Pergamon

Tetrahedron 56 (2000) 8111–8117

TETRAHEDRON

Synthesis of a Novel Sesquiterpene Isolated from the Pheromone Gland of a Stink Bug, *Tynacantha marginata* Dallas

Shigefumi Kuwahara,[a,b,*] Shiharu Hamade,[b] Walter Soares Leal,[c] Jiro Ishikawa[b] and Osamu Kodama[b]

[a]*Laboratory of Applied Bioorganic Chemistry, Division of Life Science, Graduate School of Agricultural Science, Tohoku University, 1-1 Tsutsumidori-Amamiyamachi, Aoba-ku, Sendai 981-8555, Japan*

[b]*Laboratory of Agricultural Chemicals, Faculty of Agriculture, Ibaraki University, Ami-machi, Inashiki-gun, Ibaraki 300-0393, Japan*

[c]*Department of Entomology, University of California, Davis, CA 95616-8585, USA*

Received 27 July 2000; accepted 23 August 2000

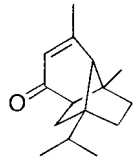
Abstract—A novel sesquiterpene, isolated as the putative sex pheromone of a stink bug (*Tynacantha marginata* Dallas) and proposed to have an unprecedented carbon framework, was synthesized as its racemate by using an intramolecular double Michael cyclization as the key step. Comparison of the spectral data of the synthetic sample with those of the natural material confirmed the proposed structure.

Introduction

The main component of the pheromone gland of a Brazilian predatory stink bug, *Tynacantha marginata* Dallas, was isolated recently by Leal et al.[1] Since the compound was male-specific, they considered it as the sex pheromone of *T. marginata*. On the basis of the ^{1}H and ^{13}C NMR, IR, UV and MS analyses, they proposed the putative pheromone to have an unprecedented tricyclic sesquiterpene skeleton as depicted by structure **1** (Fig. 1), although its absolute stereochemistry was not assigned.[1] This structural uniqueness prompted us to embark on the confirmation of the proposed structure by synthesizing **1** as its racemate. In order to construct the tricyclic carbon framework incorporated in **1**, we planned to try the double Michael cyclization of acyclic compound **4** into keto ester **3** followed by its ring expansion to (±)-**1** via tricyclic ketone **2** (Scheme 1). The cyclization substrate (**4**) was considered to be obtainable by alkylation of enone **5** with iodide **6** followed by some additional steps. As described below, we were able to accomplish the synthesis of (±)-**1** along this synthetic plan.

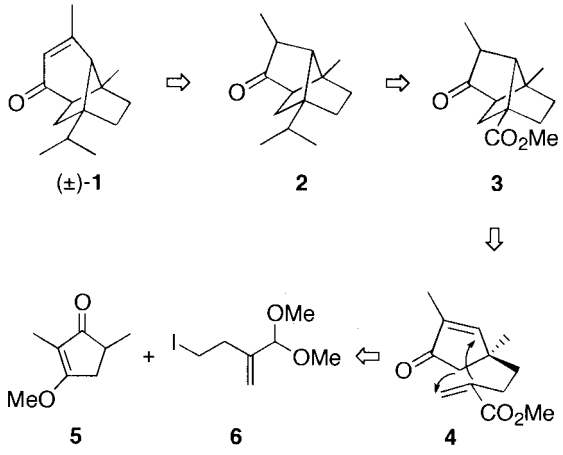
Results and Discussion

A three-step sequence for the preparation of the iodide (**6**) is shown in Scheme 2. Mono-protected butanediol **7** was



1

Figure 1. Putative sex pheromone of *T. marginata*.

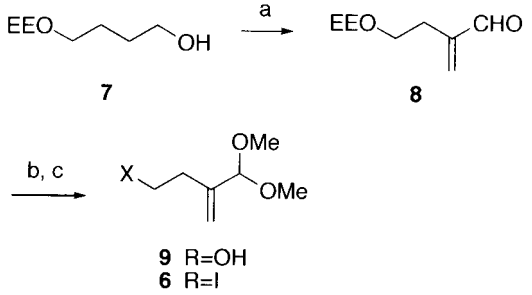


Scheme 1. Synthetic plan for (±)-**1**.

Keywords: pheromone; terpenes and terpenoids; cyclisation; Michael reactions.

* Corresponding author. Laboratory of Applied Bioorganic Chemistry, Division of Life Science, Graduate School of Agricultural Science, Tohoku University, 1-1 Tsutsumidori-Amamiyamachi, Aoba-ku, Sendai 981-8555, Japan. Tel.: +81-22-717-8784; fax: +81-22-717-8783; e-mail: skuwahar@biochem.tohoku.ac.jp

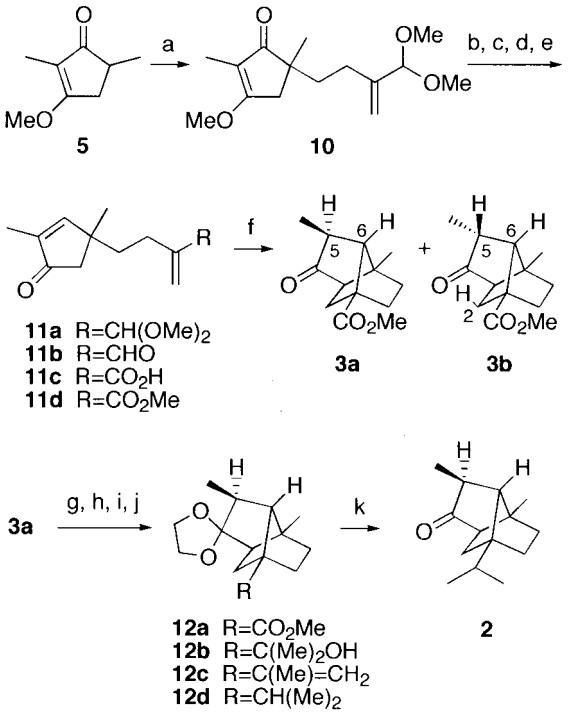
0040–4020/00/$ - see front matter
PII: S0040-4020(00)00735-3



Scheme 2. Preparation of intermediate **6**. *Reagents*: (a) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, then $CH_2{=}NMe_2I$ (64%); (b) Amberlyst 15E, MeOH; (c) I_2, Ph_3P, imidazole, THF (30%, 2 steps).

converted into α,β-unsaturated aldehyde **8** by a one-pot procedure developed by Takano et al.[2] Treatment of **8** with an acidic ion-exchange resin in absolute methanol brought about deprotection of the ethoxyethyl group and concomitant protection of the aldehyde functionality to give **9**, the hydroxyl group of which was then substituted by iodine to afford the desired alkylating agent **6**.

