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Highly Enantioselective Synthesis of a Corey Prostaglandin Intermediate

Baptiste RONAN and Henri B. KAGAN*

Laboratoire de Synthèse Asymétrique, URA CNRS 255
ICMO, Université Paris-Sud,91405-Orsay, France.

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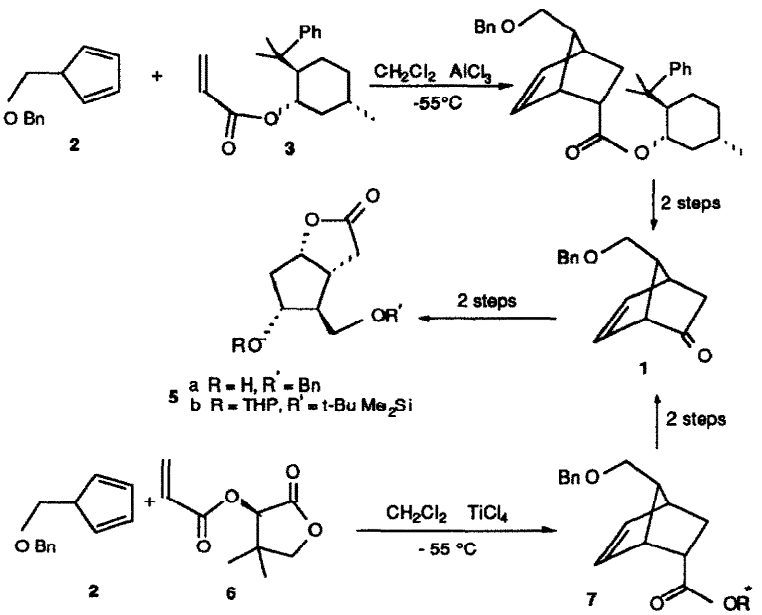
Summary

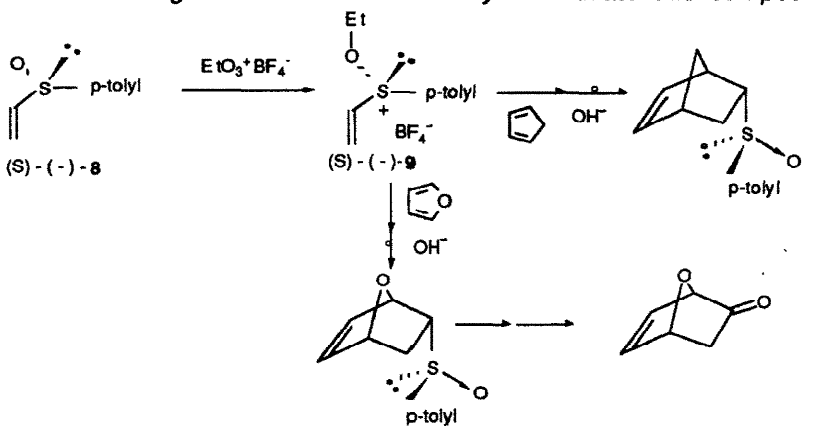
(R)-p-tolyl vinyl sulfoxide **8** was transformed into the corresponding ethoxysulfonium compound **9** which smoothly underwent reaction with 5-benzyloxymethyl-1,3-cyclopentadiene **2** to give, after basic treatment, the bicyclic sulfoxide **10** with very high de. This compound was transformed in three steps into enantiomerically pure norbornenone **1**, a key intermediate in some Corey syntheses of prostaglandins.

