Pergamon

Tetrahedron Vol. 50, No. 4, pp. 1093-1104, 1994

0040-4020/94 $6.00+0.00

0040-4020(93)E0081-P

Synthetic Approach to Stemodin (I) —— A Novel Stereocontrolled Construction Of The Stemodane System By The Successive Intramolecular Diels-Alder Reactions

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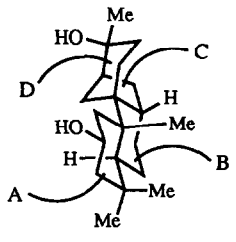
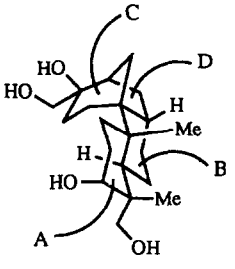
Abstract: The synthesis of the A,B,C and D ring part **17** of diterpene stemodin (**1**) from 1,4-cyclohexanedione monoethylene ketal **8** by use of the successive intramolecular Diels-Alder reactions is described.

Introduction

During the intervening years since 1973, when the structures of stemodin (**1**)[1] and aphidicolin (**2**)[2] were established, numerous total syntheses and synthetic approaches for **1** and **2** were reported[3] so far due to their unique bicyclo[3.2.1]octane moiety, constituting the CD ring system, and antitumor activity.[4] However, with a few exceptions[3] most of the synthetic studies toward the unusual carbon framework envisaged the ABC + D or ABD + C sequence for forming the ring system.



Stemodin (**1**)



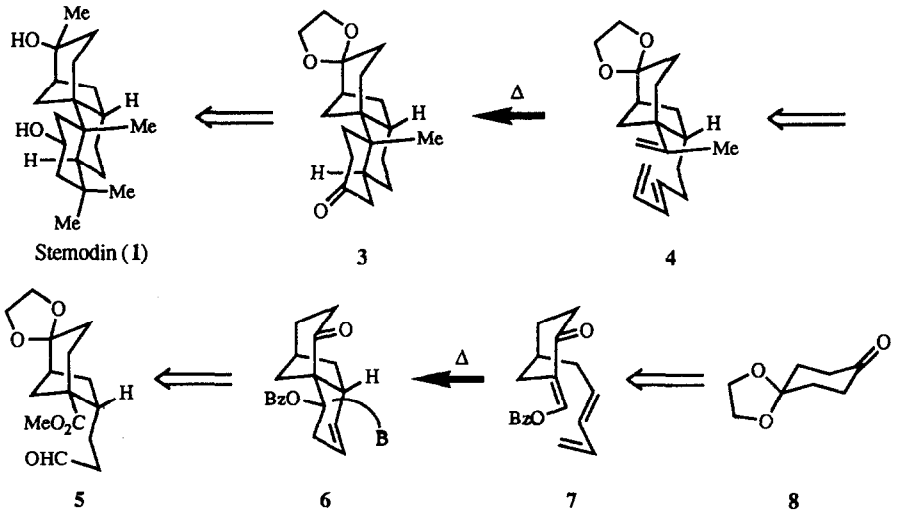
Aphidicolin (**2**)

In our first contribution to this area, we describe an approach based upon a successive intramolecular Diels-Alder reaction strategy. Our approach to stemodin (**1**) is unlike recent ones[3] as it relies on an intramolecular Diels-Alder reaction to construct the spiro fused bicyclo[3.2.1]octane ring system **6** and the tetracyclic carbon skeleton **3**.

Synthetic Plan

For preparing stemodin (**1**) in a highly diastereoselective manner, the novel synthetic strategy depicted in Scheme I was designed in which the successive intramolecular Diels-Alder reactions are ingeniously employed.

Namely, when the initial intramolecular Diels-Alder reaction of the triene **7** obtainable from 1,4-cyclohexanedione monoethylene ketal (**8**) undergoes in a highly stereoselective manner, the spiro fused bicyclo[3.2.1]octane compound **6** can be produced. Regioselective bond cleavage reaction in ring B of **6** followed by introduction of diene and dienophile portions would make the triene **4** available. And finally, the second intramolecular Diels-Alder reaction of **4** could lead to **3**, which would be convertible into stemodin (**1**).

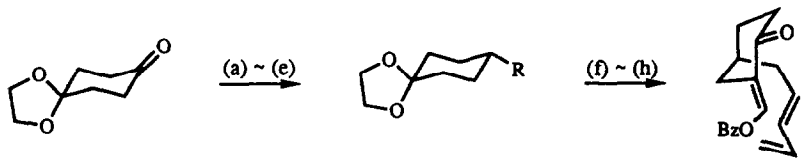


Scheme I

Results and Discussion

In order to explore the feasibility of the designed synthetic strategy, stereocontrolled synthesis of **17** was first examined as a model experiment for the construction of **3**. The requisite triene **7** for the initial intramolecular Diels-Alder reaction was readily prepared as described below. Emmons olefination[5] of **8** followed by catalytic hydrogenation of the resulting α,β-unsaturated ester led quantitatively to the corresponding saturated ester, which was subjected to lithium aluminum hydride (LAH) reduction to furnish the alcohol **9** in 95% yield. Upon treatment of **9** with sulfur trioxide pyridine complex and dimethyl sulfoxide (DMSO) in the presence of triethylamine, the desired aldehyde **10** was produced in 77% yield. Selective preparation of (E)-dienes, developed by Yamamoto[6] {$Ph_2P(O)CH_2CH{=}CH_2$, n-butyllithium, hexamethylphosphoramide (HMPA), tetrahydrofuran (THF)} was applied to **10** to give rise to the diene **11** (61%),[7] which was converted into the triene **7** in three steps. Namely, deketalization of **11** with 10% perchloric acid in THF furnished the corresponding ketone, which was condensed with ethyl formate in the presence of sodium hydride to afford the hydroxymethylene derivative, esterification of which with benzoic anhydride, pyridine, and 4-dimethylaminopyridine (DMAP) provided **7** in 87% yield from **11** (Scheme II).

