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Chiral synthesis of optically active S(+)-2,6,7,7a-tetrahydro-1β-hydroxy-4-formyl-7aβ-methylindene

D K BANERJEE, T R KASTURI* and A SARKAR
Department of Organic Chemistry, Indian Institute of Science, Bangalore 560012, India

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Abstract. The chiral aldol cyclization of the prochiral triketone 3 using l-valine afforded the optically active compound 4 in high chemical and optical yield. The configuration and optical purity of (+)4 was determined by ORD, chemical resolution and NMR chiral LSR studies. The title compound (+)7 was prepared from (+)4 following our earlier reported procedure.

Key words. Chiral synthesis; chemical resolution; optical rotatory dispersion; chiral NMR shift reagent.

1. Introduction

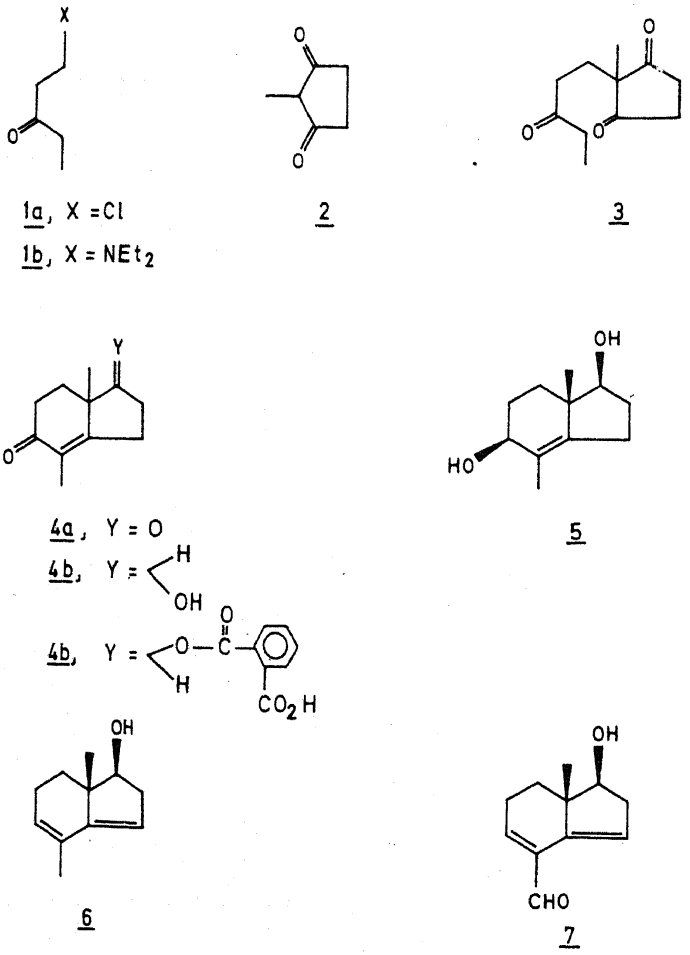
An efficient synthesis of 2,6,7,7a-tetrahydro-1β-hydroxy-4-formyl-7aβ-methylindene (7), a potential synthon for stereospecific total synthesis of natural and modified steroids, was reported earlier (Banerjee *et al* 1976). Further improvements in the method for the preparation of the compound (7) in larger quantities have been effected. Replacing the Mannich base (1b) by the parent chloroketone (1a) in the annealation reaction with the diketone (2), an yield of 92% (reported 55%, Banerjee *et al* 1976) of enedione (4a) was obtained. An improved yield of 60% (reported 55%, Banerjee *et al* 1976) of the aldehyde (7) could also be obtained by suitably modifying the reaction condition.

In the present paper, the synthesis of the aldehyde (7) in the optically-active form required for the synthesis of natural steroids, has been described. For this purpose, the triketone (3) was cyclized using l-valine as the chiral catalyst to furnish the enedione (4*a*) with the specific rotation of +250° ($CHCl_3$) in 80% yield. To determine the optical purity of the above product, the resolution of the enedione (4*a*) was undertaken following the procedure adopted by Hajos *et al* (1968) and Dutcher *et al* (1976) for similar compounds.

