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A novel method for the asymmetric synthesis of 4,4-disubstituted 2-cyclopentenones from optically active 1-chlorovinyl *p*-tolyl sulfoxides and its application to the asymmetric total synthesis of (+)-α-cuparenone

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Abstract—Enantiomerically pure 1-chlorovinyl *p*-tolyl sulfoxides having two different substituents at the 2-position were synthesized from unsymmetrical ketones and (*R*)-(−)-chloromethyl *p*-tolyl sulfoxide in three steps. Treatment of the 1-chlorovinyl *p*-tolyl sulfoxides with cyanomethyllithium at −78°C to room temperature gave optically active 2-amino-1-cyano-5,5-disubstituted-1,3-cyclopentadienes in high yields with very high asymmetric induction from the stereogenic center of the sulfoxide moiety. A mechanism for the asymmetric induction is proposed. The products were treated with phosphoric acid in acetic acid at reflux temperature to give enantiomerically pure 4,4-disubstituted 2-cyclopentenones in good yields. As an application of this synthetic method, a relatively short (seven steps) total asymmetric synthesis of (+)-α-cuparenone from methyl 4-methylphenyl ketone is described. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

Cyclopentenones are important intermediates in organic synthesis. In addition, the cyclopentenone ring system is an abundantly distributed carbon skeletal structure in natural and unnatural organic compounds. Accordingly, new methods for the synthesis of cyclopentenones, including the optically active form, have been eagerly sought in recent years.[1]

Two famous recent methods for the construction of cyclopentenones are the Nazarov cyclization[2] and the Pauson–Khand reaction.[3] The Nazarov cyclization, however, is not usually useful for the synthesis of optically active cyclopentenones. On the contrary, the Pauson–Khand reaction has recently been extensively studied and the reaction has been extended to the synthesis of optically active cyclopentenones[3g] by using, for example, brucine *N*-oxide,[4b] (*S*)-methionine-derived amides,[4c] BINAP,[4d] and chiral phosphino-oxazoline ligand[4e] as chiral sources.[4] On the other hand, the construction of a quaternary carbon center is known to be a formidable task. In particular the asymmetric synthesis of a stereogenic quaternary carbon center is an interesting and challenging target in its own right.[5]

We recently reported a novel method for the synthesis of 4,4-disubstituted 2-cyclopentenones **6** from ketones **1** and chloromethyl *p*-tolyl sulfoxide **2** via 1-chlorovinyl *p*-tolyl sulfoxides **3** and enaminonitrile **5** (Scheme 1).[6] The mechanism for the reaction of **3** with cyanomethyllithium giving the enaminonitrile **5** was shown to be as follows.[6] First, cyanomethyllithium adds to the β-carbon of the alkenylsulfoxide **3** to afford the carbenoid **4** as an intermediate. Reaction of **4** with a second cyanomethyllithium followed by the Thorpe–Ziegler reaction[7] then gives the enaminonitrile **5**.

From this mechanism, it is expected that, if unsymmetrical ketones **1** and chiral chloromethyl *p*-tolyl sulfoxide **2** were used in this reaction, optically active enaminonitriles **5** and 4,4-disubstituted 2-cyclopentenones **6** could be synthesized. This expectation was already verified, and we have previously communicated a novel asymmetric synthesis of cyclopentenones having a quaternary stereogenic carbon **6**.[8] We report herein the details of the asymmetric synthesis of 4,4-disubstituted 2-cyclopentenones and, as an application of this method,

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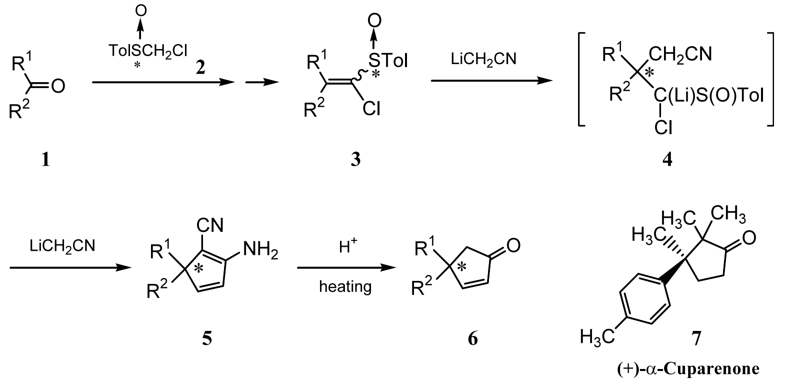
a relatively short asymmetric total synthesis of (+)-α-cuparenone **7**.

