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Efficient Diastereoselective Synthesis of Trifarane-Type Sesquiterpenes, Trifarienols A and B

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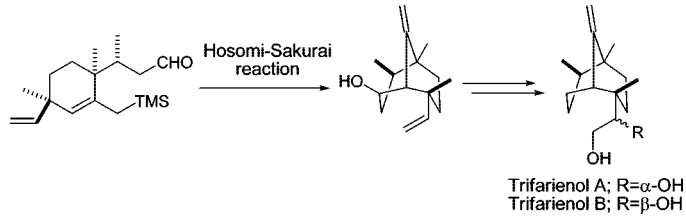

Diastereoselective total synthesis of trifarienols A and B, trifarane-type sesquiterpenes isolated from the Malaysian *Cheilolejeunea trifaria*, was achieved via an intramolecular Hosomi−Sakurai reaction of the aldehyde to construct a substituted bicyclo[3.3.1]nonane skeleton having the *exo*-methylene moiety of the target compounds in one step.

Introduction

Trifarienols A (**1**) and B (**2**) were isolated from the liverwort *Cheilolejeunea trifaria* as trifarane-type sesquiterpenes having a new carbon skeleton.

The structures of trifarienols A and B, including their absolute configurations, were established by a combination of NMR, CD, and X-ray crystallographic analyses as shown in Figure 1.[1] Regarding the synthesis of those sesquiterpenes, there are two reports to date. The first synthesis of trifarienols A and B was achieved by Huang and Forsyth,[2a] in which antiselective α′-intramolecular carbomercuration was involved as the key reaction for the assembly of a bridged bicyclic system. In this synthesis, trifarienols A and B were prepared from 2-methyl-2-cyclohexenone in 16 steps and ca. 9% and 3% overall yields, respectively. However, the synthesized target compounds were both racemic forms. Although an enantioselective synthesis of those terpenoids was developed by Tori and co-workers in 1999,[2b] the overall yields of trifarienols A and B starting from the optically active (2*RS*,3*R*)-2,3-dimethylcyclohexanone were 1.8% and 1.4%, respectively. Thus, some improvement seemed to be desired in terms of stereoselectivity and overall yields in the synthesis of optically active trifarienols A and B.

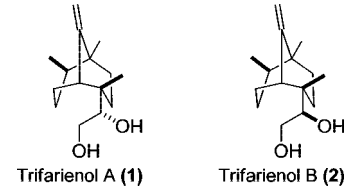

FIGURE 1. Structures of trifarienols A and B.

Trifarienols are novel, naturally occurring sesquiterpene series in bryophytes and contain a highly substituted bicyclo[3.3.1]nonane system with an *exo*-methylene unit. The bicyclo[3.3.1]nonane system is also present in several biologically attractive natural products such as hyperforin,[3] aristophenones,[4] guttiferones,[5] garsubellin A,[6] papuaforin A,[7] and upial.[8] Moreover, this ring system has received theoretical interest from the conformation point of view.[9]

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(1) (a) Hashimoto, T.; Koyama, H.; Takaoka, S.; Tori, M.; Asakawa, Y. *Tetrahedron Lett.* **1994**, *35*, 4787–4788. (b) Hashimoto, T.; Koyama, H.; Tori, M.; Takaoka, S.; Asakawa, Y. *Phytochemistry* **1995**, *40*, 171–176.

(2) (a) Huang, H.; Forsyth, C. J. *J. Org. Chem.* **1995**, *50*, 5746–5747. (b) Tori, M.; Hisazumi, K.; Wada, T.; Sono, M.; Nakashima, K. *Tetrahedron: Asymmetry* **1999**, *10*, 961–971.

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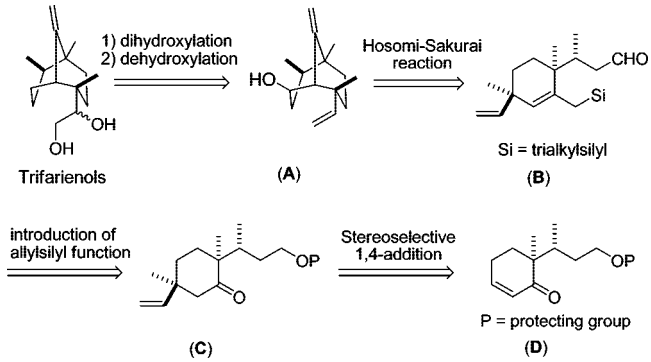
SCHEME 1. Retrosynthesis of Trifarienols A and B



Due to the unique structural features of trifarienols, we are interested in establishing a facile synthetic strategy for those natural products, since stereocontrolled construction of highly functionalized molecular frameworks with a high level of regio-, stereo-, and enantioselectivity is one of the most challenging aspects in organic synthesis.

Recently, we have developed a simple and convenient methodology for the construction of a bicyclo[3.3.1]nonane ring system with an *exo*-methylene moiety by employing an intramolecular carbonyl-ene reaction, and we have reported its application to the synthesis of (+)-upial.[10]

As part of our continuing work on enantioselective synthesis of functionalized polycyclic carbocyclic systems from readily available chiral starting material, we have developed a simple and convenient methodology for the synthesis of target compounds.

