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Total Synthesis of (±)-Scirpene

Hideo Nemoto,*,† Eiki Takahashi, and Masataka Ihara*

Department of Organic Chemistry, Graduate School of Pharmaceutical Sciences, Tohoku University, Aobayama, Sendai 980-8578, Japan

mihara@mail.pharm.tohoku.ac.jp

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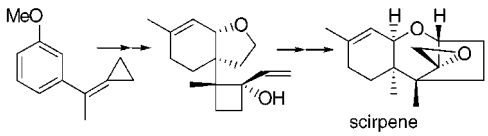
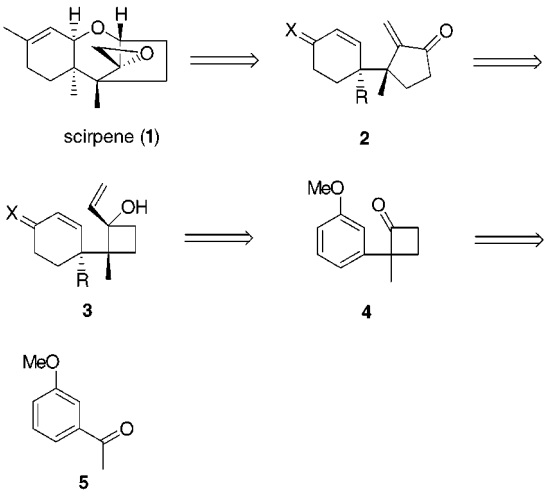
ABSTRACT



The racemate of scirpene, 12,13-epoxytrichothec-9-ene, was synthesized from 3-methoxyacetophenone. The key step in the synthesis is the palladium-mediated ring expansion reaction of the vinylcyclobutanol derivative, prepared via the oxidative ring expansion reaction of the cyclopropylidene. (3*S)-3-[(1*S**,6*S**)-3-Methyl-9-oxabicyclo[4.3.0]non-2-en-6-yl]-3-methyl-2-methylenecyclo-pentan-1-one formed from the reaction was converted into (±)-scirpene through the ring opening of tetrahydrofuran part, followed by cyclization for construction of the desired skeleton.**

Trichothecanes have attracted great attention from synthetic chemists[1] because of significant biological activities such as antifungal, antibacterial, antiviral, and antitumor activities[2] and unique structural features. We have been studying syntheses of natural products employing key reactions participating cyclobutanone[3] and achieved a total synthesis of (±)-4-deoxyverrucarol, a trichothecane-type sesquiterpenoid, by their application.[4] As an extension of this study, an alternative route to a trichothecane has been designed as shown in Scheme 1. Namely, the synthetic precursor **2** of 12,13-epoxytrichothec-9-ene (**1**),[5,6] scirpene[7] could be prepared by the palladium-catalyzed ring expansion reaction of **3**. The vinylcyclobutanol **3** would be transformed from the cyclobutanone **4**, obtainable from **5**. We now communicate a total synthesis of (±)-**1** based on this strategy.

Scheme 1



† Present address: Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Sugitani 2630, Toyama 930-0194, Japan.

(1) (a) Kupchan, S. M.; Jarvis, B. B.; Dailey, R. G., Jr.; Bright, W.; Bryan, R. F.; Shizuri, Y. *J. Am. Chem. Soc.* **1976**, *98*, 7092−7093. (b) Ueno, Y. *Trichothecenes—Chemical, Biological and Toxicological Aspects, Developments in Food Science 4*; American Elsevier: New York, 1983. (c) Iida, A.; Konishi, K.; Kubo, H.; Tomioka, K.; Tokuda, H.; Nishino, H. *Tetrahedron Lett.* **1996**, *37*, 9219−9220.

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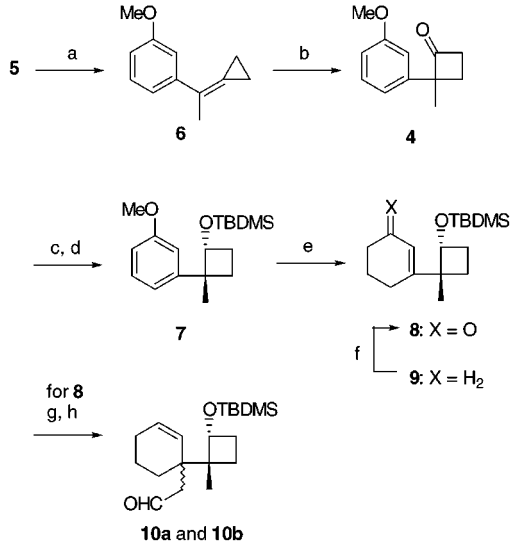
The cyclopropylidene **6**, derived from **5**, was subjected to the oxidative ring expansion reaction using *m*-CPBA to afford **4** in 84% yield (Scheme 2). Reduction of **4** with

