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Stemodin Synthesis (II) —— Highly Diastereoselective Formal Total Synthesis of (±)-Stemodin *via* Pd^{2+}-Promoted Cycloalkenylation Reaction

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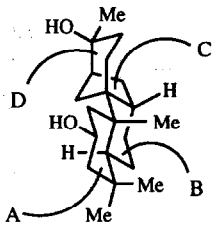
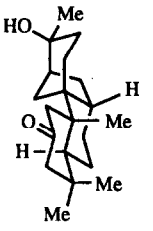
Abstract: Diastereoface-selective Pd^{2+}-promoted cycloalkenylation reaction {**22**→**24**} has been employed as the key step for a conceptually new and highly diastereocontrolled formal total synthesis of (±)-stemodin (**1**). Interestingly, the synthetic intermediates (**12**) and its stereoisomer (**29**) exhibited strong cytotoxicity.

Introduction

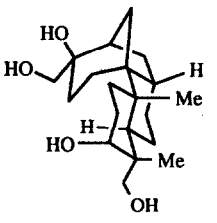
The rare littoral plant *Stemodia maritima* L (Scrophulariaceae), obtainable from the Palisadoes peninsula of Jamaica, produces an unusual tetracyclic diterpene stemodin (**1**) which was isolated and characterized by White and co-workers.[1] The unique structure of **1**, established by spectral analyses and by a single-crystal X-ray analysis of the congener, stemodinone (**2**),[1] was found to bear a close resemblance to that of the antiviral and antitumor[2] fungal metabolite aphidicolin (**3**),[3] isolated from *Cephalosporium aphidicola*. Little is known about the substantial biological activity of stemodin (**1**) itself, however, the unique bicyclo[3.2.1]octane moiety, constituting its CD ring system, has provided considerable impetus for the development of new synthetic strategies in the elaboration of stemodane family.[4]



Stemodin (**1**)



Stemodinone (**2**)



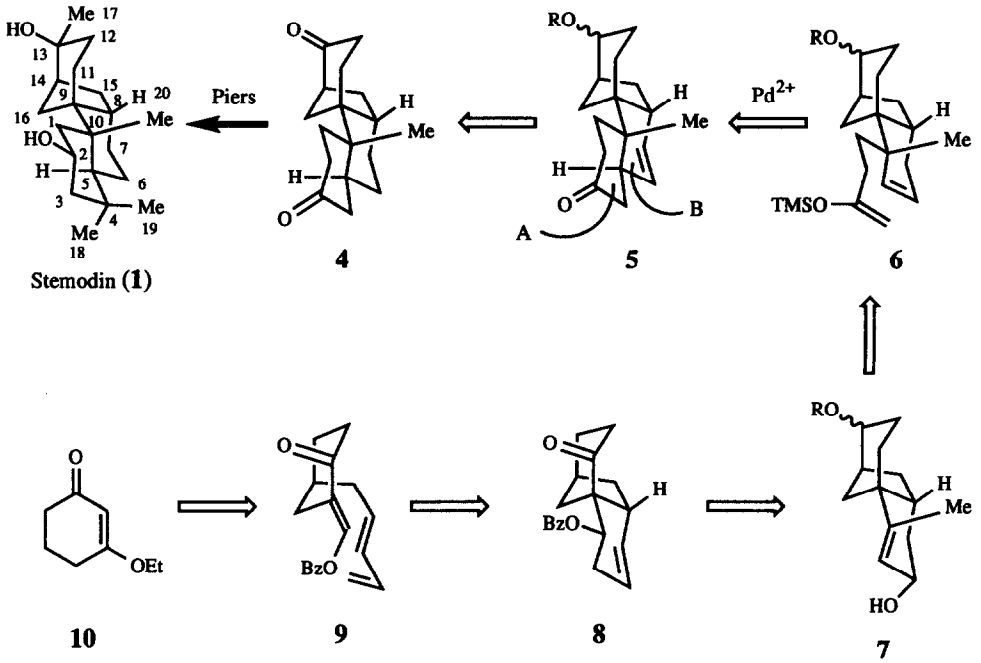
Aphidicolin (**3**)

In a preliminary communication, we outlined our synthetic approach to stemodin (**1**) by the successive intramolecular Diels-Alder reactions in a model system.[4b] After experimentation, however, it was found that the diastereoselective construction of AB *trans* ring juncture of **1** can be successfully achieved using Pd^{2+}-promoted cycloalkenylation reaction under mild conditions instead of the [4+2] cycloaddtion. In this paper we would like to describe the details of the formal total synthesis of (±)-stemodin (**1**).

In addition, in order to find out novel antitumor agents which seem to rival or surpass aphidicolin (**3**), topological relative of **1**, in term of biological promise, the selected synthetic intermediates were screened for cytotoxicity activity against murine lymphoma L1210 cells and against the human epidermoid carcinoma KB cells.

Synthetic Plan

Our basic strategy is outlined in **Scheme I**. Since the diketone (**4**) has already been converted to the natural product (**1**) by Piers and co-workers,[4f] the synthesis of **4** completes the task. The compound (**4**) was envisaged to derive from the olefinic ketone (**5**). The heart of this plan is the diastereoselective formation of **5**, and the establishment of the critical AB *trans* ring juncture, by diastereoface-selective Pd^{2+}-promoted cycloalkenylation reaciton of the olefinic silyl enol ether (**6**). Access to **6** was expected *via* a [3,3]sigmatropic rearrangement reaction of a vinyl enol ether derived from the allylic alcohol (**7**). 1,3-Transcarbonylation reaction and functionalization of the ketone (**8**), obtainable from the triene (**9**) using an intramolecular Diels-Alder reaction, would afford **7**. Finally, regioselective introduction of diene and dienophile portions into the enone (**10**) was expected to give rise to **9**.



