment with thiocarbonyl diimidazole in toluene followed by reduction with $Bu^n{}_3SnH$ by a one-pot procedure in 87% yield.[12]



Scheme 4.

Introduction of isopropyl group to the α-hydroxyketone **6** was carried out with organocerium reagent prepared from isopropylmagnesium chloride and cerium(III) trichloride in THF at 0 °C[10] to give the addition product **8** in 61% yield with high stereoselectivity.[13] Treatment of this diol **8** with Bu^nLi and carbon disulfide in THF followed by the addition of methyl iodide afforded a thiocarbonate **9** in the yield of 82%. Reductive olefination of the thiocarbonate **9** was carried out in triethyl phosphite at 140 °C to produce the desired olefin **10** in 93% yield.[9,14]

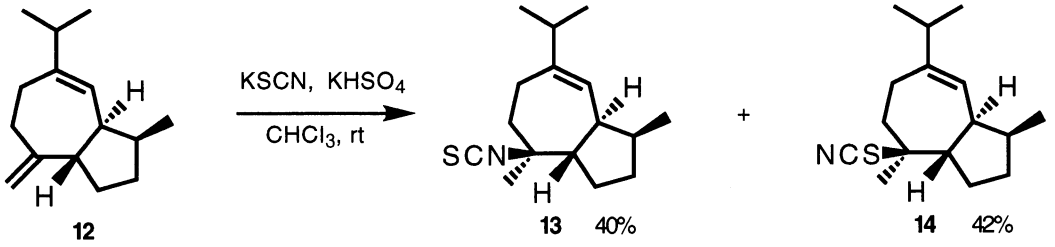
As the introduction of isopropyl group with C-2-C-3 double bond was achieved, we undertook the final operation of introducing methyl group and isothiocyano functionality at C-6 position. After deprotection of TBS group of **10** with TsOH in CH_2Cl_2 in 89% yield, the resulting alcohol was oxidized with PCC in CH_2Cl_2 to produce a ketone **11** in 85% yield. Reaction of the ketone **11** with trimethylsilylmethylmagnesium chloride followed by treatment of the crude product with TsOH[15] afforded an exo methylene derivative **12** in 73% yield.



Scheme 5.

Finally, selective addition of isothiocyanic acid to olefin **12** was attempted. Treatment of diene **12** with isothiocyanic acid generated in situ with KSCN and $KHSO_4$ in $CHCl_3$ for 3 days[16] revealed that the reaction was highly site-selective and stereoselective but gave a mixture of two compounds, which were separated easily by silica-gel column chromatography to give the desired isothiocyanide **13** in the 40% yield accompanied by the

isomeric thiocyanide **14** in 42% yield.[17] The ^{1}H and ^{13}C NMR spectra of **13** completely coincided with those of the literature.[1] Thus the first total synthesis of the isothiocyano sesquiterpene, 10-isothiocyanatoguaia-6-ene was achieved.



Scheme 6.

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3) N. Iwasawa, M. Funahashi, S. Hayakawa, and K. Narasaka, *Chem. Lett.*, **1993**, 545.
4) In this paper IUPAC nomenclature is used for the numbering of the compounds.
5) R. K. Boeckmann, Jr. and M. Ramaiah, *J. Org. Chem.*, **42**, 1581(1977).
6) S. Matsuzawa, Y. Horiguchi, E. Nakamura, and I. Kuwajima, *Tetrahedron*, **45**, 349(1989).
7) Relative stereochemistries of these isomers were not determined rigorously. The cyclization reaction was carried out using this mixture. It was expected that either isomer produced the same β-keto radical.
8) These minor products were separated at the stage of the diol **8** by recrystallization.
9) Representative spectral data are as follows; **5**: ^{1}H NMR (500 MHz, $CDCl_3$) δ=3.42 (1H, dt, J=3.4, 9.8 Hz), 2.33-2.51 (3H, m), 2.13 (1H, ddd, J=3.5, 7.2, 14.4 Hz), 2.00-2.07 (1H, m), 1.90-1.95 (1H, m), 1.67-1.85 (5H, m), 1.31-1.39 (1H, m), 1.22-1.28 (1H, m), 0.85 (9H, s), 0.79 (3H, d, J=7 Hz), 0.04 (3H, s), 0.03 (3H, s); IR (neat) 2954, 1704, 1088, 839 cm^{-1}. **10**: ^{1}H NMR (500 MHz, $CDCl_3$) δ=5.47 (1H, brs), 3.42 (1H, dt, J=4.1, 9.4 Hz), 2.12-2.24 (3H, m), 1.83-2.06 (4H, m), 1.68-1.75 (1H, m), 1.58 (1H, quintet, J=9.2 Hz), 1.18-1.37 (3H, m), 0.95 (3H, d, J=6.5 Hz), 0.94 (3H, d, J=6.7 Hz), 0.88 (3H, d, J=6.8 Hz), 0.86 (9H, s), 0.05 (3H, s), 0.04 (3H, s); IR (neat) 2954, 1464, 1375, 1257, 1086 cm^{-1}.
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13) We have not rigorously established the stereochemistry of the addition reaction at this stage. However, the result of the following reductive olefination reaction strongly supported the stereochemistry as shown in **8**.
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17) The structure of **14** was deduced from its characteristic absorption of ^{13}C NMR (δ=112) and IR (ν=2146 cm^{-1}) spectra for thiocyano group.

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