A Synthetic Study on (±)-Podosporin A

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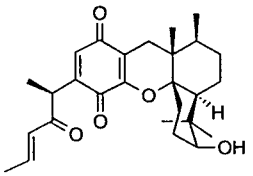
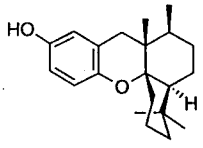
The synthesis of common skeleton of podosporin A and aureol was studied through cationic olefin cyclization as a key step. The generation of thermodynamic silyl enol ether or enol acetate under known conditions gave regioselectivity of 88 : 12. The enolate alkylation of 2,3-dimethylcyclohexanone with 2,5-dimethoxybenzyl bromide at the more substituted site *via* lithium enolate gave poor yield. In this case an organozincate or an ammonium enolate also proved to be ineffective or not practical in terms of yield. Side chain elongation of the substituted cyclohexanone **13** through Grignard reaction, Wittig reaction, or Shappiro reaction did not proceed because of steric hindrance and side reactions. However, Stille coupling reaction *via* enol triflate produced the desired product **18** in high yield. The advanced intermediate **22**, which was efficiently synthesized from **18**, produced **24** instead of the desired product under a cationic olefin cyclization condition, indicating that the cyclization occurred in a stepwise manner *via* the organomercury intermediate **23**.

Introduction

Podosporin A (**1**) is a novel antifungal metabolite from the coprophilou fungus *Podospora decipiens*. Its isolation and structural characterization by X-ray crystallography were carried out by Gloer and co-workers in 1988.[1] Podosporin A has potent activity against the early successional coprophilous fungi and also displays potent shrimp toxicity. The unusual benzo[*d*]xanthene ring system found in podosporin A was previously encountered in aureol (**2**) which was isolated from a marine sponge, *Smenospongia aurea*.[2] The biological activities, as well as the unusual benzo[*d*]xanthene skeleton of podosporin A and its structural analogs, attracted our synthetic interest. Here we wish to report our results in the construction of the common benzo[*d*]xanthene skeleton of podosporin A and aureol.



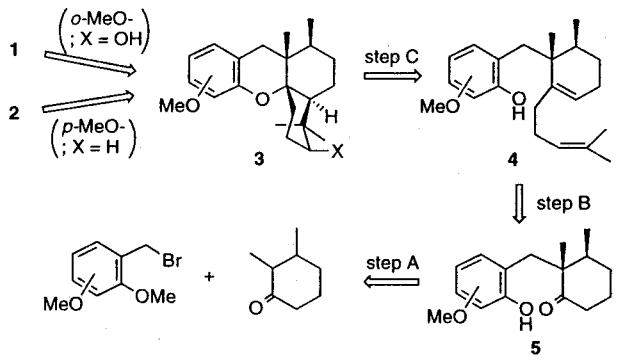
Podosporine A (1)



Aureol (2)

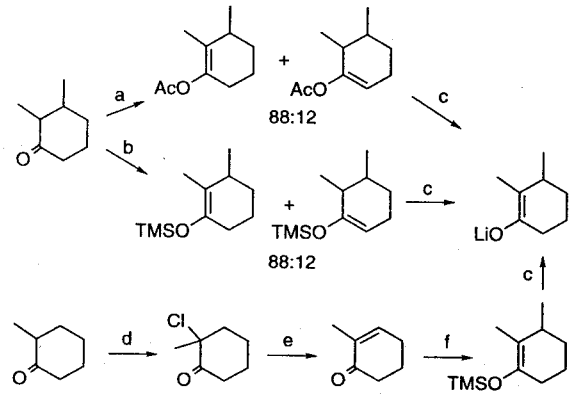
Our retrosynthetic analysis of podosporin A is depicted in Scheme 1. We planned to construct the tetracyclic skeleton of both podosporin A and aureol through a "cationic olefin cyclization" of the intermediate **4** (step C). The cationic olefin cyclization, which was pioneered by Stork-Esenmoser and systematically studied by Johnson, is well utilized in the fields of steroid synthesis.[3] But in our case, the phenolic hydroxy is the terminator group in the cyclization, which has few precedents.[4] As for the other two steps, the alkylation of 2,3-dimethylcyclohexanone at the sterically more hindered site (step A) and the conversion of **5** to **4** (step B), first seemed to be trivial but actually created a lot of problems.