With the triene **7** in hand, the crucial intramolecular Diels-Alder reaction for the construction of the BCD ring system of stemodin (**1**) was attempted. Some of conditions and yields examined for cyclization of **7** are listed in Table. Control experiments established that the products (**6a** and **6b**) do not interconvert under the

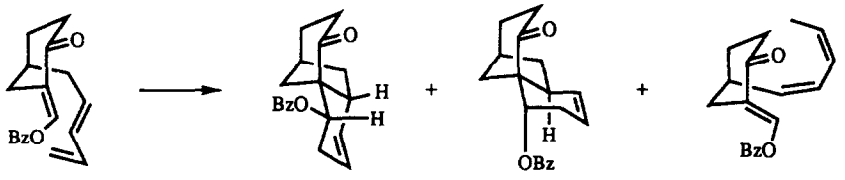


8 **9** R = CH_2CH_2OH **7**
10 R = CH_2CHO
11 R = CH_2

(a) $(EtO)_2P(O)CH_2CO_2Et$, NaH, DME, (b) H_2, 10% Pd-C, EtOAc, (c) LAH, THF, (d) SO_3·Py, DMSO, Et_3N, (e) $Ph_2P(O)CH_2CH{=}CH_2$, ^nBuLi, HMPA, THF, -78 °C → room temperature, (f) 10% $HClO_4$, THF, (g) HCO_2Et, NaH, C_6H_6, (h) Bz_2O, pyridine, DMAP.

Scheme II

reaction conditions. The Lewis acid catalyzed intramolecular Diels-Alder reaction of **7** was first attempted under various conditions, giving the unsatisfactory result even by use of dimethylaluminum chloride as a catalyst.[8] In order to determine the influence of temperature on product ratios, the cycloadditions were investigated over the temperature range from 80 °C to 280 °C. As a result of testing, the thermal reaction in *o*-dichlorobenzene at 280 °C for 3 h proceeded quite nicely to provide **6a** (62%), together with its stereoisomer **6b** and the isomerization product **12**[9] in a ratio of 16 : 1 : 0.5, and the structure of **6a** was determined by X-ray analysis (Figure I).[10]



7 **6a** **6b** **12**

Scheme III

The lack of secondary orbital control (Alder rule) in this cycloaddition is not surprising, since the endo rule is well obeyed at low temperature.[11] An explanation of the preferred formation of **6a** relies on the "concerted but nonsynchronous transition state" hypothesis[12] for unsymmetrical Diels-Alder substrates. In this case, the coefficient of the dienophile LUMO at C-1 is larger than that at C-2.[13] This results in an unsymmetrical transition state in which bond formation between C-1 and C-9 is more advanced than between C-2 and C-6 and in which formation of the nine-membered ring is considered. Therefore, importance of the steric interaction between the olefinic hydrogen and the axial hydrogen in the nine-membered ring transition state **13b**, first partially formed, makes it less favorable than the alternative transition state **13a** which affords the desired product **6a** (Figure II).

Our synthetic efforts were next focused on the ring opening and subsequent introduction of diene and dienophile portions for the second intramolecular Diels-Alder reaction. Toward this end, the carbonyl moiety of **6a** was removed by Wolff-Kishner reduction[14] and the transformation of the resulting alcohol into the ketone **14** was completed by successive catalytic hydrogenation and PCC oxidation in 69% yield from **6a**. Addition of

Table

Conditions and Yields of the Intramolecular Diels-Alder Reaction of Compound **7**

run	additive / conditions[a]	reaction time (h)	isolated yield (%)[b]			
			6a	**6b**	**6a + 6b**	**12**
1	methylene blue / 180 °C	7.5	62	8	70	4
2	$[Me_3CC_6H_2(Me)OH]_2S$ / 180 °C	7.5	54	8	62	–
3	none / 180 °C	6.0	52	7	59	2
4	Me_2AlCl / 180 °C	7.5	46	7	53	2
5	added dropwise to hot system at 180 °C	6.0	36	4	40	–
6	room temperature → 180 °C	7.5	54	6	60	4
7	none / 100 °C	72.0	38	4	42	–
8	none / 280 °C[c]	3.0	62	4	66	2
9	high pressure[d] / 10 °C → 80 °C	48.0	trace	trace	–	–

(a) All thermal cyclizations were performed in sealed tube using *o*-dichlorobenzene as solvent. (b) Yield of products isolated chromatographically. (c) The yield is not neccessarily optimum since run 8 was performed only once. (d) 11-12 kbar.

methyllithium (85.4%) followed by dehydration of the resulting alcohol with thionyl chloride and pyridine provided the corresponding endo olefin, which was immediately treated with a catalytic amount of osmium tetroxide in the presence of 4-methylmorpholine N-oxide to give rise to the diol in 39% yield from above alcohol. Oxidative cleavage of the diol with sodium periodate afforded the desired keto aldehyde, which was subjected to Wittig olefination in the same manner as previously to furnish a 70% yield of the diene **15**. Conversion of **15** into the triene **16** was achieved *via* methylation (88%) with methyllithium in n-hexane followed by dehydration (86%) of the resulting tertiary alcohol in the usual way.

With the efficient synthesis of the triene **16** realized, the stage was now set for the construction of stemodane-type ring system. An intramolecular Diels-Alder reaction was conducted in the presence of methylene blue[15] in toluene at 220 °C for 120 h in a sealed tube to produce the desired tetracyclic compound in 90% yield. The stereochemistry of **17** was deduced from the exo-conformer in the transition state during the thermolysis and the spectral evidence of **18**; due particularly to the similarity of the half-band width ($W_{h/2}$=1.00 Hz) of the angular methyl group with the reported[16] that ($W_{h/2}$=0.91 Hz) of the methyl group possessing two anticoplanar protons at the C_{10} position in *trans*-decalin derivatives. Further, in order to confirm the structure including the stereochemistry of **18**, an alternative synthesis of **18** was carried out starting from **19**.[17] Namely, successive sodium borohydride reduction of **19**, hydrolysis of methoxymethyl group, dithionoimidazolization and free radical reduction with tris(trimethylsilyl)silane in the presence of AIBN provided an 88% yield of **18** from the ketone **19** (Scheme IV). The synthetic substance **18** was identified with an authentic sample in its spectral comparison.

