

OPTICAL RESOLUTION OF KEY COMPOUNDS OF PROSTAGLANDIN SYNTHESIS  
AND RELATED COMPOUNDS

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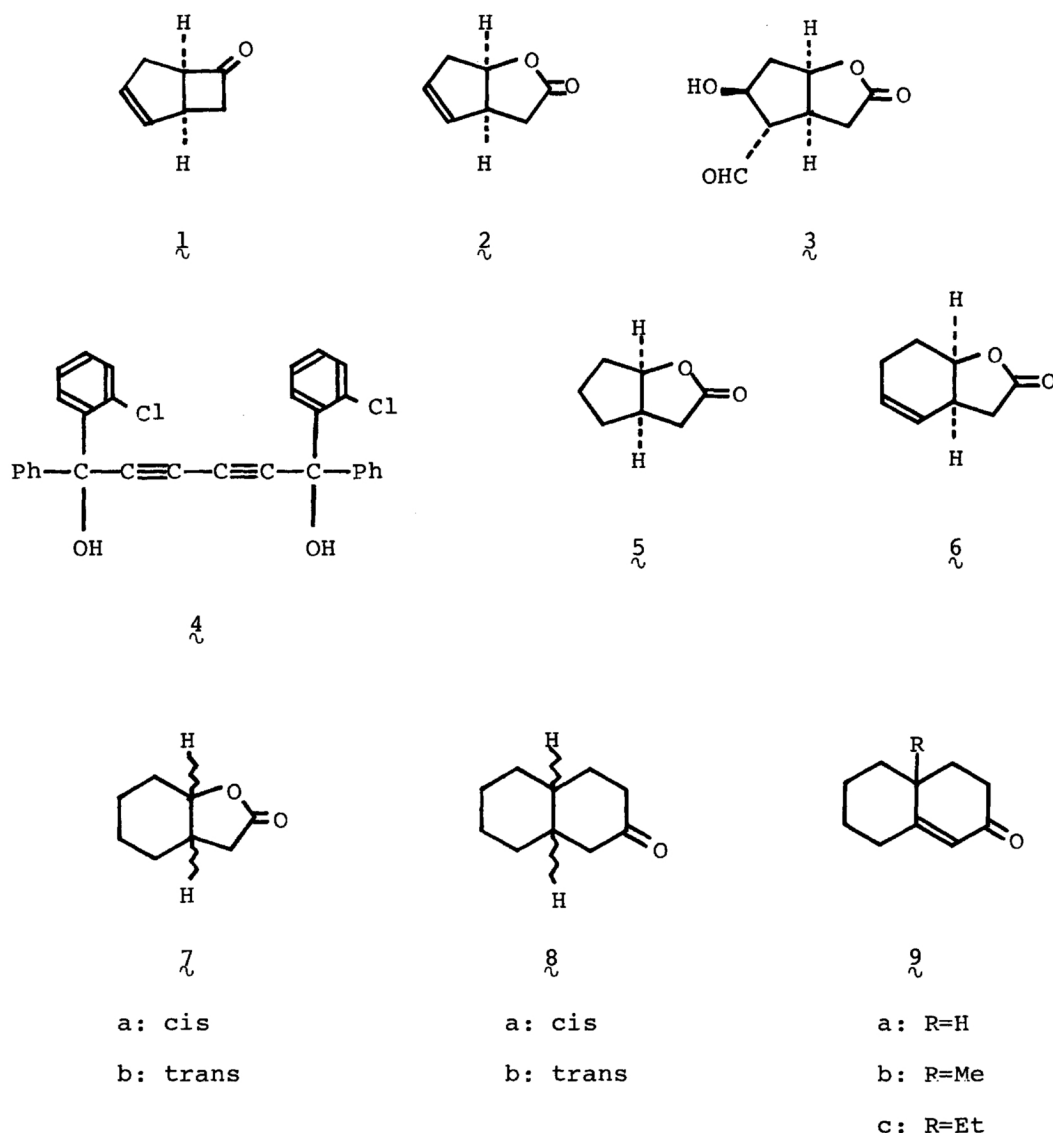
Hundred per cent optically pure bicyclic lactones and bicyclic ketones were easily obtained by complexation method with optically active 1,6-bis(2-chlorophenyl)-1,6-diphenylhexa-2,4-diyne-1,6-diol.