Lactones **5** are key compounds in the Corey synthesis of optically active prostaglandins[1-3]. A resolution step on a hydroxy acid precursor[3] was required to provide optically active material in most of these approaches. Asymmetric synthesis was also utilized by Corey to prepare ketone **1**, the precursor of lactone **5a**[4a]. Ketone **1** was obtained by the reactions depicted in Scheme 1, involving an asymmetric Diels-Alder reaction using (+)-phenylmenthol as an efficient chiral auxiliary. (+)-Phenylmenthol is derived from unnatural (S)-(-)-pulegone. This latter was prepared in two steps from (-)-citronellol. Later Corey realized a Diels-Alder reaction between 3-acrylyl-1,3-oxazolidin-2-one and **2** catalyzed by a chiral aluminum complex[4b]. The Diels-Alder adduct was obtained in 95 % ee and can also lead to ketone **1**. Very recently a research group from Nissan Chemical published another asymmetric synthesis of Corey intermediate **1** using a Diels-Alder reaction between cyclopentadiene and the acrylate of D-pantolactone **6** in presence of $TiCl_4$ (Scheme 1)[5]. The cycloadduct **7** was isolated in 79 % yield with 94 % de. A crystallization afforded **7** (100 % de) in 80 % yield. This intermediate was transformed into ketone **1** and then into the Corey lactone **5b**. This asymmetric synthesis used a commercially available chiral auxiliary (D-pantolactone). We wish to describe an alternate route to intermediate **1**, starting from a chiral vinyl sulfoxide.



Scheme 1

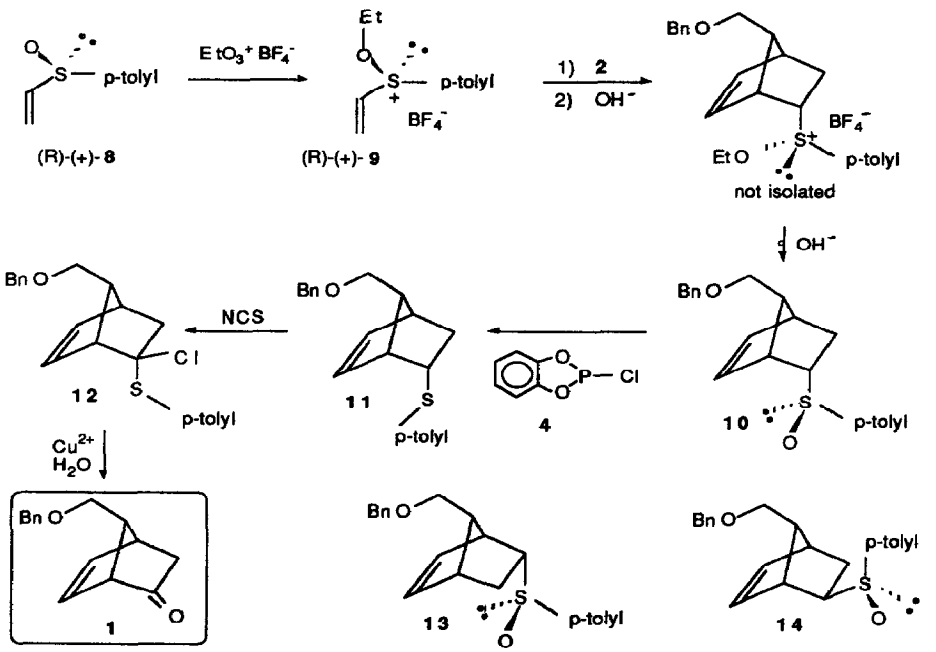
We recently described (Scheme 2) that O-alkylation of vinyl sulfoxide **8** by Meerwein's reagent was an efficient way to activate this compound in



Scheme 2 (from ref. 6)

Diels-Alder reactions, permitting them to be carried out at temperatures as low as -78°C[6]. TMSOTf was also a good activator, even, in catalytic amounts, but stereoselectivities were lower. We now apply this methodology to the synthesis of Corey intermediate **1**, as described in Scheme 3.

