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AN EFFICIENT SYNTHESIS OF ENANTIOMERIC PAIR OF VICINAL-DIOLS FROM OPTICALLY ACTIVE α-HYDROXY ACID: ITS APPLICATION TO OPTICALLY ACTIVE EPOXYTERPENE SYNTHESIS

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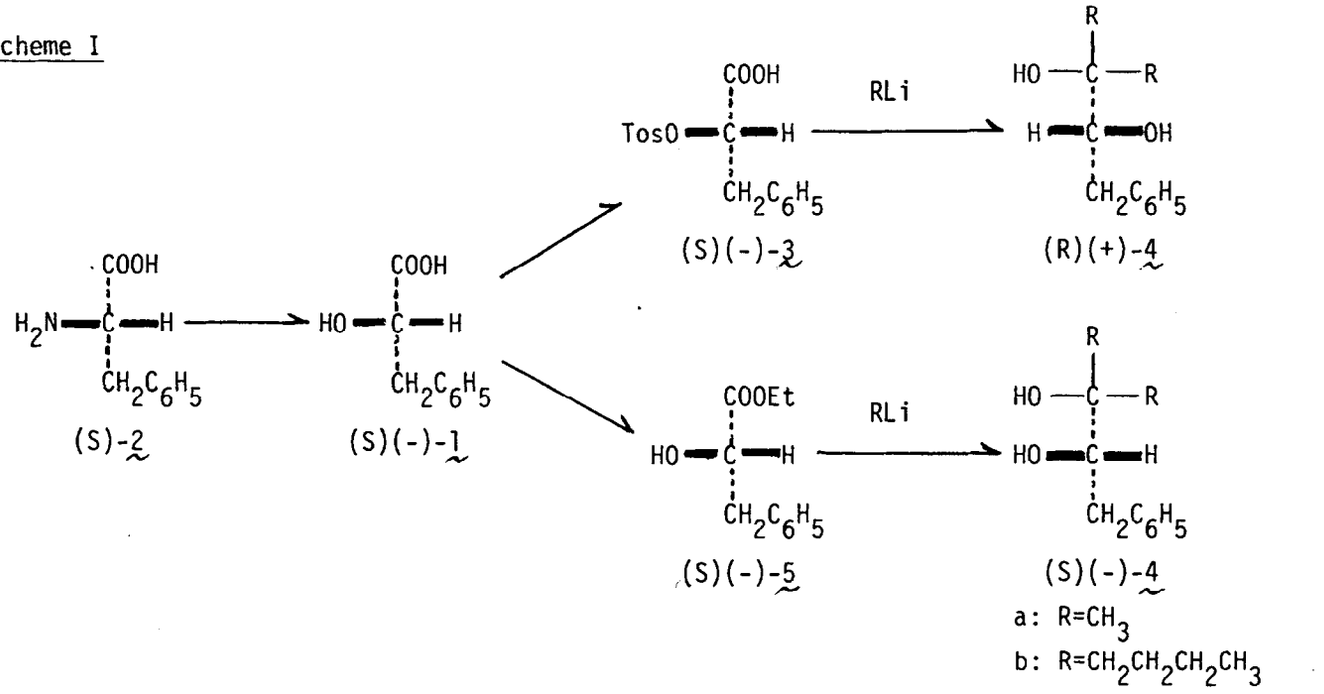
The reaction of carboxylic acids and organolithium reagents constitutes a simple general method for the synthesis of ketones.[1] Although several applications of this synthetic method to racemic[2] and optically active[3] α-hydroxy acids have been reported to produce corresponding racemic and optically active α-hydroxy ketones, the use of optically active α-tosyloxy acids having excellent leaving group at the α-position, as reaction substrates, has never been attempted.

We have now found that when optically active α-tosyloxy acid is allowed to react with organolithium reagents(5.0 eq), optically active vicinal(vic)-diols can be produced in excellent yields with full inversion at the asymmetric center. Since the reaction of optically active α-hydroxy acid ester and organolithium reagents(5.0 eq) can proceed with full retention at the asymmetric center to afford optically active vic-diols, it is now possible to prepare an enantiomeric pair of vic-diols from one enantiomer of optically active α-hydroxy acid by way of α-tosyloxy acid or α-hydroxy acid ester.

