# Asymmetric Synthesis of (+)-Dihydrokawain-5-ol

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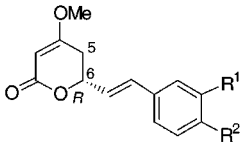
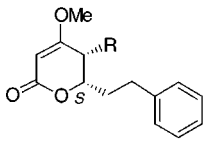
(+)-Kawain (**1**) and (+)-methysticin (**2**) were isolated from the extracts of the kava plant (*Piper methysticum* Forst.), a Polynesian shrub of the pepper family,[1] and the extracts of the roots and stem of the plant are utilized as a folk medicine and a ceremonial drink in the South Pacific. Because of its anxiolytic and analgesic properties, (±)-kawain is prepared in multigram scale and is marketed as a drug.[2] The absolute stereochemistry of **2** was established by chemical degradation to (+)-malic acid.[3] Judging from the positive Cotton effect of **2** as well as **1** in circular dichroism, the chiral center of C-6 of **1** was assigned to be the *R* configuration.[4]



**1**: $R^1 = R^2 = H$
**2**: $R^1, R^2 = OCH_2O$

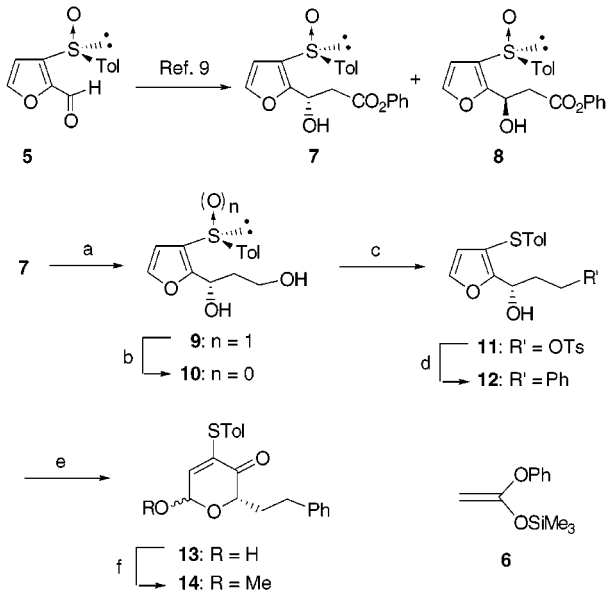


**3**: R = OH
**4**: R = H

(+)-Dihydrokawain-5-ol (**3**) was also isolated[5] and its 5*R* absolute configuration was suggested by identical transformation through $SeO_2$ allylic oxidation of (+)-dihydrokawain (**4**) derived from **1**.[6] Although **3** was thus prepared from (+)-**1** or (±)-**1**[7] by oxidation followed by hydrogenation, the oxidation step proceeds in a nonstereoselective manner and affords a poor yield of **3**. It does not seem to be suitable from synthetic viewpoint. Recently, an elegant synthesis of racemic **3** has been reported by Friesen;[8] however, no asymmetric synthesis has appeared to date.

As part of our ongoing program aimed at asymmetric reactions using chiral sulfoxides, we recently reported that the aldol reaction of sulfinyl furaldehyde **5** with 1-phenoxy-1-trimethylsilyloxyethene (**6**) proceeds smoothly to give the aldol product **7** with high diastereoselectivity.[9] High stereochemical control of the reaction led us to exploit an efficient route to a chiral pyranone moiety in **3** by degradation of the furan ring in the furyl alcohol. Herein we wish to report the first asymmetric synthesis of (+)-dihydrokawain-5-ol (**3**) based upon this strategy.

**Scheme 1**[a]



[a] Reagents and conditions: (a) DIBALH (4 equiv), $CH_2Cl_2$, −78 °C, 1.5 h, 74%; (b) $SmI_2$ (4 equiv), THF, HMPA−MeOH (25:1), 25 °C, 0.5 h, 65%; (c) TsCl (1.5 equiv), pyridine, 0 °C, 3 h; (d) $Ph_2CuLi$ (3 equiv), $Et_2O$, −30 → 0 °C, 1.5 h, 63% from **10**; (e) NBS (1.1 equiv), KOAc, THF−$H_2O$, 0 °C, 100%; (f) $CH(OMe)_3$, PPTS, MeOH 0 °C, 22 h, 85%.

Chirally functionalized furylpropanoate **7** was easily obtained by Mukaiyama aldol reaction of **5** and **6** with 90% diastereoisomeric excess in 91% combined yield. Isomerically pure **7** was separated from the minor diastereoisomer **8** by simple crystallization of the reaction mixture. The absolute stereochemistry of **7** was unequivocally established by single-crystal X-ray analysis.[10] Introduction of the phenyl group was accomplished as illustrated in Scheme 1. Reduction of the ester **7** with diisobutylaluminum hydride (DIBALH) proceeded smoothly to give the diol **9**, accompanied by a small amount of the over-reduction product **10**. Deoxygenation of the sulfinyl group in **9** with Sm(II)$I_2$−hexamethylphosphoramide (HMPA)[11] produced the sulfanyl diol **10** in 65% yield. Attempts at deoxygenation of **7** by means of other reducing agents such as trichlorosilane[12] or $TiCl_4/Zn$[13]