(R)-(+)-p-tolyl vinyl sulfoxide **8** (100 % ee) was easily prepared by the Andersen method by reaction of vinylmagnesiumchloride with commercially available (+)-menthyl (R)-p-toluenesulfinate[6,7]. Treatment of **8** with Et_3O^+ BF_4^- in methylene chloride at -78°C produced salt **9** to which was added one equivalent of 5-benzyloxy-



Scheme 3

methyl-1,3-cyclopentadiene **2**[2]. The Diels-Alder reaction smoothly occurred at -30°C. Quenching with aqueous sodium hydroxide converted the sulfonium cycloadduct into endo sulfoxide **10** (with inversion of configuration at sulfur[6]). The Diels-Alder reaction occurred with very high stereoselectivity giving mainly the endo diastereomer (endo/exo >

98:2) as detected by ^1H nmr spectroscopy. Moreover of the two possible endo cycloadducts it was diastereomer **10** which was largely predominent (de > 96 %). The transformation of cycloadduct **10** into norbornenone **1** was achieved by a standard methodology[6], reduction by 2-chloro-1,3,2-benzodioxa-phosphole **4** gave sulfide **11**. This latter was chlorinated by NCS to give α-chlorosulfide **12** which was not purified but was treated by $CuO/CuCl_2$ (oxidative cleavage) to produce enantiomerically pure norbornenone **1**. The specific rotation ($[\alpha]_D^{25}$=-454 (c=1.03, $CHCl_3$)) compared to literature data[4] indicates that the absolute configuration was as described in **1**[9]. The yield for the transformation of starting sulfoxide **8** into bicyclic sulfoxide **10** is 59 %. The degradation of **10** into the Corey intermediate **1** was achieved in 32 % yield (for the three steps) and was not optimized.
In conclusion this work shows an additional example of the usefulness of chiral sulfoxides as starting material in highly enantioselective asymmetric Diels-Alder reactions[10].

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Experimental

Apparatus
^1H nmr spectra were registered on Bruker AM 200 or 250 MHz, in $CDCl_3$ using TMS as internal standard. Chemical shifts were expressed in ppm (s=singlet, d=doublet, t=triplet, m=multiplet). Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Mass spectra were recorded on Riber Mag R10-10 instrument. Microanalyses were performed at the Service de microanalyse du CNRS (Gif sur Yvette).

Chemicals
Methylene chloride was distilled over calcium hydride and stored under argon. THF and diethyl ether were distilled over sodium benzophenone ketyl before use. Vinylmagnesium chloride, (1R,2S,5R)-(-)-Menthyl (S)-p-toluenesulfinate and Et_3O^+ BF_4^- were purchased from Fluka. Thallium cyclopentadienide and benzyl chloromethyl ether were purchased from Janssen and Aldrich respectively.

2-chloro-1,3,2-benzodioxaphosphole was synthesized according to reference 8.

(R)-(+)-p-tolyl vinyl sulfoxide **8**[6,7]

To a solution of 5 g of (1R,2S,5R)-(-)-menthyl (S)-p-toluenesufinate (17 mmol) in 50 mL of ether at rt was rapidly added 10 mL of vinylmagnesiumchloride (17 mmol, 1.73 M in THF) under argon with vigorous stirring. After 10 min, the reaction was quenched by addition of 30 mL water and 30 mL of saturated aqueous solution of NH_4Cl. An ether extraction, washing with saturated NaCl solution, drying over $MgSO_4$, concentration in vacuo and flash chromatography on silica gel (AcOEt/cyclohexane=1:1) gave 2.1 g (75 %) of **8** (100 % ee) as a colorless oil.
$[\alpha]_D^{25}$= + 446 (c=1.65, acetone), lit.[7]: $[\alpha]_D^{25}$= + 390 (c=1.2, acetone).
^1H nmr: δ 7.56-7.30 (4 H, dd). 6.59 (1 H, dd). 6.20 (1 H, dd); 5.89 (1 H, d); 2.40 (3 H, s).