Results and Discussion

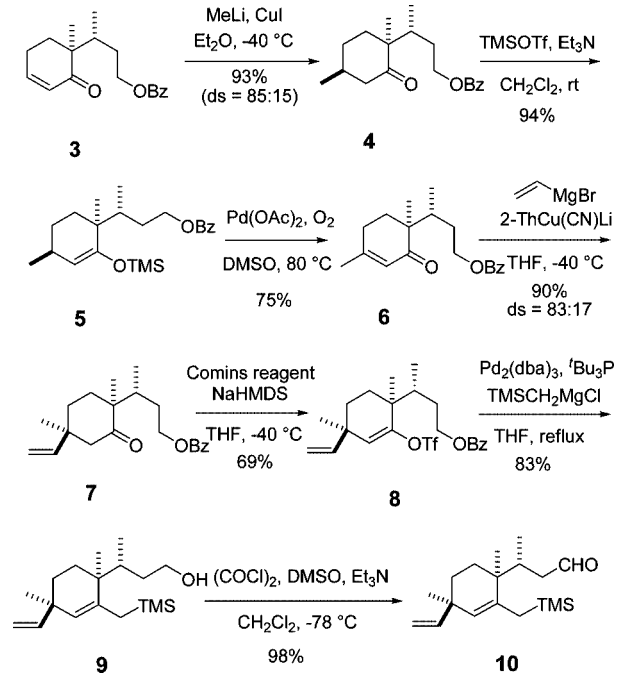
Our basic strategy for the synthesis of trifarienols A and B is outlined in Scheme 1.

We envisaged that the diol function could be installed at a later stage of the synthesis by dihydroxylation of the corresponding alkene **A**. A bicyclo[3.3.1]nonane skeleton would be constructed by an intramolecular Hosomi−Sakurai reaction of allylsilane-aldehyde **B**, which would be available from ketone **C** by introducing a silylmethyl group by palladium-mediated coupling of the corresponding triflate with a suitable Grignard reagent. Construction of a quaternary carbon center with the desired stereochemistry could be achieved by exploitation of sequential stereoselective conjugate addition of a methyl group and a vinyl group to enone **D**.

The synthesis was started by Michael addition of a methyl group to the known enone **3**[11] that was previously prepared in optically pure form by us.[10]

Treatment of enone **3** with methyllithium and copper(I) iodide in THF brought about 1,4-conjugate addition of a methyl group to give β-methyl compound **4** as the major product (dr = 85:15; the stereochemistry was depicted for the major product). Similar stereoselectivity has already been observed in our synthesis of (+)-upial.[10] A mixture of the two diastereoisomers

SCHEME 2. Preparation of Allylsilane



was able to be converted to enone **6** via Ito−Saegusa oxidation[12] of silyl enol ether **5** in the usual manner. Subsequent Michael addition of a vinyl group to enone **6** by treatment with vinylmagnesium bromide in THF at −40 °C in the presence of a higher ordered copper catalyst[13] afforded ketone **7**, as an inseparable mixture, by constructing the quaternary carbon center with the desired stereochemistry predominantly in 90% yield (dr = 83:17).

The configuration of the newly generated quaternary carbon center of **7** was assumed to have an *S* configuration arising from an axial attack of the vinyl group on enone.[10] After treatment of ketone **7** with Comins reagent[14] and sodium hexamethyldisilazide (NaHMDS), the resulting triflate **8** was coupled with trimethylsilylmethylmagnesium chloride in the presence of tris(dibenzylideneacetone)dipalladium and tri-*tert*-butylphosphine to give allylsilane derivative **9**,[15] where removal of the benzoyl group of **8** took place, simultaneously, and the diastereoisomeric mixture could be separated at this stage. Swern oxidation of alcohol **9** afforded the desired aldehyde in 98% yield (Scheme 2).

First, we attempted construction of a bicyclo[3.3.1]nonane ring system by treatment of **10** with 0.05 equiv of *p*-toluenesulfonic acid in $CHCl_3$, which was shown to be the best reaction conditions for the synthesis of (+)-upial;[10] however, the desired product **11** was isolated in only 30% yield together with the corresponding ethoxy derivative **12** in 48% yield (entry 1). Slight improvement was observed with the use of 0.1 equiv of *p*-toluenesulfonic acid in $CHCl_3$ to give **11** in 42% yield (entry 2). The ethoxy function of compound **12** might be installed from ethanol present in the solvent $CHCl_3$ as a stabilizer. When this

(9) Peters, J. A.; Baas, J. M. A.; van de Graaf, B.; van der Toorn, J. M.; van Bekkum, H. *Tetrahedron* **1978**, *34*, 3313–3323.

(10) Takahashi, K.; Watanabe, M.; Honda, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 131–133.

(11) Compound **3** was prepared from methyl (3*R*)-3-[(1*S*)-1-methyl-2-oxocyclohexyl]butanoate, which was derived by using an addition of the chiral imine of 2-methylcyclohexanone to phenyl crotonate as the key step, according to Pfau's procedure, see: Javin, I.; Revial, G.; Tomas, A.; Lemoine, P.; Pfau, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1795–1812.

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(14) Comins, D. L.; Dehghani, A. *Tetrahedron Lett.* **1992**, *33*, 6299–6302.