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(10) Crystal data for **7**: MW = 370.42, $C_{20}H_{18}O_5S$, crystal dimensions 0.30 × 0.30 × 0.20 mm, monoclinic, space group *P*21/*c* (No.14), $a$ = 10.733(2) Å, $b$ = 9.571(5) Å, $c$ = 18.714(3) Å, V = 1884(1) Å$^3$, $Z$ = 4, $D_{calc}$ = 1.306 g cm$^{-3}$, $2\theta_{max}$ = 50.0°, Mo Kα radiation ($\lambda$ = 0.71069 Å), T = 296 K. Data were collected using the Rigaku AFC7R system, and the structure was solved by direct methods, SIR92 (Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, M.; Giacovazzo, C.; Guagliardi, A.; Polidori, G. *J. Appl. Crystallogr.* **1994**, *27*, 435). Full-matrix least-squares refinement using the DIRDIF94 program system converged with final $R$ = 0.066 and $R_w$ = 0.105 for 1598 independent reflections with $I > 3.00\sigma(I)$ and 236 variable parameters.
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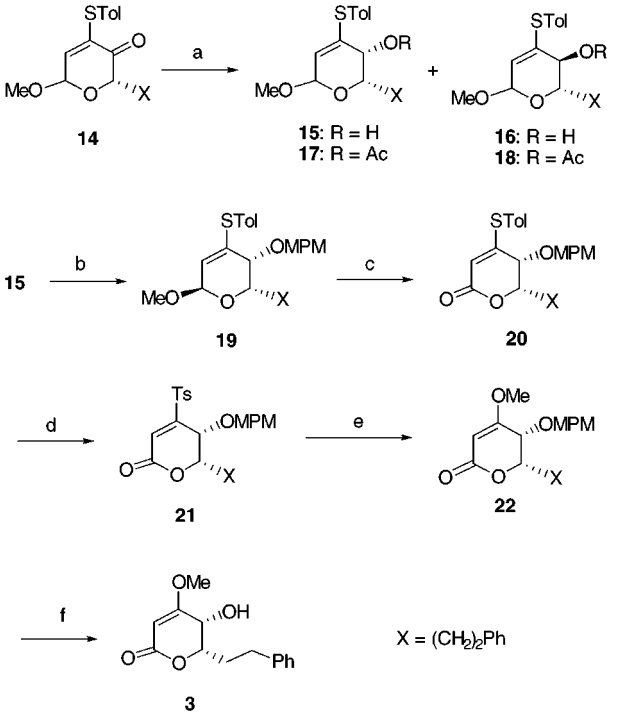
**Scheme 2**[a]




[a] Reagents and conditions: (a) DIBALH (3 equiv), 2,6-di-*tert*-butyl-4-methylphenol (6 equiv), toluene, −78 °C, 1 h, 78%; (b) MPMCl (1.2 equiv), NaH, DMF, 25 °C, 2 h, 86%; (c) TsOH (cat.), THF−$H_2O$, 0 °C → 25 °C, 6.5 h; TPAP (cat.), *N*-methylmorphorine *N*-oxide, molecular sieve 4A (powder), $CH_2Cl_2$, 25 °C, 2 h, 56%; (d) *m*-CPBA (2.5 equiv), $CH_2Cl_2$, 25 °C, 2.5 h, 89%; (e) $K_2CO_3$ (1.5 equiv), MeOH, 0 °C, 0.5 h, 100%; (f) DDQ (1.5 equiv), $CH_2Cl_2$−$H_2O$ (20:1), 25 °C, 4 h, 68%.

gave no better results. After selective monotosylation[14] of **10** with TsCl in pyridine at 0 °C, the subsequent replacement of the unstable tosylate **11** with diphenylcopperlithium gave the alcohol **12** in 63% yield from **10**.

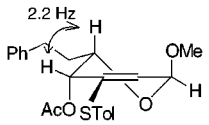
Although several methods for the conversion of furyl alcohols into the pyranones have been reported,[15] the procedure involving oxidation with *N*-bromosuccinimide (NBS) gave the best results. Namely, exposure of **12** to NBS in THF−$H_2O$[16] afforded the pyrane acetal **13**, as a 7:3 anomeric mixture, which was successively protected as the methyl acetal **14** obtained as an anomeric mixture ranging from 3:1 to 4.4:1. On the other hand, with the corresponding sulfinyl and sulfonyl derivatives of **12**, attempts at a similar oxidative degradation gave no successful results, accompanied by mass recovery of starting material, and in no cases were substantial amounts of desired product detected. The lower reactivity is consistent with the fact that furans with electron-withdrawing substituents are generally resistant to attack by protic acids.[17]

**Table 1. Reduction of Pyranone 14**

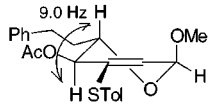
| reducing agent | solvent | temp (°C) | time (h) | yield (%)[a] | ratio **15**:**16**[b] |
|---|---|---|---|---|---|
| $NaBH_4$−$CeCl_3$ | $CH_2Cl_2$−MeOH | 0 | 0.2 | 69 | 2:3 |
| DIBALH | $CH_2Cl_2$ | −78 | 3 | 47 | 1:1 |
| L-Selectride | $CH_2Cl_2$ | −78 | 0.75 | 0 | |
| $LiBH_3Bu$ | THF | −78 | 0.3 | 0 | |
| *i*-$Bu_3Al$ | $Et_2O$ | −78 | 28 | <1 | |
| DIBALH−BHT[c] | toluene | −78 | 1 | 78 | 15:1 |

[a] Yield of combined isomers. [b] Ratio determined from the integrated value in the $^1H$ NMR spectrum of the crude reaction mixture. [c] BHT = 2,6-di-*tert*-butyl-4-methylphenol.

Our attention was then focused on the stereoselective reduction of the carbonyl group in pyranone **14** (Scheme 2). Of the several methods available, the use of the combination of DIBALH and 2,6-di-*tert*-butyl-4-methylphenol[18] was found to be most effective, giving the axial alcohol **15** and the equatorial alcohol **16** in a 15:1 ratio in 78% yield. With a β-anomer enriched pyranone **14** (3.7:1), α-anomeric alcohol of **15** was not obtained in substantial yield. Attempts at reduction of **14** by the use of other reducing agents were not fruitful (Table 1). For the reduction of **14**, $NaBH_4/CeCl_3$[19] or DIBALH had no effect in increasing the yield of desired alcohol **15**. The stereochemistry of the newly formed hydroxyl group in **15** and **16** was determined on the basis of $^1H$ NMR analysis of the acetates **17** and **18** derived from **15** and **16**, respectively. Particularly informative are the large coupling constant between the H-5 proton and the H-6 proton ($J_{5,6}$ = 9.0 Hz, axial−axial coupling) of **18** in the $^1H$ NMR



β-anomer **17**



**18**

spectrum and the small coupling constant ($J_{5,6}$ = 2.2 or 1.8 Hz) of anomeric **17** which indicates a *cis* relationship due to the H-5 equatorial hydrogen and the H-6 axial hydrogen. Protection of the resulting hydroxyl group in **15** as the *p*-methoxyphenylmethyl (MPM) ether[20] **19** and subsequent deprotection of the acetal moiety followed by oxidation with tetrapropylammonium perruthenate(VII) (TPAP)[21] produced the pyranone **20** in good yield. Exposure of **20** to *m*-chloroperoxybenzoic acid (*m*-CPBA) afforded the sulfonyl derivative **21** in 89% yield.