(R)-(+)-Ethoxy p-tolyl vinyl sulfonium tetrafluoborate **9**[6]

To a solution of 0.83 g of (+)-(R)-p-tolyl vinyl sulfoxide **8** (5 mmol) in 5 mL CH_2Cl_2 was added 0.95 g of $Et_3O^+BF_4^-$ (5 mmol). The reaction mixture was purged with argon and stirred 1.5 h at rt. Diethyl ether (20 mL) was added to precipitate the salt as an oil. This solution was cooled at -78°C and the ethereal fraction was discarded.The oil was then washed with ether 3 times. Drying under reduced pressure gave 1.27 g (90 %) of **9** as a colorless oil.
$[\alpha]_D^{25}$= +59 (c=1, $CHCl_3$)..
^1H nmr: δ 8.00-7.51 (4 H, dd); 7.28-7.16 (1 H, m); 6.80-6.62 (2 H, m); 4.57-4.38 (2 H, m); 2.50 (3 H, s); 1.46 (3 H, s).

5-Benzyloxymethyl-1,3-cyclopentadiene **2**

Preparation according to procedure of ref. 2.
To a suspension of 8.65 g $TlCp_2$ (32.1 mmol) in 13 mL of diethyl ether under argon was added at -20°C 4.9 mL of freshly distilled chloromethyl benzyl ether (35.3 mmol). After stirring 20 h at -20°C insoluble solid (TlCl) was quickly filtered at -20°C and washed 3 times by 5 mL ether at this temperature. Concentration of ether solution (under 1 mm Hg) at

-20°C for 1 h gave 5-benzyloxymethyl-1,3-cyclopentadiene **2** devoid of isomerized product as shown by ^1H nmr (7.40-7.25 (m, 5 H); 6.49 (m, 2 H); 4.55 (s, 2 H); 3.46 (s, 2 H)). The crude product was used as such for the Diels-Alder reaction. In order to have good results in the Diels-Alder reaction it is necessary to use the above workup (evaporation of ether during 1 h under 1 mm Hg) in order to also remove traces of cyclopentadiene which otherwise compete with benzyloxymethyl-cyclopentadiene **2** in the Diels-Alder reaction.

(1R,2S,4S,7R,S_S)-(-)-bicyclo [2.2.1] hep-7-benzyloxymethyl-5-ene-2-p-toluenesulfinyl **10**

5-Benzyloxymethyl-1,3-cyclopentadiene **2** prepared as above was diluted in 5 mL CH_2Cl_2 at -20°C under argon. To this solution was added 2.63 g of sulfonium salt **9** (9.3 mmol) diluted in 15 mL of CH_2Cl_2 at -20°C under argon. After stirring 50 h at -30°C the reaction was quenched by addition of 75 mL 0.15 N NaOH (11 mmol). After stirring 30 min at rt the product was extracted with CH_2Cl_2..Washing with water, drying over $MgSO_4$ and concentration in vacuo gave 7.28 g of a green oil. ^1H nmr analysis showed endo adduct (endo/exo > 95:5), as well as a very high de (> 96 %). (1R,2S,4S,7R,S_S)-(-)-bicyclo [2.2.1] hep-7-benzyloxymethyl-5-ene-2-p-toluenesulfinyl **10** was obtained pure as a yellow oil (no traces of other diastereomers) by flash chromatography on silica gel (AcOEt/cyclohexane=1:1) in 66 % yield.
$[\alpha]_D^{25}$=-181.5 (c=1.11, acetone).
^1H nmr: δ 7.57-7.26 (9 H, m); 6.23 (2 H, m); 4.42 (2 H, s); 3.41 (4 H, m); 2.88 (1 H, s); 2.40 (3 H, s); 2.11 (1 H, t); 1.61 (1 H, m); 0.85 (1 H, m).
MS: 353 (100 %) (MH^+).
Analysis $C_{22}H_{24}O_2S$= 352 Calc.(%) C 74.96, H6.86, O 9.08, S 9.10
Found (%) C 74.34, H 6.47, O 10.25, S 8.94
Diastereomeric endo sulfoxide (1S,2R,4R,7S,S_S) **13** was detected in the crude product by ^1H nmr signals: δ 6. 38 (2 H, m); 3. 20 (1 H, m) and 2.72 (1 H, s). Diastereomeric exo sulfoxide (1S,2S,4R,7S,S_S) **14** was also detectable by ^1H nmr signals: δ 5.93 (2H, m); 2.90 (1 H, s); 2.59 (1 H, dd); 2.50 (1 H, t); 1.00 (1 H, dd).