The racemic enedione (4*a*) was selectively reduced by purified sodium borohydride in methanol under controlled conditions and the compound (4*b*) was obtained in 98% yield. The monophthalate (4*c*) of the keto alcohol (4*b*) was resolved with a molar quantity of brucine in boiling acetone. The salt which separated out on cooling, was repeatedly crystallized from acetone to the constant rotation of −4·5° ($CHCl_3$). The monophthalate, (−)4*c*, was regenerated by treating with dilute hydrochloric acid and crystallized twice from acetonitrile to the constant rotation of −71° (DMSO). Saponification followed by oxidation with pyridinium dichromate furnished the

* To whom correspondence should be addressed.

Chart 1



enantiomerically pure enedione (4*a*) which had a specific rotation of $-337°$ ($CHCl_3$).

The negative rotation and the inverted ORD curve (figure 1) of the resolved compound (4*a*) led us to suspect that the brucine salt of the *R*-isomer might have selectively precipitated out unlike the separation of the S-isomer in the case of Hajos' and Heathcock's compounds (Hajos *et al* 1968, Dutcher *et al* 1976). The formation of four isomers of the hydroxyenone (4*b*) is possible, as shown in chart 2, by the two possible pathways.

To clarify whether the borohydride reduction of the compound (4*a*) actually resulted in a higher proportion of the *trans* alcohol, the enedione (4*a*) was reduced with lithium tri-(*t*-butoxy)aluminumhydride (LTBA) in tetrahydrofuran and the entire process of resolution was repeated to obtain identical result, *i.e.* the isomer (−)4*a* was formed. On the basis of the absolute rotation obtained and assuming that the other antipode has identical magnitude of rotation with opposite sign, the optical yield in the chiral transformation has been found to be 74%. Analysis of the 270 MHz PMR spectrum of the compound (+)4*a*, in the presence of Eu^{III} (trifluoroacetylcamphorato) complex (substrate:LSR = 1:0·46 M) corroborated this result. Both the angular methyl and the allylic methyl singlets split into two distinct peaks; the integration of both the signals showed the same ratio (7:3), and this compared well with the enantiomeric excess determined by the chemical resolution. The configuration at C-13 (steroid nomencla-