Transformation of **21** into **22** was readily effected using $K_2CO_3$ in MeOH[22] to provide the pyranone **22**. Finally, removal of the MPM protecting group in **22** furnished (+)-dihydrokawain-5-ol (**3**) {mp 89.5−90 °C ($Et_2O$) (lit.[5] mp 92 °C, lit.[6] mp 91−92 °C); $[\alpha]^{20}_D$ +72.6 (*c* 0.22, $CHCl_3$) for >99% ee by chiral HPLC {lit.[5] $[\alpha]^{20}_D$ +73 ($CHCl_3$); lit.[6] $[\alpha]^{20}_D$ +69 (*c* 0.001, $CHCl_3$)}.

In summary, we succeeded in the asymmetric synthesis of (+)-dihydrokawain-5-ol **3** using the highly selective aldol condensation of sulfinyl-substituted furaldehyde **5**

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with silyl ketene acetal **6** and the highly selective reduction of the carbonyl group in pyranone **14** as key steps.

## Experimental Section[23]

IR spectra were recorded on a FT-IR spectrometer in $CHCl_3$ solution or in liquid film. $^1H$ NMR spectra were measured with a 400 and 270 MHz spectrometer, and $^{13}C$ NMR spectra were obtained with 100 MHz. Extracts were dried over anhydrous $MgSO_4$ before evaporation of solvents on a rotary evaporator under reduced pressure. Dry tetrahydrofuran (THF) and diethyl ether were freshly distilled from sodium benzophenone ketyl prior to use. Dry dichloromethane was distilled from $CaH_2$ prior to use. *m*-CPBA was used after purification by washing with pH 7.5 phosphate buffer, according to the literature method.[24]

**Phenyl (3*S*,*S*$_s$)-3-Hydroxy-3-[3-(*p*-tolylsulfinyl)-2-furyl]-propanoate (7).**[25] To a suspension of $Nd(OTf)_3$ (0.607 g, 1.03 mmol) in dry THF (60 mL) was added a solution of aldehyde **5**[9] (4.81 g, 20.5 mmol) in dry THF (20 mL) at 0 °C. After being stirred at the same temperature for 15 min, silyl ketene acetal **6**[26] (8.55 g, 41.1 mmol) in dry THF (20 mL) was added dropwise and the solution was stirred for 5 h. The reaction mixture was then treated with 3% hydrochloric acid (50 mL) and stirred for 0.5 h. The organic phase was separated and the aqueous phase was extracted with AcOEt. The combined extracts were washed with brine, dried, and concentrated. The residue was purified by column chromatography on silica (hexane/EtOAc 4:1 to 1:1) to give a mixture of **7** and **8** (6.94 g, 91%) as a semisolid, which was recrystallized from benzene to afford isomerically pure **7** (6.16 g, 81%) as a crystalline solid: mp 45−48 °C (benzene); $[\alpha]^{20}_D$ −83.9 (*c* 1.0, acetone) for >99% ee by chiral HPLC [Chiralcel OD, hexane−2-propanol, 7:1, flow rate, 1.0 mL min$^{-1}$, retention time (+)-**7**, 55.8 min; (−)-**7**, 28.7 min]; IR ($CHCl_3$) 3280, 1750 cm$^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 2.38 (s, 3H), 3.12 (dd, 1H, $J$ = 16.1, 5.1 Hz), 3.25 (dd, 1H, $J$ = 16.1, 8.3 Hz), 4.69 (d, 1H, $J$ = 6.3 Hz), 5.55 (ddd, 1H, $J$ = 8.3, 6.3, 5.1 Hz), 6.30 (d, 1H, $J$ = 2.2 Hz), 7.09 (d, 2H, $J$ = 8.3 Hz), 7.2−7.4 (m, 5H), 7.33 (d, 1H, $J$ = 2.2 Hz), 7.59 (d, 2H, $J$ = 8.3 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 21.4, 40.3, 63.7, 108.4, 121.5 (2C), 124.9 (2C), 126.0 (2C), 128.3 (2C), 130.1 (2C), 140.4, 141.9, 142.5, 150.4, 156.5, 169.5. Anal. Calcd for $C_{20}H_{18}O_5S$: C, 64.85; H, 4.90. Found: C, 64.84; H, 4.91. The minor product **8** (**7**:**8** = 95:5) was inseparable from **7**, but was characterized from the $^1H$ NMR analysis of the crude product. **8**: $\delta$ 2.40 (s, 3 H), 3.23 (dd, 1 H, $J$ = 16.2, 6.5 Hz), 3.29 (dd, 1 H, $J$ = 16.2, 7.3 Hz), 4.7 (br, 1 H), 5.59 (dd, 1 H, $J$ = 7.3, 6.5 Hz), 6.20 (d, 1 H, $J$ = 2.0 Hz), 7.10 (d, 2 H, $J$ = 8.3 Hz), 7.2−7.45 (m, 6 H), 7.60 (d, 2 H, $J$ = 8.3 Hz).

For determination of the enantiomeric excess of (−)-**7**, a racemic sample (±)-**7** was prepared by reaction of (±)-**5** with the ketene acetal **6**.