In conclusion, the work described here provides a strategy for the highly diastereocontrolled synthesis of stemodin (1) with repeating intramolecular Diels-Alder reaction. Further efforts will be directed toward fine

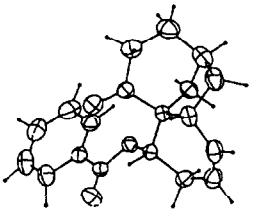


Figure I

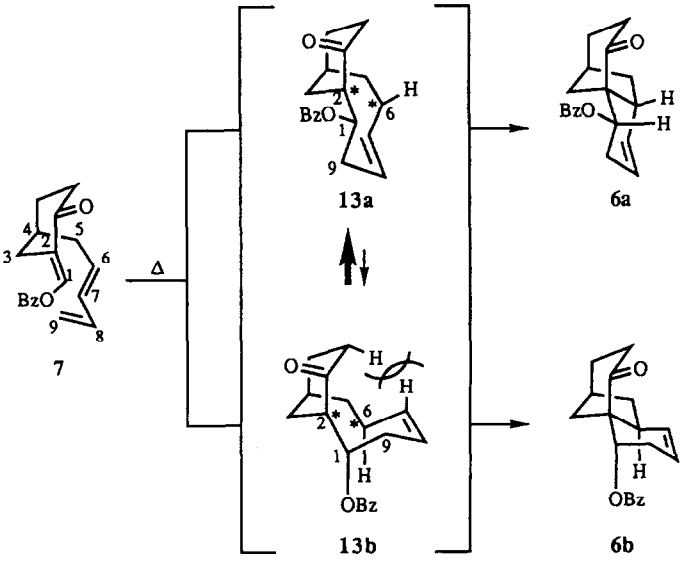
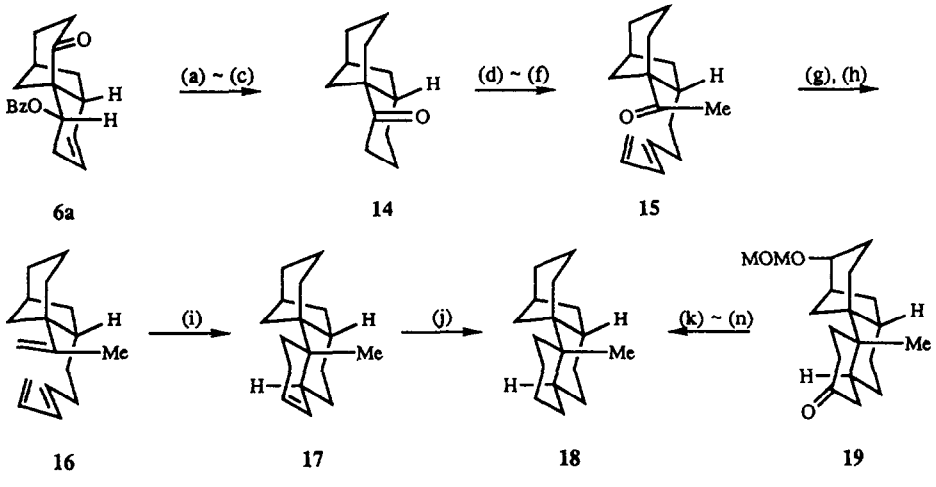


Figure II



(a) $NH_2NH_2{\cdot}H_2O$, KOH, $(HOCH_2CH_2O)_2$, 200 °C, (b) H_2, 10% Pd-C, EtOAc, (c) PCC, SiO_2, CH_2Cl_2, (d) MeLi, n-hexane, -78 °C, (e) $SOCl_2$, pyridine, -20 °C; OsO_4 (catalyst), NMO, MeCN-H_2O(2 :1 v/v), (f) $NaIO_4$, Et_2O-H_2O (1 : 1 v/v); $Ph_2P(O)CH_2CH{=}CH_2$, n-BuLi, HMPA, THF, -78 °C→0 °C, (g) MeLi, n-hexane, -78 °C, (h) $SOCl_2$, pyridine, -20 °C→0 °C, (i) toluene, 220 °C, 120 h, methylene blue, (j) H_2 10% Pd-C, EtOAc, (k) $NaBH_4$, MeOH, (l) AcOH-H_2O (1 : 1 v/v), 60 °C, (m) S=C(imid)$_2$, DMAP, CH_2Cl_2, (n) $(TMS)_3SiH$, AIBN, C_6H_6, reflux.

Scheme IV

tuning this protocol with a view to yield improvements and with synthesis of suitably functionalized tetracyclic compound for completion of the total synthesis.

EXPERIMENTAL SECTION

General: Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled under argon from sodium benzophenone immediately prior to use. Dichloromethane (CH_2Cl_2), pyridine, diisopropylamine, dimethyl sulfoxide (DMSO), toluene and benzene (C_6H_6) were distilled under argon from CaH_2 and used immediately. The concentration of commercially available solution of n-butyllithium in n-hexane was checked by titration using diphenylacetic acid.[18] All reactions involving organometallic reagents or strong bases were conducted under an argon atmosphere in dry flasks. Unless otherwise noted, reagents and solvents were added by syringe, and organic extracts were dried by being stirred over anhydrous $MgSO_4$, filtered through Celite, and concentrated under reduced pressure (aspirator) with the aid of a rotary evaporator. Chromatography was carried out using Merck 60 (230-400 mesh) silica gel according to the procedure described by Still.[19] Reactions and chromatography fractions were analyzed using precoated silica gel 60 F_{254} plates (Merck). Infrared spectra were recorded as films on NaCl plates unless otherwise noted. ^1H NMR spectra were measured as $CDCl_3$ solutions at 500 MHz. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane or relative to internal $CHCl_3$. *J* values are in hertz.

***8-(2-Hydroxyethyl)-1,4-dioxaspiro[4.5]decane* (9)**

To a solution of the Emmons reagent, prepared from 60% sodium hydride (9.0 g, 0.225 mol) and triethyl phosphonoacetate (45.0 mL, 0.226 mol), in DME (200 mL), was added dropwise a DME solution (50 mL) of the ketone **8** (25.0 g, 0.159 mol) at ambient temperature, and the mixture was stirred at room temperature for 11.5 h. After addition of water, the resulting mixture was extracted with Et_2O. The ethereal layer was dried and evaporated to leave an oil, which was chromatographed. Elution with a 5 : 1 mixture of n-hexane-EtOAc gave rise to the α,β-unsaturated ester (36.1 g, 100%) as a colorless oil. IR: 1715 cm^{-1}. ^1H NMR: δ 1.28 (3H, t, *J*=7.0), 1.73-1.81 (4H, m), 2.35-2.41 (2H, m), 2.98-3.04 (2H, m), 3.96-4.00 (4H, m), 4.15 (2H, q, *J*=7.0), 5.67 (1H, t, *J*=0.5). MS m/z: 226 (M^+). Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.52; H, 8.02.

A mixture of the above α,β-unsaturated ester (7.77 g, 34.3 mmol) and 10% palladium-charcoal (0.5 g) in EtOAc (90 mL) was stirred under an atmosphere of hydrogen until absorption of hydrogen had ceased. After filtration, the filtrate was evaporated and the residue was chromatographed. Elution with a 5 : 1 mixture of n-hexane-EtOAc afforded the saturated ester (7.48 g, 95%) as a colorless oil. IR: 1735 cm^{-1}. ^1H NMR: δ 1.26 (3H, t, *J*=7.0), 1.78-1.89 (1H, m), 2.22 (2H, d, *J*=7.0), 3.90-3.97 (4H, m), 4.13 (2H, q, *J*=7.0). MS m/z: 228 (M^+). Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. C, 63.18; H, 8.79.

