

## Chiral Acyl Anion Equivalents: Asymmetric Synthesis of 11-Deoxy-*ent*-Prostaglandin Intermediates<sup>1</sup>

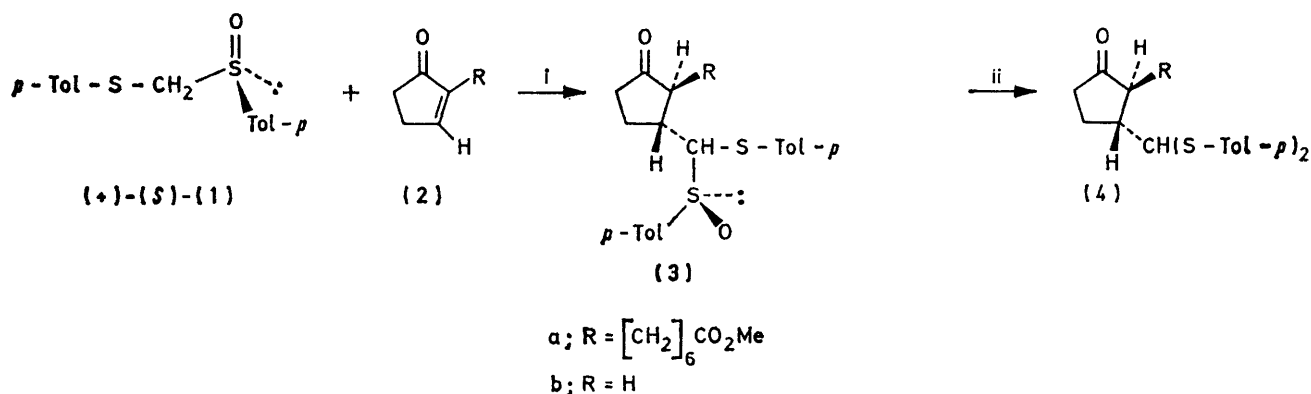
By Lino Colombo, Cesare Gennari, Giuseppe Resnati, and Carlo Scolastico,\* Istituto di Chimica Organica dell'Università, Centro C.N.R. delle Sostanze Organiche Naturali, Via C. Saldini 50, 20133 Milano, Italy

Conjugate addition of the chiral formyl anion equivalent *p*-tolyl *p*-tolylthiomethyl sulphoxide (+)-(*S*)-(1) to the cyclopentenone derivative (2a) leads to the adduct (3a) in 45% yield with high diastereoselectivity. Reduction of (3a) gives the dithioacetal (4a), an interesting optically pure intermediate in the synthesis of 11-deoxy-*ent*-prostanoids. The high selectivity, contrasting with a lower selectivity observed using cyclopentenone, is to be ascribed to more severe steric demands in the transition state.

WITHIN the past few years, the syntheses of prostaglandins *via* conjugate additions of organometallic derivatives to substituted cyclopentenones have been the subject of intensive investigations.<sup>2</sup> We now report the critical experimental details of our studies necessary for the successful elaboration of the chiral, non-racemic prostanoid acid skeleton.

### RESULTS AND DISCUSSION

The enone (2a) was added at  $-78^{\circ}\text{C}$  to the anion of (1), prepared by treating (+)-(*S*)-(1)<sup>3</sup> with  $\text{Bu}^{\text{n}}\text{Li}$  in tetrahydrofuran (THF) at  $-20^{\circ}\text{C}$ : after 30 min at  $-78^{\circ}\text{C}$ , usual work-up and chromatography on silica gel gave the 1,2-addition product in 50% yield. The same reaction gave the 1,4-addition product (3a) in 45% yield when hexamethylphosphoric triamide (HMPT) [10 mol per mol of (1)] was mixed at  $-78^{\circ}\text{C}$  with (1) prior to addition of the enone (Scheme).



