An Easy Route to (−)-10(*R*)-Isothiocyanoaromadendrane and (−)-10(*S*)-Isothiocyanoalloaromadendrane

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Isothiocyanosesquiterpenoids belong to an unusual class of bioactive (ichtiotoxic, antimicrobial, antifeedant, and anticancer[1]) marine sponge metabolites. Despite the above cited peculiarities, the total synthesis and absolute configuration of many sesquiterpene isothiocyanates remain to be determined. The same also holds true for axisothiocyanate 2, 1,[2] which was first isolated in a mixture of four compounds from *Axinella cannabina*. A sample of 1 was obtained in a pure form by semisynthesis, treating axisonitrile 2, another *A. cannabina* metabolite, with sulfur. The isothiocyano derivative of 2 was shown to be identical to one of the components of the original mixture (GLC). A literature search focusing on isothiocyanosesquiterpenes revealed that epipolasin B, 3,[3] isolated from *Epipolasis kushimotoensis* (reported in 1985), possessed an absolute configuration related to that of (−)-aromadendrene.

The similarity between the ^{1}H-NMR data of 1 and 3 and differences in physical data led Tada and Masuda[3] to suggest that these compounds were stereoisomers (Figure 1). Two years later, Fattorusso and co-workers, on the basis of a series of NMR experiments,[4] revealed that 1 possessed a relative configuration identical to that of 10-(*R*)-thiocyanoaromadendrane (3 or 4). Whether 1 and 3 are identical or enantiomers is an unanswered question. Controversies concerning the isothiocyanosesquiterpene structures are relatively common and arise from the fact that these compounds always occur in triads (isocyano, isothiocyano, and formamide derivatives) which makes purification and identification a difficult task.

Motivated by these facts, we have undertaken a synthetic program with the primary goal of providing chemists with a simple method of transforming available, chiral terpenes into their corresponding isothiocyanates. We have recently reported our preliminary results concerning this subject,[5] and in this paper we describe the application of this method to obtain enantiomerically pure (−)-10(*R*)-isothiocyanoaromadendrane, 4, and (−)-10(*S*)-isothiocyanoalloaromadendrane, 5. Other synthetic and mechanistic considerations are under investigation and will be reported shortly.

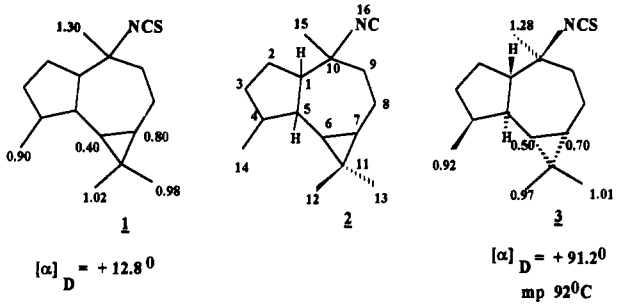
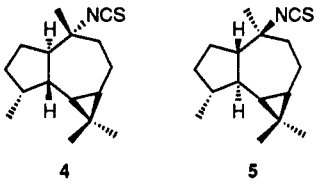
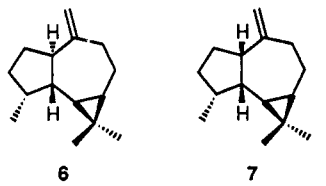


Figure 1. Structure numbering, physical data, and proton NMR assignments of 1 and 3.



Results and Discussion

Treatment of (+)-aromadendrene, 6, with thiocyanic acid in chloroform furnished after 2 days at room temperature only one addition product. Silica column chromatography with pentane as eluent produced 4 in 97% yield. Recrystallization of 4 in cold pentane (3 °C)



produced colorless needles possessing a melting point of 96–97 °C and $[\alpha]_D$ −90° (*c* 1.2, $CHCl_3$). The strong infrared absorption at 2112 cm^{-1} and molecular ion at *m/z* 263 was consistent with an isothiocyanate functionality. Its proton and carbon-13 NMR signals (Figure 2) were assigned on the basis of 1D and 2D NMR experiments (homonuclear correlations, COSY, and heteronuclear correlations, HETCOR and COLOC).