To a stirred suspension of LAH (3.2 g, 84.3 mmol) in THF (140 mL) was added dropwise a THF solution (10 mL) of the above saturated ester (9.6 g, 42.0 mmol) at ambient temperature, whereupon the mixture was continued to stir for an additional 0.5 h. After successive addition of H_2O (3.5 mL), 15% NaOH solution (3.5 mL) and H_2O (10.5 mL), followed by stirring for 0.5 h, the mixture was filtered through Celite and washed with Et_2O. Evaporation of the combined filtrate and washings gave a residue, which was chromatographed. Elution with a 5 : 4 mixture of n-hexane-EtOAc furnished the alcohol **9** (7.9 g, 100%) as a colorless oil. IR:

3410 cm^{-1}. ^1H NMR: δ 3.68 (2H, br t, *J*=6.5), 3.81-4.07 (4H, m). MS m/z: 186 (M^+). Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.50; H, 9.65.

***8-Formylethyl-1,4-dioxaspiro[4.5]decane* (10)**

To a stirred solution of the alcohol **9** (500 mg, 2.68 mmol) in DMSO (20 mL) was added Et_3N (3.73 mL, 26.8 mmol) at room temperature. After 5 min of stirring , to the mixture was added sulfur trioxide pyridine complex (1.37 g, 8.61 mmol) at ambient temperature, whereupon the resulting mixture was continued to stir at room temperature for 0.5 h. To the mixture was added saturated $NaHCO_3$ solution, then the mixture was extracted with CH_2Cl_2. The organic layers were dried and evaporated to give an oil, which was chromatographed. Elution with a 5 : 1 mixture of n-hexane-EtOAc gave rise to the aldehyde **10** (381 mg, 77%) as a colorless oil. IR: 1719 cm^{-1}. ^1H NMR: δ 1.90-2.02 (1H, m), 2.36 (2H, dd, *J*=6.9 and 1.8), 3.91-3.97 (4H, m), 9.77 (1H, t, *J*=1.8). HRMS: Calcd for $C_{10}H_{17}O_3$ (M^+ +1) 185.1178. Found: 185.1178.

***8-((E)-2,4-Pentadienyl)-1,4-dioxaspiro[4.5]decane* (11)**

To a stirred solution of allyldiphenylphosphine oxide (430 mg, 2.33 mmol) in THF (12 mL) was added HMPA (0.975 mL, 5.6 mmol), then the mixture was cooled to -78 °C. To the above mixture was added dropwise n-butyllithium (1.79 mL, 2.79 mmol) with stirring. After 10 min, to the mixture was added a THF solution (3 mL) of the aldehyde **10** (430 mg, 2.33 mmol) at -78 °C. The mixture was stirred for 0.5 h at 0 °C, then allowed to come to room temperature. Workup in the usual manner followed by chromatography (5 : 1 n-hexane-EtOAc) afforded the diene **11** (295 mg, 61%) as a colorless oil. ^1H NMR: δ 1.33-1.43 (1H, m), 1.94-2.08 (2H, m), 4.96 (1H, br d, *J*=10.5), 5.09 (1H, br d, *J*=17.0), 5.69 (1H, ddd, *J*=15.0, 7.5 and 7.5), 6.03 (1H, dd, *J*=15.0 and 4.5), 6.31 (1H, ddd, *J*=16.5, 10.5 and 10.0). Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96, H, 9.68. Found: C, 75.17; H, 9.59.

***(E)-2-Benzoyloxymethylene-4-((E)-2,4-pentadienyl)cyclohexanone* (7)**

To a stirred solution of the ketal **11** (35.7 g, 0.172 mol) in THF (350 mL) was added 10% $HClO_4$ solution (350 mL) at ambient temperature. After 2 h of stirring, the mixture was extracted with Et_2O. The ethereal phase was washed with brine, saturated $NaHCO_3$ solution and evaporated to give an oil, which was chromatographed. Elution with a 5 : 1 mixture of n-hexane-EtOAc afforded the ketone (28.2 g, 100%) as a colorless oil. IR: 1715 cm^{-1}. ^1H NMR: δ 5.00 (1H, br d, *J*=10.0), 5.12 (1H, br d, *J*=16.5), 5.96 (1H, ddd, *J*=14.5, 7.3 and 7.3), 6.07 (1H, br dd, *J*=14.5 and 10.5), 6.31 (1H, ddd, *J*=16.5, 10.5 and 10.0). Anal. Calcd for $C_{13}H_{20}O_2$: C, 80.44; H, 9.82. Found: C, 80.24; H, 9.82.

To a stirred suspension of sodium hydride (60% dispersion in mineral oil, 2.17 g, 54.3 mmol) in C_6H_6 (70 mL) was added a C_6H_6 solution (30 mL) of the above ketone (6.37 g, 38.8 mmol) at ambient temperature. After 3 h of stirring at room temperature, to the mixture was added ethyl formate (3.45 mL, 42.7 mmol), whereupon the resulting mixture was continued to stir at the same temperature for 12 h. The mixture was diluted with Et_2O and extracted with 15% NaOH solution. The aqueous layer was acidified to pH 1 with 10% H_2SO_4 solution. The resulting solution was extracted with Et_2O, then the ethereal phases were dried and evaporated to give an oil, which was used without purification in the following step.

To a stirred solution of the crude product in CH_2Cl_2 (90 mL) were added DMAP (50 mg, 0.41 mmol) and pyridine (4.49 mL, 55.5 mmol). After 1 h of stirring at room temperature, to the mixture was added a CH_2Cl_2 solution (30 mL) of benzoic anhydride (12.6 g, 55.7 mmol), whereupon it was continued to stir for an

additional 1 h. After removal of the solvent, the residue was chromatographed. Elution with a 20 : 3 mixture of n-hexane-EtOAc gave the triene **7** (10.7 g, 93%) as a colorless oil. IR: 1742 and 1692 cm^{-1}. ^1H NMR: δ 5.08 (1H, br d, *J*=10.0), 5.14 (1H, br d, *J*=17.0), 5.74 (1H, ddd, *J*=15.0, 7.5 and 7.5), 6.13 (1H, dd, *J*=15.0 and 10.0), 6.35 (1H, ddd, *J*=17.0, 10.0 and 10.0), 7.46-7.58 (2H, m), 7.62-7.69 (1H, m), 8.06-8.16 (2H, m), 8.31-8.35 (1H, m). Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.76; H, 6.80.