2. Results and discussion

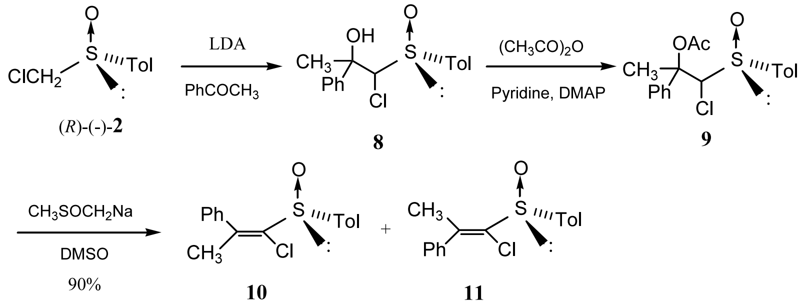
2.1. Synthesis of optically active 1-chlorovinyl *p*-tolyl sulfoxides and the reaction with cyanomethyllithium

The synthesis of optically active 1-chlorovinyl *p*-tolyl sulfoxides **10** and **11** was first investigated, starting from acetophenone and (*R*)-(−)-chloromethyl *p*-tolyl sulfoxide **2**[9] (Scheme 2). According to the previous paper,[6] (*R*)-**2** was treated with LDA at −50°C followed by acetophenone to give the adduct **8** in 99% yield as a mixture of two diastereomers. This mixture was acetylated with acetic anhydride in pyridine in the presence of DMAP at room temperature to afford the acetate **9** in 96% yield as a mixture of two diastereomers. Deacetoxylation of the acetates was successfully conducted with dimsylsodium in DMSO at room temperature to afford the optically active **10** and **11** (in a ratio of 4:1) in 90% yield. The isomers could be separated by silica gel flash column chromatography.[10] The geometry of the two isomers could be easily determined by ^{1}H NMR.[11]

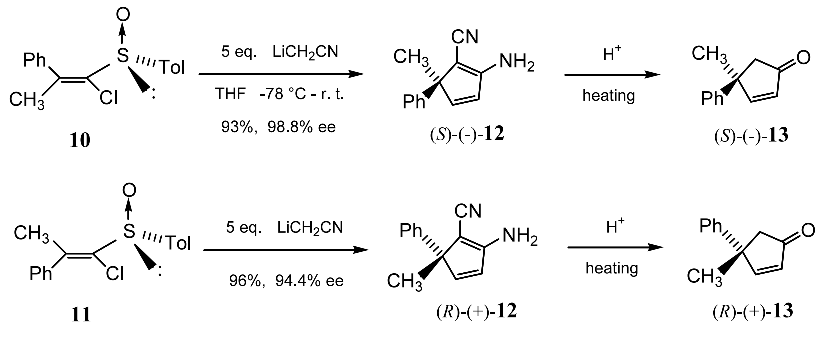
With the desired optically active 1-chlorovinyl *p*-tolyl sulfoxides in hand, we first investigated the reaction of **10** with cyanomethyllithium at −78°C to room temperature (Scheme 3). The reaction proceeded smoothly to afford the optically active enaminonitrile (−)-**12** in 93% yield. The enantiomeric purity was determined by HPLC using a chiral stationary column (Daisel CHIRALCEL OD, 10% 2-propanol in hexane) and we found that the enantiomeric purity was surprisingly



Scheme 1.



Scheme 2.



Scheme 3.

high (98.8%). The same reaction of **11** gave the enaminonitrile (+)-**12**, which was found to be the enantiomer of the product derived from **10**. The enantiomeric purity of (+)-**12** was found to be 94.4%. Interestingly, the geometrical isomers **10** and **11** gave the enantiomers of the enaminonitrile **12**, respectively, in high ee value. At this stage, the absolute configuration of (−)-**12** and (+)-**12** was not known.

2.2. Hydrolytic decyanation of the enaminonitriles giving 4,4-disubstituted-2-cyclopentenones and determination of the absolute configuration

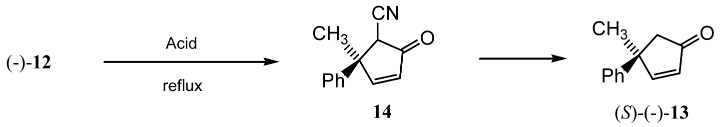
To ascertain the absolute configuration of the products ((−)-**12** and (+)-**12**), and to transform the products to the synthetically useful compound, 4,4-disubstituted-2-cyclopentenone, we investigated the hydrolytic decyanation of (−)-**12** (Table 1). The enaminonitrile (−)-**12** was heated at reflux in 1,4-dioxane with 5% H_2SO_4. The reaction gave the hydrolyzed cyano-enone **14** within 1 h; however, hydrolysis of the cyano group was found to be difficult (entry 1). After some investigation we found that phosphoric acid is effective for our purpose (entries 2 and 3). Finally, phosphoric acid in acetic acid containing a small amount of water was found to be the conditions of choice of this reaction (entries 4 and 5), and (−)-4-methyl-4-phenyl-2-cyclopentenone (−)-**13** was obtained in 86% yield. The conditions in entry 5 seem to be somewhat harsh; however, the reaction was comparatively clean and the mass balance was good (total yield 94%).

Comparing the sign of the specific rotation of the product enone (−)-**13** with that of the reported optically active **13**,[12] the absolute configuration of (−)-**13** was unambiguously determined to be *S*. At the same time, the absolute configuration of the enaminonitrile (−)-**12** was determined to be *S*.