Enolate alkylation at the more substituted site of 2,3-dimethylcyclohexanone. The generation of thermodynamically stable enolates of 2-alkyl substituted cyclohexa-



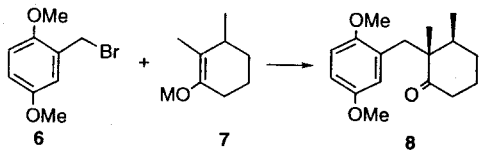
Scheme 1.

nones has been a fundamental operation and regioselectivitiy of ≥95 : 5 now can be achieved under several conditions.[5] However, we have found that the formation of the more substituted enolate of 2,3-dimethylcyclohexanone in a comparable selectivity can not be obtained under the same conditions as used for 2-methylcyclohexanone. The preparation of the enol acetate of 2,3-dimethylcyclohexanone, under the conditions reported by House,[6] gave a mixture of regioisomers in an 88 : 12 ratio. The lower selectivity was not improved and a similar selectivity was observed when silyl enol ether was generated with the BrMgN(*i*-Pr)$_2$-TMSCl system that was recently developed by Krafft.[5a] Both systems are known to give the thermodynamically stable enolate precursor with a 95 : 5 selectivity in the case of 2-methylcyclohexanone. Therefore, we indirectly synthesized the regioisomerically pure metal enolate **7** through the 1,4-addition of dimethylcuprate to 2-methyl-2-cylcohexene in the presence of TMSCl (Scheme 2).[7] The lithium enolate of **7** can be also generated from the silyl enol ether by treating with MeLi. As expected, the alkylation of the lithium enolate **7** with 2,6-dimethoxybenzyl bromide (**6**) gave a mixture of mono- and di-substituted products together with starting material. The scrambling of metal enolates during enolate alkylations with less reactive electrophiles, giving a mixture of regioiso-



Scheme 2. Reagents and Conditions: (a) Ac_2O, CCl_4, 25 ℃, 95%. (b) $BrMgN(i\text{-}Pr)_2$, Et_2O, 0→25 ℃, then TMSCl, HMPA, Et_3N, 90 %. (c) MeLi, Et_2O, 0→15 ℃. (d) SO_2Cl_2, CCl_4, 25 ℃. (e) LiCl, DMF, 100-112 ℃, 42% for two steps. (f) Me_2CuLi, TMSCl, HMPA, Et_3N, −78→25 ℃, 95%.

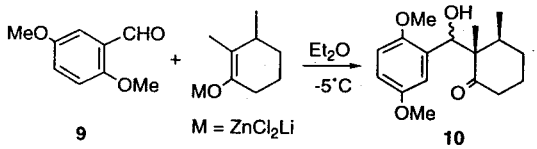
mers and overalkylation products, is a fundamental problem in carbanion chemistry.[8] This proton exchange problem has been partly solved by employing more polar media such as DME, liquid NH_3, or mixture with HMPA; by changing the counter metal ion to a quaternary ammonium ion, K^+, or Na^+; or *via* other metals such as Zn, Al, Cu, etc.[9] When the coupling (eq. 1) was carried out *via* a lithium enolate,



(1)

6 **7** **8**

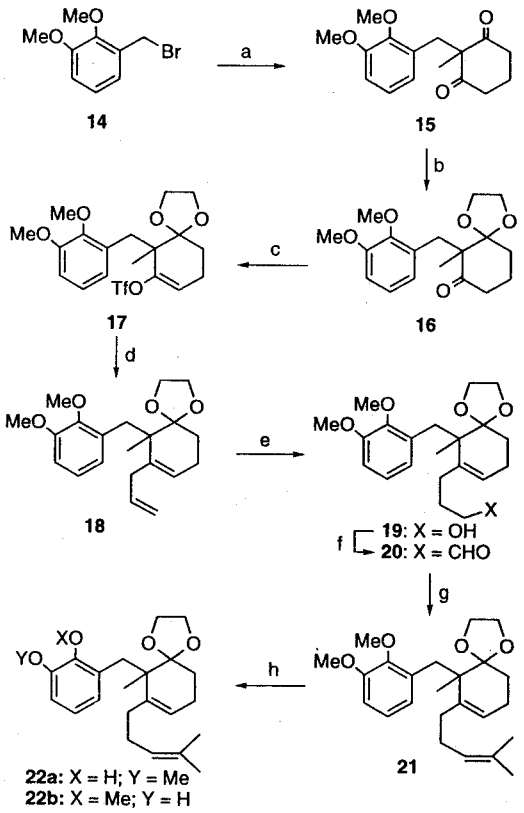
we could obtain the desired product **8** in less than 20% yield. The same alkylation *via* organozincate,[9d] which is known to suppress the proton exchange, did not proceed, indicating the poor reactivity of our system. We could obtain 30-40% of **8** in small-scale experiments (less than g-scale) *via* an ammonium enolate under the conditions reported by Kuwajima,[5c] but the yield was decreased with larger scales. The syn/anti ratio for the two methyl groups in **8** was about 9 : 1. When more electrophilic 2,5-dimethoxybenzaldehyde (**9**) was used in the Mukaiyama aldol reaction (eq. 2),[10] the aldol



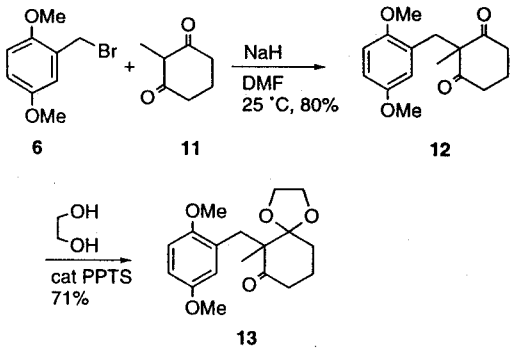
(2)