SCHEME Reagents: i,  $\text{Bu}^{\text{n}}\text{Li}$ , THF-HMPT,  $-78^{\circ}\text{C}$ ; ii,  $(\text{Me}_2\text{N})_3\text{P}$ ,  $\text{I}_2$ , KI, MeCN.

1,2-Addition is charge controlled while 1,4-addition is frontier-orbital controlled: the presence of HMPT is known to favour frontier control, strongly solvating the lithium cation and diminishing charge localization.<sup>4</sup> Protonation of the enolate, resulting from the conjugate addition, is known to provide the thermodynamically more stable *trans* relationships of the two side chains.<sup>5</sup> Therefore, only the four '*trans*-diastereoisomers,' out of the eight possible stereoisomers, are reasonably expected to be formed.

We observed the formation of significant amounts (>90%) of only two out of the four '*trans*-diastereoisomers.'

These two stereoisomers constitute a single spot on t.l.c. and have the same  $R_f$  using flash-chromatography,<sup>6</sup> and using h.p.l.c. with silica gel † or reversed phases.§ A small separation was observed only by the use of h.p.t.l.c.¶

The ratio of the two diastereoisomers (*ca.* 52 : 48) was calculated by  $^1\text{H}$  n.m.r. spectroscopy in the presence of  $\text{Eu}(\text{fod})_3$ . The other two '*trans*-diastereoisomers', characterized by analogous  $^1\text{H}$  n.m.r. spectra, represent only 8% of the overall diastereoisomeric mixture.

The two stereoisomers, representing a single t.l.c. spot and constituting 92% of the diastereoisomeric mixture, were isolated and reduced with  $(\text{Me}_2\text{N})_3\text{P-I}_2$ -KI in acetonitrile<sup>7</sup> giving (4a) in 59% yield.  $^1\text{H}$  N.m.r. spectra, in the presence of  $\text{Eu}(\text{tfc})_3$ , of racemic (4a), obtained starting from racemic (1), showed a splitting of the  $\text{CO}_2\text{CH}_3$  signal into two separate signals ( $\Delta\delta$  0.13) due to the two enantiomers. Under the same recording

conditions, the  $^1\text{H}$  n.m.r. spectra of (4a), obtained starting from (+)-(*S*)-(1), showed only lanthanide-induced shifts and no splitting. Therefore (4a) is optically pure, within the range of experimental error.

The dithioacetal (4a),  $[\alpha]_D^{20} +46^{\circ}$ , showed a positive Cotton effect in the circular dichroism (c.d.) spectrum ( $\theta \times 10^{-3} = +4.29^{\circ}$  at 296 nm) definitely characterizing

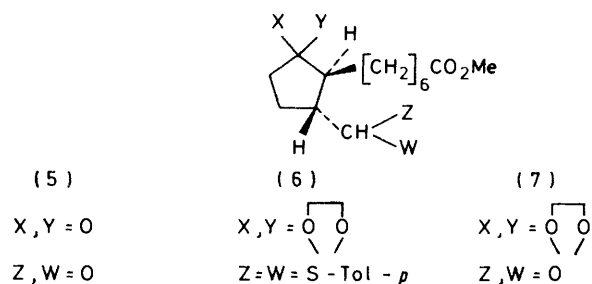
† Eluant benzene-ethyl acetate (85 : 15 v/v).

§ Zorbax C<sub>8</sub> (Dupont) (0.4 × 25 cm), eluant acetonitrile; RP 18 (Merck) 10 μm (0.4 × 25 cm), eluant acetonitrile.

¶ Kieselgel 60 F<sub>254</sub> Merck, eluant benzene-ethyl acetate (85 : 15 v/v), three runs.

the absolute configuration of C-8 of *ent*-prostanic acids.<sup>5,8</sup> Besides the positive Cotton effect of the  $n \rightarrow \pi^*$  transition of the carbonyl group at 296 nm, the c.d. spectrum showed another positive Cotton effect ( $\theta \times 10^{-3} = +10.23^\circ$  at 268 nm) of the  $\pi \rightarrow \pi^*$  transition of the *p*-tolyl groups.