**(1*S*,*S*$_s$)-3-Hydroxy-1-[3-(*p*-tolylsufinyl)-2-furyl]propan-1-ol (9).** To a stirred solution of the phenyl ester **7** (6.16 g, 16.6 mmol) in dry dichloromethane (150 mL) was added dropwise diisobutylaluminum hydride (DIBALH, 65.9 mL of 1.01 M solution in toluene, 66.5 mmol) over 10 min at −78 °C. The mixture was stirred at the same temperature for 1.5 h and then quenched by slow addition of MeOH (10 mL). The reaction mixture was warmed to room temperature and treated with saturated aqueous Rochelle's salt (200 mL) and then 3% hydrochloric acid (100 mL). After being stirred vigorously for 3 h, the mixture was extracted with dichloromethane. The combined extracts were washed with brine, dried, and concentrated. The residue was purified by column chromatography on silica. Early fractions eluted with hexane/EtOAc (1:1) afforded sulfide **10** (347 mg, 8%) as a crystalline solid: mp 104−105 °C (hexane/AcOEt); $[\alpha]^{22}_D$ −8.55 (*c* 1.03, $CHCl_3$); IR ($CHCl_3$) 3400, 1500, 1045, 995 cm$^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.9−2.3 (m, 3H), 2.29 (s, 3H), 2.80 (br, 1H), 3.7−3.95 (m, 2H), 5.20 (m, 1H), 6.38 (d, 1H, $J$ = 2.0 Hz), 7.07 (ABq, 4H, $J$ = 3.0 Hz, $\Delta\nu$ = 4.4 Hz), 7.44 (d, 1H, $J$ = 2.0 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 20.9, 37.1, 60.8, 65.2, 110.7, 115.3, 127.6 (2C), 129.8 (2C), 133.3, 135.9, 142.5, 157.8; Anal. Calcd for $C_{14}H_{16}O_3S$: C, 63.61; H, 6.10. Found: C, 63.45; H, 6.12. Further elutions with ethyl acetate afforded diol **9** (3.10 g, 66%) as a crystalline solid: mp 110−112 °C ($CH_2Cl_2$−$Et_2O$); $[\alpha]^{20}_D$ +17.1 (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) 3340, 1025 cm$^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 2.0−2.3 (m, 2H), 2.40 (s, 3H), 2.75 (dd, 1H, $J$ = 6.0, 4.9 Hz), 3.7−3.95 (m, 2H), 4.42 (d, 1H, $J$ = 5.5 Hz), 5.29 (dt, 1H, $J$ = 8.6, 5.5 Hz), 6.17 (d, 1H, $J$ = 2.0 Hz), 7.31 (d × 2, total 3H, $J$ = 7.9 and 2.0 Hz), 7.57 (d, 2H, $J$ = 7.9 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 21.4, 37.7, 59.8, 65.6, 107.9, 124.8 (2C), 125.1, 130.0 (2C), 140.0, 141.6, 142.6, 158.7. Anal. Calcd for $C_{14}H_{16}O_4S$: C, 59.98; H, 5.75. Found: C, 59.82; H, 5.76.

**(1*S*)-3-Hydroxy-1-[3-(*p*-tolylsulfanyl)-2-furyl]propan-1-ol (10).** To a well-sonicated solution of sulfoxide **9** (566 mg, 2.01 mmol) in degassed dry hexamethylphosphoramide (10 mL) and degassed dry methanol (0.4 mL) was added dropwise $SmI_2$ (80.4 mL of 0.1 M in THF, 8.04 mmol, 4 equiv) at room temperature under a stream of argon. After being stirred for 0.5 h, the purple mixture was then treated with water (5 mL). After removal of the solvents under reduced pressure, 3% hydrochloric acid was added until a clear solution was obtained. The aqueous phase was extracted with AcOEt. The combined extracts were washed with 3% hydrochloric acid and brine, dried, and concentrated. Purification of the residue by column chromatography on silica (hexane/AcOEt 1:1) provided diol **10** (345 mg, 65%) as a solid, which was identified with the minor product obtained by DIBALH reduction of **7**.

**(1*S*)-3-Phenyl-1-[3-(*p*-tolylsulfanyl)-2-furyl]propan-1-ol (12).** To a solution of diol **10** (373 mg, 1.41 mmol) in pyridine (2 mL) was added *p*-toluenesulfonyl chloride (404 mg, 1.5 equiv) in portions at 0 °C. The mixture was stirred at the same temperature for 3 h and partitioned between $Et_2O$ (20 mL) and 1% hydrochloric acid (15 mL). The aqueous layer was extracted with $Et_2O$. The combined organic phases were washed with brine, dried, and concentrated. Purification of the residue by flash chromatography on silica (hexane/AcOEt 5:1 to 3:1) afforded tosylate **11** (494 mg, 84%) as an unstable oil, which was immediately used in the next step without further purification. Tosylate **11**: $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 2.07−2.3 (m, 3H), 2.30 (s, 3H), 2.43 (s, 3H), 4.11 (dt, 1H, $J$ = 10.1, 5.5 Hz), 4.26 (ddd, 1H, $J$ = 10.1, 5.3, 5.1 Hz), 5.04 (br, 1H), 6.35 (d, 1H, $J$ = 2.0 Hz), 7.07 (s, 4H), 7.31 (d, 2H, $J$ = 8.2 Hz), 7.39 (d, 1H, $J$ = 2.0 Hz), 7.78 (d, 2H, $J$ = 8.2 Hz).

To a gray suspension of CuI (672 mg, 3.53 mmol) in dry $Et_2O$ (20 mL) was added phenyllithium (7.5 mL of 0.94 M solution in cyclohexane/$Et_2O$, 6 equiv) at −30 °C, and the resulting black suspension was stirred at the same temperature for 10 min. Essentially pure tosylate **11** (494 mg), obtained previously in the reaction, in dry $Et_2O$ (5 mL) was then added slowly and the mixture was allowed to warm to 0 °C over 1.5 h. The mixture was quenched with saturated $NH_4Cl$ (30 mL) and the organic layer was separated. The aqueous layer was extracted with $Et_2O$ and the extracts were washed brine, dried, and concentrated. Purification of the residue by flash chromatography on silica (hexane/AcOEt 7:1) gave **12** (286 mg, 75%) as a colorless oil: $[\alpha]^{21}_D$ −29.5 (*c* 1.2, $CHCl_3$) for >99% ee determined by chiral HPLC [Chiralpak AS, hexane−2-propanol, 100:1, flow rate, 1.0 mL min$^{-1}$, retention time (+)-**12**, 26.2 min; (−)-**12**, 22.2 min]; IR ($CHCl_3$) 3520 cm$^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) $\delta$ 2.0−2.3 (m, 3H), 2.29 (s, 3H), 2.5−2.75 (m, 2H), 4.96 (dt, 1H. $J$ = 6.7, 5.9 Hz), 6.38 (d, 1H, $J$ = 2.0 Hz), 7.05−7.3 (m, 9H), 7.43 (d, 1H, $J$ = 2.0 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 20.9, 31.7, 37.0, 65.4, 111.1, 115.4, 125.9, 127.7 (2C), 128.4 (4C), 129.8 (2C), 133.4, 135.9, 141.3, 142.3, 158.0; HRMS calcd for $C_{20}H_{20}O_2S$ 324.1184. found, 324.1178.