9 M = $ZnCl_2Li$ **10**

product **10** could be isolated in 40% yield. In this case it was possible to scale-up (7 g) but the compound **10** readily underwent a retroaldol reaction. Furthermore, several attempts to convert **10** to **8** such as hydrogenolysis (H_2-Pd/C) and reduction (CF_3CO_2H-Et_3SiH)[11] were unsuccessful. Therefore, we were obliged to change the aforementioned approach to an indirect route for the synthesis of the intermediate **8**, and the compound **12** was thus synthesized as a synthetic equivalent to **8** (eq. 3).



Scheme 3. Reagents and Conditions: (a) **11**, NaH, DMF, 25 ℃, 80%. (b) 1,2-ethanediol, cat PPTS, benzene, Δ (-H_2O), 70%. (c) LDA, THF, −30 ℃, then $(CF_3SO_2)_2NPh$, 0 ℃, 82%. (d) cat$(PPh_3)_4Pd$, LiCl, $(CH_2{=}CHCH_2)SnBu_3$, Δ, 24 h, 100%. (e) cat $Rh(PPh_3)_3Cl$, catecholborane, THF, 20 ℃, then $NaBO_3(4H_2O)$, 90%. (f) DMSO, $(COCl)_2$, −78 ℃, Et_3N. (g) $Ph_3P{=}C(CH_3)_2$, THF, 25 ℃, 48% for two steps. (h) *n*-PrSNa, DMF, 115-120 ℃, 94%.

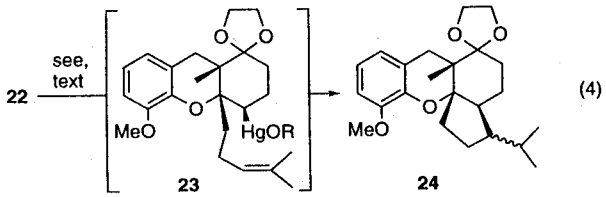


(3)

Side chain elongation of cyclohexanone 13. First we intended to convert one keto group of **12** to the methyl group as in **8**. Interestingly, both the two diketo groups in **12** underwent reduction with $NaBH_4$ or addition of MeMgBr concurrently and the corresponding monofunctionalization was not possible. However, monoprotection of **12** with ethylene glycol gave **13** in 70% yield. We tried several possible approaches for the chain extension of the ketone **13** but failed. The Wittig reaction with the phosphonium ylide generated from 4-methylpent-3-enyltriphenylphosphonium bromide did not occur. The Grignard reaction of **13** with 4-methyl-

pent-3-enylmagnesium bromide did not give the addition product, instead a carbonyl%reduced product was obtained. The steric hindrance around the carbonyl group may be a reason for the poor reactivity of **13** toward the reagents. In addition, the generation of a vinyllithium from the ketone **13** *via* hydrazone under the Shappiro reaction conditions[12] was unsuccessful. The competitive lithiation for the dimethoxyphenyl group possibly interrupted the vinyllithium formation. In the long run, we could synthesize the desired compound **21** through the Pd-catalyzed vinyl triflate-allyltin coupling that was developed by Stille.[13] The triflate **17**, prepared from the monoketone **16** which was similarly synthesized from **15** as for **13**, was subjected to the Stille coupling with allyltributyltin in the presence of $(Ph_3P)_4Pd$ catalyst to give the diene **18** in high yield. The hydroboration-oxidation of **18** with 9-BBN[14] selectively gave the primary alcohol **19** in moderate yield (42%). This conversion was greatly improved by a Rh-catalyzed hydroboration (90% yield).[15] Swern oxidation[16] of the alcohol **19** followed by the Wittig reaction with 1-methylethyltriphenylphosphorane afforded **21** in overall 48 % yield. Among several deprotection experiments for the methyl ethers in **21**, *n*-PrSNa in DMF[17] gave the best result and a mixture of mono-protected products (**22a** and **22b**) were always obtained in 70-94% yield. The ratio of **22a : 22b** was about 7 : 5, determined by ^1H NMR analysis. Other attempted deprotection with BBr_3[18] or TMSI[19] was not effective, resulting in an incomplete reaction or side products (Scheme 3).