The absolute configuration of (4a) is therefore shown to be (8*S*,12*R*). Compounds (5), (6), and (7) could be easily



obtained from (4a) by direct dithioacetal hydrolysis, using  $I_2$  and  $NaHCO_3$  in dioxan-water,<sup>4</sup> or by acetalization of the carbonyl group followed by hydrolysis of the thioacetal. The aldehydes (5) and (7) could be transformed into 11-deoxy-*ent*-prostanoids<sup>9</sup> by known methods.<sup>10-12</sup> Starting from optically pure (-)-(R)-(1),<sup>13</sup> the same reactions could provide the above mentioned products with a natural configuration.

The key step of this asymmetric synthesis consists of the addition of a chiral formyl anion equivalent to the enone (2a). The reaction proceeds with high  $\beta$ - and  $\gamma$ -asymmetric induction (92%) and with poor  $\alpha$ -stereoselection (52 : 48). We also noted a high asymmetric  $\beta$ -induction to the sulphoxide and a very poor  $\alpha$ -induction in other reactions of (+)-(S)-(1).<sup>4,14</sup>

Specifically (+)-(S)-(1), added to enone (2b), gave (3b) in 78% yield, and in the form of a mixture of four diastereoisomers (relative ratio *ca.* 37 : 32 : 16 : 15).

TABLE  
Relative ratio of the four diastereoisomers of (3a)

(3a)

| C-8 | C-12 | C-13   | S-14 |       |       |
|-----|------|--------|------|-------|-------|
| S   | R    | R or S | S    | 47.8% | } 92% |
| S   | R    | S or R | S    | 44.2% |       |
| R   | S    | R or S | S    | 5.0%  | } 8%  |
| R   | S    | S or R | S    | 3.0%  |       |

Reduction of the sulphoxide gave the dithioacetal (4b) in 39% enantiomeric excess and *R* absolute configuration.<sup>4</sup>

The relative ratio of the four (3a) diastereoisomers is shown in the Table: in this case, stereoselection is overtly

increased by the enone  $\alpha$ -substitution. Undoubtedly, the presence of C-8, C-12 substitution in (3a) creates a more demanding steric array in the transition state.

#### EXPERIMENTAL

Tetrahydrofuran was distilled from lithium aluminium hydride under nitrogen. Hexamethylphosphoric triamide was distilled from BaO at reduced pressure (20 mmHg) under argon. Acetonitrile was distilled from  $P_2O_5$  under nitrogen. I.r. spectra were recorded with a Perkin-Elmer 257 spectrophotometer, and n.m.r. spectra with a Varian XL-100 (100 MHz) instrument; optical rotations were measured with a Perkin-Elmer 141 polarimeter; u.v. spectra were recorded with a Perkin-Elmer 551 spectrophotometer, and c.d. spectra with a Jobin-Yvon Dicrograph. (+)-(S)-*p*-Tolyl *p*-tolylthiomethyl sulphoxide (+)-(S)-(1), prepared by literature methods,<sup>3</sup> had m.p. 79 °C,  $[\alpha]_D^{20} +76^\circ$  (*c.* 1 in acetone); the cyclopentenone derivative (2a) was prepared by literature methods;<sup>5</sup> tris(dimethylamino)phosphine (Fluka), Eu(fod)<sub>3</sub> (Merck), and Eu(tfc)<sub>3</sub> (Merck) were commercial products. Reactions using organolithium compounds were carried out in an inert atmosphere (purified argon).