Optically active bicyclo[3.2.0]hept-2-en-6-one ( $1_{\kappa}$ ) and 6-oxabicyclo[3.3.0]-oct-2-en-7-one ( $2_{\kappa}$ ) are key compounds of the preparation of various prostaglandins via the Corey lactone ( $3_{\kappa}$ ). The most successful preparative method of the optically pure  $2_{\kappa}$  is a biological resolution of  $1_{\kappa}$  followed by a Baeyer-Villiger oxidation to  $2_{\kappa}$ .<sup>1)</sup> Since one enantiomer of  $1_{\kappa}$  is reduced by a yeast to alcohol,  $1_{\kappa}$  can be resolved.

We found that  $2_{\kappa}$  can easily be resolved by complexation method with an artificial optically active compound, 1,6-bis(2-chlorophenyl)-1,6-diphenylhexa-2,4-diyne-1,6-diol ( $4_{\kappa}$ ).<sup>2)</sup> It was also disclosed that the method is applicable to obtain 100% optically pure 2-oxabicyclo[3.3.0]octan-3-one ( $5_{\kappa}$ ), 7-oxabicyclo[4.3.0]non-2-en-8-one ( $6_{\kappa}$ ), 7-oxabicyclo[4.3.0]nonan-8-one ( $7a_{\kappa}$ ), bicyclo[4.4.0]decan-3-one ( $8a_{\kappa}$ ), and 6-methylbicyclo[4.4.0]dec-1-en-3-one ( $9b_{\kappa}$ ).

Optically pure  $6_{\kappa}$  is an important key compound for the synthesis of 11-desoxy-prostaglandins.<sup>3)</sup> Optically pure  $9b_{\kappa}$  is also a useful starting material for the preparation of various physiologically active compounds.

When a solution of (-)- $4_{\kappa}$  (10.0 g, 20.7 mmol)<sup>2)</sup> and ( $\pm$ )- $2_{\kappa}$  (10.3 g, 82.8 mmol) in 2:1 ether-light petroleum (45 ml) was kept at room temperature for 6 h, a 1:2 complex of (-)- $4_{\kappa}$  and (+)- $2_{\kappa}$  (15.0 g, 99%)<sup>4)</sup> was obtained, which upon distillation gave 8.5% ee (+)- $2_{\kappa}$ <sup>5)</sup> (5.0 g, 97%). Ten recrystallizations of the 1:2 complex of (-)- $4_{\kappa}$  and 8.5% ee (+)- $2_{\kappa}$  (15.0 g) from ether (40 ml each) gave the complex of



(-)-**1** and 100% ee (+)-**2** (1.67 g, 11%) as colorless needles, mp 118-120 °C,  $[\alpha]_D^{25} -55.1^\circ$ , which upon distillation gave 100% ee (+)-**2** (0.52 g, 10%),  $[\alpha]_D^{25} +110^\circ$ . However, optical resolution of **1** by this complexation method is not successful. For example, when a solution of (-)-**4** (10.0 g, 20.7 mmol) and ( $\pm$ )-**1** (8.94 g, 82.8 mmol) in 1:5 ether-light petroleum (12 ml) was kept at room temperature for 6 h, a 1:2 complex of (-)-**4** and (-)-**1** (10.1 g, 70%) was obtained as colorless needles, which upon distillation gave 8.3% ee (-)-**1** (3.08 g, 69%),  $[\alpha]_D^{25} -5.2^\circ$ . Baeyer-Villiger oxidation of the (-)-**1** gave 8.3% ee (+)-**2**. However, since recrystallization of the complex of (-)-**4** and (-)-**1** is very difficult, we could not get optically pure (-)-**1**. Nonetheless, dihydro derivative of **2** (**5**) was easily resolved by the method. Four recrystallizations from 1:1 ether-light petroleum (20 ml each) of the

1:2 complex of (-)-**4** and 20% ee (+)-**5** (5.4 g) obtained in 75% yield by keeping a solution of (-)-**4** (5.1 g, 10.6 mmol) and **5** (5.34 g, 42.4 mmol) in 1:1 ether-light petroleum at room temperature for 6 h, gave a 1:2 complex of (-)-**4** and 100% ee (+)-**5** (0.85 g, 11%) as colorless prisms, mp 95-96 °C,  $[\alpha]_D -81.0^\circ$ , which upon distillation gave 100% ee (+)-**5** (0.27 g, 10%),  $[\alpha]_D +13.3^\circ$ . The  $[\alpha]_D$  value was identical to that of hydrogenation product of 100% ee (+)-**2**.