Scheme 2[a]

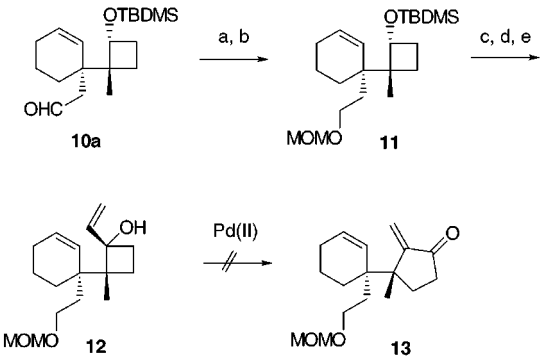


[a] Reagents and conditions: (a) cyclopropyltriphenylphosphonium bromide, NaH, 92%; (b) *m*-CPBA, $NaHCO_3$, 84%; (c) $NaBH_4$, 100%, (9:1 ds); (d) TBDMSCl, imidazole, 99%; (e) Na, liquid NH_3, EtOH; $(CO_2H)_2$, MeOH, 50% of **8** and 16% of **9**; (f) CrO_3, 3,5-DMP, 4 Å molecular sieves, 60%; (g) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 100% (1:1 ds); (h) ethyl vinyl ether, $Hg(OCOCF_3)_2$; Et_3N−toluene (1:4 v/v), 200 °C, 74%.

$NaBH_4$ gave a 9:1 mixture of the corresponding alcohols, the major of which was converted into the TBDMS ether **7**. Birch reduction of **7**, followed by acidic and basic treatments, provided the enone **8** in 50% overall yield together with the overreduced product **9** in 16% yield. The latter was convertible into **8** in 60% yield by oxidation with CrO_3 and 3,5-dimethylpyrazole.[8] Introduction of an alkyl group at the β-position of the enone **9** was performed in two steps although the diastereoselectivity was unsatisfactory. Thus, reduction of **9** with $NaBH_4$ and $CeCl_3 \cdot 7H_2O$ in MeOH afforded a 1:1 mixture of the alcohols, which was transformed into the aldehydes **10**, via [3,3]-sigmatropic rearrangement. The two stereoisomers **10a** and **10b** were separated by column chromatography on silica gel.

After transformation of the required stereoisomer **10a**[9] into the MOM ether **11**, the deprotection of the TBDMS group, followed by oxidation and addition of vinyl group to the resulting ketone provided the cyclobutanol **12** as a single stereoisomer (Scheme 3). However, the palladium(II)-mediated ring expansion reaction of **12** to **13** failed, probably due to the existence of the double bond close to the reaction site.

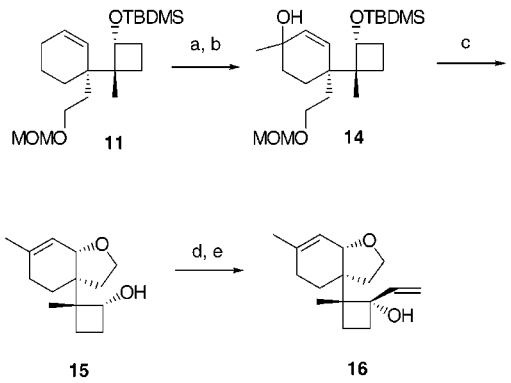
Scheme 3[a]



[a] Reagents and conditions: (a) $NaBH_4$, 100%; (b) MOMCl, *iso*-Pr_2NEt, 100%; (c) TBAF, 99%; (d) DMSO, $(COCl)_2$; Et_3N, 96%; (e) vinylmagnesium bromide, $CeCl_3$, 91%.

The introduction of one carbon unit accompanied by the transposition of the double bond converted **11**, in two steps, into the tertiary alcohol **14** as a 1:1 stereoisomeric mixture (Scheme 4). Exposure of **14** to acid produced **15** in a high yield. Ring-expansion reaction of **16**, prepared from **15** in a stereoselective manner, was examined under various conditions as shown in Table 1.