Having secured iodide **6**, we next tried the alkylation of known cyclopentenone derivative **5**[3,4] with **6** (Scheme 3). We first attempted to alkylate the lithium enolate of **5** with **6**. However, the lithium enolate prepared by treating **5** with LDA functioned as a base and induced the elimination reaction of **6** to give conjugated diene **A** (Fig. 2). Thus, the lithium enolate was first converted to the corresponding



Scheme 3. Preparation of tricyclic intermediate **2**. *Reagents*: (a) LDA, $ZnCl_2$, **6**, THF–HMPA (78%); (b) DIBAL, toluene, then SiO_2 (63%); (c) PPTS, THF–H_2O; (d) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH–H_2O; (e) $Me_3O{\cdot}BF_4$, $(i\text{-}Pr)_2NEt$, CH_2Cl_2 (75%, 3 steps); (f) TMSI, $(TMS)_2NH$, 1,2-dichloroethane (74%); (g) $HO(CH_2)_2OH$, TsOH, $(MeO)_3CH$, C_6H_6 (76%); (h) MeLi, $CeCl_3$, THF (87%); i) $MeO_2CNSO_2NEt_3$, C_6H_6 (83%); (j) H_2, 10% Pd–C, EtOH; (k) PPTS, acetone–H_2O (87%, 2 steps).

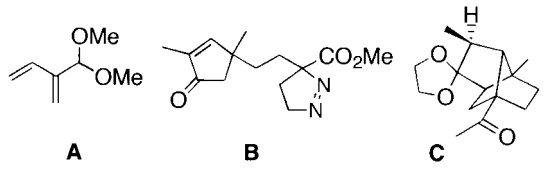
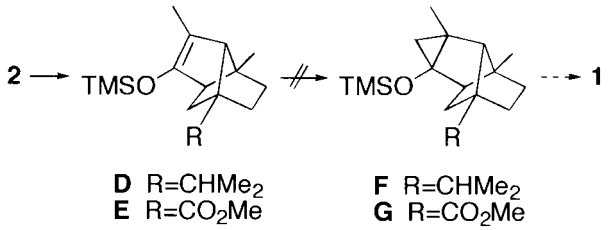


Figure 2.

zinc enolate for the purpose of reducing the basicity of the nucleophile, and then treated with **6** to give successfully the alkylation product **10** (Scheme 3). Reduction of the keto group of **10** with DIBAL afforded an intermediary allylic alcohol, which was treated with silica gel in a one-pot operation to induce the enol ether hydrolysis and subsequent dehydration to give enone **11a**. Deprotection of the **11a** to **11b** was followed by oxidation to give carboxylic acid **11c**, which was esterified with Meerwein's reagent[5] to furnish the cyclization substrate **11d**. When the esterification step was carried out with diazomethane in the usual way, a substantial amount of 1-pyrazoline derivative **B** (Fig. 2) was formed through 1,3-dipolar addition of excess diazomethane to the produced α,β-unsaturated ester (**11d**).[6] Next, we proceeded to the construction of the tricyclic skeleton via the double Michael cyclization. According to Ihara's procedure,[7] compound **11d** was treated with TMSI and bis(trimethylsilyl)amine in dichloromethane at room temperature for 4.5 h to give a separable 4:1 epimeric mixture of **3a** and **3b** in 74% combined yield. The stereochemistries of **3a** and **3b** were deduced on the basis of the ^1H NMR coupling constants between C5 and C6 protons of each epimer. In the case of **3b**, the dihedral angle between the C5 proton and C6 proton was nearly 90°, as judged by the Dreiding model, therefore the C5 proton was observed as a simple quartet (J=7.7 Hz) coupled only with the methyl protons, while the C5 proton of **3a** was observed as a double quartet (J=4.7 and 7.5 Hz). This assignment was further supported by an NOE correlation observed between the C2 and C5 protons of **3b**. This cyclization was also possible under Diels–Alder conditions reported by Snowden (TMSCl, Et_3N, $ZnCl_2$, 1,2-dichloroethene, 200°C, 46 h),[8] although the isolated yield (46% combined yield, **3a**:**3b**=1:3) did not exceed that attained in the double Michael cyclization. The major epimer (**3a**) obtained by the double Micheal cyclization was converted to the ring expansion precursor (**2**) by a five-step sequence shown in Scheme 3. The keto group of **3a** was protected as its acetal **12a** and allowed to react with methyllithium in the presence of cerium trichloride to give tertiary alcohol **12b**.[9] In this conversion, treatment of **12a** with methyllithium itself resulted in the production of intermediary ketone **C** (Fig. 2) probably through the formation of the corresponding enolate. Dehydration of **12b** with the Burgess reagent[10] gave olefin **12c**, which was then hydrogenated and deprotected to afford **2** via **12d**.