For determination of the enantiomeric excess of (−)-**12**, a racemic sample (±)-**12** was prepared starting with (±)-**5** and the ketene acetal **6**.

**(2*S*,6*S*/6*R*)-6-Methoxy-2-(1-phenylethyl)-4-(*p*-tolylsulfanyl)-2*H*-pyran-3(6*H*)-one (14).** To a stirred solution of furyl alcohol **12** (1.967 g, 6.06 mmol) and potassium acetate (655 mg, 6.67 mmol) in THF (64 mL) and $H_2O$ (16 mL) was added in portions *N*-bromosuccinimide (NBS, 1.187 g, 6.67 mmol) at 0 °C. After being stirred at the same temperature for 20 min, the reaction mixture was partitioned between $Et_2O$ (120 mL) and

(23) General experimental procedures and instrumentation are described in the following: Arai, Y.; Suzuki, A.; Masuda, T.; Masaki, Y.; Shiro, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2913.

(24) Schwartz, N. N.; Blumbergs, J. H. *J. Org. Chem.* **1964**, *29*, 1976.

(25) The symbol $S_s$ given in this text expresses that the sulfinyl center is the *S* configuration.

(26) Slougui, N.; Rousseau, G. *Synth. Commun.* **1987**, *17*, 1.

10% potassium iodide (80 mL). The organic layer was separated and the aqueous layer was extracted with $Et_2O$. The combined extracts were washed with 15% sodium thiosulfate and saturated sodium hydrogen carbonate and brine, dried, and concentrated. Purification of the residue by column chromatography on silica (hexane/AcOEt 9:1 to 4:1) yielded pyranone **13** (2.07 g, 100%) of a ca. 7:3 anomeric mixture, which was used in the next step without further purification. **13**: colorless oil; $^1$H NMR (400 MHz, $CDCl_3$, 7:3 anomeric mixture) $\delta$ 2.0−2.2 (m, 1H), 2.25−2.4 (m, 1H), 2.38 (s, 3H), 2.65−2.9 (m, 2.7H), 3.0 (br, 0.3H), 4.06 (ddd, 0.3H, $J$ = 8.5, 3.9, 1.2 Hz), 4.62 (dd, 0.7H, $J$ = 8.2, 3.8 Hz), 5.54 (br s, 0.3H), 5.57 (d, 0.7H, $J$ = 3.9 Hz), 5.92 (d, 0.7H, $J$ = 3.9 Hz), 5.95 (d, 0.3H, $J$ = 1.7 Hz), 7.05−7.45 (m, 9H); $^{13}$C NMR ($CDCl_3$, major anomer) $\delta$ 21.3, 31.0, 31.5, 73.2, 88.9, 92.0, 125.1, 126.0, 128.4 (2C), 128.6 (2C), 130.7 (2C), 133.1, 135.6 (2C), 139.9, 141.2, 192.9.

To a solution of **13** (2.618 g, 7.69 mmol) and trimethyl orthoformate (4.21 mL, 38.5 mmol) in dry methanol (40 mL) was added pyridinium *p*-toluenesulfonate (387 mg, 1.54 mmol) at 0 °C. The reaction mixture was stirred at the same temperature for 22 h and concentrated. Purification of the residue by column chromatography on silica (hexane/AcOEt 30:1 to 15:1) provided acetal **14** (2.31 g, 85%) as a colorless oil in a ratio of a ca. 3:1 anomeric mixture: $[\alpha]^{20}_D$ −7.78 (*c* 1.35, $CHCl_3$) (3:1 anomeric mixture); IR ($CHCl_3$) 1680, 1600 cm$^{-1}$; $^1$H NMR (270 MHz, $CDCl_3$, anomeric mixture) $\delta$ 2.0−2.3 (m, 2H), 2.37 (s, 3H), 2.7−2.95 (m, 2H), 3.41 (s, 2.1H), 3.50 (s, 0.9H), 4.04 (ddd, 0.3H, $J$ = 8.8, 4.0, 0.9 Hz), 4.47 (dd, 0.7H, $J$ = 8.4, 3.5 Hz), 5.01 (d, 0.7H, $J$ = 3.9 Hz), 5.13 (dd, 0.3H, $J$ = 2.2, 0.9 Hz), 5.87 (d, 0.7H, $J$ = 3.9 Hz), 5.91 (d, 0.3H, $J$ = 2.2 Hz), 7.2−7.5 (m, 9H). $^{13}$C NMR ($CDCl_3$, for major anomer) $\delta$ 21.3, 31.2, 31.5, 56.3, 73.2, 95.3, 98.0, 125.2, 126.0, 128.4 (2C), 128.5 (2C), 130.7 (2C), 132.2 (2C), 135.7, 139.9, 141.2, 193.0; HRMS calcd for $C_{21}H_{22}O_3S$ 354.1290, found 354.1281.