***rel-(1S,2S,6R,8S)-2-Benzoyloxyticyclo[6.3.1.0^{1,6}]dodec-4-en-11-one* (6a)**

(Run 1) A mixture of the triene **7** (120 mg, 0.41 mmol) and methylene blue (1 mg) in *o*-dichlorobenzene (ODB) (3 mL) was heated at 180 °C for 10 h. After cooling to room temperature, the solvent was removed under reduced pressure to yield crude products, which were chromatographed. Elution with a 10 : 1 mixture of n-hexane-Et_2O gave **6a** (74 mg), **6b** (10 mg, 8%) and **12** (5 mg, 4%) respectively. **6a**: mp 119.5-122.0 °C (n-hexane-CH_2Cl_2). IR ($CHCl_3$): 1710 cm^{-1}. ^1H NMR: δ 5.42-5.54 (2H, m), 5.80 (1H, dd, *J*=10.5 and 6.5), 7.37-7.43 (2H, m), 7.49-7.54 (1H, m), 7.94-8.00 (2H, m). ^{13}C NMR (125 MHz): δ 26.13, 30.95, 32.83, 34.60, 34.79, 37.37, 42.72, 58.20, 69.29, 120.11, 128.23, 129.61, 130.47, 130.83, 132.65, 165.72, 210.19. MS m/z: 296 (M^+). Anal. Calcd for $C_{19}H_{21}O_3$: C, 77.00; H, 6.80. Found: C, 77.18; H, 6.73. **6b**: mp 83.0-84.0 °C (n-hexane-EtOAc). IR ($CHCl_3$): 1719 cm^{-1}. ^1H NMR: δ 5.56 (1H, ddd, *J*=10.0, 3.5 and 3.4), 5.85 (1H, d, *J*=6.5), 5.95 (1H, br dd, *J*=10.0 and 2.0), 7.41-7.48 (2H, m), 7.53-7.59 (1H, m), 8.00-8.06 (2H, m). MS m/z: 296 (M^+). Anal. Calcd for $C_{19}H_{20}C_3$: C, 77.00; H, 6.80. Found: C, 76.71; H, 6.87. **12**: (colorless oil); IR: 1743 and 1695 cm^{-1}. ^1H NMR: δ 1.76 (3H, dd, *J*=3.9 and 2.2), 5.49 (1H, dq, *J*=11.0 and 3.9), 5.71 (1H, dd, *J*=15.2 and 11.0), 6.02 (1H, ddd, *J*=11.0, 11.0 and 2.2), 6.48 (1H, dd, *J*=15.2 and 11.0), 7.48-7.53 (2H, m), 7.62-7.67 (1H, m), 8.09-8.15 (2H, m), 8.36 (1H, m). MS m/z: 296 (M^+). HRMS: Calcd for $C_{19}H_{20}O_3$: 296.1412. Found: 296.1413.

(Run 2) A mixture of the triene **7** (125 mg, 0.422 mmol) and 3-*tert*-butyl-4-hydroxy-5-methylphenyl sulfide (1 mg) in toluene (3 mL) was heated at 180 °C in a sealed stainless steel tube for 7.5 h. After the same workup as (run 1), **6a** (68 mg, 54%) and **6b** (10 mg, 8%) were obtained.

(Run 3) An ODB solution (3 mL) of the triene **7** (126 mg, 0.425 mmol) was heated at 180 °C for 6 h. After the same workup as previously, **6a** (66 mg, 52%), **6b** (9 mg, 7%) and **12** (2 mg, 2%) were obtained.

(Run 4) A mixture of the triene **7** (121 mg, 0.408 mmol) and dimethylaluminum chloride (10 mg, 0.108 mmol) in ODB (3 mL) was heated at 180 °C for 7.5 h. After the same workup as previously, **6a** (55 mg, 46%), **6b** (9mg, 7%) and **12** (2 mg, 2%) were obtained.

(Run 5) To a pre-heated (180 °C) flask was added dropwise an ODB solution (3 mL) of the triene **7** (116 mg, 0.391 mmol) over a period of 10 min. After 6 h of stirring at 180 °C, the solvent was removed under reduced pressure. **6a** (42 mg, 36%) and **6b** (5 mg, 4%) were obtained after the same workup as previously.

(Run 6) An ODB solution (3 mL) of the triene **7** (130 mg, 0.439 mmol) was gradually heated to 180 °C over a period of 1 h, whereupon the mixture was continued to stir at 180 °C for an additional 6.5 h. After the workup as previously, **6a** (65 mg, 50%), **6b** (9 mg, 7%) and **12** (5 mg, 4%) were obtained.

(Run 7) An ODB solution (10 mL) of the triene **7** (100 mg, 0.338 mmol) was heated at 100 °C for 72 h. After the workup as previously, **6a** (38 mg, 38%), **6b** (3 mg, 4%) were obtained.

(Run 8) An ODB solution (30 mL) of the triene **7** (981 mg, 3.341 mmol) was heated at 280 °C in a sealed stainless steel tube for 3 h. After the usual workup as previously, **6a** (608 mg, 62%), **6b** (38 mg, 4%) and **12** (19 mg, 2%) were obtained.

(**Run 9**) A toluene solution (5 mL) of the triene **7** (27 mg, 0.091 mmol) was heated at 80 °C under 10 Katm for 48 h. After the removal of the solvent, the starting material **7** (23 mg) was recovered unchanged. However, TLC analysis of the crude product showed the presence of **6a** and **6b**.

rel-(1R,6S,8S)-tricyclo[6.3.1.0^{1,6}]dodecan-2-one **(14)**

A mixture of the ketone **6a** (1.00 g, 3.378 mmol), potassium hydroxide (1.52 g, 23.026 mmol) and hydrazine hydrate (1.64 ml, 33.809 mmol) in diethylene glycol (20 mL) was refluxed for 2 h, whereupon the excess of hydrazine hydrate was evaporated off. The reaction mixture was further heated at 200 °C for 4 h. After cooling to room temperature, the mixture was diluted with H_2O, then the resulting mixture was extracted with Et_2O. The extract was dried and evaporated to leave an oil, which was chromatographed. Elution with a 10 : 3 mixture of n-hexane-EtOAc gave rise to the alcohol (493 mg, 82%) as an oil. IR ($CHCl_3$): 3650 cm^{-1}. ^1H NMR: δ 1.20-1.30 (2H, m), 1.33-1.41 (2H, m), 1.53-1.65 (4H, m), 1.80-1.90 (2H, m), 1.95-2.05 (1H, m), 2.19-2.25 (1H, m), 2.35-2.39 (1H, br s), 3.63-3.70 (1H, m), 5.34-5.39 (1H, m), 5.42-5.46 (1H, m). MS m/z: 178 (M^+). HRMS: Calcd for $C_{12}H_{18}O$: 178.1358. Found: 178.1354.