Cationic olefin cyclization of 22. Since the alcohol **22a** and **22b** were hardly separable by column chromatography, the mixture was subjected to the cationic olefin cyclization. In spite of numerous reports regarding the utilization of cationic olefin cyclization in organic synthesis, there are only a few wherein a hydroxy group participates as a terminator in the cyclization cascade.[4] We chose the Nishizawa's reagent, mercury (II) triflate-N,N-dimethylaniline complex,[20] for the cyclization of our system because it was shown, by Gopalan recently,[4a] to be mild and very efficient, particularly for a hydroxy group-participated polyene cyclization. When the mixture **22** was treated with $Hg(OCOCF_3)_2$-$PhN(CH_3)_2$ complex in nitromethane at −20 ℃ for 2 h, followed by a saturated NaCl aqueous solution for additional 3 h at 25 ℃, a mixture containing an organomercuric intermediate was obtained after work-up and column chromatography. Treatment of the mixture with an aqueous $NaBH_4$ solution under a basic condition produced various compounds together with remaining **22**. Through a careful column chromatography, we could obtain a mixture of two major compounds, which were much less than the starting material, in the ratio of 3 : 1 determined by ^1H NMR analysis. The two compounds were believed to be diastereomers having one different stereocenter and their structures were tentatively assigned as **24** based on the following spectroscopic and mass data: (a) two double bonds (two vinylic protons at δ 5.43 and 4.88) were disappeared; (b) the chemical shifts difference of the geminal benzylic protons increased [δ 2.82 (AB, J=13.2 Hz, $\Delta\upsilon_{AB}$=23.5 Hz, 2H)→δ 2.51 (d, J=17.3 Hz, 1H) and δ 3.05 (d, J=17.3 Hz, 1H)], implying one of the benzylic protons was in a more crowded environment compared to **22**; (c) a ^{13}C DEPT experiment demonstrated that the carbon skeleton exactly matched with the structure **24** (ten methine and methyl carbons; seven methylene carbons), and (d) one isopropyl group was clearly present, and appeared as two diastereotopic groups in the ^1H NMR spectrum [δ 0.57 (d, J=6.5 Hz, 3H) and δ 0.75 (d, J=6.4 Hz, 3H)]. The formation of undesired product **24** suggests that the cyclization does not occur in a concerted fashion but a stepwise manner *via* the organomercuric intermediate **23**, which undergoes the more facile "5-exo-trig" radical cyclization[21] on treating with $NaBH_4$ (eq. 4). Another attempted cyclization with $BF_3 \cdot Et_2O$ on alumina[4b] was not also fruitful.



(4)

Although the cationic olefin cyclization occurred differently to our plan, the several important findings from this study suggest a clue for the synthesis of the desired skeleton. Minor structural modification of the intermediate **22** would lead to the desired common skeleton of podosporin A and aureol by an approach similar to the one described in this paper. A study along these lines will be the subject of a future report.

Experimental

All reagents were purchased from Aldrich Chemical Co., Inc., and were used without further purification. All reactions were carried out under an inert atmosphere. ^1H NMR and ^{13}C NMR were recorded at 300 and 75 MHz, respectively. Purification by column chromatography was carried out on silica gel with 230-400 mesh size. Melting points are uncorrected.

2-(2,5-dimethoxyphenyl)methyl-2,3-*syn*-dimethylcyclohexanone (8). Benzyltrimethylammonium fluoride (BTAF) (806 mg, 4.76 mmol) and 4 Å molecular sieves (4.76 g, 1 g/mmol) were placed under argon in a round bottom flask, and THF (10 mL) was added by a syringe. The suspension was stirred overnight at room temperature. To this fine suspension at 0 ℃, was added a THF (8 mL) solution of the silyl enol ether **7** (M=$SiMe_3$) (859 mg, 4.33 mmol) followed by 2,6-dimethoxybenzyl bromide (500 mg, 2.16 mmol). The mixture was stirred for 10 min at 0 ℃ and then for several hours at 20 ℃. It was diluted with hexane (20 mL), filtered through a small pad of silica gel, concentrated by a rotavapor, and the resulting residue was purified by column chromatography. The monoalkylated ketone **8** was obtained as an oil (246 mg, 41%): IR (neat, cm^{-1}) 2938, 2833, 1702, 1590, 1500, 1458, 1379, 1225, 1042; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (s, 3H), 0.89 (d, J=5.5 Hz, 3H), 1.50 (m, 1H), 1.77-2.08 (m, 4H), 2.32 (m, 1H), 2.70 (m,1H), 3.01 (AB , J_{AB}= 13.6 Hz, $\Delta\upsilon_{AB}$=74.0 Hz, 2H), 3.66 (s, 3H), 3.70 (s, 1H), 6.68 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.18, 18.67, 22.85, 28.59, 36.99, 38.21, 39.92, 53.42, 55.36, 55.59, 111.07, 111.73, 118.38, 128.08, 152.20, 153.06, 215.85; Mass m/e (relative intensity) 276 (M^+, 62), 151 (71), 121 (42), 83 (100), 49 (71).