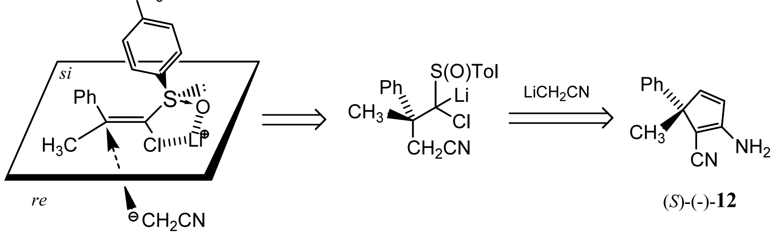
As shown in Scheme 4, (*S*)-(−)-**12** was derived from the adduct of (*E*)-1-chlorovinyl *p*-tolyl sulfoxide **10** with cyanomethyllithium, and the cyanomethyllithium must be selectively introduced from the *re* face of the vinyl sulfoxide. The observed high selectivity is most conveniently explained by assuming the formation of a five-membered chelate with the lithium ion between the oxygen of the sulfoxide and the chlorine, where the approach of the cyanomethyl anion takes place from the less-hindered *re* face avoiding the bulky *p*-tolyl group. This is the first example of asymmetric synthesis by conjugate addition to an α,β-unsaturated sulfoxide bearing a halogen atom on the α-position.[13]

To investigate the generality of these reactions, we studied this procedure further, starting from 2-hexanone (Scheme 5). The vinyl sulfoxides (*E*)-**15** and (*Z*)-**16** were synthesized from 2-hexanone in a similar way as described for the synthesis of **10** and **11**. In the deacetylation step, in this case, the ratio of **15** and **16** was almost 1:1. The vinyl sulfoxide **15** was treated with cyanomethyllithium in the same way as described above to obtain the desired enaminonitrile (−)-**17** in 97% yield with higher enantiomeric excess (99.2% ee) than the case of (*S*)-(−)-**12**.

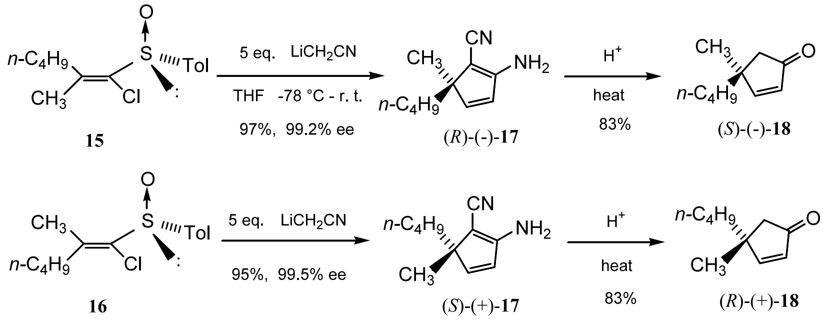
Table 1. Hydrolytic decyanation of (−)-**12** with acids under reflux conditions



Entry	Acid	Solvent	Time (h)	Yield (%)	
				14	(*S*)-(−)-**13**
1	5% H_2SO_4	1,4-Dioxane	77	65	Trace
2	AcOH, H_3PO_4	1,4-Dioxane	77	78	Trace
3	H_3PO_4	1,4-Dioxane	77	33	42
4	H_3PO_4	AcOH	16	39	50
5	H_3PO_4	AcOH	44	8	86



Scheme 4.



Scheme 5.

The enaminonitrile (−)-**17** was heated in a solution of phosphoric acid in acetic acid to give the enone (−)-**18** in 83% yield. Comparing the sign of the specific rotation of the enone (−)-**18** with that of the reported optically active **18**,[12] the absolute configuration of the enone was determined to be *S*. The result from the vinyl sulfoxide **16** is shown in Scheme 5. Again, the asymmetric induction is explained by the chelate model shown in Scheme 4. It is worth noting that the level of asymmetric induction reported in this paper is one of the highest attained in asymmetric synthesis using chiral sulfoxide.[13]

2.3. An application of this chiral synthesis of 4,4-disubstituted-2-cyclopentenone to an asymmetric synthesis of (+)-α-cuparenone

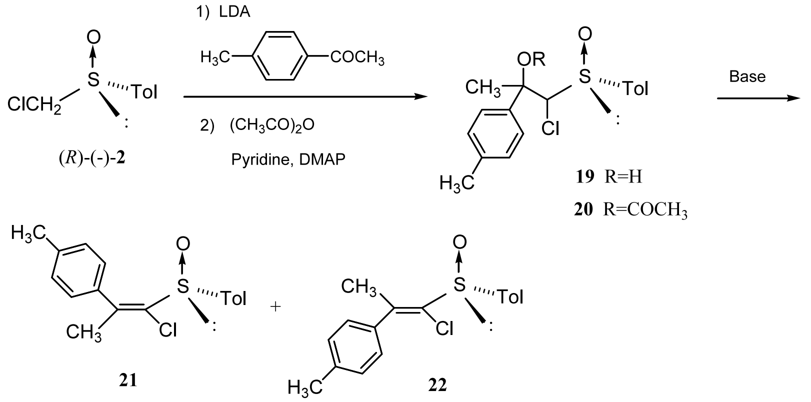
(+)-α-Cuparenone **7** was isolated from *Mayur Pankhi*,[14] and the absolute configuration was determined by Irie et al.[15] Interestingly, the enantiomer (−)-**7** was also isolated from the liverwort *Mannia fragrans*.[16] Several papers have been published for the synthesis of racemic α-cuparenone;[17] however, only few methods have been applied to the asymmetric synthesis of (+)-α- and (−)-α-cuparenone **7**.[18]