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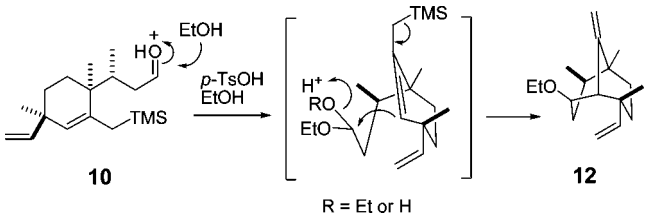
SCHEME 3. Formation of Ethoxy Derivative 12



cyclization was carried out with 0.1 equiv of *p*-toluenesulfonic acid in $CHCl_3$ containing amylene as a stabilizer, **11** was isolated in 57% yield without formation of the ethoxy derivative (entry 3). Similar reaction with 0.1 equiv of *p*-toluenesulfonic acid in the presence of water (5 equiv) instead of ethanol with the expectation of obtaining a desired alcohol in better yield afforded **11** in 49% yield (entry 4). With the use of *p*-toluenesulfonic acid, the cyclization of **10** to **11** required relatively longer reaction times compared to the case observed in the synthesis of upial,[10] probably due to the steric repulsion between the carbonyl group and the quaternary carbon center adjacent to the reaction site of the starting aldehyde. Since the Hosomi−Sakurai reaction will be competitive to acetal (or half acetal) formation under the reaction conditions for entries 1 and 2, the decreased reactivity of **10** by steric hindrance may lead to the formation of the unfavorable ethoxy derivative (Scheme 3). Thus, we attempted to use an alternative Lewis acid as an initiator for the Hosomi−Sakurai reaction.

Fortunately, we were able to find that the desired alcohol **11** was obtained as the sole product in 93% yield when aldehyde **10** was treated with zinc chloride (1 equiv) in refluxing $CHCl_3$ for 0.5 h (entry 5). It is noteworthy that an intramolecular Hosomi−Sakurai reaction of **10** proceeded in an entirely stereoselective manner, and the newly generated stereogenic center at the secondary hydroxyl group of **11** was unambiguously determined by NOE experiments as depicted in Figure 2 (also see Table 1).

Since the basic carbon framework of the target compounds was thus constructed, our attention was focused on conversion of **11** into natural products by installation of the diol function and subsequent deoxygenation of the secondary hydroxyl group. For deoxygenation of the secondary hydroxyl group, we decided to exploit a radical reaction of the corresponding toluoyl group originally developed by Markó.[16] Acylation of **11** with toluoyl chloride in CH_2Cl_2 in the presence of TMEDA at room temperature afforded ester **13** in 98% yield.

Dihydroxylation of **13** was first carried out by using a catalytic amount of OsO_4 and 1.2 equiv of *N*-methylmorphorine *N*-oxide (NMO) in *t*-BuOH−THF−H_2O (5:5:1, v/v) at ambient temperature for 3 days to give separable diols **14** and **15** in 23% and 64% yields, respectively. To obtain a better diastereoselectivity, AD-mix α and *β* were applied to alkene **13**; however, the expected improvement was not observed and the reactivity was decreased even for longer reaction times, unfortunately, as shown in Table 2.

Since the configurations of diols could not be determined at this stage, the major diol **15** was subjected to deoxygenation with samarium diiodide to provide trifarienol B (**2**) in 25% yield (Scheme 4). This conversion led to the determination of the stereochemistry of diol **15** unambiguously. Although the reason for the observed stereoselectivity in dihydroxylation of **13** leading

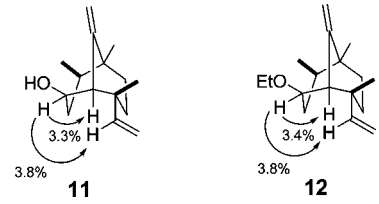
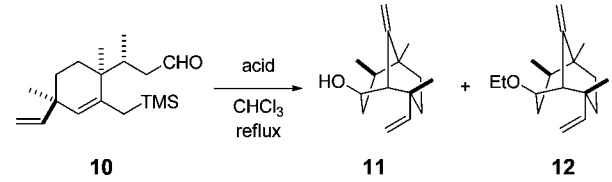


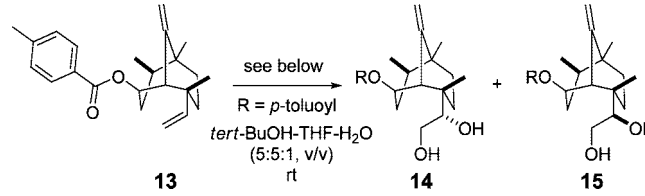
FIGURE 2. Structure determination of compounds **11** and **12**. Observed NOEs are indicated by arrows.

TABLE 1. Synthesis of the Bicyclo[3.3.1]nonane System



entry	acid (equiv)	solvent stabilizer	additive (equiv)	reaction time (h)	product yield (%) 11	12
1	*p*-TsOH (0.05)	EtOH		3	30	48
2	*p*-TsOH (0.1)	EtOH		0.5	42	25
3	*p*-TsOH (0.1)	amylene		12	57	0
4	*p*-TsOH (0.1)	amylene	H_2O (5)	12	49	0
5	$ZnCl_2$ (1)	amylene		0.5	93	0

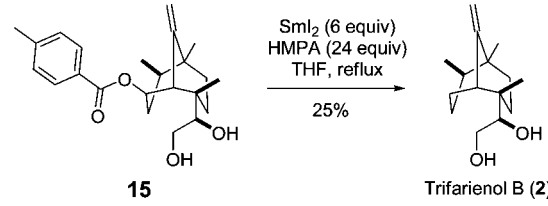
TABLE 2. Dihydroxylation of 13



reagents	reaction time	additive	yield (%)	dr (**14**:**15**)
OsO_4, NMO	3 days		87	1:3
AD-mix α	7 days	$MeSO_2NH_2$	no reaction	
AD-mix *β*	7 days	$MeSO_2NH_2$	25[a]	1:2

[a] 53% yield based on the consumed starting material.