According to the synthetic plan, we set about the ring expansion of **2**. Scheme 4 represents our initial synthetic plan which consists of enol etherification of **2** to **D**, cyclopropanation of **D** to **F**, and finally oxidative cleavage[11] of the cyclopropane ring of **F** to form (±)-**1**. TMS-enol etherification of **2** by treating with TMSOTf and $(i\text{-}Pr)_2NEt$ in dichloromethane proceeded smoothly to give **D**.[12] However,



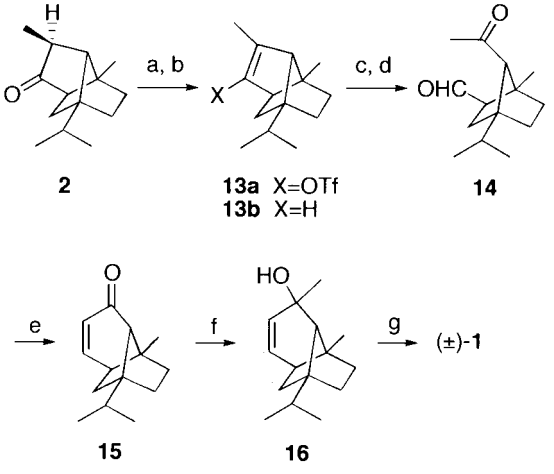
Scheme 4. Initial plan for the conversion of **2** into (±)-**1**.

all reaction conditions attempted for the cyclopropanation of **D**, including CH_2I_2–$ZnEt_2$,[13] CH_2I_2–Zn–CuCl,[14] CH_2N_2–$Pd(OAc)_2$,[15] CH_2I_2–$AlMe_3$,[16] CH_2I_2–Zn–Ag[17] and CH_2I_2–Sm[18] were unsuccessful, resulting only in the recovery of **D** or its hydrolysis product, probably due to severe steric hindrance on both faces of the double bond. Cyclopropanation of **E**, which was derived from **3a** under the same conditions as employed for the preparation of **D**, leading to **G** was not successful, either, and the minor cyclization product **3b** did not even afford the corresponding enol ether (**E**). Eventually, we had to alter this desirable three-step conversion of **2** to **1** into a ring cleavage-recyclization pathway shown in Scheme 5.

Thus, the tricyclic ketone (**2**) was converted to olefin **13b** via enol triflate **13a** according to Cacchi's procedure (Scheme 5).[19] The double bond of **13b** was then cleaved oxidatively, and the resulting keto aldehyde **14** was cyclized under aldol condensation conditions to produce α,β-unsaturated ketone **15**. Finally, enone **15** was subjected to alkylative 1,3-dicarbonyl transposition protocol developed by Dauben and Michno[20] to provide the desired target compound (±)-**1** via tertiary alcohol **16**. The ^1H and ^{13}C NMR, MS and GLC data of the synthetic sample were identical with those of the natural material, which enabled us to confirm the structure proposed by Leal et al.

Conclusion

The synthesis of the novel tricyclic sesquiterpene (±)-**1** isolated as the putative sex pheromone of *T. marginata* was accomplished in 18 steps and 4.2% overall yield from the known cyclopentenone derivative **5** by using the double Michael cyclization as the key step. The spectral data and GLC retention time of the synthetic sample were identical with those of the natural material. These results supported the structural determination by Leal et al. The synthesis of both the enantiomers of **1** are now in progress, aiming at the determination the absolute configuration of this putative pheromone.



Scheme 5. Coversion of intermediate **2** into (±)-**1**. *Reagents*: (a) Tf_2O, $(i\text{-}Pr)_2NEt$, CH_2Cl_2 (98%); (b) HCO_2H, $Pd(OAc)_2(PPh_3)_2$, $(n\text{-}Bu)_3N$, DMF (75%); (c) OsO_4, C_5H_5N; (d) $NaIO_4$, ether–H_2O (80%, 2 steps); (e) K_2CO_3, *t*-BuOH (90%); (f) MeLi, ether; (g) PCC, CH_2Cl_2 (62%, 2 steps).

Experimental

IR spectra were measured as films on a Jasco FT/IR-5000 spectrometer. ^1H (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded with TMS as an internal standard in $CDCl_3$ by a JEOL JNM-A500 spectrometer. High resolution mass spectra (70 eV) were measured on a Shimadzu GCMS 9020-DF spectrometer. Tetrahydrofuran was purified by distilling from sodium benzophenone ketyl. Dichloromethane was purified by drying with P_2O_5 followed by distillation from CaH_2. Merck silica gel 60 (70–230 mesh) was used for silica gel column chromatography unless otherwise stated.

2-[2-(1-Ethoxyethoxy)ethyl]propenal (8). To a stirred solution of oxalyl chloride (2.54 ml, 29.1 mmol) in dichloromethane (72 ml) was added dropwise a solution of dimethyl sulfoxide (2.84 ml, 40.0 mmol) in dichloromethane (5 ml) at −78°C, and the mixture was stirred for 15 min. To the mixture was added dropwise a solution of **7** (1.58 g, 9.75 mmol) in dichloromethane (10 ml), and the mixture was allowed to warm gradually to −30°C over a period of 30 min. Triethylamine (15.2 ml, 109 mmol) was then added to the mixture, and the mixture was stirred for 15 min at room temperature. After the addition of Eschenmoser's salt (3.62 g, 19.6 mmol), the mixture was stirred overnight at room temperature. The mixture was diluted with dichloromethane and washed with sat. aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over silica gel (60 g, hexane/EtOAc=30:1) to give 1.07 g (64%) of 8: IR 1692 (s), 1381 (s), 1342 (m), 1135 (s), 1089 (s), 1060 (s), 949 (m) cm^{-1}; ^1H NMR δ 1.19 (3H, t, J=7.0 Hz), 1.29 (3H, d, J=5.2 Hz), 2.54 (2H, t, J=6.5 Hz), 3.46 (1H, dq, J=9.5, 7.0 Hz), 3.55 (1H, dt, J=9.5 Hz, 6.5 Hz), 3.62 (1H, dq, J=9.5, 7.0 Hz), 3.69 (1H, dt, J=9.5, 6.5 Hz), 4.67 (1H, q, J=5.2 Hz), 6.08 (1H, s), 6.39 (1H, br s), 9.55 (1H, s); HRMS m/z (M^+) 172.1064 (calcd for $C_9H_{16}O_3$, 172.1099).