As an application of our above-mentioned method to synthesis of optically active natural products, we investigated a synthesis of enantiomerically pure (+)-α-cuparenone **7** (Scheme 6). Enantiomerically pure (*R*)-(−)-**2** was treated with LDA at −50°C followed by commercially available methyl 4-methylphenyl ketone to afford the adduct **19** in 98% yield as a mixture of two diastereomers. The hydroxyl group in **19** was acetylated to afford the acetate **20** in 95% yield. As mentioned above, in order to obtain the 1-chlorovinyl *p*-tolyl sulfoxide **21**, the acetate **20** was treated with base (see Table in Scheme 6). First, **20** was treated with dimsylsodium in DMSO under similar conditions to those described above; however, we came across a problem in this step: the reaction gave a mixture of **21** and **22** in up to 81% yield, but the outcome of the reaction was found to be quite sensitive to the conditions employed, especially with regard to the base employed. Sometimes, the reaction gave complex mixtures of products and low yields. In order to refine this step and to determine whether we could obtain the desired isomer **21** with higher selectivity, the reaction was investigated with other bases, and the results are shown in Scheme 6. The alkoxides worked; however, the yields were usually lower than those obtained using dimsylsodium. Finally, lithium diphenylamide was found to be the reagent of choice for this elimination. The reaction of the acetate with lithium diphenylamide gave over 93% yield of the desired 1-chlorovinyl *p*-tolyl sulfoxide **21** and **22** with good reproducibility. Despite the fact that we could not improve the ratio of **21**:**22**, the two isomers were easily separable by silica gel flash chromatography.[10]

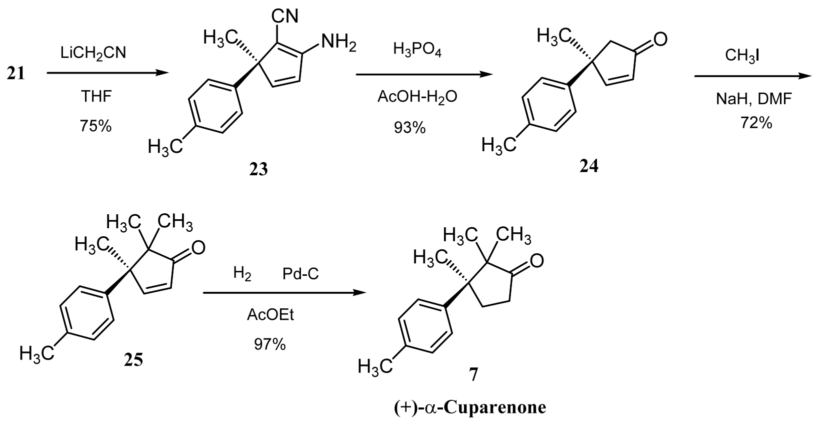
The major isomer **21** was treated with 5 equiv. of cyanomethyllithium to give optically active enaminonitrile **23** in 75% yield and the enantiomeric purity was found to be 96% by HPLC. One recrystallization of the product from ethyl acetate–hexane gave enantiomerically pure **23** ($[\alpha]_D^{20}$ −373.6). The enaminonitrile **23** was heated under reflux with H_3PO_4 in acetic acid to give the desired cyclopentenone **24** in 93% yield, which was treated with excess sodium hydride and iodomethane in DMF at room temperature to afford the dimethylated product **25** ($[\alpha]_D^{27}$ +35.6) in 72% yield. Finally, **25** was hydrogenated in ethyl acetate with catalytic Pd–C under atmospheric pressure of hydrogen to give a quantitative yield of (+)-α-cuparenone **7** as a crystalline solid (mp 51.5–52°C; $[\alpha]_D^{28}$ +172.5 (*c* 0.49 $CHCl_3$; over 99% ee); lit.[14] mp 52–53°C, $[\alpha]_D^{30}$ +177.1; lit.[18c] mp 53–54°C, $[\alpha]_D^{23}$ +163 (*c* 0.82, $CHCl_3$).

3. Experimental

All melting points are uncorrected. ^1H NMR spectra were measured in a $CDCl_3$ solution with JEOL JNM-LA 400 and 500 spectrometer. Electron-impact mass spectra (MS) were obtained at 70 eV by direct insertion. Silica gel 60 (Merck) containing 0.5% fluorescence reagent 254 and a quartz column were used for column chromatography and the products having UV absorption were detected by UV irradiation. In experiments requiring a dry reagent and solvent, diisopropylamine, acetonitrile, pyridine, DMF and DMSO were distilled from CaH_2 and THF was distilled from diphenylketyl. Acetone was dried over $CaSO_4$ and distilled before use.



Base	Solvent	21 and 22 Yield / %	21: 22
$CH_3S(O)CH_2Na$	DMSO	81	3 : 1
CH_3OK	THF	58	3.4 : 1
$(CH_3)_3COK$	THF	61	3 : 1
Ph_2NLi	THF	93	3 : 1



Scheme 6.