SCHEME 4. Synthesis of Trifarienol B



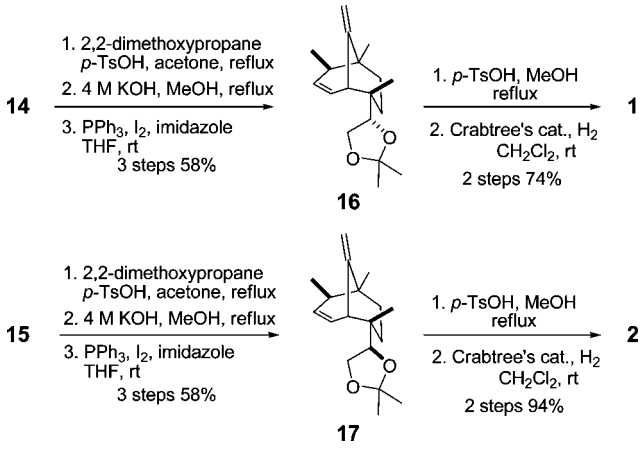
to diol **15** as a major isomer was not clear at present, we presumed that the presence of a sterically bulky toluoyl group might prevent the attack of OsO_4 from the other side leading to diol **14**.

Although the asymmetric synthesis of trifarienol B (**2**) was achieved as above, the yield of the final deoxygenation step was not sufficient. Thus, an alternative synthetic route to the target compounds was examined as follows.

Diol **14** was converted to acetonides, which on hydrolysis of the toluoyl group with methanolic NaOH solution gave the corresponding alcohol. Treatment of alcohol with iodine in the presence of triphenylphosphine and imidazole in THF at room temperature afforded the corresponding olefin **16** in 58% yield from **14** in three steps (Scheme 5). Finally, removal of acetonide by acid treatment of **16**, followed by site-selective hydrogenation

(16) Lam, K.; Markó, I. E. *Org. Lett.* **2008**, *10*, 2773–2776.

SCHEME 5. Synthesis of Trifarienols A and B



of a carbon−carbon double bond of the diol over Crabtree's catalyst[17] gave the desired product, trifarienol A (**1**), in 74% yield from **16**, whose spectroscopic data (^{1}H and ^{13}C NMR, MS, IR) and TLC behavior, including its melting point and specific optical rotation [mp 71−72 °C (lit.[1a] mp 59−60 °C, lit.[2b] mp 82−82.5 °C); $[\alpha]_D$ +11.5 (*c* 0.9, $CHCl_3$) {lit.[1a] $[\alpha]_D$ +10.2 (*c* 0.63, $CHCl_3$); lit.,[2b] $[\alpha]_D$ +15 (*c* 0.57, $CHCl_3$)}], were similar to those reported in the literature.[1]

Similarly, diol **15** was transformed to alkene **17** in 58% yield, which was further converted to trifarienol B (**2**), successfully, in 94% yield from **17**. Again, the spectroscopic data (^{1}H and ^{13}C NMR, MS, IR) and TLC behavior of the synthesized compound, including its melting point and optical rotation [mp 99−100 °C (lit.[1a] mp 105−105.5 °C, lit.[2b] mp 108−109.5 °C); $[\alpha]_D$ −6.0 (*c* 1.53, $CHCl_3$) {lit.[1a] $[\alpha]_D$ −3.6 (*c* 1.62, $CHCl_3$); lit.,[2b] $[\alpha]_D$ −3.5 (*c* 1.017, $CHCl_3$)}], were comparable to those reported in the literature.[1]

Conclusions

In summary, we were able to establish a concise synthetic route for trifarienols A (**1**) and B (**2**) by employing an intramolecular Hosomi−Sakurai reaction of an allylsilane derivative as the key reaction. In this synthesis, remarkable stereoselectivities and site-selectivities were observed during the construction of a bicyclo-[3.3.1]nonane ring system by the Hosomi−Sakurai reaction and also in catalytic reduction of a carbon−carbon double bond. Finally, trifarienols A and B were prepared from enone **3** in 15 steps in 2% and 9% yields, respectively. Further applications of this methodology to various types of natural product synthesis are now under investigation in our laboratory.