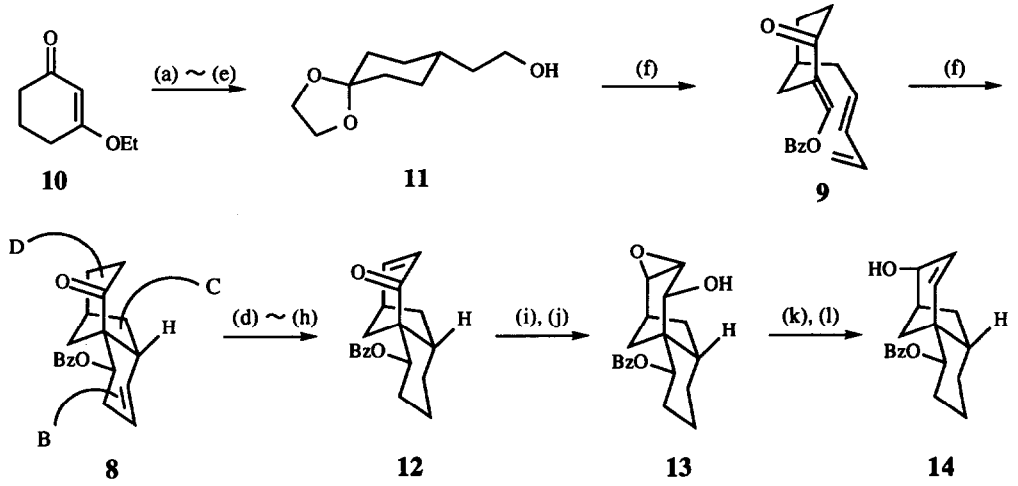
Scheme I

Results and Discussion

In an earlier study,[4b] we were able to demonstrate that the intramolecular Diels-Alder reaction (**9**→**8**) for the construction of BCD ring system of stemodin (**1**) provided a 6 : 1 ratio of diastereomers with the major isomer being formed through "*concerted but nonsynchronous*" transition state.[4b,5] After considerable experimentations with a variety of reaction conditions, the thermolysis at 280 °C proved to be uniquely effective. Optimum conditions involved treatment of the triene (**9**) in *o*-dichlorobenzene at 280 °C for 3 h to provide the tricyclic ketone (**8**) in 62% yield together with its stereoisomer in a ratio of 16 : 1.

Having firmly established an efficient methodology to construct BCD ring system of stemodin (**1**), our synthetic efforts were next focused on the improvement of the previous synthetic route[4b] to get the alcohol (**11**).

The prohibitive cost of commercial 1,4-cyclohexanedione monoethylene ketal caused us to examine the various methods for its preparation. Of these, Stork's procedure[6] was notably effective and provided for the ready acquisition of large amounts of **11** from inexpensive starting material (**10**). Namely, alkylation of 3-ethoxy-2-cyclohexen-1-one (**10**) under the kinetically controlled conditions (LDA, HMPA, THF, -45 °C) with ethyl bromoacetate afforded, in 97% yield, the desired monoalkylated product, which was smoothly elaborated to **11** by sequential reduction with LAH in THF, acidic treatment (3% HCl, THF), hydrogenation in the presence of 10% palladium-charcoal, and ketalization (ethylene glycol, TsOH, benzene, reflux) in 98% overall yield. The transformation of **11** into the tricyclic ketone (**8**) *via* the triene (**9**) using intramolecular Diels-Alder reaciton was accomplished in the same way as previously.[4b] The next hurdle to be surmounted was 1,3-transposition reaction of the carbonyl group in **8**. After numerous attempts[7] an approach by radical mediated epoxide fragmentation reaction of the thionoimidazolide of the epoxy alcohol (**13**) was found to give rise to the desired product in good yield. This procedure proved significantly more amenable to scale up than alternative methods that utilize Wharton process.[8] Catalytic hydrogenation of **8** in the presence of 10% palladium-charcoal led to the corresponding ketone (89%), which was subjected to bromination reaction (pyridinium bromide perbromide, acetic acid, room temperature) followed by dehydrobromination of the resulting α-bromo ketone with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in THF under reflux to furnish the enone (**12**) in 74% yield from **8**. Epoxidation of **12** with 30% hydrogen peroxide and 2.5% NaOH in methanol was next conducted to give the epoxy ketone (88%), which was converted into the epoxy alcohol (**13**) after sodium borohydride reduction in the presence of cerium (III) chloride heptahydrate (94%). After treatment of **13** with 1,1'-thiocarbonyldiimidazole and 4-dimethylaminopyridine (DMAP) in dichloromethane, the corresponding thioimidazolide, obtained in 88% yield, was allowed to react with tributyltin hydride in the presence of 2,2'-azobisisobutyronitrile (AIBN) in benzene under reflux, giving the allylic alcohol (**14**) in 79% yield (**Scheme II**).

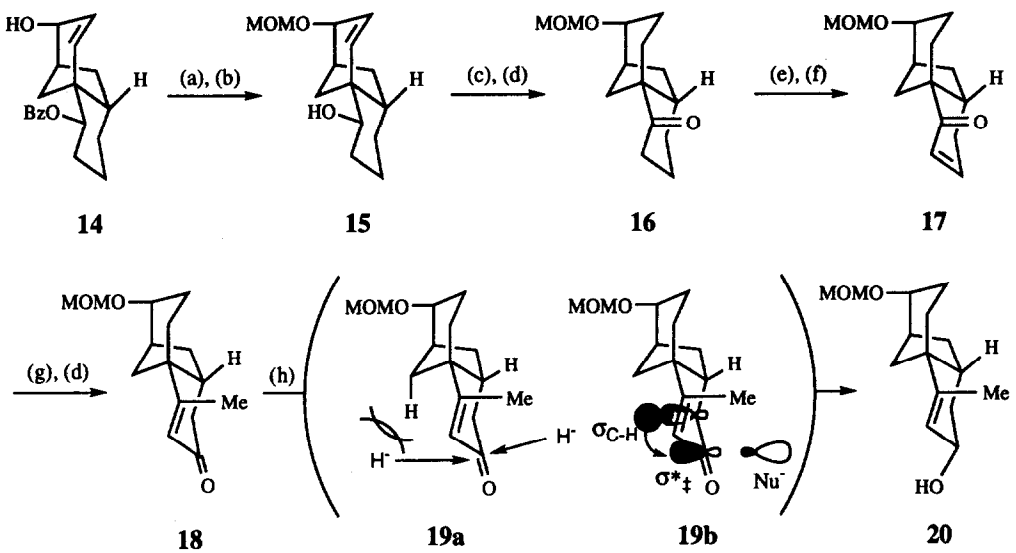


(a) LDA, THF, -78 °C; $BrCH_2CO_2Et$, -45 °C, (b) LAH, THF, (c) 1N HCl, THF, (d) H_2, 10% Pd-C, EtOAc, (e) $HOCH_2CH_2OH$, TsOH, C_6H_6, reflux, (f) ref. 4b, (g) $C_5H_5N^+HBr_3^-$, AcOH, (h) DBU, C_6H_6, reflux, (i) 30% H_2O_2, 2.5% NaOH, MeOH, (j) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, (k) $(Imid)_2C=S$, DMAP, CH_2Cl_2, (l) n-Bu_3SnH, AIBN, C_6H_6, reflux

Scheme II

With convenient access to **14** secure, we then examined on the synthesis of the allylic alcohol (**20**). Toward this end, the hydroxyl group of **14** was protected with chloromethyl methyl ether and diisopropylethylamine, and the transformation of the resulting MOM ether into the alcohol (**15**) was completed by hydrolysis with lithium hydroxide monohydrate in 85% yield form **14**. Hydrogenation (10% palladium-charcoal, EtOAc) of **15** followed by PCC oxidation in the presence of sodium acetate afforded the ketone (**16**) in 95% yield. Dehydrogenation of **16** was accomplished by a selenenylation / selenoxide elimination procedure.[9] Careful temperature control during the selenenylation reaction helped to minimize the formation of diselenide by-product. Exposure of the resulting selenide to 30% hydrogen peroxide, followed by addition of sodium hydrogen carbonate, provided the enone (**17**) in 55% yield. In order to construct **18**, successive methylation (MeLi, n-hexane, -78 °C) and PCC oxidation were attempted, proceeding nicely to provide the enone (**18**) in 69% yield.