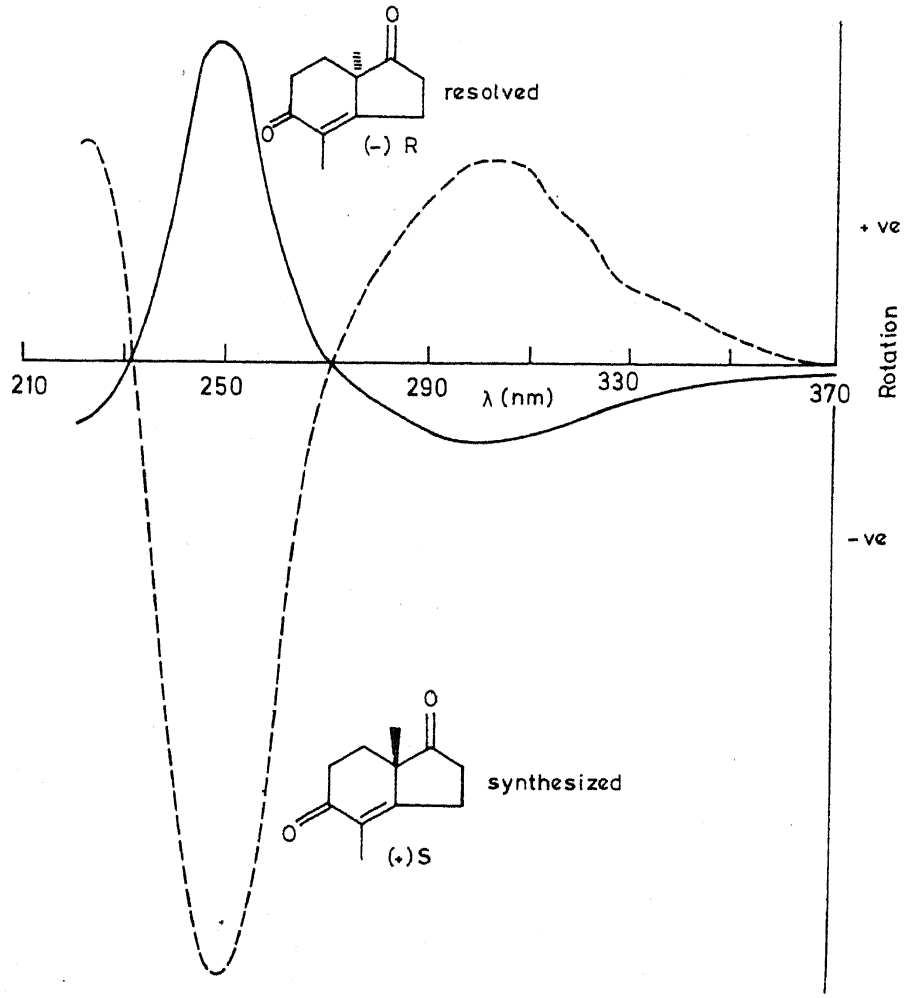
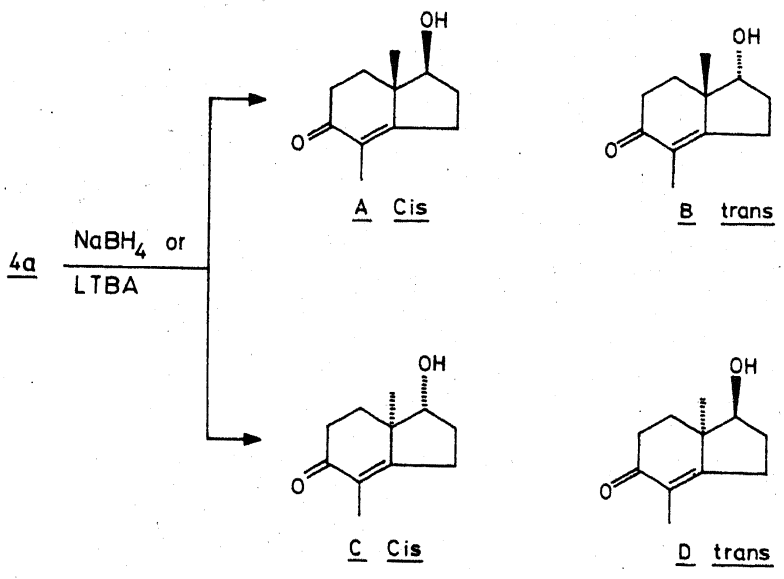


Figure 1. ORD spectrum of 4*a* in EtOH —— for (−) 4*a*; ---- for (+) 4*a*.

Chart 2



ture) was further confirmed to be 'S' by comparison of the CD-spectrum of the enedione (4*a*) with the data published by Hajos and Parrish (1974) for a related compound (figure 2).

The optically-active enedione (4*a*), possessing the required chirality for the synthesis of natural steroids, was then reduced with sodium borohydride to obtain the diol (5), m.p. 142°, $\alpha_D + 2{\cdot}5°$ (EtOH). The dienol (6), m.p. 74–75°, obtained after the acid-catalyzed dehydration of the diol (5), had a negative rotation of $-80°$ ($CHCl_3$). Such a change in the sign of the specific rotation is in accordance with an earlier report in the literature for the cholestane series (Fieser and Fieser 1959). Selenium dioxide oxidation resulted in a relatively improved yield (64%) of the title compound (7), mp. 84°, $\alpha_D + 12°$ ($CHCl_3$).

2. Experimental

All melting points (hot stage) and boiling points (bath-temperature) are uncorrected. The UV spectra were recorded in 95% ethanol on a Unicam SP 700A recording