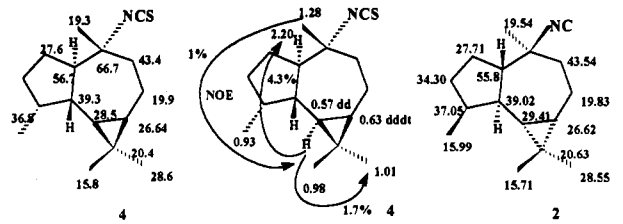


Figure 2. Carbon and proton assignments of (−)-10(*R*)-isothiocyanoaromadendrane, 4, and those reported for 2.[4]

The 10*R* stereochemistry at carbon-10 was inferred from NOE difference experiments (enhancement of methyl-12 at 0.98 ppm upon irradiation of methyl-15 at 1.28 ppm). We confirmed our results with an X-ray crystallographic structure determination which provided the unquestionable proof of 4 depicted in Figure 3. A complete crystallographic report will be published elsewhere.[8]

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(1) Edenborough, M. S.; Herbert, R. B. *Nat. Prod. Rep.* **1988**, 229–245 (epipolasin B was reported in this review article with a drawing misinterpretation of the original article; the same is true for the bisabolene derivatives structures 113–118). Faulkner, D. J. *Nat. Prod. Rep.* **1992**, 323–364; **1991**, 97–147; **1990**, 269–309; **1988**, 613–663; **1987**, 539–575. Fraga, B. M. *Nat. Prod. Rep.* **1990**, 61–84; **1990**, 515–537; **1992**, 217–241.

(2) Fattorusso, E.; Magno, S.; Mayol, L.; Santacroce, C.; Sica, D. *Tetrahedron* **1975**, *31*, 269–270.

(3) Tada, H.; Yasuda, F. *Chem. Pharm. Bull.* **1985**, *33*, 1941–1945.

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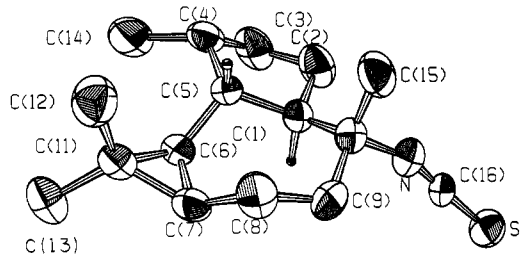

Figure 3. ORTEP drawing of compound 4 and atom labeling.

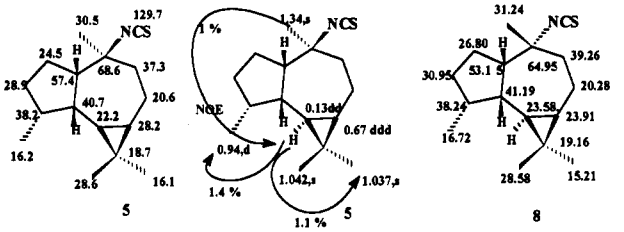

Figure 4. Carbon and proton assignments of (–)-10(*S*)-isothiocyanoalloaromadendrane, **5**, and those reported for **8**.

From the similarity of the carbon-13 NMR signals of **2**[4] (Figure 2) with those of **4**, we conclude that both possess the same relative configuration, which also confirms the configuration of axisothiocyanate 2, 1. The optical rotation of **4** ($[\alpha]_D$ –90°) clearly indicates that **4** and **3** ($[\alpha]_D$ +91.2°) are enantiomers. Contamination might be the cause of the low optical rotation ($[\alpha]_D$ +12.8°) of compound 1, and if so, both epipolasin B, **3**, and axisothiocyanate 2, 1, have the same structure and absolute configuration.

Following the same synthetic method, we have performed the addition of thiocyanic acid to (–)-alloaromadendrene, **7**. Usual workup and purification over a silica gel column eluted with pentane yielded (–)-10(*S*)-isothiocyanoalloaromadendrane, **5** ($[\alpha]_D$ –5.9°), in 40% yield (based on the reacted alloaromadendrene **7**). Compound **5** displayed a molecular ion at *m/z* 263 and a strong infrared absorption at 2100 cm^{-2} (–NCS). A full spectroscopic analysis (1D and 2D, ^1H and ^{13}C NMR, COSY, HETCOR, and COLOC) led to the assignments depicted in Figure 4. The 10*S* stereochemistry was suggested on the basis of NOE difference experiments in which the enhancement of H-6 was observed upon methyl-15 irradiation. The (–)-10(*R*)-isothiocyanoalloaromadendrane, **8**, was isolated from *A. cannabina*,[4] but the 10*S* epimer has not been reported in the literature. Both ^1H and ^{13}C NMR signal assignments of **8**[4] and of **5** are depicted in Figure 4 for a better visualization of the differences in chemical shifts.