Scheme 4[a]



[a] Reagents and conditions: (a) $CrCO_3$, 3,5-DMP, 4 Å molecular sieves, 82%; (b) MeLi, 100% (1.2:1 ds); (c) dilute HCl, 91%; (d) DMSO, $(COCl)_2$; Et_3N, 93%; (e) vinylmagnesium bromide, $CeCl_3$, 97%.

The desired reaction did not proceed with $Pd(OAc)_2$ (entry 1), but the target compound **17** was obtained by the use of $PdCl_2(MeCN)_2$ (entry 2). It is interesting that the acetylcyclobutene **18** was produced as a byproduct, although the mechanism of the reaction is obscure. The yield of **17** was improved to 62% by the presence of an oxidizing agent in dimethylacetamide (DMA) (entry 3).[10] It is noteworthy that

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(8) Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 2057−2059.
(9) Stereochemistries of two isomers were tentatively assigned by NOE experiments after their conversions into **27** and **28**, respectively.

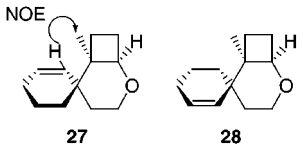
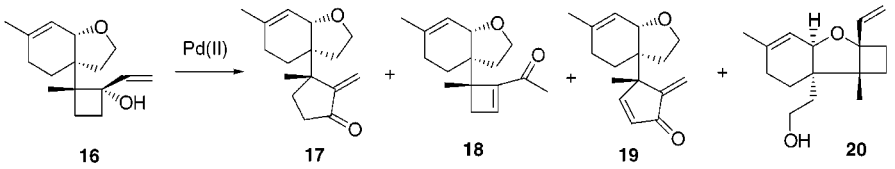


Table 1. Reaction of **16** with Pd(II)

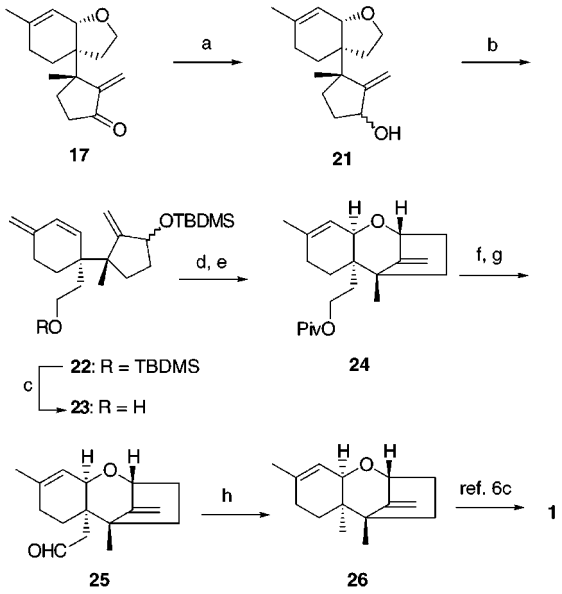


entry	reagents	solvent	yield (%) 17	18	19	20
1	$Pd(OAc)_2$ (2 eq)	THF	0	0	0	50
2	$PdCl_2(MeCN)_2$ (1.2 eq)	DMF	36	32	0	31
3	$PdCl_2(MeCN)_2$ (1.0 eq), *p*-quinone (2 eq)	DMA	62	34	4	trace
4	$PdCl_2(MeCN)_2$ (0.1 eq), *p*-quinone (2 eq)	DMA	42	27	4	trace
5	$PdCl_2(MeCN)_2$ (0.1 eq), $CuCl_2$ (2 eq)	DMA	43	41	0	trace

the reaction has taken place by a catalytic amount of $PdCl_2(MeCN)_2$ in the presence of *p*-quinone or $CuCl_2$ (entries 4 or 5).

With the ring-expanded compound in hand, the ring opening of the tetrahydrofuran part was then investigated. Fortunately, the process could be performed after reduction of the carbonyl group of **17**. Namely, **17** was reduced with DIBALH to give a 1.5:1 epimeric mixture of **21** (Scheme 5). Treatment of **21** with TBDMSOTf in the presence of 2,6-lutidine caused the ring-opening reaction to afford **22**. Subsequent removal of one of the TBDMS groups of **22** provided, in 95% overall yield for two steps, a 1.5:1 mixture of **23**,[11] separable by chromatography. Protection of the primary hydroxyl group of the major product **23** with a pivaloyl group, followed by the action of 10-camphorsulfonic acid (CSA) in MeOH, quantitatively furnished the tricyclic compound **24**. Removal of one carbon unit was carried out in three steps through the aldehyde **25** to afford **26**, spectral data of which were consistent with the reported ones.[6c] Since **26** had been converted into scirpene (**1**) by epoxidation with *m*-CPBA,[6c] the total synthesis of (±)-**1** has been accomplished.