**1,2-Addition of (+)-(S)-(1).**—A solution of (+)-(S)-(1) (0.2 g, 0.725 mmol) in dry tetrahydrofuran (3 ml) was cooled to -40 °C and a solution of 1.52*N*-*n*-butyl-lithium in *n*-hexane (0.63 ml) added. The resulting pale yellow solution was stirred at -20 °C for 20 min and then cooled to -78 °C. To this solution a solution of the cyclopentenone derivative (2a) (0.178 g, 0.797 mmol) in dry tetrahydrofuran (3 ml) was added. After stirring for 30 min at -78 °C, the reaction was quenched with saturated ammonium chloride solution and the product isolated with ether. Flash chromatography<sup>6</sup> of the residue on silica gel (eluant *n*-hexane-ethyl acetate, 3 : 2 v/v) and subsequent preparative t.l.c. of mixed fractions gave the following compounds: unchanged enone (0.066 g), unchanged (+)-(S)-(1) (0.060 g), and the 1,2-addition product (0.126 g, 50%) (Found: C, 67.0; H, 7.4.  $C_{28}H_{36}O_4S_2$  requires C, 67.2; H, 7.2%),  $\nu_{max}$  (CHCl<sub>3</sub>) 3 400, 1 735, 1 170, and 1 020  $cm^{-1}$ ;  $\delta$  (CDCl<sub>3</sub>) 1.0—2.6 (m, 16 H); 2.25 (s, 3 H), 2.43 (s, 3 H), 3.7 (s, 3 H, OCH<sub>3</sub>), 4.30 (s, 1 H, SCHSO), 5.75 (m, 1 H, CH=C), and 6.4—8.0 (m, 8 H arom.).

**1,4-Addition of (+)-(S)-(1).**—A solution of (+)-(S)-(1) (6.0 g, 21.7 mmol) in dry tetrahydrofuran (90 ml) was cooled to -40 °C and a solution of 1.52*N*-*n*-butyl-lithium in *n*-hexane (18.8 ml) added. The resulting pale yellow solution was stirred at -20 °C for 20 min and then cooled to -78 °C. To this solution hexamethylphosphoric triamide (37 ml) and then a solution of the cyclopentenone derivative (2a) (5.36 g, 23.9 mmol) in dry tetrahydrofuran (90 ml) were added. After stirring for 30 min at -78 °C, the reaction mixture was quenched with saturated ammonium chloride solution and the product isolated with ether. Flash chromatography<sup>6</sup> of the residue on silica gel (eluant benzene-ethyl acetate, 85 : 15 v/v) and subsequent preparative t.l.c. of mixed fractions gave the following compounds: unchanged enone (3.80 g), unchanged (+)-(S)-(1) (4.10 g), by-products deriving from the decomposition of the reagents (0.71 g), and the 1,4-addition products (1.55 g, 45%) (Found: C, 67.1; H, 7.2.  $C_{28}H_{36}O_4S_2$  requires C, 67.2; H, 7.2%),  $\nu_{max}$  (CHCl<sub>3</sub>) 1 740, 1 170, and 1 035  $cm^{-1}$ ,  $\lambda_{max}$  (Et<sub>2</sub>O) 223 and 258 nm. The four diastereoisomers were characterized by their analogous <sup>1</sup>H n.m.r. spectra: (i)