2-Dimethoxymethyl-4-iodo-1-butene (6). A mixture of **8** (1.00 g, 5.81 mmol) and Amberlyst® 15E (0.100 g) in methanol (30 ml) was stirred overnight at room temperature, and then filtered. The filtrate was mixed with triethylamine (0.1 ml) and concentrated in vacuo to give 0.301 g of **9** [^1H NMR δ 2.33 (1H, t, J=6.0 Hz), 2.37 (2H, t, J=6.0 Hz), 3.35 (6H, s), 3.73 (1H, q, J=6.0 Hz), 4.58 (1H, s), 5.15 (1H, br s), 5.24 (1H, br s)], which was then dissolved in THF (4.5 ml). To the solution was added in sequence imidazole (0.320 g, 4.70 mmol), triphenylphosphine (0.595 g, 2.27 mmol) and iodine (0.576 g, 2.27 mmol), and the mixture was stirred for 1 h at room

temperature. The mixture was diluted with 5% aq. $Na_2S_2O_3$ and extracted with ether. The ethereal solution was washed with 5% aq. $Na_2S_2O_3$ and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over silica gel (15 g, hexane/benzene=3:2 with 1% triethylamine) to give 0.440 g (30%, 2 steps) of **6**: IR 3080 (w), 1660 (w), 1210 (m), 1190 (m), 1170 (m), 1110 (s), 1070 (s), 1050 (s), 980 (m), 920 (m) cm^{-1}; ^1H NMR δ 2.65 (2H, br t, J=7.6 Hz), 3.30 (2H, t, J=7.6 Hz), 3.31 (6H, s), 4.59 (1H, s), 5.11–5.13 (1H, m), 5.28 (1H, br s); HRMS m/z (M^+) 255.9997 (calcd. for $C_7H_{13}O_2I$ 255.9960).

3-Methoxy-2,5-dimethyl-2-cyclopenten-1-one (5). The preparation of this enone had been reported earlier,[3] but we prepared **5** from 3-methoxy-2-methyl-2-cyclopenten-1-one[4] in a different way as follows. To a stirred solution of LDA, prepared by treating diisopropylamine (7.50 ml, 53.5 mmol) in THF (75 ml) with butyllithium (1.54 M in hexane, 34.5 ml, 53.1 mmol) at 0°C for 50 min, was added dropwise a solution of 3-methoxy-2-methyl-2-cyclopenten-1-one (6.10 g, 48.4 mmol) in THF (61 ml) at −78°C, and the mixture was stirred for 1.5 h. To the mixture was added dropwise a solution of iodomethane (3.3 ml, 53.0 mmol) in THF–HMPA (1:1, 32 ml) and the resulting mixture was stirred at −78°C for 1 h before being quenched with sat. aq. NH_4Cl. The mixture was extracted with ethyl acetate, and the organic layer was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by silica gel column chromatography (150 g, hexane/ethyl acetate=3:2) and distillation to give **5**. 10 g (76%) of **5**: bp 89–90°C (3 Torr); IR 1690 (s), 1630 (vs), 1340 (vs), 1260 (s), 1125 (s), 980 (s) cm^{-1}; ^1H NMR δ 1.20 (3H, d, J=7.5 Hz), 1.63 (3H, t, J=1.8 Hz), 2.21 (1H, ddq, J=17.5, 2.0, 1.8 Hz), 2.43 (1H, qdd, J=7.5, 7.2, 2.0 Hz), 2.88 (1H, ddq, J=17.5, 7.2, 1.8 Hz), 3.94 (3H, s); HRMS m/z (M^+) 140.0842 (calcd for $C_8H_{12}O_2$, 140.0837).

5-(3-Dimethoxymethyl-3-butenyl)-3-methoxy-2,5-dimethyl-2-cyclopenten-1-one (10). To a stirred solution of LDA, prepared by treating diisopropylamine (0.950 ml, 6.78 mmol) in THF (9 ml) with *n*-BuLi (1.63 M in hexane, 4.10 ml, 6.68 mmol) at 0°C for 20 min, was added dropwise a solution of **5** (900 mg, 6.42 mmol) in THF (9 ml) at −78°C. After 1 h, a solution of zinc chloride (470 mg, 3.45 mmol) in THF (4.7 ml) was added, and the mixture was stirred for 15 min. To the mixture was added dropwise a solution of **6** (400 mg, 1.56 mmol) in THF-HMPA (1:3, 8 ml) and the mixture was stirred for 45 min at −78°C. The reaction mixture was allowed to warm gradually to −20°C, quenched by the addition of a mixture of water and THF (1:10, 1.65 ml) and extracted with ether. The ethereal solution was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over silica gel (15 g, hexane/EtOAC=5: 1 with 1% triethylamine) to give 327 mg (78%) of **10**: IR 1690 (m), 1635 (vs), 1340 (s), 1110 (s), 1075 (m), 1050 (m), 985 (m), 915 (m), 730 (s) cm^{-1}; ^1H NMR δ 1.15 (3H, s), 1.63 (3H, t, J=1.7 Hz), 1.65–1.69 (2H, m), 1.81–1.87 (1H, m), 1.94–2.01 (1H, m), 2.34 (1H, dq, J=18.0, 1.7 Hz), 2.61 (1H, dq, J=18.0, 1.7 Hz), 3.236 (3H, s), 3.243 (3H, s), 3.92 (3H, s), 4.56 (1H, s), 5.03–5.04 (1H, m), 5.15–5.16 (1H, m); HRMS m/z (M^+) 268.1689 (calcd for $C_{15}H_{24}O_4$, 268.1674).

4-(3-Dimethoxymethyl-3-butenyl)-2,4-dimethyl-2-cyclopenten-1-one (11a). To a stirred solution of **10** (880 mg, 3.28 mmol) in toluene (8.8 ml) was added dropwise a solution of DIBAL (1.01 M in toluene, 5.17 ml, 5.22 mmol) at −78°C. The mixture was stirred for 2 h and quenched with EtOAc (0.97 ml, 9.9 mmol). After 5 min, silica gel and 2-propanol was added and the resulting slurry was stirred for 30 min at room temperature. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was chromatographed over silica gel (15 g, hexane/ether=8:1 with 1% triethylamine) to give 499 mg (63%) of **11a**: IR 1710 (vs), 1640 (w), 1410 (w), 1330 (w), 1215 (w), 1195 (w), 1110 (s), 1070 (s), 1055 (s), 985 (m), 915 (m), 730 (m) cm^{-1}; ^1H NMR δ 1.19 (3H, s), 1.58–1.69 (2H, m), 1.75 (3H, d, J=1.6 Hz), 1.90–1.97 (1H, m), 1.98–2.06 (1H, m), 2.17 (1H, d, J=19.0 Hz), 2.36 (1H, d, J=19.0 Hz), 3.29 (6H, s), 4.57 (1H, s), 5.01–5.02 (1H, m), 5.17 (1H, br s), 7.0 7(1H, q, J=1.6 Hz); HRMS m/z (M^+) 238.1600 (calcd for $C_{14}H_{22}O_3$, 238.1568).