(1R,2S,4S,7R)-(-)-Bicyclo [2.2.1] hept-7-benzyloxymethyl-5-ene-2-p-tolylsulfenyl **11**

To a stirred solution of 1.38 g (4 mmol) of **10** and 0.32 mL of pyridine in 7 mL benzene was slowly added 0.69 g (4 mmol) of 2-chloro-1,3,2-

benzodioxaphosphole **4**[8] (4 mmol) A precipitate formed almost immediately. After 1 h, 2N NaOH (5 mL) was added and the benzene layer washed several times with aqueous NaOH (4 %) and finally with water. The benzene solution was dried ($MgSO_4$), the solvent evaporated and the residue purified by flash chromatography on silica gel (ether/hexane=1:5) to give 1.03 g of **11** (77 %) as a colorless oil.
$[\alpha]_D^{25}$=-121.4 (c=0.98, acetone).
^1H nmr: δ 7.38-7.07 (9 H, m); 6.05 (2 H, m); 4.41 (2 H, s); 3.65 (1 H, m); 3.35 (2 H, d); 3.00 (1 H, s); 2.83 (1 H, s); 2.31, 4 H, m); 2.10 (1 H, t); 0.93 (1 H, dd).
MS (NH_3, CI): m/z 337 (66%)(MH^+); 354 (2%) (MNH_4^+).
Analysis $C_{22}H_{24}OS$ = 336 Calc(%): C 78.53, H 7.19, O 4.75, S 9.53
Found(%): C 78.31, H 7.02, O 5.18, S 9.48

(1R,4S,7R)-(-)-Bicyclo [2.2.1] hept-7-benzyloxymethyl-5-ene-2-one **1**

A mixture of 0.84 g of sulfide (-)-**11** (2.5 mmol), 0.34 g of NCS (2.5 mmol) and 4 mmL CCl_4 was treated under reflux under argon for 1 h. Cooling, fitration and evaporation furnished a residue which was immediately treated with acetone (1.1 mL), water (0.36 mL), $CuCl_2$ (0.36 mL), CuO (0.71 g) and the mixture was heated under reflux for 30 min. It was then cooled, filtered, diluted with water (10 mL) and extracted with ether. Drying ($MgSO_4$) and evaporation of the ether gave a yellow oil (0.60 g) which was purified by flash chromatography on silica gel (ether/hexane=1:3) (R_f of **1** is 0.2; reagent for visualization was prepared from 10 g vanilin, 2.7 g H_2SO_4 and 100 mL 95 % ethanol) giving **1** (0.24 g.Yield: 42 %) as a yellow oil.
$[\alpha]_D^{25}$=-454 (c=1.03, $CHCl_3$), (lit[4]: $[\alpha]_D^{25}$=-365 (c=1.29, $CHCl_3$)).
^1H nmr: δ 7.31 (5 H, m); 6.40 (1 H, m); 5.94 (1 H, m); 4.48 (2 H, s); 3.53 (2 H, d); 3.15 (1 H, s); 3.01 (1 H, m); 2.74 (1 H, t); 2.00 (2 H, m).
Analysis $C_{15}H_{16}O_2$ = 228 Calc (%): C 78.92, H 7.06, O 14.02
Found (%): C 78.50, C 7.14, O 14.87

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(9) This is in agreement with our previous results concerning Diels-Alder reaction with cyclopentadiene or furan (Scheme 2)[6], where (S)-(-)-vinyl p-tolyl sulfoxide led to cycloadducts whose absolute configurations are as indicated in Scheme 2.
(10) In addition to ref.6 see for example refs 11-14.
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