As shown in Scheme I, optically pure (S)(-)-α-hydroxy acid((S)(-)-1),[4] mp 125-126°C,

Scheme I

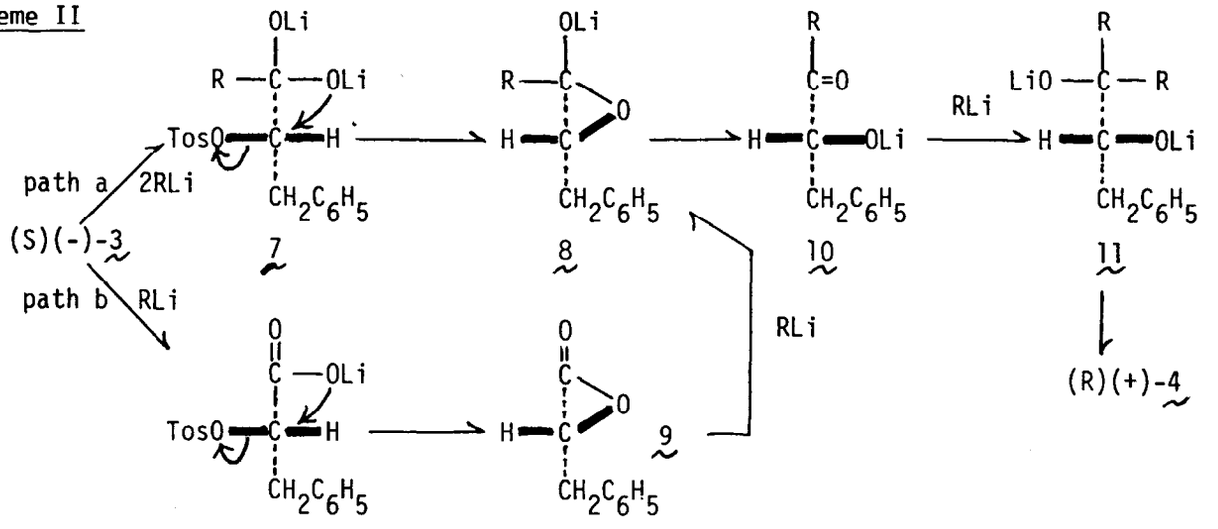


$[\alpha]_D^{25}$-27.2°(c=3.8, acetone), readily obtainable from (S)-phenylalanine((S)-2) by nitrous acid deamination,[4] was transformed into optically pure (S)(-)-α-tosyloxy acid((S)(-)-3),[5] mp 122-124°C, $[\alpha]_D^{20}$-46.9°(c=1.5, chloroform), in 84% yield by successive esterification with benzyl alcohol, tosylation, and reductive cleavage of the benzyl ester.[6] When (S)(-)-3 was treated with methyllithium(5.0 eq) in ether(-10°C, 3.5 hr), (+)-vic-diol((+)-4a),[5] mp 74-75°C, $[\alpha]_D^{20}$+58.9°(c=0.91, chloroform), could be obtained in 81% yield. On the other hand, the reaction of optically pure (S)(-)-α-hydroxy acid ester((S)(-)-5),[4] mp 47-49°C, $[\alpha]_D^{24}$-21.4°(c=4.6, benzene), prepared from (S)(-)-1,[4] with methyllithium(5.0 eq) in ether (-10°C, 3.5 hr), was found to give (-)-vic-diol((-)-4a),[5] mp 74.5-75.5°C, $[\alpha]_D^{20}$-59.0°(c=0.86, chloroform), in 98% yield. It is quite clear that (-)-4a can be produced with full retention of the configuration because the alcoholic function of (S)(-)-5 might be immediately converted to the lithium alkoxide when (S)(-)-5 was treated with methyllithium. Therefore, the absolute configuration of (+)- and (-)-4a could be assigned as (R)- and (S)-series, respectively. This assignment was further ascertained by the successful synthesis of (S)(-)-ketone((S)(-)-6), a key intermediate of optically active epoxyterpene synthesis,[7,8] from (-)-4a(vide infra).

In a similar manner, when butyllithium(5.0 eq) was used in place of methyllithium, (R)(+)-vic-diol((R)(+)-4b),[5a] mp 109-112°C, $[\alpha]_D^{20}$+24.8°(c=2.4, chloroform), and (S)(-)-vic-diol ((S)(-)-4b),[5a] mp 110-111°C, $[\alpha]_D^{20}$-26.1°(c=2.3, chloroform), were obtained from (S)(-)-3 and (S)(-)-5 in 92% and 97% yields.