Methyl 2-[2-(1,3-dimethyl-4-oxo-2-cyclopenten-1-yl)ethyl]-propenoate (11d). A mixture of **11a** (2.60 g, 10.9 mmol) and pyridinium *p*-toluenesulfonate (500 mg, 1.99 mmol) in THF–water (1:1, 26 ml) was stirred for 3 h at room temperature. The mixture was diluted with sat. aq. $NaHCO_3$ and extracted with ether. The ethereal solution was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo to give 2.20 g of crude **11b**. This aldehyde was then dissolved in *t*-butyl alcohol (22 ml). To the solution was added in sequence 2-methyl-2-butene (6.00 ml, 56.6 mmol), a solution of sodium dihydrogen phosphate dihydrate (2.50 g, 16.0 mmol) in water (37.5 ml) and finally sodium chlorite (5.00 g, 55.3 mmol). The mixture was stirred for 1.5 h at room temperature. After the addition of oxalic acid dihydrate (4.00 g, 31.7 mmol), the mixture was poured into brine and extracted with ether. The ethereal solution was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo to give 3.50 g of crude **11c**. This acid was dissolved in dichloromethane (140 ml). To the solution was added trimethyloxonium tetrafluoroborate (2.90 g, 19.6 mmol) and *N*,*N*-diisopropylethylamine (2.90 ml, 16.6 mmol) and the mixture was stirred for 1 h at room temperature. The mixture was poured into water and extracted with ether. The ethereal solution was washed with 0.5 M hydrochloric acid, sat. aq. $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over silica gel (50 g, hexane/ethyl acetate=8:1) to gve 1.82 g (75% from **11a**) of **11d**: IR 1710 (s), 1635 (m), 1440 (m), 1419 (w), 1330 (m), 1250 (m), 1200 (m), 1175 (m), 1145 (m), 1120 (w), 1065 (w), 990 (w), 950 (w), 895 (w), 820 (w) cm^{-1}; ^1H NMR δ 1.21 (3H, s), 1.57–1.68 (2H, m), 1.76 (3H, d, J=1.7 Hz), 2.18 (1H, d, J=19.0 Hz), 2.16–2.30 (2H, m), 2.40 (1H, d, J=19.0 Hz), 3.75 (3H, s), 5.53 (1H, q, J=1.5 Hz), 6.13–6.14 (1H, m), 7.07 (1H, q, J=1.7 Hz); HRMS m/z (M^+) 222.1289 (calcd for $C_{13}H_{18}O_3$, 222.1255).

Methyl (1*R,3*S**,5*R**,6*S**,7*S**)-5,7-dimethyl-4-oxotricyclo-[4.3.0.0^{3,7}]nonane-1-carboxylate (3a).** To a stirred solution of **11d** (666 mg, 3.00 mmol) in 1,2-dichloroethane (106 ml) was added in sequence 1,1,1,3,3,3-hexamethyldisilazane (1.00 ml, 4.74 mmol) and iodotrimethylsilane (0.550 ml, 3.86 mmol) at 0°C and the mixture was stirred for 4.5 h at

room temperature. The mixture was poured into sat. aq. NH_4Cl and extracted with ether. The ethereal solution was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over silica gel (Katayama Chemical K230W, 35 g, hexane/ethyl acetate=9:1) to give 394 mg (59%) of **3a** and 98 mg (15%) of its C5-epimer (**3b**). Data for **3a**: IR 1750 (vs), 1730 (vs), 1435 (m), 1340 (m), 1310 (m), 1230 (s), 1145 (m), 1080 (s), 1060 (m), 840 (m) cm^{-1}; ^1H NMR δ 1.06 (3H, s), 1.08 (3H, d, J=7.5 Hz), 1.73–1.78 (2H, m), 1.79–1.82 (3H, m), 2.02–2.10 (1H, m), 2.23 (1H, br d, J=5.5 Hz), 2.40 (1H, dq, J=4.7, 7.5 Hz), 2.45 (1H, br d, J=4.7 Hz), 3.69 (3H, s); HRMS m/z (M^+) 222.1237 (calcd for $C_{13}H_{18}O_3$, 222.1255). Data for **3b**: ^1H NMR δ 1.10 (3H, s), 1.18 (3H, d, J=7.7 Hz), 1.66–1.79 (4H, m), 1.93 (1H, dd, J=13.5, 2.9 Hz), 2.07–2.12 (1H, m), 2.11 (1H, br s), 2.19 (1H, dd, J=6.0, 1.9 Hz), 2.42 (1H, q, J=7.7 Hz), 3.71 (3H, s); HRMS m/z (M^+) 222.1241 (calcd for $C_{13}H_{18}O_3$, 222.1255).

Methyl (1*R,3*S**,5*R**,6*S**,7*S**)-4,4-ethylenedioxy-5,7-dimethyltricyclo[4.3.0.0^{3,7}]nonane-1-carboxylate (12a).** To a stirred solution of **3a** (442 mg, 1.99 mmol) in benzene was added in sequence ethylene glycol (1.30 ml, 23.3 mmol), trimethyl orthoformate (435 μl, 3.98 mmol) and *p*-toluenesulfonic acid monohydrate (18.9 mg, 99 μmol) and the mixture was stirred at reflux for 5 h. The mixture was poured into sat. aq. $NaHCO_3$ and extracted with ether. The ethereal solution was washed with water and brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over silica gel (15 g, hexane/ethyl acetate=15:1) to give 404 mg (76%) of **12a**: 1735 (vs), 1320 (m), 1265 (s), 1230 (m), 1190 (m), 1155 (m), 1110 (s), 1085 (s), 1060 (m), 1040 (m), 950 (m) cm^{-1}; ^1H NMR δ 0.88 (3H, d, J=7.8 Hz), 1.25 (3H, s), 1.37 (1H, br dd, J=13.3, 6.0 Hz), 1.50–1.60 (2H, m), 1.68–1.76 (2H, m), 1.84–1.91 (1H, m), 2.07 (1H, br d, J=4.6 Hz), 2.28 (1H, dq, J=4.6, 7.8 Hz), 2.29 (1H, dd, J=13.4, 2.8 Hz), 3.65 (3H, s), 3.73–3.81 (3H, m), 3.91–3.95 (1H, m); HRMS m/z (M^+) 266.1564 (calcd for $C_{15}H_{22}O_4$, 266.1517).