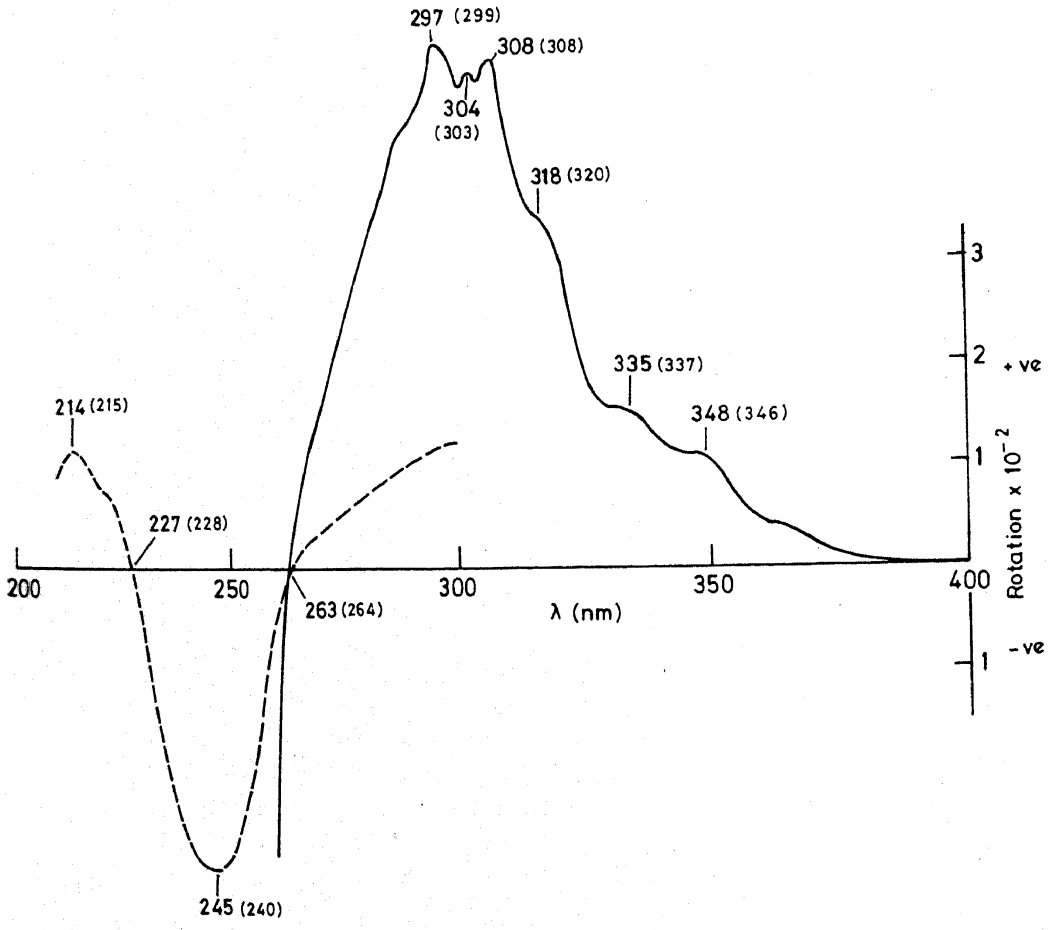


Figure 2. CD spectrum (dioxan) of (+) 4*a*. The figures in parentheses are taken from Hajos *et al* 1974.
—— Conc 3·5 mg/ml } in 1 mm cell.
--- Conc 0·7 mg/ml }

spectrometer and Shimadzu double-beam UV spectrophotometer. The IR spectra were recorded on Perkin-Elmer 397 and Perkin-Elmer 700 spectrophotometers. The NMR spectra were recorded on a Varian T-60, Varian HA-100D or Bruker WH-270 FT NMR spectrometer. Chemical shifts are quoted relative to TMS ($\delta = 0$ ppm) as internal standard. Anhydrous sodium sulphate has been used for drying organic solutions. The optical rotations were recorded on a JASCO-J20 automatic recording ORD/CD machine.

2.1 *2-methyl-2-(3-oxopentyl)-cyclopentane-1,3-dione* (3)

Freshly-distilled ethyl vinyl ketone (14 g) and 2-methylcyclopentane-1,3-dione (2, 18·6 g) were stirred in 35 ml of demineralized water for 7 days at room temperature under nitrogen. Benzene (100 ml) was then added and the mixture filtered. The residue was repeatedly washed with boiling benzene (30 ml × 3). The combined benzene layer was concentrated and chromatographed over neutral alumina (600 g) using benzene-chloroform (3 : 1) as the eluent. The triketone (3) was obtained (19·9 g, 60%) as a pale yellow liquid, b.p. 145–150°/2 mm (reported 94°/0·01 mm, Swaminathan *et al* 1970); IR (neat): ν_{max} 1770, 1730, 1710 cm^{-1}; NMR (CCl_4): 0·95 (t, J = 7 Hz, 3H, $CH_2\underline{CH_3}$), 1·02 (s, 3H, CH_3), 1·80 (q, J = 7 Hz, 2H, $\underline{CH_2}CH_3$), 2·20–2·60 (m, 4H, methylenes) and 2·74 δ (s, 4H, ring methylenes).