**(2*S*,3*R*/3*S*,6*R*/6*S*)-3-Hydroxy-6-methoxy-2-(1-phenylethyl)-4-(*p*-tolylsulfanyl)-3,6-dihydro-2*H*-pyran (15 and 16).** To a solution of 2,6-di-*tert*-butyl-4-methylphenol (2.63 g, 11.9 mmol) in dry toluene (30 mL) was added DIBALH (5.9 mL of 1.01 M in toluene, 5.97 mmol) at 0 °C. The mixture was stirred for 10 min and cooled to −78 °C. Pyranone **14** (705 mg, 1.99 mmol, 3.7:1 anomeric mixture) in dry toluene (10 mL) was then added and stirred at the same temperature for 0.5 h. The reaction mixture was quenched with saturated Rochelle's salt (150 mL) and diluted with AcOEt (100 mL). The mixture was stirred vigorously at room temperature for 2 h. The organic layer was separated and the aqueous layer was extracted with AcOEt. The combined extracts were washed with brine, dried, and concentrated. The product ratio (**15**:**16** = 15:1) was estimated by the olefinic signals in the $^1$H NMR spectrum of the crude product. Purification of the residue was carried out by column chromatography on silica (hexane/AcOEt 9:1 to 3:1). Initial fractions contained **16** (57 mg, 8%) as an unstable oil, contaminated with **15**. Later fractions gave pure **15** (497 mg, 70%) as an almost single $\beta$-anomer. By using a ≥3.7:1 anomeric mixture **14** for this reduction, α-anomer of **15** was not obtained in substantial yield. **15**: mp 111−113 °C ($\beta$-anomer, hexane/AcOEt); $[\alpha]^{20}_D$ +83.4 (*c* 1.03, $CHCl_3$); IR ($CHCl_3$) 3400 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.85−1.95 (m, 1H), 1.98 (d, 1H, $J$ = 8.8 Hz), 2.05−2.15 (m, 1H), 2.35 (s, 3H), 2.65−2.75 (m, 1H), 2.8−2.9 (m, 1H), 3.42 (s, 3H), 3.55 (dd, 1H, $J$ = 8.8, 1.8 Hz), 3.95 (ddd, 1H, $J$ = 8.8, 4.4, 1.8 Hz), 4.87 (d, 1H, $J$ = 3.1 Hz), 5.47 (d, 1H, $J$ = 3.1 Hz), 7.14−7.3 (m, 7H), 7.37 (d, 2H, $J$ = 8.1 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 21.2, 31.9, 32.2, 55.5, 65.8, 70.6, 96.2, 121.7, 125.9, 126.6, 127.6, 128.3 (2C), 128.4, 129.8, 130.2 (2C), 134.4 (2C), 139.1, 141.7. Anal. Calcd for $C_{21}H_{24}O_3S$: C, 70.76; H, 6.79. Found: C, 70.53; H, 6.82. **16**: $^1$H NMR (270 MHz, $CDCl_3$, ca.. 6:1 anomeric mixture) $\delta$ 1.75−1.9 (m, 1H), 2.05 (br, 1H), 2.2−2.3 (m, 1H), 2.35 (s, 3H), 2.65−2.8 (m, 1H), 2.85−3.0 (m, 1H), 3.41 (s, 2.55H), 3.47 (s, 0.45H), 3.75 (dt, 0.85H, $J$ = 9.3, 2.2 Hz), 3.95 (br, 1.15H), 4.85 (d, 0.85H, $J$ = 3.2 Hz), 4.95 (t, 0.15H, $J$ = 1.7 Hz), 5.36 (dd, 0.85H, $J$ = 3.2, 1.7 Hz), 5.48 (dd, 0.15H, $J$ = 1.5, 1.0 Hz), 7.17 (d, 2H, $J$ = 7.9 Hz), 7.1−7.3 (m, 5H), 7.36 (d, 2H, $J$ = 7.9 Hz).

**(2*S*,3*R*/3*S*,6*R*/6*S*)-3-Acetoxy-6-methoxy-2-(1-phenylethyl)-4-(*p*-tolylsulfanyl)-3,6-dihydro-2*H*-pyran (17 and 18).** A crude mixture of **15** and **16**, obtained by stereoselective reduction of **14** (3:1 ratio, 21 mg, 0.059 mmol), was treated with acetic anhydride and pyridine in the usual manner. The product was submitted to column chromatography on silica (hexane/AcOEt 50:1 to 9:1) to afford a 15:1 mixture of **17** and **18** (18 mg, 78%),[27] which was separated by preparative TLC (hexane/AcOEt 7:1, two developments). Acetate **17** (7:3 anomeric mixture): mp 86−88 °C (for $\beta$-anomer); IR ($CHCl_3$) 1730 cm$^{-1}$; $^1$H NMR (270 MHz, $CDCl_3$, 7:3 anomeric mixture) $\delta$ 1.7−2.1 (m, 2H), 2.10, 2.11 (each s, total 3H), 2.35 (s, 3H), 2.6−2.75 (m, 1H), 2.75−2.95 (m, 1H), 3.44, 3.50 (each s, total 3H), 3.55 (ddd, 0.3H, $J$ = 9.5, 3.7, 1.8 Hz), 4.07 (ddd, 0.7H, $J$ = 9.2, 3.7, 2.2 Hz), 4.94 (d, 0.3H, $J$ = 1.5 Hz), 4.95 (d, 0.7H, $J$ = 3.3 Hz), 5.16 (d, 0.7H, $J$ = 2.2 Hz), 5.20 (t, 0.3H, $J$ = 1.8 Hz), 5.55 (d, 0.3H, $J$ = 1.5 Hz), 5.65 (d, 0.7H, $J$ = 3.3 Hz), 7.14−7.34 (m, 5H), 7.26 (d, 0.6H, $J$ = 8.3 Hz), 7.27 (d, 1.4H, $J$ = 8.3 Hz), 7.32 (d, 2H, $J$ = 8.3 Hz); HRMS calcd for $C_{23}H_{26}O_4S$ 398.1552, found 398.1542. Anal. Calcd for $C_{23}H_{26}O_4S$: C, 69.32; H, 6.58. Found: C, 69.16; H, 6.69. Acetate **18** (single $\beta$-anomer): $[\alpha]^{20}_D$ −61.9 (*c* 1.0, $CHCl_3$); IR (film) 1749 cm$^{-1}$; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 1.7−1.9 (m, 2H), 2.06 (s, 3H), 2.35 (s, 3H), 2.55−2.65 (m, 1H), 2.85−3.0 (m, 1H), 3.41 (s, 3H), 3.95 (dt, 1H, $J$ = 9.0, 3.7 Hz), 4.86 (d, 1H, $J$ = 3.2 Hz), 5.27 (dd, 1H, $J$ = 3.2, 1.6 Hz), 5.48 (dt, 1H, $J$ = 9.0, 1.6 Hz), 7.2−7.4 (m, 5H), 7.17 (d, 2H, $J$ = 7.9 Hz), 7.35 (d, 2H, $J$ = 7.9 Hz); HRMS calcd for $C_{23}H_{26}O_4S$ 398.1552, found 398.1547.