All systems were now ready for the all-important stereoselective introduction of a carbon unit to generate A ring of stemodin (**1**). Of particular note was the highly stereoselective 1,2-reduction of the enone (**18**) with diisobutylaluminum hydride at -78 °C in dichloromethane. The high preference for a hydride ion to add to **18** from *re*-face can be explained by both the steric interaction between the equatorial hydrogen and nucleophile, and the "Cieplak" effect by hyperconjugative stabilization (or electron delocalization) of neighboring group electrons into the σ*-orbital of the incipient carbon-nucleophile bond (**Scheme III**).[10]



(a) MOMCl, $^{i}Pr_2NEt$, $ClCH_2CH_2Cl$, (b) $LiOH{\cdot}H_2O$, MeOH, H_2O, (c) H_2, 10% Pd-C, EtOAc, (d) PCC, NaOAc, Florisil®, CH_2Cl_2, (e) LDA, THF, -78 °C; PhSeBr, (f) 30% H_2O_2, THF, $NaHCO_3$, (g) MeLi, n-hexane, -78 °C, (h) DIBAH, CH_2Cl_2, -78 °C

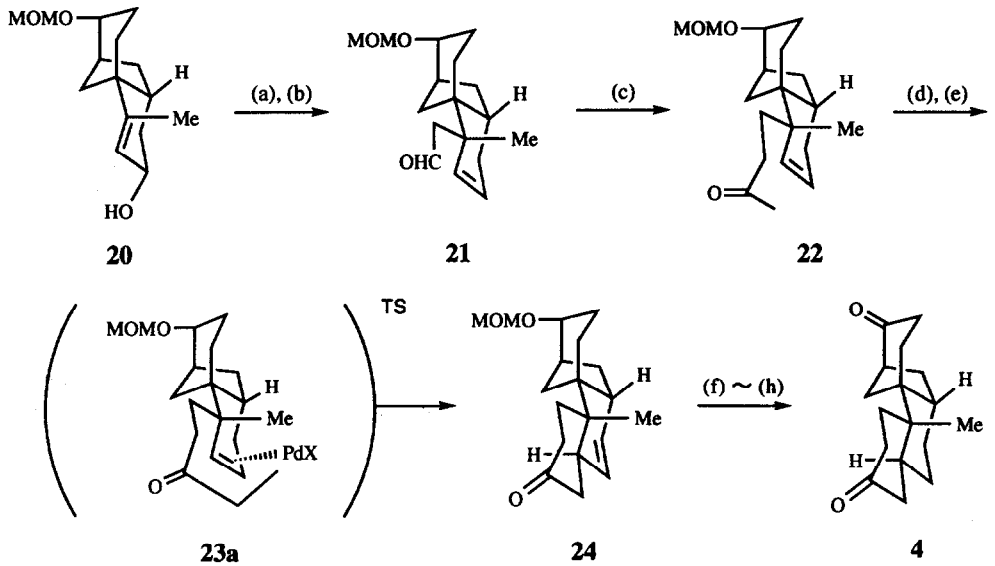
Scheme III

With **20** in hand, we turned our attention to the sigmatropic rearrangement of vinyl enol ether of the compound (**20**). First of all, the accelerating influence of water as a solvent on the rate of the Claisen rearrangement was tested.[11] However, our material was unfit to aqueous solvent system such as water-pyridine (3 : 1). In an attempt to optimize this step, thermal Claisen rearrangement[4d,12] of vinyl enol ether of **20** was

conducted at 220 °C for 52 h to give rise to the aldehyde (**21**) in 91% yield. Chain extension was next accomplished by sequential Wittig-like olefination[13] ($Ph_2P(O)CH(OMe)Me$, LDA, HMPA, THF) and acidic treatment (2.5 % $HClO_4$, THF) (2 steps : 67%).

With the efficient synthesis of the highly functionalized ketone (**22**) realized, the stage was now set for the completion of the synthesis. Although the Pd^{2+}-promoted cycloalkenylation reaction[14] of an olefinic silyl enol ether is a powerful strategy for construction of polycyclic system, little is known about successful application of the above reaction to biologically active natural product syntheses.[15] Careful consideration of molecular model of the compound (**22**) suggested that **22** was an attractive progenitor of the ketone (**24**) since diastereoface-selective Pd^{2+}-promoted cycloalkenylation reaction of the TMS enol ether of **22** from the less hindered face would set the stereochemistry required for stemodin synthesis. As expected, upon treatment of the silyl enol ether of **22** with palladium acetate in acetonitrile, the desired ketone (**24**) was produced in 56% yield, presumably through the intermediacy of the alkylpalladium (II) complex (**23a**).[16]

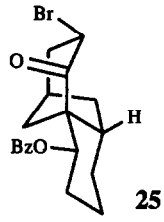
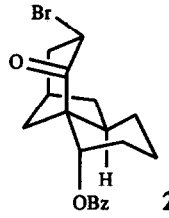
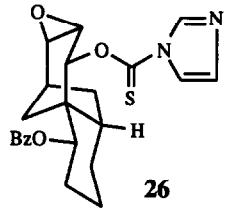
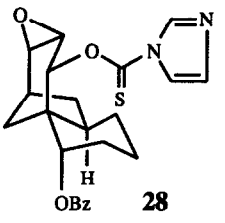
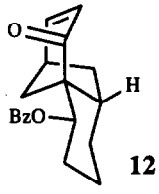
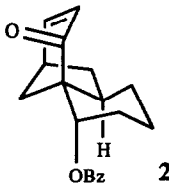
Finally, consecutive catalytic hydrogenation (10% palladium-charcoal, EtOAc : 65%), deprotection (50% acetic acid, 65 °C : 58%) and PCC oxidation (90%) provided the diketone (**4**), which displayed spectral properties identical with those reported by Piers and co-workers in a total synthesis of stemodin (**1**),[4f] thus completing a formal synthesis of the latter.