3.1. (R_S)-(E)-1-Chloro-2-phenyl-1-(p-tolylsulfinyl)-1-propene, 10 and (R_S)-(Z)-isomer, 11

A solution of (R)-**2** (377 mg; 2.0 mmol) in the minimum amount of dry THF (about 2 ml) was added dropwise with stirring to a solution of LDA (2.4 mmol) in 6.0 ml of THF in a flame-dried flask at −50°C. After 5 min, a solution of acetophenone (0.28 ml, 2.4 mmol) in THF was added to the reaction mixture and the reaction mixture was stirred for 3 min. The reaction was quenched with sat aq. NH_4Cl. The whole was extracted with AcOEt–hexane. The organic layer was dried over $MgSO_4$, and the solvent was evaporated to leave colorless crystals, which were purified by silica gel column chromatography to give 612 mg (99%) of **8** as colorless crystals (a mixture of two diastereomers). IR (KBr) 3332 (OH), 1036 (SO) cm^{-1}.

4-(Dimethylamino)pyridine (489 mg, 0.4 mmol) was added to a solution of **8** (612 mg, 2.0 mmol) in a mixture of acetic anhydride (3 ml) and pyridine (3 ml). The mixture was stirred at room temperature for 11 h. The acetic anhydride and pyridine were evaporated under vacuum and the residue was purified by silica gel column chromatography to give 667 mg (96%) of **9** as a colorless oil (a mixture of two diastereomers). IR (neat) 1746 (CO), 1241 (COC), 1059 (SO) cm^{-1}.

NaH (33 mg, 0.83 mmol) was added to DMSO (2.9 ml) and the suspension was stirred at room temperature for 4 h to afford dimsylsodium. To this was added with stirring a solution of **9** (100 mg, 0.29 mmol) in minimum amount (about 0.5 ml) of dry THF. After 8 min, the solution was diluted with ether (4 ml) and cooled in an ice bath. The reaction was quenched by adding a solution of acetic acid (1 ml) in 10 ml of ether. The whole was extracted with AcOEt–hexane, washed once with sat aq. NH_4Cl. The organic layer was dried over $MgSO_4$ and the products were purified by column chromatography to give **10** (60 mg; 72%) and **11** (15 mg; 18%). **10**: Colorless crystals; mp 82–83°C (AcOEt–hexane). IR (KBr) 1594, 1086, 1060 (SO), 813, 760, 700, 520 cm^{-1}; ^1H NMR δ 2.32 (3H, s, vinyl-CH_3), 2.40 (3H, s), 7.28–7.46 (9H, m). Anal. calcd for $C_{16}H_{15}ClOS$: C, 66.19; H, 5.21; Cl, 12.05; S, 11.04. Found: C, 66.35; H, 5.21; Cl, 12.05; S, 11.04%. $[\alpha]_D^{21}$ +280.5 (*c* 0.40, acetone). **11**: Colorless crystals; mp 77–78°C (AcOEt–hexane). IR (KBr) 1596, 1088, 1055 (SO), 892, 807, 705, 525 cm^{-1}; ^1H NMR δ 2.43 (3H, s), 2.62 (3H, s, vinyl-CH_3), 7.24–7.58 (9H, m). Anal. calcd for $C_{16}H_{15}ClOS$: C, 66.19; H, 5.21; Cl, 12.05; S, 11.04. Found: C, 66.28; H, 5.14; Cl, 12.00; S, 10.98%. $[\alpha]_D^{27}$ −9.3 (*c* 0.20, acetone).

3.2. (*S*)-(−)-2-Amino-1-cyano-5-methyl-5-phenyl-1,3-cyclopentadiene, 12

Acetonitrile (0.094 ml, 1.8 mmol) was added to a solution of *n*-BuLi (1.5 mmol) in 3 ml of dry THF at −78°C with stirring. The solution was stirred for 15 min, then a solution of **10** (87 mg, 0.3 mmol) in THF (1 ml) was added. The temperature of the reaction mixture was gradually allowed to warm to room temperature for 2 h and the reaction mixture was stirred at room temperature for 15 min. The reaction was quenched by sat aq. NH_4Cl. The whole was extracted with AcOEt–hexane. The organic layer was washed once with sat aq. NH_4Cl. The product was isolated by silica gel column chromatography to give (*S*)-**12** as colorless crystals (55 mg, 93%); mp 114–116°C (AcOEt–hexane). IR (KBr) 3454, 3423, 3353, 3231, 2168 (CN), 1642, 1610, 1544, 1420, 780, 766, 700 cm^{-1}; ^1H NMR δ 1.68 (3H, s), 4.69 (2H, br s), 6.07, 6.67 (each 1H, d, *J*=5.5 Hz), 7.2–7.3 (5H, m). ^{13}C NMR δ 22.2, 59.0, 88.0, 118.1, 125.1, 125.8, 126.9, 128.6, 140.4, 153.6, 158.9. MS *m*/*z* (%) 196 (M^+, 100), 181 (89), 152 (12). Calcd for $C_{13}H_{12}N_2$: M, 196.1000. Found: *m*/*z* 196.1004. $[\alpha]_D^{21}$ −428.5 (*c* 0.40, acetone; over 99% ee). (*R*)-**12**: $[\alpha]_D^{31}$ +418.8 (*c* 0.40, acetone; 98.1% ee).