(1*R,3*S**,5*R**,6*S**,7*S**)-4,4-Ethylenedioxy-α,α,5,7-tetramethyltricyclo[4.3.0.0^{3,7}]nonane-1-methanol (12b).** THF (22 ml) was added to anhydrous cerium trichloride (1.47 g, 5.96 mmol) and the mixture was stirred for 3 h at room temperature, and then cooled to −78°C. To the mixture was added dropwise a solution of methyllithium (1.1 M in ether, 5.40 ml, 5.94 mmol). After 30 min, a solution of **12a** (394 mg, 1.48 mmol) in THF (3.9 ml) was added and the mixture was stirred for 1 h at −78°C. The reaction temperature was then gradually raised to −30°C. The reaction mixture was quenched with sat. aq. NH_4Cl (0.91 ml) and extracted with ether. The ethereal solution was washed with water and brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over silica gel (15 g, hexane/ethyl acetate=10:1) to give 382 mg (95%) of **12b**: IR 3500 (w), 1365 (m), 1285 (m), 1220 (m), 1160 (s), 1105 (vs), 1035 (s), 955 (s) cm^{-1}; ^1H NMR δ 1.09 (1H, dd, J=12.6, 6.0 Hz), 1.13 (3H, s), 1.20 (3H, d, J=7.7 Hz), 1.210 (3H, s), 1.214 (3H, s), 1.27–1.39 (2H, m), 1.45–1.52 (1H, m), 1.56 (1H, br s), 1.61 (1H, ddd, J=12.8, 9.3, 7.0 Hz), 1.68 (1H, dd, J=6.0, 1.7 Hz), 2.03 (1H, dd, J=12.6, 3.1 Hz), 2.45 (1H, dq, J=3.8, 7.7 Hz), 3.72–3.82 (3H, m), 3.91–3.95 (1H, m); HRMS m/z (M^+) 266.1877 (calcd for $C_{16}H_{26}O_3$, 266.1881).

(1*R,3*S**,5*R**,6*S**,7*S**)-4,4-Ethylenedioxy-1-isopropenyl-5,7-dimethyltricyclo[4.3.0.0^{3,7}]nonane (12c).** To a stirred solution of the Burgess reagent (334 mg, 1.40 mmol) in benzene (3.3 ml) was added a solution of **12b** (250 mg, 0.939 mmol) in benzene (2.5 ml) and the mixture was stirred at reflux for 1.8 h. The mixture was diluted with water and extracted with ether. The ethereal solution was washed with water and brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over silica gel (15 g, hexane/ethyl acetate=50:1) to give 195 mg (83%) of **12c**: IR 3080 (vw), 1635 (m), 1315 (w), 1280 (w), 1160 (m), 1135 (m), 1110 (vs), 1040 (m), 960 (m), 885 (m) cm^{-1}; ^1H NMR δ 0.97 (3H, d, J=7.8 Hz), 1.09 (1H, ddd, J=11.2, 9.0, 2.1 Hz), 1.23 (3H, s), 1.35 (1H, br dd, J=12.7, 6.3 Hz), 1.40 (1H, ddd, J=12.9, 11.5, 2.1 Hz), 1.65–1.72 (2H, m), 1.74–1.81 (2H, m), 1.77 (3H, br s), 2.09 (1H, dd, J=12.7, 2.9 Hz), 2.29 (1H, dq, J=4.8, 7.8 Hz), 3.73–3.82 (3H, m), 3.90–3.95 (1H, m), 4.72–4.74 (2H, m); HRMS m/z (M^+) 248.1763 (calcd for $C_{16}H_{24}O_2$, 248.1775).

(1*R,2*R**,4*S**,6*S**,9*S**)-6-Isopropyl-2,9-dimethyltricyclo[4.3.0.0^{4,9}]nonan-3-one (2).** A mixture of **12c** (195 mg, 0.786 mmol) and 10% Pd–C (58 mg) in ethanol (1.9 ml) was stirred for 5 h at room temperature under an atmospheric pressure of hydrogen. The mixture was filtered through a Celite® pad and the filtrate was concentrated in vacuo to give 187 mg of crude **12d**, which was then dissolved in acetone–water (4:1, 2.5 ml). To the solution was added pyridinium *p*-toluenesulfonate (18.0 mg, 0.07 mmol) and the mixture was stirred at reflux for 3 h. The mixture was poured into sat. aq. $NaHCO_3$ and extracted with ether. The ethereal solution was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over silica gel (15 g, hexane/ethyl acetate=25:1) to give 141 mg (87% from **12c**) of **2**: IR 1750 (vs), 1360 (w), 1210 (w), 1140 (w), 1020 (w), 935 (w), 890 (w), 835 (w) cm^{-1}; ^1H NMR δ 0.82 (3H, d, J=6.9 Hz), 0.96 (3H, d, J=6.9 Hz), 1.01 (3H, s), 1.16 (1H, dd, J=13.5, 3.1 Hz), 1.28 (3H, d, J=7.8 Hz), 1.32 (1H, ddd, J=12.3, 9.2, 2.2 Hz), 1.52 (1H, dt, J=2.3, 12.3 Hz), 1.59–1.64 (1H, m), 1.69 (1H, ddd, J=12.3, 9.2, 6.7 Hz), 1.81 (1H, br dd, J=13.5, 6.7 Hz). 1.93 (1H, dm, J=4.8 Hz), 2.03 (1H, sep, J=6.9 Hz), 2.17 (1H, br d, J=6.7 Hz), 2.47 (1H, dq, J=4.8, 7.8 Hz); HRMS m/z (M^+) 206.1689 (calcd for $C_{14}H_{22}O$, 206.1670).