(a) CH_2=CHOEt, $Hg(OAc)_2$, (b) 220 °C, toluene, (c) $Ph_2P(O)CH(OMe)Me$, LDA, HMPA, THF, (d) LDA, THF, -78 °C; TMSCl, (e) $Pd(OAc)_2$, MeCN, r.t. → 45 °C, (f) H_2, 10% Pd-C, EtOAc, (g) aq. AcOH, 65 °C, (h) PCC, Florisil®, CH_2Cl_2

Scheme IV

Our interest in exploiting this chemistry further was heightened upon finding that the following synthetic intermediates such as **12**, **25**, **26**, **27**,[17] **28**[17] and **29**[17] exhibited cytotoxicities against L1210 murine leukemia cells with IC_{50} values of 0.019, 0.18, 0.27, 2.6, 0.13 and 0.02 μg/mL and KB human epidermoid carcinoma cells with those of 0.027, 0.26, 2.7, 4.2, 0.23 and 0.02 μg/mL *in vitro*, respectively.

Compound	L1210	KB	Compound	L1210	KB
 **25**	0.18	0.26	 **27**	2.6	4.2
 **26**	0.27	2.7	 **28**	0.13	0.23
 **12**	0.019	0.027	 **29**	0.02	0.02

IC_{50} (L1210 and KB) (μg/ml)

Table Cytotoxicity of the synthetic intermediates (**12**, **25**, **26**, **27**, **28**, and **29**).

In conclusion, a new and highly diastereocontrolled route for the synthesis of stemodin (**1**) has been developed. Our methodology based upon diastereoface-selective Pd^{2+}-promoted cycloalkenylation reaction should prove an efficient tool in the synthesis of other complex diterpene systems, such as stemodinone (**2**)[1] and maritimol.[4a]

Experimental Section

General: Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) was distilled under argon from sodium benzophenone immediately prior to use. Dichloromethane (CH_2Cl_2), pyridine, acetonitrile (MeCN), hexamethylphosphoric triamide (HMPA), benzene (C_6H_6), toluene, dimethyl sulfoxide (DMSO) and diisopropylamine were distilled under argon from CaH_2 and used immediately. The concentration of commercially available n-butyllithium in n-hexane was checked by titration using diphenylacetic acid.[18] All reactions involving organometallic reagents or strong bases (e.g. LDA) 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 300 or 500 MHz. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane or relative internal $CHCl_3$. *J* values are in hertz. Since all synthetic products were sufficiently pure by 300 or 500 MHz ^1H NMR spectral analyses, they were directly subjected to *in vitro* cytotoxicity assay.

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

To a stirred solution of LDA, prepared from diisopropylamine (2.5 mL, 17.87 mmol) and n-butyllithium (10% solution in n-hexane, 11.46 mL, 17.87 mmol) in THF (30 mL), at -78 °C were added dropwise HMPA (2.60 mL, 14.90 mmol) and 3-ethoxy-2-cyclohexen-1-one (2.0 mL, 13.76 mmol), and the mixture was then allowed to warm to -45 °C. After 0.5 h of stirring, the mixture was re-cooled to -78 °C, whereupon ethyl bromoacetate (1.7 mL, 15.33 mmol) was added to the above mixture. After 5 min, the resulting mixture was allowed to warm to -45 °C. The mixture was continued to stir at the same temperature for 1 h, and then quenched with saturated NH_4Cl solution (50 mL). The resulting solution was extracted with Et_2O (2 × 50 mL). The ethereal layers were washed with brine, dried and evaporated to leave an oil, which was chromatographed. Elution with a 2 : 1 mixture of n-hexane - EtOAc gave the ester (3.0 g, 97%) as a colorless oil IR: 1720 and 1650 cm^{-1}. ^1H NMR (300 MHz): δ 1.27 (3H, t, *J*=7.3), 1.37 (3H, t, *J*=7.0), 1.70 - 1.87 (1H, m), 2.04 - 2.16 (1H, m), 2.28 (1H, dd, *J*=16.5 and 7.5), 2.39 (1H, ddd, *J*=17.5, 5.0 and 3.0), 2.50 - 2.64 (1H, m), 2.67 - 2.79 (1H, m), 2.93 (1H, dd, *J*=16.5 and 5.0), 3.82 - 3.98 (2H, m), 4.10 - 4.21 (2H, m), 5.35 (1H, d, *J*=1.5). HRMS: calcd for $C_{12}H_{18}O_4$ 226.1205, found 226.1193.

To a stirred suspension of LAH (0.30 g, 7.91 mmol) in THF (10 mL) was added dropwise a THF solution (5 mL) of the above ester (0.30 g, 1.33 mmol) at ambient temperature, and the mixture was stirred at room temperature for 0.5 h. After successive addition of H_2O (0.3 mL), 15% NaOH solution (0.3 mL), and H_2O (0.9 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 dissolved in THF (10 mL). To the solution was added 3% HCl solution (2 mL) at ambient temperature. After 5 min of stirring, the solution was neutralized with saturated $NaHCO_3$ solution at 0 °C, then the resulting mixture was extracted with EtOAc (2 × 20 mL). The organic layers were washed with brine, dried and evaporated to give an oil, which was used without purification in the following step.

A mixture of the above product and 10% Pd-C (5 mg) in EtOAc (5 mL) was stirred at room temperature under a hydrogen atmosphere. After 2 h of stirring, the catalyst was removed through Celite, and the filtrate was concentrated to give rise to an oil.

A solution of the above ketone, ethylene glycol (5 mL, 89.66 mmol) and toluene-*p*-sulfonic acid (3 mg) in C_6H_6 (10 mL) was refluxed under a Dean-Stark water separator for 3 h. The solution was cooled to room temperature and the solvent was removed under reduced pressure. The residue was taken up in CH_2Cl_2 (10 mL) and washed with saturated $NaHCO_3$ solution (2 × 30 mL) and brine (20 mL). The organic phases were dried and evaporated to afford an oil. Chromatography (elution with a 10 : 3 mixture of n-hexane - EtOAc) gave the alcohol (11) (168 mg, 98%) as a colorless oil. IR: 3410 cm^{-1}. ^1H NMR (500 MHz): δ 3.68 (2H, br t, *J*=6.5), 3.81 - 4.07 (4H, m). *Anal.* Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.50; H, 9.65.

***(1S*,2S*,6S*,8S*)-2-Benzoyloxytricyclo[6.3.1.0^{1,6}]dodec-9-en-11-one* (12)**

A mixture of the olefin (**8**) (7.00 g, 23.4 mmol) and 10% palladium-charcoal (0.5 g) in EtOAc (70 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 : 1 mixture of n-hexane-EtOAc afforded the ketone (6.24 g, 89%) as needles, mp 110-113 °C. IR ($CHCl_3$): 1718 cm^{-1}. ^1H NMR (500 MHz): δ 5.83 (1H, dd, *J*=11.0 and 4.2), 7.37 - 7.43 (2H, m), 7.49 - 7.54 (1H, m), 7.94 - 7.99 (2H, m). *Anal.* Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.42; H, 7.40.