Experimental Section

(3*R*)-3-{(1*S*,4*R*)-1,4-Dimethy-2-[(trimethylsilyl)methyl]-4-vinylcyclohex-2-en-1-yl}butan-1-ol (9). To a stirred solution of triflate **8** (153 mg, 0.333 mmol) in THF (6.7 mL) were added $Pd_2(dba)_3$ (15.3 mg, 16.7 μmol), ^{t}Bu$_3$P (4.4 M toluene solution; 19 μL, 83.3 μmol), and trimethylsilylmethylmagnesium chloride (1.0 M Et_2O solution; 1.7 mL, 1.67 mmol) at rt under Ar, and the resulting mixture was heated at reflux for 12 h. After treatment with saturated aq ammonium chloride, the mixture was extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with *n*-hexane−AcOEt (9:1, v/v) afforded allylsilane **9** (82 mg, 83%) as a colorless oil: $[\alpha]^{25}_D$ −15.2 (*c* 1.4, $CHCl_3$); IR ν_{max} 3369, 1213 cm^{-1}; ^{1}H NMR ($CDCl_3$; 400 MHz) δ 5.69 (1H, dd, *J* = 17.4 and 10.4 Hz), 5.06 (1H, s), 4.93 (1H, dd, *J* = 17.4 and 2.0 Hz), 4.88 (1H, dd, *J* = 10.4 and 2.0 Hz), 3.72−3.78 (1H, m), 3.56−3.63 (1H, m), 1.69−1.79 (2H, m), 1.25−1.56 (6H, m), 1.05−1.24 (2H, m), 1.02 (3H, s), 0.97 (3H, s), 0.74 (3H, d, *J* = 6.9 Hz), 0.05 (9H, s); ^{13}C NMR ($CDCl_3$; 100 MHz) δ 147.2, 141.6, 129.7, 112.6, 62.6, 40.6, 39.2, 35.8, 33.8, 32.2, 29.8, 26.3, 24.1, 19.1, 14.9, 0.2 (3), −29.8; MS (EI) 294 (M^+); HRMS (EI) calcd for $C_{18}H_{34}OSi$ 294.2379, found 294.2353.

(3*R*)-3-{(1*S*,4*R*)-1,4-Dimethyl-2-[(trimethylsilyl)methyl]-4-vinylcyclohex-2-en-1-yl}butanal (10). To a stirred solution of oxalyl chloride (83 μL, 0.582 mmol) in dry CH_2Cl_2 (2 mL) was added a solution of DMSO (83 μL, 0.164 mmol) in dry CH_2Cl_2 (1 mL) dropwise at −78 °C under Ar, and the whole was stirred for an additional 10 min. To this solution was added a solution of alcohol **9** (57 mg, 0.194 mmol) in CH_2Cl_2 (2 mL) and the resulting mixture was stirred at the same temperature for 2 h. After addition of Et_3N (135 μL, 0.97 mmol), the mixture was stirred at 0 °C for 30 min, and the whole was subjected to column chromatography on silica gel. Elution with *n*-hexane:Et_3N (99:1, v/v) gave aldehyde **10** (55 mg, 98%) as a colorless oil: $[\alpha]^{24}_D$ −30.6 (*c* 2.1, $CHCl_3$); IR ν_{max} 2957, 1728 cm^{-1}; ^{1}H NMR ($CDCl_3$; 400 MHz) δ 9.77 (1H, dd, *J* = 3.2 and 1.8 Hz), 5.68 (1H, dd, *J* = 17.3 and 10.4 Hz), 5.10 (1H, s), 4.93 (1H, dd, *J* = 10.4 and 1.9 Hz), 4.86 (1H, dd, *J* = 17.3 and 1.9 Hz), 2.49 (1H, dd, *J* = 16.2 and 1.8 Hz), 2.28−2.36 (1H, m), 2.10 (1H, ddd, *J* = 16.2, 10.6, and 3.2 Hz), 1.54 (1H, dt, *J* = 13.3 and 3.2 Hz), 1.43−1.49 (3H, m), 1.39 (1H, dd, *J* = 13.3 and 2.7 Hz), 1.34 (1H, d, *J* = 15.6 Hz), 1.02 (3H, s), 0.97 (3H, s), 0.77 (3H, d, *J* = 6.7 Hz), 0.05 (9H, s); ^{13}C NMR ($CDCl_3$; 100 MHz) δ 203.4, 147.0, 140.6, 130.3, 112.8, 45.9, 40.3, 39.2, 34.4, 32.0, 29.7, 26.6, 24.3, 19.1, 15.7, −0.3 (3); MS (EI) 292 (M^+); HRMS (EI) calcd for $C_{18}H_{32}OSi$ 292.2222, found 292.2233.

(2*S*,4*R*,8*R*)-4,5,8-Trimethyl-9-methylene-8-vinylbicyclo-[3.3.1]nonan-2-ol (11). To a stirred solution of aldehyde **10** (30 mg, 0.103 mmol) in $CHCl_3$ (3.4 mL) was added $ZnCl_2$ (0.5 M THF solution; 0.2 mL, 0.103 mmol) at rt under Ar, and the resulting mixture was heated at reflux for 30 min. The mixture was treated with saturated aq $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with *n*-hexane−AcOEt (9:1, v/v) afforded alcohol **11** (21.2 mg, 93%) as white crystals: $[\alpha]^{26}_D$ −17.6 (*c* 1.2, $CHCl_3$); mp 63−65 °C; IR ν_{max} 2927, 1220 cm^{-1}; ^{1}H NMR ($CDCl_3$; 400 MHz) δ 5.84 (1H, dd, *J* = 17.5 and 10.9 Hz), 5.01 (1H, dd, *J* = 10.9 and 0.6 Hz), 4.98 (1H, dd, *J* = 17.5 and 0.6 Hz), 4.94 (1H, d, *J* = 1.6 Hz), 4.90 (1H, d, *J* = 1.6 Hz), 3.91 (1H, br), 2.19−2.26 (1H, m), 2.05−2.14 (1H, m), 2.02 (1H, s), 1.59−1.74 (4H, m), 1.45 (1H, d, *J* = 15.3 Hz), 1.25−1.33 (1H, m), 0.99 (6H, s), 0.95 (3H, d, *J* = 7.3 Hz); ^{13}C NMR ($CDCl_3$; 100 MHz) δ 148.9, 147.7, 111.3, 110.8, 70.8, 59.5, 39.9, 39.7, 39.2, 38.7, 37.8, 29.9, 26.9, 25.1, 21.0; MS (CI) 221 (M + 1)$^+$; HRMS (CI) calcd for $C_{15}H_{24}O$ + H 221.1905, found 221.1899. Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.50; H, 10.93.