**(2*S*,3*R*,6*R*)-6-Methoxy-3-(4-methoxybenzyloxy)-2-(1-phenylethyl)-4-(*p*-tolylsulfanyl)-3,6-dihydro-2*H*-pyran (19).** To a suspension of NaH (18 mg, 0.45 mmol, 60% oil dispersion) in dry DMF (2.5 mL) was added **15** (80 mg, 0.22 mmol) in dry DMF (2 mL) at 0 °C. After being stirred for 10 min, *p*-methoxybenzyl chloride (40 $\mu$L, 0.29 mmol) was added and the mixture was stirred at room temperature for 2 h. The mixture was poured into a pH 7.5 phosphate buffer solution (10 mL), and the aqueous layer was extracted with AcOEt. The combined extracts were washed with water and brine, dried, and concentrated. Purification of the residue by column chromatography on silica (hexane/AcOEt 8:1) yielded **19** (92 mg, 86%) as a single $\beta$-anomer **19**: $[\alpha]^{26}_D$ +131.5 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3016, 1515 cm$^{-1}$; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 1.75−1.9 (m, 1H), 2.05−2.2 (m, 1H), 2.36 (s, 3H), 2.63 (ddd, 1H, $J$ = 13.9, 9.6, 6.4 Hz), 2.86 (ddd, 1H, $J$ = 13.9, 10.0, 5.2 Hz), 3.41 (s, 3H), 3.61 (d, 1H, $J$ = 2.5 Hz), 3.78 (s, 3H), 3.96 (ddd, 1H, $J$ = 9.1, 4.0, 2.5 Hz), 4.63 (AB q, 2H, $J$ = 10.8 Hz, $\Delta\nu$ = 38 Hz), 4.92 (d, 1H, $J$ = 3.2 Hz), 5.55 (d, 1H, $J$ = 3.2 Hz), 6.85 (d, 2H, $J$ = 8.5 Hz), 7.1−7.35 (m, 9H), 7.37 (d, 2H, $J$ = 8.1 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 21.2, 32.1, 32.5, 55.2, 55.4, 71.2, 71.3, 71.4, 96.3, 113.7 (2C), 123.4, 125.8, 127.1, 128.3 (4C), 129.9 (2C), 130.3 (2C), 130.5, 134.3 (2C), 138.9, 139.1, 141.8, 159.2; HRMS calcd for $C_{29}H_{32}O_4S$ 476.2022, found 476.2028. Isolative workup for acid-sensitive **19** often resulted in production of variable amounts of the corresponding hemiacetal, which was used in TPAP oxidation.

**(5*R*,6*S*)-5-(4-Methoxybenzyloxy)-6-(1-phenylethyl)-4-(*p*-tolylsulfanyl)-5,6-dihydro-2*H*-pyran-2-one (20).** To an ice-cooled solution of **19** (85.5 mg, 0.18 mmol) in THF−$H_2O$ (4:1, 7.5 mL) was added *p*-TsOH·$H_2O$ (6.8 mg). The reaction mixture was then allowed to warm to room temperature. After being stirred for 6.5 h, the resulting mixture was extracted with $CHCl_3$. The combined extracts were washed with saturated sodium hydrogen carbonate and brine, dried, and concentrated. Since the hemiacetal was labile to silica gel and could not be separated from small amounts of unidentified byproducts by silica gel column chromatography, the purification was achieved in the subsequent step.

To a stirred suspension of *N*-methylmorphorine *N*-oxide (105 mg, 0.9 mmol) and molecular sieve 4A powder (90 mg) in dry dichloromethane (2.5 mL) was added the above hemiacetal in dry dichloromethane (2.5 mL) at 0 °C. After being stirred at the same temperature for 10 min, tetrapropylammonium perruthenate (TPAP, 3.2 mg) was added to the suspension. The mixture was stirred at room temperature for 1 h and filtered with the aid of a short pad of Celite. The filtrate was concentrated and the residue was purified by column chromatography on silica (hexane/AcOEt 6:1) to afford **20** (46.1 mg, 56% from **19**) as a crystalline solid: mp 109−110 °C (hexane/AcOEt); $[\alpha]^{28}_D$ +159.6 (*c* 1.0, $CHCl_3$); IR ($CDCl_3$) 1702 cm$^{-1}$; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 1.8−2.0 (m, 1H), 2.3−2.4 (m, 1H), 2.40 (s, 3H), 2.68 (dt, 1H,

(27) The product ratio was determined by the peak intensities in the 1H NMR spectrum: 5.16 and 5.20 ppm for the H-5 protons of **17**; 5.48 ppm for the H-3 proton of **18**.

$J$ = 14.0, 7.9 Hz), 2.84 (ddd, 1H, $J$ = 14.0, 8.6, 5.3 Hz), 3.81 (s, 3H), 3.91 (d, 1H, $J$ = 2.8 Hz), 4.25 (ddd, 1H, $J$ = 9.2, 4.1, 2.8 Hz), 4.70 (AB q, 2H, $J$ = 11.3 Hz, $\Delta\nu$ = 47 Hz), 5.28 (s, 1H), 6.89 (d, 2H, $J$ = 8.7 Hz), 7.1−7.4 (m, 11H); $^{13}$C NMR ($CDCl_3$) $\delta$ 21.4, 31.0, 31.5, 55.3, 71.7, 72.2, 78.7, 111.5, 114.0 (2C), 123.4, 126.1, 128.5 (2C), 128.6 (2C), 129.1, 129.9 (2C), 131.0 (2C), 135.2 (2C), 140.8, 141.2, 159.6, 160.6, 162.8. Anal. Calcd for $C_{28}H_{28}O_4S$: C, 73.02; H, 6.13. Found: C, 72.76; H, 6.15.