A mixture of the above compound (493 mg, 2.770 mmol) and 10% palladium-charcoal (10 mg) in EtOAc (15 mL) was stirred under an atmosphere of hydrogen until absorption of hydrogen had ceased. After filtration, the filtrate was evaporated and the residue was chromatographed. Elution with a 10 : 3 mixture of n-hexane-EtOAc afforded the alcohol (446 mg, 90%) as powders. IR ($CHCl_3$): 3670 cm^{-1}. ^1H NMR: δ 0.93-1.11 (1H, m), 1.15-1.21 (3H, m), 1.26-1.31 (5H, m), 1.50-1.83 (5H, m), 1.84-1.94 (1H, m), 2.21-2.27 (1H, m), 3.38-3.45 (1H, m). MS m/z: 180 (M^+). HRMS: Calcd for $C_{12}H_{20}O$: 180.1514. Found: 180.1507.

To a stirred mixture of PCC (3.08 g, 14.288 mmol) and silica gel (1.5 g) in CH_2Cl_2 (15 mL) was added dropwise a CH_2Cl_2 solution (5 mL) of the above alcohol (444 mg, 2.467 mmol) at ambient temperature. The resulting mixture was continued to stir at the room temperature for 10 h. After dilution with Et_2O, filtration followed by evaporation of the filtrate, gave a residue, which was chromatographed. Elution with a 5 : 1 mixture of n-hexane-EtOAc afforded the ketone **14** (408 mg, 93%) as a colorless oil. IR: 1695 cm^{-1}. ^1H NMR: δ 1.20-1.68 (9H, m), 1.80-1.98 (5H, m), 2.05-2.14 (1H, m), 2.25-2.38 (3H, m). MS m/z: 178 (M^+). HRMS: Calcd for $C_{12}H_{18}O$: 178.1358. Found: 178.1376.

rel-(1R,5S,7S)-1-Acetyl-7-((E)-hexa-3,5-dienyl)-bicyclo[3.2.1]octane **(15)**

To a stirred n-hexane solution (5 mL) of **14** (58 mg, 0.326 mmol) was added dropwise methyllithium (72 mg, 3.273 mmol) at -78 °C, whereupon the mixture was allowed to warm to room temperature over a period of 4 h. Saturated aqueous NH_4Cl solution was added to the above mixture at 0 °C, then the resulting mixture was extracted with Et_2O. The ethereal layer was washed with brine, dried and evaporated to leave an oil which was chromatographed. Elution with a 20 : 3 mixture of n-hexane-EtOAc furnished the alcohol (54 mg, 94%) and the starting material (5 mg). IR: 3450 cm^{-1}. ^1H NMR: δ 1.04-1.73 (16H, m), 1.19 (3H, s), 1.80 (1H, dd, J=7.0 and 4.0), 1.92-1.98 (1H, m), 2.20-2.26 (1H, m). MS m/z: 194 (M^+). HRMS: Calcd for $C_{13}H_{22}O$: 194.1671. Found: 194.1682.

To a stirred solution of the above alcohol (37 mg, 0.191 mmol) in pyridine (4 mL) was added dropwise thionyl chloride (0.116 mL, 1.339 mmol) at -20 °C. After 0.5 h of stirring at the same temperature, the mixture was diluted with Et_2O. The ethereal layer was washed with saturated aqueous $KHSO_4$ solution (thrice), brine, dried and evaporated to give an oil, which was chromatographed. Elution with n-hexane afforded the olefin {^1H NMR: δ 1.66 (3H, br s), 5.36-5.40 (1H, br s)}, which was dissolved in MeCN-H_2O (6 ml; 2 : 1 v/v). Osmium

tetroxide (*ca.* 3 mg) and 4-methylmorpholine N-oxide (152 mg, 1.297 mmol) were added to the above solution at ambient temperature. The resulting mixture was continued to stir at room temperature for 15.5 h under argon. The mixture was diluted with Et_2O, whereupon the resulting mixture was washed with saturated aqueous $Na_2S_2O_3$ solution (thrice), brine, dried and evaporated to give an oil, which was chromatographed. Elution with a 10 : 9 mixture of n-hexane-EtOAc gave rise to the diol (29 mg, 72%) as a colorless oil. IR: 3450 cm^{-1}. ^1H NMR: δ 1.18 (1.5H, s), 1.24 (1.5H, s), 2.14-2.25 (3H, m), 3.50-3.56 (1H, m), 3.66-3.70 (1H, br s). MS m/z: 210 (M^+). HRMS: Calcd for $C_{13}H_{22}O_2$: 210.1620. Found: 210.1626.

A mixture of the above diol (85 mg, 0.405 mmol) and solium periodate (866 mg, 4.05 mmol) in Et_2O-H_2O (9 mL; 2 : 1) was stirred at room temperature for 1 h. The mixture was diluted with H_2O, whereupon the resulting solution was extracted with C_6H_6. The organic layer was dried and evaporated to give an oil, which was chromatographed. Elution with a 20 : 7 mixture of n-hexane-EtOAc afforded the ketone (45 mg, 93%) and the starting material (36 mg). IR: 1700 cm^{-1}. ^1H NMR: δ 2.15 (3H, s), 2.38 (2H, br t, *J*=7.0), 9.98 (1H, t, *J*=1.0).

To a stirred solution of allyldiphenylphosphine oxide (50 mg, 0.229 mmol) in THF (5 mL) was added HMPA (0.05 mL, 0.287 mmol), then the mixture was cooled to -78 °C. To the above mixture was added dropwise n-butyllithium (11 mg, 0.173 mmol) with stirring. After 10 min, to the mixture was added a THF solution (1 mL) of the above aldehyde (24 mg, 0.115 mmol) at -78 °C. The mixture was stirred for 0.5 h at 0 °C then allowed to come to room temperature. Workup in the usual way gave rise to an oil, which was chromatographed. Elution with a 10 : 1 mixture of n-hexane-EtOAc furnished **15** (25 mg, 93%) as a colorless oil. IR: 1700 cm^{-1}. ^1H NMR: δ 2.10 (3H, s), 4.96 (1H, br d, *J*=10), 5.09 (1H, br d, *J*=17.0), 5.64 (1H, ddd, *J*=15.0, 7.5 and 7.5), 6.02 (1H, dd, *J*=15.0 and 10.0), 6.29 (1H, ddd, *J*=17.0, 10.0 and 10.0). MS m/z: 233 (M^+ +1). HRMS: Calcd for $C_{16}H_{25}O$: 233.1906. Found: 233.1890.