2-(2,3-dimethoxyphenyl)methyl-2-methylcyclohexan-1,3-dione (15). To a stirred suspension of sodium

hydride (2.35 g, 58.7 mmol) in DMF (30 mL) was added a DMF (90 mL) solution of 2-methylcyclohexan-1,3-dione (7.40 g, 58.7 mmol) in small portions over a 20 min period at 0 ℃. To the mixture was added a DMF (35 mL) solution of 2,3-dimethoxybenzyl bromide (15.18 g, 65.7 mmol) over a 30 min period. The resulting mixture was stirred 1-2 h at 25 ℃ and then poured into a Et_2O-H_2O (1 : 1, v/v) solution (300 mL). The organic phase was washed with water, dried ($MgSO_4$), and concentrated by a rotavapor. The residue was recrystallized from EtOAc-petroleum ether to give the 1,3-diketone **15** as white crystals (12.86 g, 80%): mp 93.6-94.4 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (s, 3H), 1.85 (m, 2H), 2.60 (m, 4H), 3.07 (s, 2H), 3.74 (s, 3H), 3.80 (s, 3H), 6.59 (dd, J=1.4, 7.7 Hz, 1H), 6.77 (dd, J=1.4, 8.2 Hz, 1H), 6.90 (dd, 7.9, 8.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.48, 19.36, 38.54, 38.80, 55.66, 60.05, 65.21, 111.70, 123.42, 123.78, 129.62, 147.42, 152.51, 210.17; IR (NaCl) cm^{-1} 3012, 2931, 2828, 1724 (vs), 1695 (vs), 1584, 1482, 1439, 1324, 1268, 1223, 1066; MS m/e (rel intensity) 276 (M^+, 40), 189 (18), 151 (87), 136 (100), 106 (10), 91 (49).

2-(2,3-Dimethoxyphenyl)methyl-2-methyl-3-oxo-spirocyclohexane-2′-[1,3]dioxolane (16). A mixture of the 1,3-diketone **15** (4.0 g, 14.5 mmol), ethylene glycol (0.892 mL, 15.9 mmol), *p*-toluenesulfonic acid (30 mg, 0.16 mmol), and benzene (20 mL) was refluxed for 12 h with azeotropic removal of water. The solution was cooled, washed with water (10 mL), dried ($MgSO_4$), and concentrated by a rotavapor. The solid residue was recrystallized from EtOAc-petroleum ether to give the monoketal **15** as white crystals (3.24 g, 70%): mp 94.3-95.8 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (s, 3H), 1.82 (m,3H), 2.18 (m, 1H), 2.39 (m, 1H), 2.95 (m, 1H), 3.17 (AB, J_{AB}=13.4 Hz, $\Delta\upsilon_{AB}$=60.8 Hz, 2H), 3.98 (m, 4H), 6.64 (dd, J=1.5, 7.8 Hz, 1H), 6.76 (dd, J=1.5, 8.1Hz, 1H), 6.89 (dd, J=7.9, 8.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.27, 19.53, 29.98, 34.77, 37.03, 55.68, 60.02, 60.29, 65.39, 65.42, 111.21, 113.85, 122.97, 123.92, 130.89, 147.68, 152.41, 211.36; IR (NaCl) cm^{-1} 3005, 2952, 2879, 2839, 1712, 1587, 1462, 1308, 1272, 1227, 1175, 1112, 1068, 1030, 1002; MS m/e (rel intensity) 320 (M^+, 17), 151 (12), 136 (6), 99 (100).

2-(2,3-Dimethoxyphenyl)methyl-2-methyl-3-trifluoromethane-sulfonylspiro3-cyclohexene-2′-[1,3]dioxolane (17). A DME (26 mL) solution of the ketone **16** (2.80 g, 8.74 mmol) was added to a THF (20 mL) solution of lithium diisopropylamide (9.6 mmol) at −78 ℃, and the reaction temperature was slowly raised to −30 ℃ for 2 h. The enolate solution was recooled to −78 ℃ and it was treated with a DME (19 mL) solution of N-phenyltrifluoromethanesulfonimide (3.34 g, 9.35 mmol). The reaction mixture was allowed to warm to 0 ℃ and further stirred for 9 h at the same temperature. Most of the solvent was removed by a rotavapor, and the resultant yellow oil was dissolved in ether, then washed sequentially with water, aqueous sodium bicarbonate, and brine. Drying ($MgSO_4$), concentration by a rotavapor, and purification by column chromatography (1-2% EtOAc in petroleum ether) gave the enol triflate **17** as an oil (3.22 g, 82%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (s, 3H), 1.62 (m, 1H), 1.82 (m, 1H), 2.13 (m, 1H), 2.23 (m, 1H), 2.93 (AB, J_{AB}=12.9, $\Delta\upsilon_{AB}$=18.4 Hz, 2H), 3.76 (s, 3H), 3.80 (s, 3H), 4.01 (m, 4H), 5.72 (dd, J=4.97, 4.99 Hz, 1H), 6.77 (dd, J=1.6, 8.0 Hz), 6.81 (dd, J=1.6, 7.9 Hz, 1H), 6.90 (dd, J=7.7, 7.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.35, 20.73, 26.49, 37.54, 48.96, 55.62, 60.08, 64.96, 65.21, 111.05, 111.10, 115.63, 122.82, 124.38, 131.33, 148.14, 151.16, 152.46; IR (NaCl) cm^{-1} 3060, 2990, 2957, 2882, 2829, 1675, 1588, 1479, 1397, 1212, 1110; MS m/e (rel intensity) 452 (M^+, 26), 302 (12), 216 (14), 151 (100), 136 (73), 113 (18), 99 (40), 91(45).