Optical resolutions of **6** and **7a** were also very successful. Two recrystallizations from 1:1 ether-light petroleum (10 ml each) of the 1:2 complex of (-)-**4** and (+)-**6** (2.0 g) obtained in 47% yield by keeping a solution of (-)-**4** (2.7 g, 5.6 mmol) and **6** (3.1 g 22.5 mmol) in 1:1 ether-light petroleum for 6 h, gave a 1:2 complex of (-)-**4** and 100% ee (+)-**6** (0.55 g, 13%) as colorless needles, mp 95-97 °C,  $[\alpha]_D -72.6^\circ$  (CHCl<sub>3</sub>). Three recrystallizations from 2:1 ether-light petroleum (30 ml each) of the 1:2 complex of (-)-**4** and (+)-**7a** (9.7 g) obtained in 88% yield by keeping a solution of (-)-**4** (7.0 g, 14.5 mmol) and **7a** (8.1 g, 58.0 mmol) in 1:1 ether-light petroleum (40 ml) for 6 h, gave a 1:2 complex (-)-**4** and (+)-**7a** (3.65 g, 33%) as colorless prisms, mp 103-105 °C,  $[\alpha]_D -61.1^\circ$ , which upon distillation gave 100% ee (+)-**7a** (1.3 g, 32%),  $[\alpha]_D +50.3^\circ$  (CHCl<sub>3</sub>). The  $[\alpha]_D$  value was identical to that of hydrogenation product of 100% ee (+)-**6**. However, the  $[\alpha]_D$  value of 100% ee (+)-**7a** was higher than that ( $[\alpha]_D +41.9^\circ$  (CHCl<sub>3</sub>)) of the sample resolved previously.<sup>7)</sup>

It is interesting that the trans-isomer of **7a** (**7b**) does not form complex with (-)-**4**. Shape of molecule might be important for the formation of complex. Non-planar molecule such as **1**, **2**, **5**, **6**, or **7a** rather than planar one such as **7b** would be convenient for the formation of complex. This is well supported by an efficient resolution of **8a** by the complexation method and by no complex formation of **8b**. Two recrystallizations from 1:1 ether-light petroleum (20 ml each) of the 1:2 complex of (-)-**4** and (-)-**8a** (4.4 g) obtained in 54% yield by keeping a solution of (-)-**4** (5.0 g, 10.4 mmol) and **8a** (6.32 g, 41.6 mmol) in 1:1 ether-light petroleum (20 ml) for 6 h, gave a 1:2 complex of (-)-**4** and 100% ee (-)-**8a** (1.8 g, 22%) as colorless needles, mp 118-112 °C,  $[\alpha]_D -92.3^\circ$ , which upon distillation gave 100% ee (-)-**8a** (0.66 g, 20%),  $[\alpha]_D -3.9^\circ$ .

It is also interesting that **9b** is resolved efficiently, even though neither **9a** nor **9c** forms complex with (-)-**4**. For example, two recrystallizations from 1:1 ether-light petroleum (50 ml each) of the 1:2 complex (5.4 g) obtained in 63% yield by keeping a solution of (-)-**4** (5.1 g, 10.6 mmol) and **9b** (7.0 g, 42.7 mmol) in 1:2

ether-light petroleum (15 ml) for 6 h, gave a 1:2 complex of (-)-**4** and 100% ee (+)-**9b** (2.1 g, 24%) as colorless prisms, mp 122-123 °C,  $[\alpha]_D +15.6^\circ$ , which upon distillation gave 100% ee (+)-**9b** (0.8 g, 23%),  $[\alpha]_D +219^\circ$ . These results show that (-)-**4** can recognize not only the chirality of **9b** but also whether the substituent R of **9** is larger or smaller than Me.

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- 3) E. J. Corey and T. Ravindranathan, *Tetrahedron Lett.*, 1971, 4753.
- 4) All distillations were carried out with using Kugelrohr apparatus in vacuo.
- 5) Hundred per cent optical purity of **2** was determined by referring its reported  $[\alpha]_D$  value.<sup>1)</sup> Hundred per cent optical purity of **5**, **6**, **7a**, **8a**, and **9b** was determined by no change of their  $[\alpha]_D$  values on further resolution. Authentic samples of the 100% ee **5** and **7a** were also prepared by hydrogenation of the 100% ee **2** and **6**, respectively.
- 6) All the  $[\alpha]_D$  values were measured at a concentration of  $\leq 0.1$ , in MeOH at 20 °C unless otherwise stated. All yields of the optically resolved compounds were based on the theoretical amount of the optical isomer contained in the initial ( $\pm$ )-compound.
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