***rel-(1R,5S,7S)-7-((E)-Hexa-3,5-dienyl)-1-isopropenyl-bicyclo[3.2.1]octane* (16)**

To a stirred solution of the ketone **15** (18 mg, 0.078 mmol) in hexane (5 mL) was added methyllithium (17 mg, 0.776 mmol) at 0 °C. After 0.5 h of stirring at the same temperature, the mixture was diluted with saturated aqueous NH_4Cl solution. The resulting mixture was extracted with Et_2O, whereupon the ethereal layer was dried and evaporated to give an oil, which was chromatographed. Elution with a 10 : 1 mixture of n-hexane-EtOAc gave rise to the alcohol (17 mg, 86%). IR: 3475 cm^{-1}. ^1H NMR: δ 1.22 (3H, s), 1.27 (3H, s), 4.95 (1H, br d, *J*=10), 5.08 (1H, br d, *J*=17.0), 5.72 (1H, ddd, *J*=15.0, 7.5 and 7.5), 6.05 (1H, dd, *J*=15.0 and 10.0), 6.31 (1H, ddd, *J*=17.0, 10.0 and 10.0). MS m/z: 189 (M^+ -59).

To a stirred solution of the above alcohol (5 mg, 0.020 mmol) in pyridine (3 mL) was added dropwise thionyl chloride (0.035 mL, 0.404 mmol) at -20 °C. After 10 min of stirring at the same temperature, H_2O was added to the mixture at 0 °C, whereupon the resulting mixture was extracted with Et_2O. The ethereal layer was washed with saturated aqueous $KHSO_4$ solution, brine, dried and evapotated to give an oil, which was chromatographed. Elution with n-hexane afforded the triene **16** (4 mg, 86%) as a colorless oil. ^1H NMR: δ 4.65 (1H, br d, *J*=1.8), 4.71 (1H, br d, *J*=1.2), 4.94 (1H, br d, *J*=9.8), 5.08 (1H, br d, *J*=17.1), 5.68 (1H, ddd, *J*=15.0, 7.5 and 7.5), 6.03 (1H, dd, *J*=15.0 and 10.0), 6.30 (1H, ddd, *J*=17.0, 10.0 and 10.0). MS m/z: 230 (M^+). HRMS: Calcd for $C_{17}H_{26}$: 230.2034.

***Trinorstemod-3-ene* (17)**

A mixture of the triene **16** (4.0 mg, 0.0714 mmol) and methylene blue (1 mg) in toluene (2 mL) was heated at 220 °C in a sealed stainless steel tube for 120 h. After cooling to room temperature, the solvent was removed under reduced pressure, whereupon the residue was chromatographed. Elution with n-hexane provided the teracyclic compound **17** (3.6 mg, 90%) as a colorless oil. IR: 1450 cm^{-1}. ^1H NMR: δ 0.82 (3H, s), 5.30-5.70 (2H, m). MS m/z: 230 (M^+). HRMS: Calcd for $C_{17}H_{26}$: 230.2034. Found: 230.2038.

***Trinorstemodane* (18)**

A mixture of the olefin **17** (4.0 mg, 0.0174 mmol) and 10% palladium-charcoal (2 mg) in EtOAc (2 mL) was stirred under an atmosphere of hydrogen until absorption of hydogen had ceased. After filtration, the filtrate was evaporated to give an oil, which was chromatographed. Elution with n-hexane furnished **18** (4 mg, 99%) as a colorless oil. ^1H NMR: δ 0.75-1.80 (25H, m), 0.81 (3H, s). MS m/z: 232 (M^+). HRMS: Calcd for $C_{17}H_{28}$: 232.2191. Found: 232.2187.

19→18

To a stirred solution of **19** (5.0 mg, 0.0163 mmol) in EtOH (2 mL) was added sodium borohydride (5.1 mg, 0.1348 mmol) at 0 °C. After 0.5 h of stirring at the same temperature, the solvent was evaporated to leave a residue, which was dissolved in CH_2Cl_2-H_2O (5 mL; 1/1 v/v). The resulting mixture was extracted with CH_2Cl_2, whereupon the organic layer was washed with brine, dried and evaporated to afford an oil, which was chromatographed. Elution with a 5 : 1 mixture of n-hexane-EtOAc gave rise to the alcohol (4.9 mg, 96%) as a colorless oil. IR: 3380 cm^{-1}. ^1H NMR: δ 0.86 (3H, s), 3.36 (3H, s), 3.47-3.63 (2H, m), 4.65 (2H, dd, J=9.5 and 6.5). MS m/z: 308 (M^+). HRMS: Calcd for $C_{19}H_{32}O_3$: 308.2351. Found: 308.2318.

A mixture of the above alcohol (2.1 mg, 0.0068 mmol) and acetic acid (2 mL) in H_2O (2 mL) was heated at 60 °C for 6 h. After removal of the solvent under reduced pressure, the residue was diluted with H_2O, then the solution was extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous K_2CO_3 solution, brine, dried and evaporated to gave the crude diol, which was used without purification in the next step.

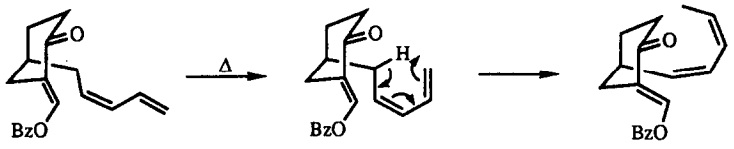
A mixture of the above diol (1.8 mg. 0.0068 mmol), 1,1'-thiocarbonyldiimidazole (4.8 mg, 0.0269 mmol) and DMAP (2.9 mg, 0.0237 mmol) in CH_2Cl_2 (4 ml) was refluxed for 16 h. After removal of the solvent, the residue was chromatographed. Elution with a 1 : 5 mixture of n-hexane-EtOAc provided the dithioimidazoyloxy compound (2.9 mg, 88%) as a colorless oil. IR: 1465, 1390, 1285 and 1218 cm^{-1}. ^1H NMR: δ 1.00 (3H, s), 5.34-5.48 (2H, m), 7.03 (1H, br s), 7.06 (1H, br s), 7.64 (2H, br s), 8.34 (1H, br s), 8.37 (1H, br s). MS m/z: 228 (M^+ -256).