In the two reactions above two unusual facts attracted our attention: the reaction was stereoselective and little or no thiocyano derivatives were formed. Usually the thiocyanic acid addition products are a mixture of the thiocyanic and the isothiocyanic derivatives in an approximate 1:1 ratio.[5]

Mechanistic considerations to explain the observed selectivity took into consideration the extensive work on the isothiocyano and thiocyano derivative kinetics.[6] We suppose that the thiocyanic acid adds almost exclusively to the less hindered *Re* face of the aromadendrene and *Si* face of the alloaromadendrene double bonds. The kinetic products, the thiocyanic derivatives, form intimate ion pair intermediates at room temperature which rearrange (on the same face) to the thermodynamic product isothiocyanate (the formation of the intermediate thiocyanic derivative was monitored by GC). Had both *Re* and *Si* faces of the aromadendrene, **6**, and alloaromadendrene, **7**, double bond presented equal steric hindrance, the intimate ion pair could have been attacked by the thiocyano moiety from the opposite face, leading to a 10*R* and 10*S* mixture of thiocyanic and isothiocyanic derivatives in both cases.

(6) Giles, D. E. Kinetics and mechanisms of reactions of cyanates and related compounds. In *The Chemistry of cyanates and their derivatives*; Patai, S., Ed.; John Wiley & Sons: New York, 1977; Part 1.

Experimental Section

General Procedures. Melting points were determined on a Reichert hot-stage microscope and are uncorrected. Optical rotations were measured on an automatic Carl Zeiss polarimeter, Polaromat A, using a 20-mm cell and mercury lamp. The optical rotation values were then corrected using the equation $[\alpha]_{Hg} = 1.17543[\alpha]_D$. The IR spectra were recorded on a Perkin-Elmer 1600 FTIR instrument. Proton NMR spectra were run at 300 MHz in $CDCl_3$ solutions (Bruker AC-300P or Varian Gemini-300 spectrometer). Carbon-13 NMR spectra were determined at 75 MHz in $CDCl_3$ solutions (Bruker AC-300P or a Varian Gemini-300 spectrometer). Chemical shifts were reported in ppm (δ) from TMS ($\delta = 0$), the internal reference. Carbon-13 NMR peak assignments were confirmed by DEPT, HETCOR, and COLOC. Mass spectra were measured at 70 eV using a GC/MS HP 5970-MSD connected to a gas chromatograph HP-5890. Merck silica gel 60 (70–230 mesh) was used for column and Merck silica gel 60 F 254 for thin-layer chromatographies.

Preparation of the Thiocyanic Acid[7] In an Aldrich atmosbag, a slurry of 7.3 g (75 mmol) of powdered KSCN in 30 mL of $CHCl_3$ was triturated with 11.2 g (82 mmol) of $KHSO_4$ in a mortar for 5 min. The HSCN chloroform solution was decanted, and an additional 10 mL of $CHCl_3$ was added to the solid mixture. The combined solutions totaled 30 mL.

(–)-10(*R*)-Isothiocyanoaromadendrane, 4. To aromadendrene **6** ($[\alpha]_D$ +12°) (Fluka, 110 mg, 0.54 mmol), in chloroform (1 mL) was added a HSCN–chloroform solution (10 mL), prepared as described above. The mixture was stirred at room temperature for 2 days. The reaction was filtered and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (pentane) gave **4** (137 mg, 97%) as a colorless oil. Crystallization from pentane gave **4** as colorless plates: mp 97–98 °C, $[\alpha]_D$ –90° (c, 2.4, $CHCl_3$); IR $\nu(cm^{-1})$ 2112 (–NCS); ^1H- and ^{13}C-NMR (see Figure 1); MS *m/z* 263 (2), 248 (20), 230 (18), 181 (60), 161 (30), 149 (55), 107 (80), 69 (100).

(–)-10(*S*)-Isothiocyanoalloaromadendrane, 5. To alloaromadendrene, **7** ($[\alpha]_D$ –39°) (Fluka) (204 mg, 2.45 mmol), in chloroform (1 mL) was added a HSCN–chloroform solution (10 mL), prepared as described above. The mixture was stirred at room temperature for 2 days. The mixture was filtered and concentrated in vacuo. Purification of the residue by column chromatography on silica gel (pentane) gave alloaromadendrene (53 mg) and **5** (78.5 mg, 40%, based on the reacted alloaromadendrene) as a colorless oil. Crystallization from pentane gave **5** as colorless needles: mp 63–66 °C; $[\alpha]_D$ –5.9° (c, 2.1, $CHCl_3$); IR $\nu(cm^{-1})$ 2095 (–SCN); ^1H- and ^{13}C-NMR (see Figure 2); MS *m/z* 263 (M^+), 248 (20), 230 (15), 161 (45), 69 (100).

Anal. Calcd for $C_{16}H_{25}NS$: C, 72.95; H, 9.57; N, 5.32; S, 12.16. Found: C, 73.00; H, 9.53; N, 6.55; S, 10.92.

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(8) The author has deposited atomic coordinates for $C_{16}H_{25}NS$ with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.