3-Allyl-2-(2,3-Dimethoxyphenyl)methyl-2-methylspiro-3-cyclohexene-2′-[1,3]dioxolane (18). To a dry THF (15 mL) solution of lithium chloride (835 mg, 19.7 mmol) and tetrakis(triphenylphospine)palladium (0) (150 mg, 2 mol %) under argon, was added a THF (15 mL) solution of the enol triflate **17** (2.89 g, 6.39 mmol) and allyltributyltin (2.33 g, 7.04 mmol) at 25 ℃. This slurry was heated at reflux for 24 h. The reaction mixture was cooled to room temperature, and diluted with diethyl ether (200 mL), then it was washed sequentially with water, a 10% aqueous ammonium hydroxide solution, water, and brine. The ethereal solution was dried over $MgSO_4$, filtered through a small pad of silica gel, and concentrated by a rotavapor to yield **18** as an oil (2.20 g, 100%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 3H), 1.24 (m, 1H), 1.16 (m, 1H), 2.02 (m, 1H), 2.17 (m, 1H), 2.34 (m, 1H), 2.90 (AB, J_{AB}=13.0, $\Delta\upsilon_{AB}$=25.3 Hz, 2H), 3.76 (s, 3H), 3.82 (s, 3H), 4.01 (m, 2H), 4.77-4.91 (m, 2H), 5.36 (br s, 1H), 5.64 (m, 1H), 6.75 (dd, J=1.8, 7.8 Hz, 1H), 6.83 (dd, J=1.8, 7.8 Hz, 1H), 6.90 (dd, J=7.6, 7.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.68, 23.88, 26.42, 36.82, 38.68, 47.66, 55.65, 60.24, 64.87, 65.08, 110.47, 112.78, 115.54, 121.68, 122.78, 124.66, 133.19, 137.53, 140.87, 148.21, 152.63; MS m/e (rel intensity) 344 (M^+, 63), 313 (19), 258 (50), 193 (66), 151 (86), 136 (50), 91 (83), 73 (100).

2-(2,3-Dimethoxyphenyl)methyl-2-methyl-3-(3-hydroxypropyl)spiro-3-cyclohexene-2′-[1,3]dioxolane (19). To a THF (26 mL) solution of the diene **18** (3.0 g, 8.71 mmol) and $Rh(PPh_3)_3Cl$ (242 mg, 3 mol %) was added catecholborane (22.0 mL, 1.0 M in THF) at 20 ℃. The resulting yellow solution was stirred at the same temperature for 20 min. The reaction mixture was treated with water (9 mL) and $NaBO_3 \cdot 4H_2O$ (4.02 g, 26.1 mmol) sequentially and then vigorously stirred at 25 ℃ for 2 h. The mixture was extracted with Et_2O, the organic phase was washed with 2 N aqueous NaOH solution and dried over $MgSO_4$. Concentration of solvent and column chromatography of the residue (10-20% ethyl acetate in petroleum ether) afforded the alcohol **19** as an oil (2.85 g, 90%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (s, 3H), 1.43-1.75 (m, 3H), 2.01-2.11 (m, 1H), 2.23 (br s, 2H), 2.90 (AB, J_{AB}=12.9, $\Delta\upsilon_{AB}$=21.5 Hz, 2H), 3.40-3.51 (m, 2H), 3.77 (s, 3H), 3.84 (s, 3H), 3.94-4.05 (m, 4H), 5.40 (br s, 1H), 6.76 (dd, J=1.6, 7.8 Hz, 1H), 6.81 (dd, J=1.6, 7.8 Hz, 1H), 6.91 (t, J=7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.43, 23.65, 26.36, 28.48, 31.39, 39.04, 47.64, 55.66, 60.28, 62.85, 64.90, 65.19, 110.37, 112.82, 119.96, 122.81, 124.67, 133.37, 141.89, 148.16, 152.65; IR (NaCl) cm^{-1} 3411 (vs and br), 2927 (vs), 2839, 1705, 1584, 1472, 1431, 1273, 1222, 1078; MS m/e (rel intensity) 362 (M^+, 68), 331 (62), 276 (93), 261 (23), 217 (76), 211 (100), 183 (33), 151 (85), 73 (82).