To a degassed solution of the above compound (2.9 mg, 0.0060 mmol) in C_6H_6 (2 mL) was added dropwise a degassed C_6H_6 solution (1 mL) of tris(trimelhylsilyl)silane (0.0057 mL, 0.0179 mmol) and AIBN (0.5 mg, 0.0030 mmol) under reflux. After 1 h of refluxing, the solvent was removed under reduced pressure to give a residue, which was chromatographed. Elution with n-hexane provided **18** (1.4 mg, 100%) along with a small of tris(trimethylsilyl)silane. ^1H NMR: δ 0.75-1.80 (25H, m), 0.81 (3H, s).

References and Notes

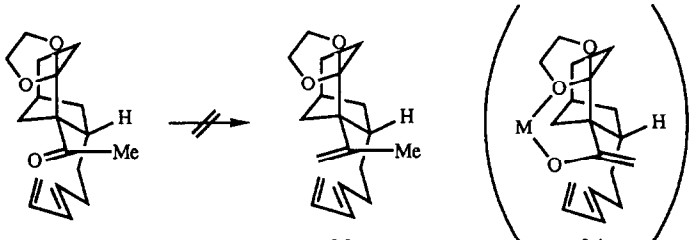
1. Manchand, P. S.; White, D. J.; Wright, H.; Clardy, J. *J. Am. Chem. Soc.*, **1973**, *95*, 2705-2706.
2. Dalziel, W.; Hesp, B.; Stevenson, K. M.; Jarvis, J. A. J. *J. Chem. Soc., Perkin Trans. 1*, **1973**, 2841-2851.

3. Recent formal syntheses of stemodin and aphidicolin: (a) Germanas, J.; Aubert, C.; Vollhardt, K. P. C. *J. Am. Chem. Soc.*, **1991**, *113*, 4006-4007, and refs sited therein. (b) Iwata, C.; Morie, T.; Maezaki, N.; Yamashita, H.; Kuroda, T.; Inoue, T.; Kamei, K.; Imanishi, T.; Tanaka, T.; Kim, S.; Murakami. K. *Abstracts of 32nd Symposium on the Chemistry of Natural Products*, **1990**, 455-462.
4. Bucknall, R. A.; Moores, H.; Simms, R.; Hesp, B. *Antimicrob. Agents Chemother.*, **1973**, *4*, 294-298.
5. Wadsworth, W. S. *Org, React.*, **1977**, *25*, 73-253.
6. Ukai, J.; Ikeda, Y.; Ikeda, N.; Yamamoto, H. *Tetrahedron Lett.*, **1983**, *24*, 4029-4032.
7. E/Z ratio (34 : 1) was determined after the initial intramolecular Diels-Alder reaction (**7** → **6a+6b+12**).
8. Roush, W. R.; Peseckis, S. M. *J. Am. Chem. Soc.*, **1981**, *103*, 6696-6704.
9. The compound **12** was obtained through 1,5-sigmatropic rearrangement of **20** under the thermal conditions.



20 **21** **12**

10. The compound **6a** crystallizes in the monoclinic P2 $_{1/n}$ space group with a=10.743 (1), b=12.322 (3), c=12.108 (1) Å, α=90.0, β=90.719 (12), γ=90.0 °, V=1602.8 (4), and Z=4. The final coordinates were solved by direct methods and refined by block diagonal least squares methods with R=0.071, Rw=0.062. Final crystallographic coordinates are deposited in Cambridge Crystallographic Data Centre.
11. (a) Sauer, J.; Sustmann, R. *Angew. Chem. Int. Ed. Engl.*, **1980**, *19*, 779-807. (b) Ciganek, E. *Org. React.*, **1984**, *32*, 1-374, and refs cited therein.
12. Semi-empirical calculations: Dewar, M. J. S.; Olivella, S.; Stewart, J. J. P. *J. Am. Chem. Soc.*, **1986**, *108*, 5771-5779, and refs cited therein.
Recent reviews: (a) Roush, W. R. "Comprehensive Organic Synthesis", Pergamon Press, Oxford, New York, Seoul, Tokyo, **1991**, *5*, 513-550, and refs cited therein. (b) Roush, W. R. "Advances in Cycloaddition", JAI Press Inc, Greenwich, Connecticut, London, England, **1990**, *2*, 91-146.
Recent examples: (a) Toyota, M.; Wada, Y; Fukumoto, K. *Heterocycles*, **1993**, *35*, 111-114. (b) Hall, D. G.; Müller, R.; Deslongchamps, P. *Tetrahedron Lett.*, **1992**, *33*, 5521-5224. (c) Toyota, M.; Seishi, T. Yokoyama, M.; Fukumoto, K.; Kabuto, C. *Tetrahedron Lett.*, **1992**, *33*, 4581-4584, and refs cited therein.
13. Fleming, I. "Frontier Orbitals and Organic Chemical Reactions", Wiley, New York, 1976.
14. All attempts (a: $Ph_3P^+MeBr^-$, n-BuLi; b: CH_2Br_2, Zn, $TiCl_4$; c: MeLi, n-hexane the $SOCl_2$, pyridine) in the conversion (**22**→**23**) led to failure, and the starting material **22** was recovered unchanged due probably to the metal chelated imtermediate **24**.



22 **23** **24**

15. (a) Taber, D. F.; Saleh, S. A. *J. Am. Chem. Soc.*, **1980**, *102*, 5085-5088. (b) Taber, D. F.; Campbell, C.; Gunn, B. P.; Chiu, I.-C. *Tetrahedron Lett.*, **1981**, *22*, 5141-5144.
16. Williamson, K. L.; Howell, T.; Spencer, T. A. *J. Am. Chem. Soc.*, **1966**, *88*, 325-334.
17. The compound **19** was synthesized by the different procedure and successful transformation of **19** into the known compound definitely comfirmed **19**'s stereochemistry. Toyota, M.; Seishi, T.; Fukumoto, K. *Tetrahedron Lett.*, **1993**, 34, 5947-5950.
18. Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.*, **1976**, *41*, 1879-1880.
19. Still, W. C.; Kahn, M.; Mitra, A. *J. Org, Chem.*, **1978**, *43*, 2923-2925.

(*Received in Japan* 4 *October* 1993; *accepted* 1 *November* 1993)