3.3. (*S*)-4-Methyl-4-phenyl-2-cyclopntenone, 13

To a solution of (*S*)-**12** (29 mg, 0.15 mmol) in 10 ml of acetic acid was added phosphoric acid (85%, 4 ml) and water (0.6 ml). The reaction mixture was stirred and heated under reflux for 44 h. The reaction mixture was neutralized with 5% aq. NaOH followed by sat aq. NH_4Cl and the whole was extracted with AcOEt–hexane. The organic layer was dried over $MgSO_4$ and the solvent was evaporated to give an oil, which was purified by silica gel column chromatography to afford 22 mg (86%) of (*S*)-**13** as a colorless oil; IR (neat) 1714, 1588, 1495, 805, 762, 700 cm^{-1}; ^1H NMR δ 1.64 (3H, s), 2.57, 2.65 (each 1H, d, *J*=18.8 Hz), 6.21 (1H, d, *J*=5.5 Hz), 7.23–7.37 (5H, m), 7.69 (1H, d, *J*=5.5 Hz). MS *m*/*z* (%) 172 (M^+, 89), 157 (100), 129 (49), 43 (37). Calcd For $C_{12}H_{12}O$: M, 172.0888. Found: *m*/*z* 172.0883. $[\alpha]_D^{27}$ −119.0 (*c* 0.40, toluene; over 99% ee). (*R*)-**13**: $[\alpha]_D^{32}$ +115.1 (*c* 0.30, toluene; 94.4% ee).

3.4. (R_S)-(*E*)-1-Chloro-2-methyl-1-(*p*-tolylsulfinyl)-1-hexene, 15 and (R_S)-(*Z*)-isomer, 16

These 1-chrolovinyl *p*-tolyl sulfoxides were synthesized from 2-hexanone and (*R*)-(−)-**2** according to the procedure described above in similar yields. **15**: Light yellow oil; IR (neat) 2957, 2930, 1603, 1465, 1083, 1057 (SO), 807, 520 cm^{-1}; ^1H NMR δ 0.98 (3H, t, *J*=7.2 Hz), 1.44 (2H, sextet, *J*=7.2 Hz), 1.49–1.57 (1H, m), 1.58–1.66 (1H, m), 2.00 (3H, s), 2.41 (3H, s), 2.70–2.77 (2H, m), 7.31, 7.48 (each 2H, d, *J*=8.3 Hz). MS *m*/*z* (%) 270 (M^+, 18), 255 (38), 253 (100), 175 (28), 91 (33). Calcd for $C_{14}H_{19}ClOS$: M, 270.0843. Found: *m*/*z* 270.0841. $[\alpha]_D^{24}$ +187.6 (*c* 0.40, acetone). **16**: Colorless crystals; mp 68–70°C (AcOEt–hexane). IR (KBr) 2954, 2927, 1684, 1085, 1054 (SO), 884, 809 cm^{-1}; ^1H NMR δ 0.91 (3H, t, *J*=7.3 Hz), 1.29–1.37 (2H, m), 1.40–1.51 (2H, m), 2.31 (3H, s), 2.34 (2H, t, *J*=7.8 Hz), 2.41 (3H, s), 7.31, 7.46 (each 2H, d, *J*=8.1 Hz). MS *m*/*z* (%) 270 (M^+, 85), 253 (93), 211 (62), 140 (72), 92 (96), 89 (100). Anal. calcd for $C_{14}H_{19}ClOS$: C, 62.09; H, 7.07; Cl, 13.09; S, 11.84. Found: C, 62.22; H, 6.89; Cl, 12.98; S, 11.89%. High Mass: M, 270.0845. Found: *m*/*z* 270.0851. $[\alpha]_D^{27}$ +133.4 (*c* 0.40, acetone).

3.5. (*R*)-2-Amino-5-butyl-1-cyano-5-methyl-1,3-cyclopentadiene, 17

Colorless crystals; mp 56–58°C (AcOEt–hexane). IR (KBr) 3451, 3350, 3236, 2929, 2169 (CN), 1660, 1640, 1610, 1547, 1420, 782 cm^{-1}; ^1H NMR δ 0.85 (3H, t, *J*=7.3 Hz), 1.08–1.16 (2H, m), 1.21–1.28 (2H, m), 1.25 (3H, s), 1.61–1.66 (2H, m), 4.51 (2H, s, NH), 6.00, 6.42 (each 1H, d, *J*=5.5 Hz). MS *m*/*z* (%) 176 (M^+, 27), 133 (50), 120 (66), 119 (100). Anal. calcd for $C_{11}H_{16}N_2$: C, 74.96; H, 9.15; N, 15.89. Found: C, 75.06; H, 8.98; N, 15.78%. High Mass: M, 176.1313. Found: *m*/*z* 176.1323. $[\alpha]_D^{29}$ −176.5 (*c* 0.40, acetone). (*S*)-**17**: $[\alpha]_D^{28}$ +172.7 (*c* 0.40, acetone).