(1*R,4*S**,6*S**,9*S**)-6-Isopropyl-2,9-dimethyl-3-(trifluoromethanesulfonyloxy)tricyclo[4.3.0.0^{4,9}]non-2-ene (13a).** To a stirred solution of **2** (121 mg, 0.587 mmol) in dichloromethane (1.2 ml) was added in sequence *N*,*N*-diisopropylethylamine (0.615 ml, 3.53 mmol) and trifluoromethanesulfonic anhydride (0.287 ml, 1.71 mmol) at 0°C and the mixture was stirred for 1.5 h at room temperature. The mixture was diluted with sat. aq. $NaHCO_3$, stirred for 30 min and then extracted with ether. The ethereal solution was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over silica gel (10 g, hexane) to give 195 mg (98%) of **13a**: IR 1680 (w), 1580 (m), 1425 (vs), 1250 (s), 1210 (vs), 1145

(vs), 1120 (s), 1105 (s), 1090 (s), 900 (m), 870 (s), 845 (m) cm^{-1}; ^1H NMR δ 0.85 (3H, d, J=6.9 Hz), 0.93(3H, d, J=6.9 Hz), 1.03 (3H, s), 1.11 (1H, dd, J=11.5, 2.3 Hz), 1.34–1.47 (3H, m), 1.51–1.58 (2H, m), 1.66 (1H, dd, J=11.5, 4.5 Hz), 1.74 (3H, s), 2.14 (1H, d, J=2.1 Hz), 2.35 (1H, dd, J=4.5, 2.1 Hz); HRMS m/z (M^+) 338.1127 (calcd for $C_{15}H_{21}O_3SF_3$, 338.1162).

(1*R,4*S**,6*R**,9*S**)-6-Isopropyl-2,9-dimethyltricyclo-[4.3.0.0^{4,9}]non-2-ene (13b).** To a solution of **13a** (190 mg, 0.562 mmol) in DMF (2 ml) was added in sequence tributylamine (0.651 ml, 2.73 mmol), a solution of bis-(acetato)bis(triphenylphosphine)palladium (II) (13.5 mg, 0.018 mmol) in DMF (0.2 ml) and formic acid (99%, 0.101 ml, 2.68 mmol), and the mixture was stirred at 60°C for 1 h. The mixture was diluted with sat. aq. $NaHCO_3$, stirred for 30 min and then extracted with ether. The ethereal solution was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over silica gel (15 g, pentane) to give 80.0 mg (75%) of **13b**: IR 3055 (w), 1320 (w), 1280 (w), 1220 (w), 1155 (w), 1085 (w), 810 (m) cm^{-1}; ^1H NMR δ 0.67 (1H, dd, J=10.8, 2.6 Hz), 0.82 (3H, d, J=7.0 Hz), 0.90 (3H, s), 0.91 (3H, d, J=7.0 Hz), 1.30–1.41 (3H, m), 1.46–1.52 (2H, m), 1.52–1.57 (1H, m), 1.74 (3H, d, J=1,7 Hz), 1.96 (1H, brs), 1.96–1.99 (1H, m), 5.62–5.64 (1H, m); HRMS m/z (M^+) 190.1739 (calcd for $C_{14}H_{22}$, 190.1720).

(1*R,2*S**,4*S**,7*R**)-7-Acetyl-4-isopropyl-1-methylbicyclo-[2.2.1]heptane-2-carbaldehyde (14).** To a stirred solution of **13b** (54.6 mg, 0.287 mmol) in pyridine (0.55 ml) was added osmium tetroxide (73.0 mg, 0.287 mmol) and the mixture was stirred overnight at room temperature. After the addition of a solution of sodium bisulfite (166 mg, 1.60 mmol) in water-pyridine (3:2, 5 ml), the mixture was stirred for 1 h and then extracted with ether. The ethereal solution was washed with sat. aq. $CuSO_4$, water and brine, dried ($MgSO_4$) and concentrated in vacuo to give an oil (60.8 mg), which was then dissolved in ether (0.6 ml). To the solution was added water (0.87 ml) and sodium periodate (116 mg, 0.542 mmol) and the mixture was stirred for 3 h at room temperature. The mixture was diluted with water and extracted with ether. The ethereal solution was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over silica gel (15 g, hexane/ethyl acetate=10:1) to give 38.3 mg (60%) of **14**: IR 2730 (vw), 1715 (m), 1705 (m), 1260 (m), 1175 (w), 1090 (m), 1020 (m), 800 (m) cm^{-1}; ^1H NMR δ 0.87 (3H, d, J=6.8 Hz), 0.98 (3H, d, J=6.8 Hz), 1.23 (1H, ddd, J=11.9, 9.0, 5.3 Hz), 1.28 (3H, s), 1.43 (1H, ddd, J=11.9, 9.0, 3.7 Hz), 1.51 (1H, dt, J=5.3, 11.9 Hz), 1.70 (1H, tt, J=11.9, 3.7 Hz), 1.81 (1H, br dd, J=11.9, 9.0 Hz), 1.84 (1H, sep, J=6.8 Hz), 2.09 (1H, dd, J=9.0, 5.3 Hz), 2.13–2.18 (1H, m), 2.15 (3H, s), 2.47 (1H, br s), 9.64 (1H, br s); HRMS m/z (M^+) 222.1635 (calcd for $C_{14}H_{22}O_2$, 222.1619).

(1*R,2*R**,6*R**,8*S**)-8-Isopropyl-1-methyltricyclo[4.4.0.0^{2,8}]-dec-4-en-3-one (15).** To a stirred solution of **14** (35.5 mg, 0.160 mmol) in *t*-butyl alcohol (1.2 ml) was added potassium carbonate (33 mg, 0.239 mmol) and the mixture was stirred at reflux for 3 h. The mixture was diluted with ether and filtered. The filtrate was concentrated in vacuo and the residue was chromatographed over silica gel (15 g, hexane/ethyl acetate=20:1) to give 27.0 mg (83%) of **15**: IR 3040 (vw), 1670 (vs), 1290 (w), 1260 (w), 1230 (w), 1125 (w) cm^{-1}; ^1H NMR δ 0.82 (3H, d, J=6.9 Hz), 1.00 (3H, d, J=6.9 Hz), 1.08 (3H, s), 1.39–1.53 (5H, m), 1.63–1.69 (1H, m), 1.93 (1H, dd, J=12.2, 7.3 Hz), 2.29 (1H, br t, J=7.3 Hz), 2.33 (1H, br s), 5.96 (1H, br d, J=9.4 Hz), 7.37 (1H, dd, J=9.4, 7.3 Hz); HRMS m/z (M^+) 204.1511 (calcd for $C_{14}H_{20}O$, 204.1513).