2-(2,3-Dimethoxyphenyl)methyl-2-methyl-3-[(2-formyl)ethyl)]spiro-3-cyclohexene-2′-[1,3]dioxolane (20). To a CH_2Cl_2 (6.0 mL) solution of DMSO (289 μL, 4.07 mmol) was added $(COCl)_2$ dropwise under an argon atmosphere. After being stirred for 5 min at −78 ℃, the reaction mixture was treated with a dichloromethane (1.6 mL) solution of the alcohol **19** (568 mg, 1.57 mmol). The resulting

mixture was stirred for 15 min, then treated with Et_3N (1.3 mL, 9.4 mmol) at −78 ℃. The reaction temperature was allowed to rise to 0 ℃ and stirred for 30 min further. The reaction mixture was subjected to extractive work-up with dichloromethane and purification by column chromatography to give the aldehyde **20**, which was contaminated with an unknown of similar structure (about 20%). It can be eliminated at the next stage: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (s, 3H), 1.62-1.70 (m, 1H), 1.75-1.86 (m, 1H), 1.90-2.08 (m, 2H), 2.12-2.22 (m, 2H), 2.24-2.40 (m, 2H), 2.89 (AB, J_{AB}=12.9, $\Delta\upsilon_{AB}$=24.5 Hz, 2H), 3.75 (s, 3H), 3.82 (s, 3H), 3.90-4.03 (m, 4H), 5.28 (br s, 1H), 6.74 (dd, J=1.6, 7.8 Hz, 1H), 6.79 (dd, J=1.6, 7.9 Hz, 1H), 6.89 (t, J=7.7 Hz, 1H), 9.52 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.71, 23.80, 24.40, 26.32, 38.66, 42.54, 47.68, 55.68, 60.22, 64.92, 65.15, 110.60, 112.65, 120.58, 122.90.67, 124.57, 133.11, 140.79, 148.23, 152.86, 202.93; MS m/e (rel intensity) 360 (M^+, 10), 319 (8), 209 (26), 151 (100), 136 (58), 91 (64).

2-(2,3-Dimethoxyphenyl)methyl-2-methyl-3-(4-methyl-3-pentenyl)-spiro-3-cyclohexene-2′-[1,3]dioxolane (21). To the phospholane that was prepared from isopropyltriphenylphosphonium iodide (1.33 g, 3.09 mmol) in DMSO (3 mL) and NaH (129 mg, 60% dispersion, 3.23 mmol) under a nitrogen atmosphere, was added the foregoing impure aldehyde **20** (371 mg) in THF (0.7 mL). The mixture was stirred for 40 min at 25 ℃, poured on to crushed ice, and extracted with ethyl ether. The organic extract is dried over $MgSO_4$ and concentrated by a rotavapor. Purification of the residue by column chromatography gave pure **21** as an oil (288 mg, 48% from 19): ^{1}H NMR (300 MHz, CD_3CN) δ 1.01 (s, 3H), 1.62 (s, 3H), 1.57 (s, 3H), 1.4-1.7 and 1.8-2.2 (m, 8H), 2.86 (AB, J_{AB}=13.0, $\Delta\upsilon_{AB}$=10.3 Hz, 2H), 3.72 (s, 3H), 3.80 (s, 3H), 3.84-3.99 (m, 4H), 4.95 (br t, J=8.5 Hz, 1H), 5.33 (br s, 1H), 6.8-6.9 (m, 3H); ^{13}C NMR (75 MHz, CD_3CN) δ 16.70, 17.00, 23.90, 25.02, 26.33, 27.49, 38.83, 47.64, 55.59, 58.79, 64.66, 65.02, 111.06, 112.64, 120.23, 122.86, 124.86, 124.97, 131.03, 133.52, 142.26, 148.50, 152.90; IR (NaCl) cm^{-1} 3441 (s and br), 2931 (vs), 2837, 1639, 1584, 1472, 1271, 1222, 1084, 1012; MS m/e (rel intensity) 386 (M^+, 25), 355 (10), 300 (20), 257 (41), 235 (42), 163 (93), 151 (68), 136 (43), 99 (100), 91 (54), 73 (99), 69 (86).

2-(2-hydroxy-3-methoxyphenyl)methyl-2-methyl-3-(4-methyl-3-pentenyl)spiro-3-cyclohexene-2′-[1,3]dioxolane (22a) and its regioisomer 22b. To a DMF (1 mL) solution of **21** (350 mg, 0.91 mmol) at 25 ℃ was added a DMF (6 mL) solution of *n*-PrSNa that was prepared by treating *n*-PrSH (492 μL, 5.43 mmol) with NaH (145 mg, 3.62 mmol) at 25 ℃ for 15 min. The reaction mixture was heated at 115-120 ℃ for 6 h, then cooled to 25 ℃. It was diluted with Et_2O, and acidified to pH 4 with 1 N aqueous HCl solution. The organic phase was separated, dried over $MgSO_4$, concentrated. The residue was purified by column chromatography (eluant: 5-10% ethyl acetate in petroleum ether) to give a mixture of mono deprotected compounds **22a** and **22b** in a ratio of 7 : 5 (317 mg, 94%). Both compounds exhibited similar ^{1}H NMR spectra. The major isomer was purified to a relatively pure state by a careful column chromatography: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.98 (s, 3H), 1.47 (s, 3H), 1.56 (s, 3H), 1.5-2.2 (m, 8H), 2.82 (AB, J_{AB}=13.2, $\Delta\upsilon_{AB}$=23.5 Hz, 2H), 3.70 (s, 3H), 3.94-3.97 (m, 4H), 4.88 (m, 1H), 5.34 (br s, 1H), 5.43 (br s, 1H), 6.65-6.79 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.56, 17.61, 23.63, 25.64, 26.52, 26.98, 31.92, 38.73, 47.97, 60.91, 64.88, 65.21, 112.71, 113.57, 119.70, 123.94, 124.33, 124.68, 130.96, 133.73, 142.26, 146.37, 148.87; MS m/e (rel intensity) 372 (M^+, 3), 311 (2), 234 (8), 165 (11), 137 (9), 99 (13), 69 (19).