To a stirred solution of the above ketone (4.17 g, 14.0 mmol) in acetic acid (40 mL) was added pyridinium bromide perbromide (4.48 g, 14.0 mmol) at ambient temperature, whereupon it was continued to stir at room temperature for an additional 1 h. The reaction solution was neutralized with saturated $NaHCO_3$ solution at 0 °C, then the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The organic layers were washed with saturated $KHSO_4$ solution, brine, dried and evaporated to leave a crude bromide. Chromatography (elution with a 5 : 1 mixture of n-hexane - EtOAc) gave the bromide (**25**) (4.63 g, 88%) as needles, mp 153-157 °C. IR ($CHCl_3$): 1715 cm^{-1}. ^1H NMR (500 MHz): δ 4.71 (1H, dd, *J*=11.5 and 8.1), 5.81 (1H, dd, *J*=10.6 and 5.2), 7.38 - 7.44 (2H, m), 7.50 - 7.55 (1H, m), 7.91 - 8.00 (2H, m). *Anal.* Calcd for $C_{19}H_{21}BrO_3$: C, 60.49; H, 5.61; Br, 21.18. Found: C, 60.39; H, 5.63; Br, 21.25.

To a stirred solution of the above α-bromoketone (**25**) (4.59 g, 12.2 mmol) in C_6H_6 (50 mL) was added DBU (18.2 mL, 122 mmol) at ambient temperature, whereupon the mixture was refluxed for 8.5 h. After cooling to room temperature, the mixture was poured into brine (100 mL). Extraction with Et_2O (2 × 100 mL), drying of the combined organic layers, and evaporation of the solvent gave a crude material, which was chromatographed. Elution with a 5 : 1 mixture of n-hexane - EtOAc afforded the enone (**12**) (3.05 g, 85%) as needles, mp 146.0 - 148.0 °C. IR ($CHCl_3$): 1712 and 1662 cm^{-1}. ^1H NMR (500 MHz): δ 5.91 (1H, d, *J*=9.2), 6.08 (1H, dd, *J*=10.8 and 5.4), 7.36 - 7.48 (3H, m), 7.48 - 7.56 (1H, m), 7.92 - 7.99 (2H, m). *Anal.* Calcd for $C_{19}H_{20}O_3$: C, 77.0; H, 6.80. Found: C, 77.06; H, 7.02.

(1S*,2S*,6S*,8S*,9R*,10R*,11R*)-2-Benzoyloxy-9,10-epoxytricyclo[6.3.1.0^{1,6}]dodecan-11-ol (**13**)

To a stirred solution of the enone (**12**) (2.98 g, 10.1 mmol) in MeOH (120 mL) were added 30% H_2O_2 solution (3.08 mL, 30.3 mmol) and 2.5% NaOH solution (10 mL) at room temperature, whereupon it was continued to stir at the same temperature for an additional 0.5 h. The mixture was diluted with H_2O (50 mL) and extracted with EtOAc (3 × 50 mL). The organic phases were washed with brine, dried and evaporated to leave a crude material. Chromatography (elution with a 5 : 1 mixture of n-hexane - EtOAc) gave rise to the epoxy ketone (2.75 g, 88%) as needles, mp 152 - 153 °C. IR ($CHCl_3$): 1708 cm^{-1}. ^1H NMR (500 MHz): δ 3.23 (1H, d, *J*=4.0), 3.51 (1H, dd, *J*=4.0 and 4.0), 5.88 (1H, dd, *J*=11.0 and 5.1), 7.38 - 7.45 (2H, m), 7.50 - 7.56 (1H, m), 7.94 - 8.00 (2H, m). HRMS: calcd for $C_{19}H_{20}O_4$ 312.1362, found 312.1357.

To a stirred solution of the above epoxy ketone (120 mg, 0.385 mmol) and $CeCl_3 \cdot 7H_2O$ (172 mg, 0.462 mmol) in MeOH (5 mL) was added $NaBH_4$ (total 17.5 mg, 0.462 mmol) in *ca.* 6 mg portions at 0 °C over a period of 3 min. After 10 min of stirring, the mixture was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were washed with brine, dried and concentrated to give an oil, which was chromatographed with a 5 : 2 mixture of n-hexane - EtOAc to yield the epoxy alcohol (**13**) (114 mg, 94%) as a colorless oil. IR ($CHCl_3$): 3480 and 1708 cm^{-1}. ^1H NMR (500 MHz): δ 2.85 (1H, br d, *J*=5.8), 2.93 (1H, d, *J*=4.2), 3.13 (1H, br dd, *J*=4.2 and 4.2), 3.74 (1H, br d, *J*=5.8), 5.39 (1H, dd, *J*=11.2 and 6.0), 7.42 - 7.48 (2H, m), 7.54 - 7.60 (1H, m), 7.95 - 8.25 (2H, m). HRMS: calcd for $C_{19}H_{22}O_4$ 314.1518, found 314.1488.

(1R*,2S*,6S*,8S*,9R*)-2-Benzoyloxytricyclo[6.3.1.0^{1,6}]dodec-10-en-9-ol **(14)**

To a stirred solution of the epoxy alcohol (**13**) (3.52 g, 11.2 mmol) in CH_2Cl_2 (40 mL) were added DMAP (1.51 g, 12.3 mmol) and 1,1'-thiocarbonyldiimidazole (2.44 g, 12.3 mmol) at room temperature, whereupon the mixture was heated under reflux for 20 h. After removal of the solvent, the residue was chromatographed. Elution with a 10 : 9 mixture of n-hexane - EtOAc gave the thioester (**26**) (4.18 g, 88%) as needles, mp 174 - 176 °C. IR ($CHCl_3$): 1712 cm^{-1}. ^{1}H NMR (300 MHz): δ 3.02 (1H, d, *J*=3.7), 3.23 (1H, br dd, *J*=3.7 and 3.7), 5.01 (1H, dd, *J*=10.6 and 5.5), 5.75 (1H, s), 7.06 - 7.12 (1H, m), 7.41 - 7.50 (2H, m), 7.54 - 7.62 (1H, m), 7.63 - 7.68 (1H, m), 7.97 - 8.05 (1H, m). HRMS: calcd for $C_{23}H_{24}N_2O_4S$ 424.1257, found 424.1269.