2.2 (+)*5,6,7,7a-tetrahydro-4,7a-dimethylindane-1,5-dione* (4*a*)

A stirred mixture of the triketone (3, 3·4 g), l-valine (2·4 g), perchloric acid (0·7 ml) in acetonitrile (15 ml) was heated under reflux for 72 hr, filtered and concentrated. Dry benzene (20 ml) and a few crystals of *p*-toluene sulphonic acid were added to the concentrate and the solution heated for 4 hr in a Dean-Stark apparatus for azeotropic removal of water. The solution was concentrated and passed through silica gel (150 g). Elution with hexane-ethyl acetate (3 : 1) yielded 2·5 g (80%) of the (+) enedione (4*a*), b.p. 160–165°/6 mm (reported 120°/0·8 mm), $\alpha_D = +250°$ ($CHCl_3$), (Found: C 74·29 H 7·88; $C_{11}H_{14}O_2$ requires C 74·13, H 7·92%).

2.3 (+)*5,6,7,7a-tetrahydro-1,5-dihydroxy-4,7a-dimethylindane* (5)

This was prepared following the reported procedure for the preparation of the recemic compound (Banerjee *et al* 1976); from 4·5 g of the enone (+)4*a*, 1·25 g of sodium borohydride and 25 ml of ethanol was obtained the required diol (+)5 (3·8 g, 94%) m.p. 142°; $\alpha_D = +2·5°$ (EtOH); (Found: C 72·68, H 9·77; $C_{11}H_{18}O_2$ requires C 72·49, H 9·96%).

2.4 (−)*2,6,7,7a-tetrahydro-1-hydroxy-4,7a-dimethylindene* (6)

Following the earlier procedure for the preparation of the racemate from 2·1 g of the diol (+) 5, was obtained 1·75 g (92·5%) of the compound (−) 6, m.p. 74–75°; $\alpha_D = -80°$ ($CHCl_3$); (Found: C 80·53, H 9·62; $C_{11}H_{16}O$ requires 80·44, H 9·83%).

2.5 (+)*2,6,7, 7a-tetrahydro-1-hydroxy-4-formyl-7a-methylindene* (7)

This was prepared by modifying the reported procedure (Banerjee *et al* 1976). A mixture of 1·6 g of the dienol (−) 6 and 2·5 g of selenium dioxide was stirred in 25 ml of dimethyl sulphoxide under nitrogen at 120 for 1·5 hr. The mixture was poured into

water and extracted with ether. The ether layer was washed with water, aqueous $NaHCO_3$, water and brine and dried. The residue left on removal of the solvent was subjected to short path distillation (140–143°/2 mm) to afford the aldehyde (+)7 (7·1 g, 64%), m.p. 84°, $\alpha_D = +12°$ ($CHCl_3$). (Found: C 74·25, H 7·79; $C_{11}H_{14}O_2$ requires C 74·15, H 7·86%).

2.6 (±)5,6,7,7*a*-tetrahydro-4,7*a*-dimethylindane-1,5-dione (4*a*)

This was prepared following the procedure of Zoretic *et al* (1976), but was obtained in a much better yield. Thus, from 32·3 g of β-chloroethyl ethylketone and 25 g of 2-methylcyclopentane-1, 3-dione, was obtained 36·5 g (92%, reported [Eder *et al* 1971] 78%) of the title compound, b.p. 160–165°/6 mm (reported 94–98°/0·01 mm).

2.7 (±)5,6,7,7*a*-tetrahydro-1-hydroxy-4,7*a*-dimethylindan-5-one (4*b*)

This was earlier prepared by Crispin *et al* (1970), but now we report different methods which considerably improved the yield.

(a) A solution of 18·5 g of the enedione (4*a*) in methanol (400 ml) was treated with purified sodium borohydride (0·989 g) at 0–5° in small portions for 90 min. The course of the reaction was monitored by TLC. One drop of acetic acid was added to the reaction mixture and the solvent distilled off. Usual work-up afforded the pure compound (4*b*), b.p. 134–136°/1 mm (reported 128–130°/0·5 mm, Crispin *et al* 1970) as a pale yellow liquid (18·65 g, 97%).