(2*R*,4*S*,6*R*)-4-Ethoxy-1,2,6-trimethyl-9-methylene-6-vinylbicyclo[3.3.1]nonane (12). $[\alpha]^{29}_D$ −8.8 (*c* 1.6, $CHCl_3$); IR ν_{max} 2975, 1119 cm^{-1}; ^{1}H NMR ($CDCl_3$; 400 MHz) δ 5.84 (1H, dd, *J* = 17.6 and 10.9 Hz), 5.00 (1H, dd, *J* = 10.9 and 1.3 Hz), 4.96 (1H, dd, *J* = 17.6 and 1.3 Hz), 4.81 (1H, d, *J* = 1.9 Hz), 4.76 (1H, d, *J* = 1.9 Hz), 3.45 (1H, dt, *J* = 5.0 and 2.2 Hz), 3.31−3.43 (2H, m), 2.07 (1H, s), 1.93−2.02 (2H, m), 1.42−1.65 (2H, m), 1.25−1.36 (3H, m), 1.11 (3H, t, *J* = 7.0 Hz), 0.98 (3H, s), 0.96 (3H, s), 0.90 (3H, d, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$; 100 MHz) δ 149.9, 148.4, 111.0, 108.9, 77.4, 63.0, 56.7, 40.1, 39.2, 38.8, 37.6, 35.1, 29.5, 26.4, 24.4, 19.5, 15.6; MS (EI) 248 (M^+); HRMS (EI) calcd for $C_{17}H_{28}O$ 248.2140, found 248.2144.

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(2*S*,4*R*,8*R*)- 4,5,8-Trimethyl-9-methylene-8-vinylbicyclo[3.3.1]-non-2-yl 4-Methylbenzoate (13). To a stirred solution of alcohol **11** (55 mg, 0.25 mmol) in CH_2Cl_2 (3 mL) were added TMEDA (83 μL, 0.55 mmol) and *p*-toluoyl chloride (73 μL, 0.55 mmol) at 0 °C under Ar, and the resulting mixture was stirred at rt for 1 h. The mixture was treated with saturated aq $NaHCO_3$ and extracted with AcOEt. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with *n*-hexane−AcOEt (50:1, v/v) afforded ester **13** (83 mg, 98%) as a colorless oil: $[\alpha]^{20}_D$ +46.7 (*c* 1.6, $CHCl_3$); IR ν_{max} 1712, 1277 cm^{-1}; ^1H NMR ($CDCl_3$; 400 MHz) δ 7.89 (2H, d, J = 8.1 Hz), 7.21 (2H, d, J = 8.1 Hz), 5.97 (1H, dd, J = 17.6 and 10.9 Hz), 5.30 (1H, br), 5.09 (1H, dd, J = 10.9 and 1.1 Hz), 5.05 (1H, dd, J = 17.6 and 1.1 Hz), 4.88 (1H, d, J = 1.8 Hz), 4.86 (1H, d, J = 1.8 Hz), 2.47 (1H, ddd, J = 16.0, 6.9, and 4.8 Hz), 2.39 (3H, s), 2.24 (1H, s), 2.18 (1H, dt, J = 13.7 and 6.9 Hz), 1.59−1.82 (4H, m), 1.38 (1H, dd, J = 14.3 and 6.3 Hz), 1.04 (3H, s), 1.02 (3H, d, J = 7.3 Hz), 1.01 (3H, s); ^{13}C NMR ($CDCl_3$; 100 MHz) δ 165.8, 148.3, 147.5, 143.2, 129.5 (2), 128.9 (2), 128.3, 111.6, 109.9, 74.4, 55.4, 40.0, 39.7, 39.5, 38.5, 34.7, 30.5, 27.0, 25.5, 21.6, 20.2; MS (EI) 338 (M^+); HRMS (EI) calcd for $C_{23}H_{30}O_2$ 338.2246, found 338.2251.