To a degassed solution of the above thioester (**26**)(146 mg, 0.344 mmol) in C_6H_6 (17 mL) was added dropwise a degassed C_6H_6 solution (3 mL) of n-Bu_3SnH (0.210 mL, 0.757 mmol) and AIBN (5.70 mg, 0.034 mmol) under reflux. After 5 min of stirring, to the mixture was added 12.5 % NH_4OH solution (20 mL), then the resulting mixture was continued to stir for 0.5 h. The aqueous layer was neutralized with saturated NH_4Cl solution, whereupon the aqueous layer was extracted with Et_2O (2 × 20 mL). The ethereal layers were washed with brine, dried and evaporated to leave a crude material. Chromatography (elution with a 5 : 2 mixture of n-hexane - EtOAc) afforded the allylic alcohol (**14**) (81 mg, 79%) as needles, mp 115 - 117 °C. IR ($CHCl_3$): 3450 and 1715 cm^{-1}. ^{1}H NMR (300 MHz): δ 3.79 (1H, br d, *J*=3.3), 5.26 (1H, dd, *J*=11.4 and 4.8), 5.54 (1H, ddd, *J*=9.5, 4.4 and 1.8), 5.91 (1H, dd, *J*=9.5 and 1.1), 7.38 - 7.48 (2H, m), 7.50 - 7.59 (1H, m), 7.98 - 8.06 (2H, m). HRMS: calcd for $C_{19}H_{22}O_3$ 298.1569, found 298.1570.

(1R*,2S*,6S*,8S*,9R*)-9-Methoxymethoxytricyclo[6.3.1.0^{1,6}]dodec-10-en-2-ol **(15)**

To a stirred solution of the allylic alcohol (**14**) (1.22 g, 4.09 mmol) in freshly distilled 1,2-dichloroethane (15 mL) were added dropwise diisopropylethylamine (2.86 mL, 16.4 mmol) and chloromethyl methyl ether (0.93 mL, 12.3 mmol) at room temperature, whereupon the mixture was stirred at the same temperature for 16 h. The mixture was poured into H_2O (30 mL), then the resulting mixture was extracted with CH_2Cl_2 (2 × 20 mL). The organic layers were dried and concentrated to give a crude product, which without purification was used in the next step.

To a stirred solution of the above ether in MeOH (30 mL) were added $LiOH·H_2O$ (749 mg, 17.9 mmol) and H_2O (10 mL), whereupon the mixture was heated under reflux for 6 h. After cooling to room temperature, the solution was neutralized with saturated NH_4Cl solution. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL), then the organic phases were dried and evaporated to yield an oil. Chromatography (elution with a 5 : 4 mixture of n-hexane - EtOAc) gave rise to the alcohol (**15**) (834 mg, 85%) as a colorless oil. IR: 3450 cm^{-1}. ^{1}H NMR (300 MHz): 3.39 (3H, s), 3.66 - 3.78 (2H, m), 4.70 (2H, dd, *J*=12.1 and 7.0), 5.66 (1H, ddd, *J*=9.5, 4.0 and 1.8), 5.97 (1H, br d, *J*=9.5). HRMS: calcd for $C_{14}H_{22}O_3$ 238.1569, found 238.1577.

(1S*,6S*,8S*,9S*)-9-Methoxymethoxytricyclo[6.3.1.0^{1,6}]dodecan-2-one **(16)**

A mixture of the olefin (**15**) (113 mg, 0.475 mmol) and 10% palladium-charcoal (100 mg,) in EtOAc (7 mL) was stirred for 21 h at room temperature under hydrogen. The catalyst was filtered off and washed with CH_2Cl_2. Concentration of the combined filtrates and washings afforded a residue, which was used in the following step.

To a stirred mixture of the above alcohol (124 mg), Florisil® (250 mg) and NaOAc (127 mg, 1.55 mmol) in CH_2Cl_2 (4 mL) was added PCC (233 mg, 1.03 mmol) at ambient temperature. The resulting mixture was

continued to stir at room temperature for 2.5 h. Filtration, followed by evaporation of the filtrate, gave a residue which was chromatographed. Elution with a 10 : 3 mixture of n-hexane - EtOAc yielded the ketone (**16**) (107 mg, 95%) as an oil. IR: 1689 cm^{-1}. ^1H NMR (300 MHz): δ 3.36 (3H, s), 3.52-3.60 (1H, m), 4.63 (2H, s). HRMS: calcd for $C_{14}H_{22}O_3$ 238.1569, found 238.1571.

***(1S*,6S*,8S*,9S*)-9-Methoxymethoxytricyclo[6.3.1.0^{1,6}]dodec-3-en-2-one* (17)**

To a stirred solution of LDA, prepared from diisopropylamine (0.078 mL, 0.540 mmol) and n-butyllithium (10% solution in n-hexane) in THF (2.5 mL), at -78 °C was added dropwise a THF solution (2 mL) of the ketone (**16**) (107 mg, 0.450 mmol), whereupon the mixture was stirred at the same temperature for 40 min. After the addition of a THF solution (2 mL) of phenylselenenyl bromide (130 mg, 0.540 mmol) at -78 °C, the resulting mixture was continued to stir for an additional 1 h. The reaction was quenched with saturated NH_4Cl solution (20 mL) at 0 °C, then extracted with Et_2O (2 × 20 mL). The ethereal layers were dried and evaporated to leave a clear viscous yellow oil, which without purification is used in the next step.

To a stirred solution of the above selenide in THF (3 mL) were added $NaHCO_3$ (302 mg, 3.59 mmol) and 30% H_2O_2 solution (0.46 mL, 4.52 mmol) at room temperature. After 2 h of stirring at the same temperature, to the mixture was added H_2O (10 mL). Extraction with Et_2O (2 × 20 mL), drying of the combined organic layers, and evaporation of the solvents gave a crude material, which was chromatographed. Elution with a 4 : 1 mixture of n-hexane - EtOAc afforded the enone (**17**) (59 mg, 55%) as a colorless oil. IR: 1662 cm^{-1}. ^1H NMR (500 MHz): δ 3.38 (3H, s), 3.55 - 3.60 (1H, m), 4.66 (2H, s), 6.01 (1H, dd, *J*=9.8 and 3.1), 6.82 (1H, ddd, *J*=9.8, 6.1 and 1.8). HRMS: calcd for $C_{14}H_{20}O_3$ 236.1412, found 236.1412.

***(1S*,6S*,8S*,9S*)-9-Methoxymethoxy-2-methyltricyclo[6.3.1.0^{1,6}]dodec-2-en-3-one* (18)**

To a stirred solution of methyllithium (1.4 M solution in Et_2O, 3.52 mL, 4.93 mmol) in n-hexane (10 mL) was added dropwise a n-hexane solution (5 mL) of the enone (**17**) (233 mg, 0.99 mmol) at 0 °C, whereupon it was stirred at the same temperature for 15 min. The mixture was quenched with saturated NH_4Cl solution (20 mL) and extracted with EtOAc (2 × 20 mL). The organic layers were dried and evaporated to give rise to a crude alcohol, which was immediately used in the next step without purification.