0.046 g (3% of the stereoisomeric mixture) showed  $\delta$  (CDCl<sub>3</sub>) 1.0—3.0 (m, 18 H), 2.28 (s, 3 H), 2.40 (s, 3 H), 3.62 (s, 3 H, OCH<sub>3</sub>), 3.90 (d, *J* 4 Hz, 1 H, SCHSO), and 6.45—7.60 (m, 8 H arom.); (ii) 0.077 g (5% of the stereoisomeric mixture) showed  $\delta$  (CDCl<sub>3</sub>) 1.0—3.0 (m, 18 H), 2.20 (s, 3 H), 2.30 (s, 3 H), 3.60 (s, 3 H, OCH<sub>3</sub>), 3.80 (d, *J* 2.5 Hz, 1 H, SCHSO), and 6.4—7.5 (m, 8 H arom.); and (iii) 1.427 g (92% of the stereoisomeric mixture) showed  $\delta$  (CDCl<sub>3</sub>) 1.0—3.0 (m, 18 H), 2.34 (s, 3 H), 2.42 (s, 3 H), 3.70 (s, 3 H, OCH<sub>3</sub>), 4.08 (d, *J* 2.5 Hz, 1 H, SCHSO), and 6.9—7.9 (m, 8 H arom.). To a solution of this compound in CDCl<sub>3</sub> (50 mg ml<sup>-1</sup>), Eu(fod)<sub>3</sub> [0.02 mmol per mmol of (3a)] was added: the parent-overlapped OCH<sub>3</sub> signals ( $\delta$  3.70) were split into two separate signals ( $\delta$  3.74, 3.80), relative ratio *ca.* 52 : 48.

**Reduction of (3a).**—Iodine (0.66 g, 2.6 mmol) was suspended in dry acetonitrile (2.5 ml) with magnetic stirring under dry nitrogen. To this suspension tris(dimethylamino)phosphine (0.85 g, 5.2 mmol) was slowly added at 0 °C with continuous stirring. Soon iodine dissolved and a solution of (3a) (1.3 g, 2.6 mmol) in dry acetonitrile (6.5 ml) was slowly added. Powdered potassium iodide (1.73 g, 10.4 mmol) was then added. The reaction mixture was warmed to 45 °C for 5 h, then taken up in ether and washed successively with aqueous sodium thiosulphate, water, and brine. The crude mixture was immediately purified by preparative t.l.c. (eluant benzene-ethyl acetate, 9 : 1 v/v), affording the *dithioacetal* (4a) (0.74 g, 59%) (Found: C, 69.5; H, 7.45. C<sub>28</sub>H<sub>36</sub>O<sub>3</sub>S<sub>2</sub> requires C, 69.42; H, 7.43%);  $\nu_{\max}$  (CHCl<sub>3</sub>) 1 740 and 1 165 cm<sup>-1</sup>;  $[\alpha]_D^{20} + 46^\circ$ ,  $[\alpha]_{578}^{20} + 51^\circ$ ,  $[\alpha]_{546}^{20} + 58^\circ$ ,  $[\alpha]_{436}^{20} + 127^\circ$ ,  $[\alpha]_{365}^{20} + 289^\circ$  (*c*, 0.55 in CHCl<sub>3</sub>);  $[\theta]_{298}^{20} + 4 290$ ,  $[\theta]_{268}^{20} + 10 230$  (*c*, 10<sup>-4</sup> in CHCl<sub>3</sub>);  $\delta$  (CCl<sub>4</sub>) 1.0—2.5 (m, 18 H), 2.36 (s, 6 H), 3.62 (s, 3 H, OCH<sub>3</sub>), 4.36 (d, 1 H, *J* 1.0 Hz, SCHS), and 6.96—7.38 (m, 8 H, arom.).

**Determination of the Optical Purity of (4a).**—To a solution of racemic (4a) in CCl<sub>4</sub> (45 mg ml<sup>-1</sup>), aliquots of Eu(tfc)<sub>3</sub> were added, in the range 0.1—0.45 mmol per mmol of (4a).

Under these conditions, the parent singlet of the OCH<sub>3</sub> protons of (4a) ( $\delta$  3.62) was split into two signals: plotting lanthanide-induced shift (L.I.S.) *vs.* mg of added Eu(tfc)<sub>3</sub>, two straight lines with the same intercept (3.62) and different slope (0.073, 0.090) were obtained. Under the same conditions, (+)-(4a),  $[\alpha]_D^{20} + 46^\circ$ , showed only a signal due to the OCH<sub>3</sub> protons, fitting the line with slope 0.090. This indicates that (+)-(4a), obtained as above described, is optically pure within experimental error.

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