(2*S*,4*R*,8*S*)-8-[(1*S*)-1,2-Dihydroxyethyl]-4,5,8-trimethyl-9-methylenebicyclo[3.3.1]non-2-yl 4-Methylbenzoate (14) and (2*S*,4*R*,8*S*)-8-[(1*R*)-1,2-Dihydroxyethyl]-4,5,8-trimethyl-9-methylenebicyclo[3.3.1]non-2-yl 4-Methylbenzoate (15). To a stirred solution of alkene **13** (63 mg, 0.186 mmol) in ^{t}BuOH−THF−H_2O (5:5:1, 1.1 mL) were added NMO (26 mg, 0.223 mmol) and OsO_4 (0.02 M ^{t}BuOH solution; 0.9 mL, 18.6 μmol) at rt, and the resulting solution was stirred for an additional 3 days. The mixture was treated with $Na_2S_2O_5$ and H_2O, and extracted with $CHCl_3$. The extract was washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with *n*-hexane−AcOEt (2:1, v/v) afforded diol **14** (16 mg, 23%) as the first eluate (colorless oil): $[\alpha]^{20}_D$ +27.9 (*c* 1.9, $CHCl_3$); IR ν_{max} 3446, 1708 cm^{-1}; ^1H NMR ($CDCl_3$; 400 MHz) δ 7.89 (2H, d, J = 8.1 Hz), 7.23 (2H, d, J = 8.1 Hz), 5.41(1H, d, J = 5.4 Hz), 4.79 (2H, dd, J = 16.7 and 1.6 Hz), 4.08 (1H, br), 3.88 (1H, dd, J = 8.8 and 2.5 Hz), 3.67 (1H, dd, J = 11.0 and 8.8 Hz), 3.60 (1H, dd, J = 11.0 and 2.5 Hz), 2.70 (1H, br), 2.53−2.63 (1H, m), 2.41 (3H, s), 1.59−1.89 (5H, m), 1.28−1.33 (2H, m), 1.11 (3H, d, J = 7.2 Hz), 1.02 (3H, s), 0.87 (3H, s); ^{13}C NMR ($CDCl_3$; 100 MHz) δ 167.5, 147.0, 143.9, 129.6 (2), 129.1 (2), 127.4, 111.1, 77.9, 73.1, 62.8, 51.3, 40.0, 39.7, 39.6, 38.0, 34.8, 31.6, 25.6, 21.7, 19.9, 18.5; MS (EI) 372 (M^+); HRMS (EI) calcd for $C_{23}H_{32}O_4$ 372.2300, found 372.2295.

Further elution with *n*-hexane−AcOEt (1:1 v/v) afforded diol **15** (44 mg, 64%) as white crystals: $[\alpha]^{19}_D$ +27.5 (*c* 1.5, $CHCl_3$); mp 148−149 °C; IR ν_{max} 3393, 1708 cm^{-1}; ^1H NMR ($CDCl_3$; 400 MHz) δ 7.87 (2H, d, J = 8.1 Hz), 7.20 (2H, d, J = 8.1 Hz), 5.50 (1H, br), 4.79 (2H, dd, J = 10.9 and 1.6 Hz), 4.15 (1H, dd, J = 11.0 and 2.5 Hz), 3.83 (1H, dd, J = 9.5 and 2.5 Hz), 3.55 (1H, dd, J = 11.0 and 9.5 Hz), 3.22 (2H, br), 2.57−2.64 (1H, m), 2.39 (3H, s), 2.20 (1H, s), 1.89−1.99 (1H, m), 1.78−1.85 (1H, m), 1.57−1.69 (4H, m), 1.05 (3H, d, J = 7.2 Hz), 1.02 (3H, s), 0.89 (3H, s); ^{13}C NMR ($CDCl_3$; 100 MHz) δ 166.3, 148.0, 143.5, 129.6 (2), 129.0 (2), 127.9, 110.2, 78.1, 73.1, 62.3, 53.3, 40.3, 39.59, 39.55, 38.4, 34.8, 31.8, 25.7, 21.6, 20.5, 18.8; MS (EI) 372 (M^+); HRMS (EI) calcd for $C_{23}H_{32}O_4$ 372.2300, found 372.2278. Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 73.90; H, 8.70.

(4*S*)-2,2-Dimethyl-4-[(2*S*,6*R*)-2,5,6-trimethyl-9-methylenebicyclo[3.3.1]non-7-en-2-yl]-1,3-dioxolane (16). To a stirred solution of diol **14** (16.6 mg, 44.6 μmol) in acetone (2 mL) were added 2,2-dimethoxypropane (0.01 mL, 89.2 μmol) and *p*-TsOH (0.01 M acetone solution; 0.2 mL, 2.23 μmol) at rt, and the whole was heated at reflux for 2 h. The mixture was treated with saturated aq $NaHCO_3$ and extracted with AcOEt. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a crude acetonide (16.6 mg), which without further purification was used in the next reaction. A solution of acetonide obtained above was dissolved in 4 M NaOH−MeOH (1:1) (2 mL), and the resulting solution was heated at reflux for 12 h. The solution was carefully acidified with 1 M HCl, and extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4, and concentrated to give alcohol (20.4 mg), which was used in the next reaction without further purification. To a solution of alcohol obtained above in THF (2 mL) were added imidazole (36 mg, 0.535 mmol), I_2 (112 mg, 0.446 mmol), and PPh_3 (117 mg, 0.446 mmol) at rt, and the whole was stirred at the same temperature for 12 h. The mixture was treated with 10% aq $Na_2S_2O_3$, and extracted with AcOEt. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with *n*-hexane−AcOEt (50:1, v/v) afforded diene **16** (7.2 mg, 58%) as a colorless oil: $[\alpha]^{19}_D$ −80.6 (*c* 1.6, $CHCl_3$); IR ν_{max} 2930, 1070 cm^{-1}; ^1H NMR ($CDCl_3$; 400 MHz) δ 5.75 (1H, ddd, J = 9.8, 5.7, and 1.5 Hz), 5.68 (1H, dd, J = 9.8 and 3.4 Hz), 4.80 (1H, d, J = 1.8 Hz), 4.64 (1H, d, J = 1.8 Hz), 3.95 (1H, dd, J = 7.9 and 6.6 Hz), 3.83 (1H, dd, J = 7.9 and 6.6 Hz), 3.66 (1H, t, J = 7.9 Hz), 2.69 (1H, d, J = 5.7 Hz), 1.99−2.07 (1H, m), 1.44−1.68 (4H, m), 1.43 (3H, s), 1.34 (3H, s), 0.99 (3H, s), 0.91 (3H, s), 0.81 (3H, d, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$; 100 MHz) δ 150.4, 136.2, 126.7, 108.3 105.9, 79.8, 65.1, 48.6, 43.8, 39.8, 39.4, 39.2, 27.4, 26.3, 25.2, 24.7, 17.6, 15.3; MS (EI) 276 (M^+); HRMS (EI) calcd for $C_{18}H_{28}O_2$ 276.2089, found 276.2116.