Scheme 5[a]



[a] Reagents and conditions: (a) DIBALH, 86% (1.5:1 ds); (b) TBDMSOTf, 2,6-lutidine; (c) AcOH−H_2O−THF (3:1:1 v/v/v), 95% for two steps; (d) PivCl, pyridine, DMAP, 99%; (e) CSA, 100%; (f) DIBALH, 93%; (g) DMSO, $(COCl)_2$; Et_3N, 100%; (h) $Rh(Ph_3)_3Cl$, toluene, reflux, 70%.

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(10) **Procedure for the Ring Expansion Reaction** (Table 1, entry 3). To a stirred mixture of **16** (24.9 mg, 0.100 mmol) and *p*-quinone (27.7 mg, 0.201 mmol) in DMA (3 mL) was added $PdCl_2(MeCN)_2$ (26.0 mg, 0.100 mmol), and the mixture was stirred for 0.5 h at ambient temperature. After addition of $MgSO_4$ and Celite, filtration followed by concentration of the filtrate gave a residue, which was chromatographed on silica gel. Elution with hexanes−AcOEt (9:1 v/v) provided **17** (15.3 mg, 62%), **18** (8.4 mg, 34%), and **19** (1.0 mg, 4%). **17**: IR (neat) 1710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (3H, s), 1.71 (3H, s), 1.62−1.86 (5H, m), 2.03−2.26 (3H, m), 2.38−2.46 (2H, m), 3.69 (1H, dd, J = 8.9 Hz), 3.80 (1H, dt, J = 4.2 and 8.9 Hz), 4.31 (1H, m), 5.28−5.30 (1H, m), 5.41 (1H, s), 6.14 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.3, 26.0, 26.6, 28.5, 31.4, 31.7, 36.0, 49.0, 50.1, 65.5, 77.2, 119.7, 122.5, 139.6, 152.6, 208.8; MS *m*/*z* 246 (M^+). Anal. Calcd for $C_{16}H_{22}O_2$: C, 78, 01; H, 9.00%. Found: C, 77.63; H, 9.34%.

(11) **Procedure for the Conversion of 21 into 23.** To a stirred solution of **21** (15.1 mg, 0.061 mmol) and 2,6-lutidine (0.04 mL, 0.304 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C was added TBDMSOTf (0.06 mL, 0.243 mmol), and the mixture was stirred for 1 h at 0 °C. The mixture was partitioned between H_2O and Et_2O. The combined organic layers were washed with saturated NaCl, dried ($MgSO_4$), and evaporated. The products **22** were treated with AcOH−THF−H_2O (3:1:1 v/v/v, 5 mL) for 3 h at ambient temperature. After addition of H_2O, the mixture was extracted with Et_2O three times. The combined organic layers were washed with saturated $NaHCO_3$ and saturated NaCl, dried ($MgSO_4$), and evaporated. Column chromatography on silica gel eluting with hexanes−AcOEt (96:4 v/v) provided **23** (12.4 mg, 56%) and its epimer (8.6 mg, 39%). **23**: IR (neat) 3300 cm^{-1}; ^1H NMR (300 Mz, $CDCl_3$) δ 0.07 (3H, s), 0.08 (3H, s), 0.88-(9H, s), 1.04 (3H, s), 1.26−2.39 (11H, m), 3.69 (2H, t, J = 7.6 Hz), 4.35 (1H, br s), 4.77 (1H, s), 4.82 (1H, s), 5.09 (1H, s), 5.17 (1H, s), 5.88 (1H, d, J = 10.0 Hz), 6.25 (1H, d, J = 10.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.7, −4.5, 18.1, 25.8, 26.0, 28.0, 30.5, 32.7, 34.9, 40.3, 42.2, 51.1, 61.8, 78.7, 110.9, 112.0, 130.0, 135.4, 142.4, 161.2; MS *m*/*z* 362 (M^+). Anal. Calcd for $C_{22}H_{38}O_2Si$: C, 72.87; H, 10.56%. Found: C, 72.73; H, 10.52%.