3.6. (*S*)-4-Butyl-4-methyl-2-cyclopentenone, 18

Colorless oil; IR (neat) 2959, 2930, 2872, 1716, 1586, 1459, 1411, 802 cm^{-1}; ^1H NMR δ 0.89 (3H, t, *J*=7.0 Hz), 1.14–1.33 (4H, m), 1.21 (3H, s), 1.42–1.56 (2H, m), 2.12, 2.30 (each 1H, d, *J*=18.8 Hz), 6.03, 7.44 (each 1H, d, *J*=5.6 Hz). MS *m*/*z* (%) 152 (M^+, 28), 96 (82), 95 (100), 67 (65), 41 (50), 18 (76). Calcd for $C_{10}H_{16}O$: M, 152.1200. Found: *m*/*z* 152.1205. $[\alpha]_D^{32}$ −43.1 (*c* 0.40, toluene). (*R*)-**18**: $[\alpha]_D^{30}$ +41.6 (*c* 0.35, toluene).

3.7. (R_S)-(*E*)-1-Chloro-2-(4-methylphenyl)-1-(*p*-tolylsulfinyl)-1-propene, 21 and (R_S)-(*Z*)-isome, 22

A solution of (*R*)-**2** (1.89 g, 10.0 mmol) in dry THF (7 ml) was added dropwise with stirring to a solution of LDA (12.0 mmol) in THF (30 ml) in a flame-dried flask at −50°C. After 5 min, a solution of 4′-methylacetophenone (1.6 ml, 12.0 mmol) in THF was added to the reaction mixture and the reaction mixture was stirred for 2 min. The reaction was quenched with sat aq. NH_4Cl. The whole was extracted with AcOEt–hexane. The organic layer was dried over $MgSO_4$, and the solvent was evaporated to leave a colorless oil, which was purified by silica gel column chromatography to give **19** as a colorless oil (3.16 g, 98% mixture of two diastereomers). IR (neat) 3313 (OH), 1041 (SO), 819 cm^{-1}.

4-(Dimethylamino)pyridine (208 mg, 1.7 mmol) was added to a solution of **19** (3.1 g, 9.54 mmol) in a mixture of acetic anhydride (13 ml) and pyridine (13 ml). The mixture was stirred at room temperature for 19.5 h. The acetic anhydride and pyridine were evaporated under vacuum and the residue was purified by silica gel column chromatography to give **20** as a colorless oil (3.32 g, 95% a mixture of two diastereomers). IR (neat) 1749 (CO), 1239 (COC), 1059 (SO), 812 cm^{-1}.

A solution of **20** (624 mg, 1.71 mmol) in 11 ml of dry THF was added dropwise with stirring to a solution of Ph_2NLi (2.4 mmol) in 11 ml of THF in a flame-dried flask at 0°C. After 8 min, the reaction was quenched by adding sat aq. NH_4Cl. The whole was extracted with AcOEt–hexane, washed once with sat. aq. NH_4Cl. The organic layer was dried over $MgSO_4$. The products were purified by column chromatography to give a mixture of **21** and **22** (484 mg, 93%). These were separated on silica gel flash column chromatography and the ratio of **21** and **22** was found to be 3:1. **21**: Colorless oil. IR (neat) 2923, 1589, 1492, 1274, 1084, 1048 (SO), 808, 754 cm^{-1}; ^{1}H NMR δ 2.30 (3H, s, vinyl-CH_3), 2.39 (3H, s) 2.40 (3H, s), 7.19–7.44 (8H, m). MS *m*/*z* (%) 304 (M^+, 42), 256 (48), 195 (19), 153. (41), 129 (100), 115 (45), 91 (32). Calcd for $C_{17}H_{17}ClOS$: M, 304.0687. Found: *m*/*z* 304.0685. $[\alpha]_D^{21}$ +369 (*c* 0.60, acetone). **22**: Colorless oil. IR (neat) 2921, 1588, 1494, 1089, 1061 (SO), 891, 811 cm^{-1}; ^{1}H NMR δ 2.35 (3H, s, vinyl-CH_3), 2.42 (3H, s), 2.60 (3H, s) 7.15–7.57 (8H, m). $[\alpha]_D^{21}$ −18.8 (*c* 0.40, acetone).

3.8. (*S*)-(−)-2-Amino-1-cyano-5-methyl-5-(4-methylphenyl)-1,3-cyclopentadiene, 23

Acetonitrile (0.105 ml, 2.0 mmol) was added to a solution of *n*-BuLi (2.0 mmol) in 6 ml of dry THF at −78°C with stirring. The solution was stirred for 15 min, then a solution of **21** (120 mg, 0.4 mmol) in THF (1 ml) was added dropwise. The temperature of the reaction mixture was gradually allowed to warm to room temperature for 2 h and the reaction mixture was stirred at room temperature for 30 min. The reaction was quenched by sat aq. NH_4Cl. The whole was extracted with AcOEt–hexane. The organic layer was washed once with sat aq. NH_4Cl. The product was isolated by silica gel column chromatography to give 62.4 mg (75%) of (*S*)-**23** as colorless crystals; mp 85–86°C (AcOEt–hexane). IR (KBr) 3463, 3344, 2925, 2172 (CN), 1646, 1609, 1541, 1514, 1420, 1237, 1088, 1060, 822, 780 cm^{-1}; ^{1}H NMR δ 1.66 (3H, s), 2.31 (3H, s), 4.60 (2H, brs, NH), 6.06, 6.67 (each 1H, d, $J=5.5$ Hz), 4.10, 7.20 (each 2H, d, $J=7.9$ Hz). MS *m*/*z* (%) 211 (M^+, 18), 210 (100), 209 (20), 195 (90), 168 (11). Anal. calcd for $C_{14}H_{14}N_2$: C, 79.97; H, 6.71; N, 13.32. Found: C, 79.79; H, 6.57; N, 13.20%. $[\alpha]_D^{20}$ −373.6 (*c* 0.40, acetone; over 99% ee).