(b) To a stirred suspension of lithium tri-*t*-butoxyaluminumhydride, prepared from 3·8 g of lithium aluminumhydride and 25 ml of *t*-butanol in THF (100 ml), maintained at 0°, was added dropwise a solution of 16·8 g of the enedione (4*a*) in 60 ml of THF. After 30 min, 15 ml of acetone and 200 ml of water were carefully added to the mixture, followed by acidification with 2N H_2SO_4 and extraction with ether. The ether layer was washed with brine and dried. Removal of the solvent yielded 15·7 g of the compound as an yellow oil (TLC single spot) (93%).

2.8 (±)5,6,7,7*a*-tetrahydro-1-phthaloyloxy-4,7*a*-dimethylindan-5-one (4*c*)

A mixture of hydroxy enone (4*b*, 11 g), resublimed phthalic anhydride (10 g) and 50 ml of pyridine was stirred under nitrogen at room temperature for two days. It was then poured into ice-water and carefully acidified with 2N HCl. The solid, which separated on cooling, was crystallized from acetonitrile to yield the analytically pure compound (4*c*) in 40% yield (8 g), m.p. 225–226°; IR (nujol): ν_{max} 2625, 2500, 1720, 1710, 1620, 1600 and 1590 cm^{-1}; NMR (DMSO-d_6): 1·2 (s, 3H, CH_3), 1·65 (s, 3H, vinylic CH_3), 1·7–2·8 (*m*, 8H, methylenes), 5·0 (bt, J = 10 Hz, 1H, –CH–O-phthaloyl), 7·65 (m, 4H, Ar-H) and 11·15 δ (broad peak, 1H, CO_2H, exchanges with D_2O); Mass: M^+ m/z 328; (Found: C 69·11, H 6·3; $C_{19}H_{20}O_5$ requires C 69·5, H 6·14%).

2.9 (−)5,6,7,7*a*-tetrahydro-1-phthaloyloxy-4,7*a*-dimethylindan-5-one (4*c*)

The brucine salt of 4*c* was prepared as follows: To a hot solution of 6 g of the monophthalate (4*c*) in boiling acetone (250 ml) was slowly added 9·2 g of brucine dissolved in 120 ml of hot acetone. The solution was concentrated to a volume of 80 ml. Refrigeration for three days yielded crystals which were thrice crystallized from acetone

to furnish the brucine salt of 4*c* having the constant rotation of $-4{\cdot}5°$ ($CHCl_3$), 3·5 g, m.p. 154–155°; NMR ($CDCl_3$); 1·25 (s, 3H, CH_3), 1·67 (bs, 3H, vinylic CH_3) and 4·98 δ (dd, J = 7 Hz, 1H, –CH–COOAr).

A solution of the above brucine salt (2 g) in 30 ml of acetone was slowly added to ice and water containing 3 ml of 5% HCl. The product was crystallized twice from acetonitrile to afford the constant rotation $\alpha_D = -71°$ ($CHCl_3$), m.p. 224–226° (Found: C 69·21, H 6·15; $C_{19}H_{20}O_5$ requires C 69·50, H 6·14%).

2.10 (−)5,6,7,7*a*-*tetrahydro*-4,7*a*-*dimethylindane*-1,5-*dione* (4*a*)

A stirred mixture of 602 mg of the compound (−) 4*c* and 10 ml of 40% aqueous KOH was attached to a continuous extraction apparatus and extracted with ether at room temperature for 24 hr. The ether was removed to obtain the hydroxy enone (4*b*, 309 mg), a stirred solution of which in 5 ml of methylene chloride was oxidized by 1 g of pyridinium dichromate at room temperature under nitrogen for 22 hr. The mixture was diluted with ether (50 ml) and filtered through $MgSO_4$ to obtain the pure enedione, (−) 4*a* (257 mg) $\alpha_D = -337°$ ($CHCl_3$) (Found: C 74·35, H 7·86; $C_{11}H_{14}O_2$ requires C 74·13, H 7·92%).

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