(1*R,5*R**,6*R**,9*R**)-9-Isopropyl-4,6-dimethyltricyclo-[4.4.0.0^{5,9}]dec-3-en-2-one (±)-1.** To a stirred solution of **15** (16.8 mg, 0.0823 mmol) in ether (0.2 ml) was added a solution of methyllithium (1.14 M in ether, 0.216 ml, 0.246 mmol) at 0°C. The mixture was allowed to warm gradually to room temperature over 2 h, diluted with sat. aq. NH_4Cl and extracted with ether. The ethereal solution was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo to give 16.8 mg of crude **16**, which was then dissolved in dichloromethane (0.3 ml). To the solution was added pyridinium chlorochromate (33.0 mg, 0.153 mmol) and the mixture was stirred at room temperature for 1.3 h. The mixture was diluted with ether and filtered through a pad of Florisil®. The filtrate was concentrated in vacuo and the residue was chromatographed over silica gel (15 g, hexane/ethyl acetate=10:1) to give 9.7 mg (54% from **15**) of (±)-**1**: IR 2960 (s), 2920 (s), 2865 (s), 1670 (vs), 1625 (m), 1460 (m), 1375 (m), 1315 (w), 1285 (m), 1250 (w), 1230 (m), 1100 (w), 1060 (w), 1015 (w), 975 (w), 925 (w), 885 (m), 870 (w), 790 (w) cm^{-1}; ^1H NMR δ 0.86 (3H, d, J=6.8 Hz), 0.99 (3H, s), 1.02 (3H, d, J=6.8 Hz), 1.28 (1H, ddd, J=13.3, 3.5, 1.5 Hz), 1.39–1.48 (2H, m), 1.53–1.62 (2H, m), 1.64–1.70 (1H, m), 1.83 (1H, dd, J=7.9, 13.3 Hz), 1.98 (3H, d, J=1.4 Hz), 2.05 (1H,br s), 2.22 (1H, dq, J=7.9, 1.5 Hz), 5.84 (1H, br s); ^{13}C NMR δ 17.00, 18.79, 19.07, 25.01, 28.65, 31.11, 34.35, 37.83, 55.22, 56.88, 58.33, 59.48, 124.68, 160.82 (as in the case of the natural material, the signal for the carbonyl carbon was not observed); HRMS m/z (M^+) 218.1691 (calcd for $C_{15}H_{22}O$, 218.1670). The ^1H and ^{13}C NMR spectra were identical with those of the natural product.

Acknowledgements

This work was supported, in part, by a Grant-in-Aid for Scientific (C) Research from the Ministry of Education, Science, Sports and Culture, Japan (No. 11660101) and by the Program for Promotion of Basic Research Activities for Inovative Bioscience (BRAIN). The financial support given to S. K. by Kato Memorial Bioscience Foundation is also greatly appreciated.

References

1. Leal, W. S.; Xu, S.-C.; Kuwahara, S.; Aldrich, J. R.; Zarbin, P. H.; Nemoto, T. The 1st Asia-Pacific Conference on Chemical Ecology, Shanghai, China, 1–4 November 1999, Abstracts p 51.
2. Takano, S.; Inomata, K.; Samizu, K.; Tomita, S.; Yanase, M.; Suzuki, M.; Iwabuchi, T.; Sugahara, T.; Ogasawara, K. *Chem. Lett.* **1989**, 1283–1284.

3. Matoba, M.; Miyabayashi, N.; Yamazaki, T. *Yakugaku Zasshi* **1973**, *93*, 1401–1405.
4. Quesada, M. L.; Schlessinger, R. H.; Parsons, W. H. *J. Org. Chem.* **1978**, *43*, 3968–3970.
5. Raber, D. J.; Gariano Jr., P.; Brod, A. O.; Gariano, A. L.; Guida, W. C. *Organic Synthesis Collected Volume 6*; , 1988, pp 576–580.
6. Brook, A. G.; Jones, P. F. *Can J. Chem.* **1971**, *49*, 1841–1847.
7. Ihara, M.; Makita, K.; Fujiwara, Y.; Tokunaga, Y.; Fukumoto, K. *J. Org. Chem.* **1996**, *61*, 6416–6421.
8. Snowden, R. L. *Tetrahedron* **1986**, *42*, 3277–3290.
9. Imamoto, T.; Takiyama, N.; Nakamura, K.; Hahajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392–4398.
10. Burgess, E. M.; Penton Jr., H. R.; H, R.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26–31.
11. Moriarty, R. M.; Vaid, R. K.; Kopkins, T. E.; Vaid, B. K.; Prakash, O. *Tetrahedron Lett.* **1990**, *31*, 197–200.
12. Hiroya, K.; Kurihara, Y.; Ogasawara, K. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2287–2289.
13. Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron* **1968**, *24*, 53–58.
14. Murai, S.; Aya, T.; Sonoda, N. *J. Org. Chem.* **1973**, *38*, 4354–4356.
15. Kottwitz, J.; Vorbrüggen, H. *Synthesis* **1975**, 636–637.
16. Maruoka, K.; Fukutani, Y.; Yamamoto, H. *J. Org. Chem.* **1985**, *50*, 4412–4414.
17. Denis, J. M.; Girard, C.; Conia, J. M. *Synthesis* **1972**, 549–551.
18. Molander, G. A.; Etter, J. B. *J. Org. Chem.* **1987**, *52*, 3942–3944.
19. Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1984**, *25*, 4821–4824.
20. Dauben, W. G.; Michno, D.; M, . *J. Org. Chem.* **1977**, *42*, 682–685.