**(5*R*,6*S*)-5-(4-Methoxybenzyloxy)-6-(1-phenylethyl)-4-(*p*-tolylsulfonyl)-5,6-dihydro-2*H*-pyran-2-one (21).** To a solution of **20** (76 mg, 0.16 mmol) in dry dichloromethane (3 mL) was added dropwise *m*-CPBA (71 mg, 0.41 mmol) in dry dichloromethane (5 mL) at room temperature. The mixture was stirred for 2.5 h and diluted with $Et_2O$ (20 mL). The organic phase was washed with 1% NaOH and brine, dried, and concentrated to yield essentially pure **21** (72 mg, 89%) as a crystalline solid: mp 132−134.5 °C (hexane/AcOEt); $[\alpha]^{26}_D$ +105.2 (*c* 1.03, $CHCl_3$); IR ($CHCl_3$) 1728 cm$^{-1}$; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 1.8−1.96 (m, 1H), 2.2−2.4 (m, 1H), 2.44 (s, 3H), 2.68 (dt, 1H, $J$ = 14.0, 8.0 Hz), 2.82 (ddd, 1H, $J$ = 14.0, 8.5, 5.6 Hz), 3.79 (s, 3H), 4.18 (ddd, 1H, $J$ = 9.2, 4.3, 2.2 Hz), 4.41 (d, 1H, $J$ = 2.2 Hz), 4.43 (AB q, 2H, $J$ = 10.6 Hz, $\Delta\nu$ = 46 Hz), 6.60 (s, 1H), 6.81 (d, 2H, $J$ = 8.7 Hz), 7.05 (d, 2H, $J$ = 8.7 Hz), 7.1−7.35 (m, 5H), 7.34 (d, 2H, $J$ = 8.3 Hz), 7.80 (d, 2H, $J$ = 8.3 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 21.7, 30.8, 31.7, 55.2, 67.3, 72.3, 81.2, 113.7 (2C), 126.0, 126.3, 128.4 (2C), 128.6 (3C), 128.9 (2C), 129.7 (2C), 130.3 (2C), 134.1, 140.1, 146.3, 155.2, 159.5, 161.7; Anal. Calcd for $C_{28}H_{28}O_6S$: C, 68.27; H, 5.73. Found: C, 68.23; H, 5.80.

**(5*R*,6*S*)-4-Methoxy-5-(4-methoxybenzyloxy)-6-(1-phenylethyl)-5,6-dihydro-2*H*-pyran-2-one (22).** A mixture of **21** (49.2 mg, 0.10 mmol) and anhydrous potassium carbonate (21 mg) in dry MeOH (8 mL) was stirred at 0 °C for 0.5 h and then was treated with saturated $NH_4Cl$ solution (10 mL). The mixture was extracted with AcOEt and the extracts were washed with brine, dried, and concentrated to produce **22** (36.6 mg, 100%) as a colorless oil; $[\alpha]^{21}_D$ +161.0 (*c* 1.01, $CHCl_3$) for >99% ee determined by chiral HPLC [Chiralpak AS, hexane−2-propanol, 5:1, flow rate, 1.0 mL min$^{-1}$, retention time (+)-**22**, 47.4 min; (−)-**22**, 73.4 min]; IR ($CDCl_3$) 1704 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.88 (dddd, 1H, $J$ = 13.9, 8.7, 8.1, 4.9 Hz), 2.32 (dddd, 1H, $J$ = 13.9, 8.7, 8.1, 5.7 Hz), 2.66 (dt, 1H, $J$ = 13.9, 8.1 Hz), 2.78 (ddd, 1H, $J$ = 13.9, 8.7, 5.7 Hz), 3.70 (dd, 1H, $J$ = 2.5, 1.2 Hz), 3.75 (s, 3H), 3.80 (s, 3H), 4.18 (ddd, 1H, $J$ = 8.7, 4.9, 2.5 Hz), 4.57 (AB q, 2H, $J$ = 11.6 Hz, $\Delta\nu$ = 79 Hz), 5.20 (d, 1H, $J$ = 1.2 Hz), 6.86 (d, 2H, $J$ = 8.8 Hz), 7.05−7.4 (m, 7H); $^{13}$C NMR ($CDCl_3$) $\delta$ 30.9, 31.3, 55.3, 56.1, 70.8, 72.0, 77.6, 78.0, 92.4, 113.8 (2C), 126.1, 128.5 (3C), 129.2, 129.7 (2C), 140.9, 159.5, 166.1, 171.8, HRMS calcd for $C_{22}H_{24}O_5$ 368.1624, found 368.1621.

**(+)-Dihydrokawain-5-ol (3).** To a solution of **22** (14.8 mg, 0.04 mmol) was added DDQ (14 mg, 0.06 mmol) in $CH_2Cl_2$−$H_2O$ (20:1, 2.1 mL) at room temperature. The mixture was stirred vigorously for 4 h and quenched with an aqueous saturated sodium hydrogen carbonate (5 mL). The aqueous layer was extracted with $CHCl_3$, and the extracts were washed with brine, dried, and concentrated. The residue was purified by column chromatography on silica (hexane/AcOEt 1:1) to afford (+)-**3** (6.8 mg, 68%), whose NMR spectrum was in good agreement with that reported in the literature by Friesen et al.:[8] mp 89.5−90 °C ($Et_2O$) (lit.[5] mp 92 °C, lit.[6] mp 91−92 °C); $[\alpha]^{20}_D$ +72.6 (*c* 0.22, $CHCl_3$) for >99% ee determined by chiral HPLC [Chiralcel OD, hexane−2-propanol, 10:1, flow rate, 1.0 mL min$^{-1}$, retention time (+)-**3**, 33.3 min; (−)-**3**, 42.8 min][lit.[5] $[\alpha]^{20}_D$ +73 ($CHCl_3$); lit.[6] $[\alpha]^{20}_D$ +69 (*c* 0.001, $CHCl_3$)].

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**Supporting Information Available:** $^1$H NMR spectra for compounds **7**−**22** and X-ray crystallographic data for compound **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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