(4*R*)-2,2-Dimethyl-4-[(2*S*,6*R*)-2,5,6-trimethyl-9-methylenebicyclo[3.3.1]non-7-en-2-yl]-1,3-dioxolane (17). Acetonide formation of diol **15** (69 mg, 0.185 mmol), followed by subsequent hydrolysis and elimination were carried out by the same procedure as described for the preparation of **16** to give the corresponding diene **17** (29.7 mg, 58%) as a colorless oil: $[\alpha]^{17}_D$ −121.3 (*c* 2.0, $CHCl_3$); IR ν_{max} 2933, 1219 cm^{-1}; ^1H NMR ($CDCl_3$; 400 MHz) δ 5.68 (1H, dd, J = 9.8 and 3.6 Hz), 5.54 (1H, ddd, J = 9.8, 5.7, and 1.5 Hz), 4.74 (1H, d, J = 1.6 Hz), 4.63 (1H, d, J = 1.6 Hz), 3.91−3.97 (2H, m), 3.72−3.78 (1H, m), 2.21 (1H, d, J = 5.7 Hz), 2.05−2.09 (1H, m), 1.78−1.87 (1H, m), 1.50−1.54 (2H, m), 1.40−1.45 (1H, m), 1.39 (3H, s), 1.33 (3H, s), 0.99 (3H, s), 0.88 (3H, s), 0.79 (3H, d, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$; 100 MHz) δ 149.9, 136.7, 125.5, 108.5, 105.8, 82.2, 64.6, 50.0, 43.7, 40.0, 39.7, 39.2, 29.1, 26.3, 25.3, 24.7, 17.5, 15.6; MS (CI) 277 ($M + 1$)$^+$; HRMS (CI) calcd for $C_{18}H_{28}O_2$ + H 277.2167, found 277.2148.

Trifarienol A (1). A solution of diene **16** (15 mg, 54.3 μmol) in MeOH (2 mL) in the presence of *p*-TsOH (41 mg, 0.217 mmol) was heated at reflux for 12 h. The mixture was treated with water and extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give diol (13.5 mg), which was used in the next reaction without further purification. To a stirred solution of diol obtained above in CH_2Cl_2 (2 mL) was added Crabtree catalyst (4.4 mg, 5.43 μmol), and the resulting mixture was stirred at rt under an atmospheric pressure of hydrogen for 12 h. Removal of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with *n*-hexane−AcOEt (1:1, v/v) furnished trifarienol A (9.6 mg, 74%), whose spectroscopic data, including its specific optical rotation, were comparable to those reported: mp 71−72 °C (lit.[1a] mp 59−60 °C, lit.[2b] mp 82−82.5 °C); $[\alpha]^{18}_D$ +11.5 (*c* 0.9, $CHCl_3$) {lit.[1a] $[\alpha]^{20}_D$ +10.2 (*c* 0.63, $CHCl_3$), lit.[2b] $[\alpha]^{21}_D$ +15 (*c* 0.5, $CHCl_3$)}; MS (EI) 238 (M^+); HRMS (EI) calcd for $C_{15}H_{26}O_2$ 238.1933, found 238.1929.

Trifarienol B (2): Method A: Trifarienol B (16.2 mg, 94%) was synthesized from diene **17** (20 mg, 72.5 μmol) by the same procedure as described for the preparation of trifarienol A. Spectroscopic data of the synthesized compound, including its specific optical rotation, were similar to those reported: mp 99−100 °C (lit.[1a] mp 105−105.5 °C, lit.[2b] mp 108−109.5 °C); $[\alpha]^{18}_D$ −6.0 (*c* 1.5, $CHCl_3$) {lit.[1a] $[\alpha]^{20}_D$ −3.6 (*c* 1.62, $CHCl_3$), lit.[2b] $[\alpha]^{20}_D$ −3.5

(*c* 1.01, $CHCl_3$)}; MS (EI) 238 (M^+); HRMS (EI) calcd for $C_{15}H_{26}O_2$ 238.1933, found 238.1934.

Method B: To a stirred solution of SmI_2 (0.1 M THF solution; 6.8 mL, 0.68 mmol) was added HMPA (0.47 mL, 2.71 mmol) at reflux under Ar. To this mixture was added a solution of ester **15** (41.4 mg, 0.113 mmol) in THF (1 mL), and the resulting mixture was stirred for an additional 5 min. After treatment with saturated aq ammonium chloride, the mixture was extracted with $CHCl_3$. The extract was washed with brine, dried over Na_2SO_4, and concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with *n*-hexane−AcOEt (1:1, v/v) furnished trifarienol B (6.7 mg, 25%), which was identical with the authentic specimen obtained above.

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Supporting Information Available: Complete synthetic details and characterization for new compounds **4**−**8**, as well as copies of ^1H and ^{13}C NMR spectra for compounds **1**, **2**, and **4**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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