The compound 24. To a suspension of mercuric oxide (HgO, 138 mg, 0.636 mmol) in nitromethane (6.0 mL) was added triflic anhydride (107 μL, 0.636 mmol) and the mixture was stirred for 2 h at 25 ℃. To this suspension of mercury (II) triflate was added N,N-dimethylaniline (81 μL, 0.636 mmol) at 25 ℃, then the mixture was cooled to −20 ℃ and treated with a nitromethane (2.0 mL) solution of **22** (a mixture of **22a/22b**=*ca* 7 : 5, 158 mg, 0.424 mmol). After being stirred for 2 h at −20 ℃, the reaction mixture was treated with brine before being warmed to room temperature, where it was further stirred for 3 h. The precipitate was filtered off through a cotton-Celite pad, and the filtrate was subjected to an extractive work-up (with dichloromethane). Column chromatography of the extracts (2-5% ethyl acetate in petroleum ether) gave **24** (38 mg, 24%). As discussed in the text, the structure of **24** was tentatively assigned based on the following spectroscopic data: major isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.57 (d, J=6.5 Hz, 3H), 0.75 (d, J=6.4 Hz, 3H), 0.93 (s, 3H), 0.65-0.85, 1.12-1.29, 1.48-1.52, and 1.52-1.95 (m, 10 H), 2.28-2.45 (m, 1H), 2.51 (d, J=17.3 Hz, 1H), 3.05 (d, J=17.3 Hz, 1H), 3.72 (s, 3H), 3.80-3.99 (m, 4H), 6.55-6.78 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.55, 21.63, 22.15, 27.50, 29.54, 29.75, 33.11, 33.30, 34.42, 41.89, 42.49, 54.44, 55.79, 64.50, 65.56, 91.57, 109.16, 112.97, 119.09, 121.13, 121.49, 141.59, 148.61; DEPT (135 deg) methine and methyl carbons: 15.57, 21.68, 22.22, 33.13, 42.40, 54.37, 55.75, 108.93, 119.11, 121.08; methylene carbons: 27.52, 29.55, 29.74, 33.27, 34.38, 64.53, 65.58; MS m/e (rel intensity) 372 (M^+, 17), 235 (82), 163 (46), 149 (72), 137 (38), 121 (17), 91 (35), 73 (40).

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Intramolecular Excimer Formation Processes of 1,3-Dipyrenylpropane in Silicate Sol-Gel

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The steady-state emission and fluorescence lifetimes of 1,3-dipyrenylpropane were measured in silicate sol-gel and xerogel matrices. In sol solution, the fluorescence emission spectra of monomer and excimer resemble those in hydrocarbon solvents. In gel and xerogel condition, however, the fluorescence spectra exhibit significant change, largely confirming the intramolecular motions in gel pores are influenced by microviscosity. The rate constants for intramolecular excimer formation were obtained from the measured fluorescence lifetimes and the rate processes for excimer forming in silicate sol-gel are described by a simple kinetic scheme.

Introduction

Organic molecules or polymers embedded in amorphous silica glass have drawn considerable attention during past few years as a new promising material.[1] They have a potential application in solar energy converter, solid-state laser dyes, and photonic devices. The organic/inorganic composites can not be prepared with high temperature glass melting technique, because the organic dopants decompose at much lower temperature than the melting point of inorganics. For this purpose, the sol-gel method, a room temperature processing technique, is usually employed to disperse guest organic molecules within the network of silica glass.[2]

To prepare organic/inorganic composite materials of high quality, it is necessary to understand the physical properties of organic dopants in microscopic sol-gel environment. The photophysical and photochemical properties of organic molecules in the inorganic matrices are expected to be quite different from those in organic solvents. For this purpose, many organic chromophores such as naphthalene, pyrene, and organic dyes have been studied in silica glass using absorption, fluorescence excitation and emission, and fluorescence anisotropy techniques.[3~6] The host matrix has been recently extended to other materials such as alumina, titania and zirconia.[7~11]

Pyrene has been widely used as a fluorescence probe to