To a stirred mixture of PCC (1.16 g, 5.38 mmol), NaOAc (629 mg, 7.67 mmol) and Florisil® (1.50 g) in CH_2Cl_2 (10 mL) was added dropwise a CH_2Cl_2 solution (5 mL) of the above alcohol (193 mg) at ambient temperature. The resulting mixture was continued to stir at room temperature for 0.5 h. Filtration, followed by evaporation of the filtrate gave a residue. Chromatographic purification, eluting with a 2 : 1 mixture of n-hexane - EtOAc, yielded the enone (**18**) (171 mg, 69%) as a colorless oil. IR: 1670 cm^{-1}. ^1H NMR (500 MHz): δ 1.96 (3H, d, *J*=1.2), 3.39 (3H, s), 3.60 - 3.65 (1H, m), 4.68 (2H, s), 5.79 (1H, br s). HRMS: calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1573.

***(1S*,4S*,6R*,8S*,9R*)-9-Methoxymethoxy-2-methyltricyclo[6.3.1.0^{1,6}]dodec-2-en-4-ol* (20)**

To a stirred solution of the enone (**18**) (171 mg, 0.68 mmol) was added dropwise DIBAH (0.93 M solution in n-hexane, 0.81 mL, 0.75 mmol) at -78 °C, and the mixture was stirred at the same temperature for an additional 0.5 h. After addition of H_2O (1.05 mL) at -78 °C, the resulting mixture was allowed to warm to room temperature over a period of 1 h. After 5 h of stirring at the same temperature, a heavy white precipitate began to form. $MgSO_4$ (3 g) was added to the above mixture with stirring, whereupon the resulting mixture was filtered

through Celite and washed with Et_2O. Evaporation of the combined filtrate and washings gave an oil. Chromatography with a 2 : 1 mixture of n-hexane - EtOAc afforded the allylic alcohol (**20**) (151 mg, 88%) as a colorless oil. IR: 3410 cm^{-1}. ^1H NMR (300 MHz): δ 3.38 (3H, s), 3.55 - 3.62 (1H, m), 4.06 - 4.19 (1H, m), 4.66 (2H, s), 5.32 - 5.39 (1H, m). HRMS: calcd for $C_{15}H_{24}O_3$ 252.1725, found 252.1713.

***(1S*,2S*,6S*,8S*,9S*)-2-Formylmethyl-9-methoxymethoxy-2-methyltricyclo[6.3.1.0^{1,6}]-dodec-3-ene* (21)**

To a stirred solution of the above allylic alcohol (**20**) (37.9 mg, 0.150 mmol) in freshly distilled ethyl vinyl ether (10 mL) was added $Hg(OA)_2$ (26.0 mg, 0.082 mmol) at room temperature, then the resulting mixture was refluxed for 50 h. After removal of the solvent, the residual oil was subjected to column chromatography on Al_2O_3 with a 20 : 1 mixture of n-hexane - EtOAc to afford the vinyl ether (34.6 mg, 83%) as a colorless oil, together with the starting material (**20**) (3.3 mg).

A toluene solution (4 mL) of the above vinyl ether (34.6 mg, 0.124 mmol) was heated at 220 °C in a sealed tube for 52 h, then the solvent was removed under reduced pressure. The residual oil was chromatographed. Elution with a 5 : 1 mixture of n-hexane - EtOAc gave rise to the aldehyde (**21**) (31.3 mg, 91%) as a colorless oil. IR: 1719 cm^{-1}. ^1H NMR (500 MHz): δ 1.11 (3H, s), 3.36 (3H, s), 3.55 - 3.60 (1H, m), 4.65 (2H, s), 5.77 (1H, ddd, *J*=9.5, 6.2 and 2.2), 5.87 (1H, dd, *J*=9.5 and 3.5), 9.92 (1H, t, *J*=3.0). HRMS: calcd for $C_{17}H_{26}O_3$ 278.1881, found 278.1866.

***(1S*,2S*,6S*,8S*,9S*)-9-Methoxymethoxy-2-methyl-2-(3-oxobutyl)tricyclo[6.3.1.0^{1,6}]-dodec-3-ene* (22)**

To a stirred solution of LDA, prepared from diisopropylamine (0.044 mL, 0.317 mmol) and n-butyllithium (10% solution in n-hexane, 0.203 mL, 0.317 mmol) in THF (2 mL), at 0 °C was added dropwise a THF solution (1 mL) of $Ph_2P(O)CH(OMe)Me$ (82.5 mg, 0.317 mmol), whereupon it was continued to stir at the same temperature for an additional 0.5 h. The mixture was cooled to -78 °C with stirring, then to the mixture was added dropwise a THF solution (2 mL) of the aldehyde (**21**) (29.4 mg, 0.106 mmol) at the same temperature. After 0.5 h of stirring, HMPA (0.074 mL, 0.424 mmol) was added, then the resulting mixture was allowed to warm to room temperature. After 16.5 h, the mixture was quenched with saturated NH_4Cl solution and extracted with Et_2O (2 × 20 mL). The ethereal layers were washed with brine, dried and evaporated to give the crude enol ether, which was chromatographed. Elution with a 10 : 1 mixture of n-hexane - EtOAc afforded the enol ether (23.7 mg, 74% based upon the recovered starting material) as a colorless oil, together with the aldehyde (**21**) (1.7 mg). This material was immediately used in the following step.

To a stirred solution of the enol ether (23.7 mg, 0.074 mmol) in THF (3 mL) was added 2.5% perchloric acid (1 mL) at room temperature, whereupon it was continued to stir for an additional 2 h. The aqueous layer was neutralized with saturated $NaHCO_3$ solution and extracted with Et_2O (2 × 15 mL). The ethereal layers were washed with brine, dried and evaporated to leave an oil, which was chromatographed. Elution with a 20 : 3 mixture of n-hexane - EtOAc gave rise to the ketone (**22**) (21.7 mg, 67%) as a colorless oil. IR: 1710 cm^{-1}. ^1H NMR (500 MHz): δ 0.87 (3H, s), 3.36 (3H, s), 3.54 - 3.60 (1H, m), 4.65 (2H, s), 5.60 - 5.80 (2H, m). HRMS: calcd for $C_{19}H_{30}O_3$ 306.2195, found 306.2204.

***(5R*,8R*,9R*,10S*,13S*,14S*)-13-Methoxymethoxy-17,18,19-trinorstemod-6-en-3-one* (24)**

To a stirred solution of LDA, prepared from diisopropylamine (0.022 mL, 0.159 mmol) and n-butyllithium (10% solution of n-hexane, 0.102 mL, 0.159 mmol) in THF (2 mL), at -78 °C was added dropwise a THF solution (2.5 mL) of the ketone (**22**) (4.3 mg, 0.016 mmol), whereupon it was allowed to warm to 0 °C. After 0.5 h of stirring, the mixture was cooled to -78 °C. Chlorotrimethylsilane (0.014 mL, 0.032 mmol) was added, then the resulting mixture was allowed to warm to room temperature over a period of 2 h. The mixture was quenched with saturated $NaHCO_3$ solution at 0 °C and extracted with Et_2O (2 × 10 ml). The ethereal layers were dried and evaporated to give a crude material, which without purification was used in the next step.