3.9. (*S*)-4-Methyl-4-(4-methylphenyl)-2-cyclopntenone, 24

To a solution of **23** (336 mg, 1.59 mmol) in acetic acid (112 ml) was added phosphoric acid (85%, 43 ml) and water (6.4 ml). The reaction mixture was stirred and heated under reflux for 50 h. The reaction mixture was neutralized with 3% aq. NaOH followed by sat aq. NH_4Cl and the whole was extracted with AcOEt–hexane. The organic layer was dried over $MgSO_4$ and the solvent was evaporated to give an oil, which was purified by silica gel column chromatography to afford 275 mg (93%) of **24** as a colorless oil; IR (neat) 2965, 2923, 1713, 1588, 1514, 1408, 1339, 1203, 1169, 1054, 818, 763 cm^{-1}; ^{1}H NMR δ 1.62 (3H, s), 2.33 (3H, s), 2.55, 2.63 (each 1H, d, $J=8.8$ Hz), 6.19 (1H, d, $J=5.5$ Hz, d), 7.15 (4H, s), 7.66 (1H, d, $J=5.5$ Hz). MS *m*/*z* (%) 186 (M^+, 43), 171 (100), 143 (20), 128 (25), 115 (14), 91 (8). Calcd for $C_{13}H_{14}O$: M, 186.1044. Found: *m*/*z* 186.1053. $[\alpha]_D^{27}$ −134.3 (*c* 0.46, toluene; over 99% ee).

3.10. (*S*)-4,5,5-Trimethyl-4-(4-methylphenyl)-2-cyclopentenone, 25

A solution of cyclopentenone **24** (132 mg, 0.71 mmol) in the minimum amount (about 0.2 ml) of dry DMF wad added over 0.25 h to a stirred solution of NaH (60% in mineral oil, 67.2 mg) in DMF (0.6 ml). The reaction was stirred for 30 min, and CH_3I was added dropwise (0.31 ml, 1.68 mmol). The mixture was stirred for 24 h at 20°C. The reaction was quenched with sat aq. NH_4Cl. The whole was extracted with AcOEt–hexane, washed once with sat aq. NH_4Cl. The organic layer was dried over $MgSO_4$ and the product was purified by column chromatography to give 109 mg (72%) of **25** as a colorless oil. IR (neat) 2972, 2923, 1709, 1588, 1512, 1450, 1385, 1264, 1185, 1122, 815 cm^{-1}; ^{1}H NMR δ 0.53 (3H, s), 1.19 (3H, s), 1.45 (3H, s) 2.34 (3H, s), 6.22 (1H, d, $J=5.8$ Hz), 7.05, 7.14 (each 2H, d, $J=5.5$ Hz), 7.75 (1H, d, $J=5.8$ Hz). MS *m*/*z* (%) 214 (M^+, 34), 199 (100), 185 (20), 171 (10), 156 (11), 141 (20), 128 (20). Calcd for $C_{15}H_{18}O$: M, 214.1356. Found: *m*/*z* 214.1354. $[\alpha]_D^{27}$ +35.6 (*c* 0.40, acetone; over 99% ee).

3.11. (*S*)-(+)-α-Cuparenone, 7

A solution of the cyclopentenone **25** (122 mg, 0.57 mmol) and 10% Pd–C (174 mg) in ethyl acetate (6 ml) was evacuated and purged three times with hydrogen and then stirred under 1 atm of hydrogen for 1 h. The catalyst was then filtered off through a short pad of silica gel and the solution was concentrated and the product was purified by silica gel column chromatography to yield α-cuparenone (120 mg, 97%): mp 51.5–52°C (hexane). IR (KBr) 2968, 2923, 2868, 1731, 1512, 1463, 1407, 1378, 1259, 1096, 1059, 817 cm^{-1}; ^{1}H NMR δ 0.62 (3H, s), 1.17 (3H, s), 1.90 (1H, m), 1.26 (3H, s), 2.34 (3H, s), 2.40 (2H, m), 2.60 (1H, m) 7.15–7.28 (4H, m). MS *m*/*z* (%) 216 (M^+, 16), 145 (20), 132 (11), 97 (11), 85 (11), 71 (16), 57 (24), 43 (16), 28 (19), 18 (100), 17 (22). Calcd for $C_{15}H_{20}O$: M, 216.1516. Found: *m*/*z* 216.1514. $[\alpha]_D^{28}$ +172.5 (*c* 0.49, $CHCl_3$; over 99% ee).

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