A solution of the above silyl enol ether dissolved in MeCN (2 mL) was added dropwise to a stirred solution of $Pd(OAc)_2$ (9.47 mg, 0.042 mmol) dissolved in MeCN (2 mL). The mixture was continued to stir at room temperature for 13.5 h and then at 45 °C for 6 h. The reaction mixture was filtered through Celite, then the filtrate was concentrated to give an oil, which was subjected to column chromatography with a 5 : 1 mixture of n-hexane - EtOAc to give rise to the tetracyclic compound (**24**) (2.4 mg, 56%) as a colorless oil. IR: 1701 cm^{-1}. ^1H NMR (300 MHz): δ 1.02 (3H, s), 3.37 (3H, s), 3.58 - 3.63 (1H, m), 4.64 (2H, s), 5.06 (1H, br d, *J*=9.9), 5.59 (1H, br dt, *J*=9.9 and 3.0). HRMS: calcd for $C_{19}H_{28}O_3$ 304.2037, found 304.2010.

***(dl)-17,18,19-Trinorstemodane-3,13-dione* (4)**

A mixture of the olefin (**24**) (8.3 mg, 0.027 mmol) and 10% palladium-charcoal (5 mg) in EtOAc (5 mL) was stirred for 39.5 h at room temperature under hydrogen. The catalyst was filtered off and washed with CH_2Cl_2. Concentration of the combined filtrates and washings afforded a residue, which was chromatographed. Elution with a 10 : 3 mixture of n-hexane - EtOAc gave the ketone (5.4 mg, 65%) as a colorless oil. IR: 1708 cm^{-1}. ^1H NMR (300 MHz): δ 1.07 (3H, s), 3.36 (3H, s), 3.47 - 3.54 (1H, m), 4.65 (2H, dd, *J*=10.4 and 6.7). HRMS: calcd for $C_{19}H_{30}O_3$ 306.2195, found 306.2191.

To a stirred solution of the above ketone (5.4 mg, 0.018 mmol) in acetic acid (1.5 mL) was added H_2O (1.5 mL), whereupon the resulting mixture was stirred at 60 °C for 25 h and then 80 °C for 6 h. This aqueous layer was neutralized with saturated $NaHCO_3$ solution at 0 °C. After extraction with Et_2O (2 × 15 mL), the ethereal layers were dried and concentrated to yield a crude material, which was chromatographed. Elution with a 5 : 4 mixture of n-hexane - EtOAc gave rise to the alcohol (2.7 mg, 58%) as powders. IR ($CHCl_3$): 1715 cm^{-1}. ^1H NMR (300 MHz): δ 1.07 (3H, s), 3.64 - 3.76 (1H, m). HRMS: calcd for $C_{17}H_{26}O_2$ 262.1933, found 262.1952.

To a stirred mixture of PCC (11.1 mg, 0.052 mmol) and Florisil® (20 mg) in CH_2Cl_2 (1.5 mL) was added dropwise a CH_2Cl_2 solution (1.5 mL) of the above alcohol (2.7 mg, 0.010 mmol) at ambient temperature. The resulting mixture was continued to stir at room temperature for 1 h. Filtration, followed by evaporation of the filtrate, gave a residue, which was subjected to column chromatography with a 5 : 4 mixture of n-hexane - EtOAc to afford the diketone (**4**) (2.4 mg, 90%) as colorless cubes, mp 130 - 131 °C. (lit.,[4f] mp 132 °C). IR ($CHCl_3$): 1710 cm^{-1}. ^1H NMR (500 MHz): δ 1.15 (3H, s), 1.73 (1H, m), 1.85 (1H, m), 1.90 - 2.05 (4H, m), 2.09 (1H, m), 2.14 - 2.44 (7H, m), 2.52 (1H, ddt, *J*=18.0, 9.0 and 1.0), 2.70 (1H, t, *J*=7.0). HRMS: calcd for $C_{17}H_{24}O_2$ 260.1776, found 260.1776.

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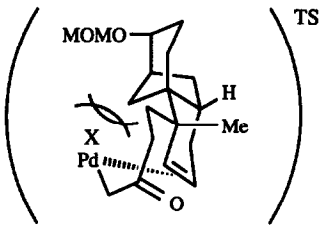
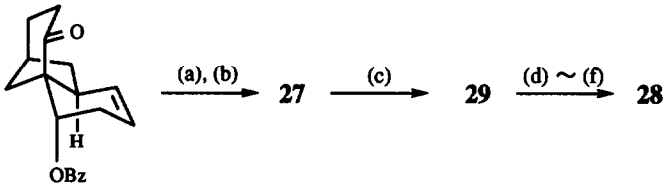
16. (a) Davis, G. D. Jr. "Advances in Metal-Organic Chemistry", 1991, **2**, 59. (b) The steric congestion in the transition state **23b** makes it less favorable than the alternative transition state **23a** which gives rise to the desired ketone (**24**).



23b

17. According to the same procedure as mentioned for the synthesis of **26**, the preparations of **27**, **28** and **29** were achieved from the ketone **30**.[4b, 20]



30

(a) H_2, 10% Pd-C, EtOAc (73%), (b) $C_5H_5N^+HBr_3^-$, AcOH (100%), (c) DBU, C_6H_6, reflux (80%), (d) 30% H_2O_2, 2.5% NaOH, MeOH (93%), (e) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH (83%), (f) $(Imid)_2C=S$, DMAP, CH_2Cl_2 (84%)

27; IR: 1725 cm^{-1}. ^1H NMR (500 MHz): δ 4.64 (1H, dd, *J*=11.6 and 7.9), 5.91 (1H, dd, *J*=3.1 and 3.1), 7.42 - 7.48 (2H, m), 7.54 - 7.60 (1H, m), 8.01 - 8.08 (2H, m). HRMS: calcd for $C_{19}H_{21}BrO_3$ 376.0674, found 376.0627. **29**; IR ($CHCl_3$): 1710 cm^{-1}. ^1H NMR (300 MHz): δ 5.66 (1H, dd, *J*=2.5 and 2.5), 5.84 (1H, d, *J*=9.5), 7.30 - 7.80 (4H, m), 7.90 - 8.40 (2H, m). HRMS: calcd for $C_{19}H_{20}O_3$ 296.1412, found 296.1409. **28**; IR ($CHCl_3$): 1710 cm^{-1}. ^1H NMR (300 MHz): δ 2.94 (1H, d, *J*=2.2), 3.28 (1H, dd, *J*=2.2 and 2.2), 5.20 - 5.50 (1H, m), 6.07 (1H, s), 7.05 - 7.25 (1H, m), 7.35 - 7.85 (4H, m). 7.90 - 8.25 (2H, m), 8.38 (1H, s). HRMS: calcd for $C_{23}H_{24}N_2O_4S$ 424.1257, found 424.1255.

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