Formation of the inverted vic-diols((R)(+)-4) from (S)(-)-3 might be rationalized by the two possible paths shown in Scheme II. Thus, addition of two moles of organolithium to (S)(-)-3 directly gives the dilithium salt(7) in which S_N2-type substitution of the tosyloxy group by the intramolecular alkoxide anion occurs to give the epoxy alkoxide(8)(path a). Formation of the same intermediate(8) is also possible by the stepwise addition of organolithium to (S)(-)-3 by way of the α-lactone(9)(path b).[9] The epoxy alkoxide(8) can isomerize to the α-keto alkoxide(10) and the addition of organolithium to 10 would produce the inverted dilithium salt(11), from which (R)(+)-4 can be liberated on acidic workup.

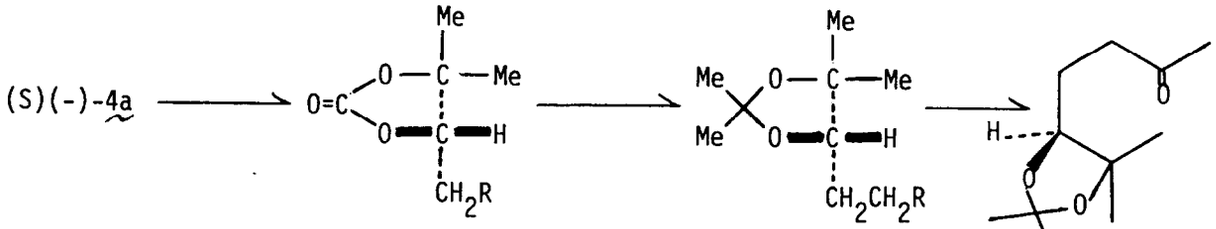
Scheme II



Next, aiming to realize the utility of the optically active vic-diols in natural product synthesis, preparation of (S)(-)-6 was examined by using (S)(-)-4a as a starting material. Several versatile synthetic schemes to optically active epoxyterpenes such as epoxygeraniol, epoxyfarnesol, and epoxysqualene, had been exploited from (S)(-)-6.[7,8] Although partial racemization had been observed in the previous synthesis of (S)(-)-6 from (S)-glutamic acid,[7] we succeeded in readily obtaining optically pure (S)(-)-6 from (S)(-)-4a.

Thus, protection of vic-diol function of (S)(-)-4a as a cyclic carbonate(diethyl carbonate-sodium ethoxide(catalytic amount), reflux, 16 hr) afforded (S)(-)-carbonate((S)(-)-12)[5] (100%), mp 84-85.5°C, $[\alpha]_D^{20}$-75.2°(c=0.97, chloroform). Ozonolysis of (S)(-)-12 in acetic

Scheme III



(S)(-)-12: R=C_6H_5
(S)(-)-13: R=COOMe

(S)(-)-14: R=OH
(S)(-)-15: R=OTos
(S)(-)-16: R=CN
(S)(-)-17: R=COOH

(S)(-)-6

acid(rt, 12 hr), followed by oxidative workup(aq. 30% hydrogen peroxide), esterification with diazomethane, and separation with a silica gel column(benzene-ethyl acetate 4:1), cleanly gave (S)(-)-ester((S)(-)-13)[5](69%, 81% corrected for the recovery of (S)(-)-12), mp 64-65°C, $[\alpha]_D^{20}$-29.7°(c=0.66, chloroform), with the recovery of (S)(-)-12(14%). Reduction of (S)(-)-13(lithium aluminum hydride(5.0 eq) in tetrahydrofuran, -23°C, 2 hr; rt, 1.5 hr; reflux, 2 hr), and acetalization of the vic-diol function(acetone-p-toluenesulfonic acid(catalytic amount)), gave (S)(-)-alcohol((S)(-)-14)[5a] as a pale yellow oil(two steps 94%), which, without purification, was directly treated with tosyl chloride(1.4 eq) in pyridine, yielding (S)(-)-tosylate((S)(-)-15)[5,10](89%), mp 61.5-64.5°C, $[\alpha]_D^{20}$-17.6°(c=0.99, chloroform). Treatment of (S)(-)-15 with potassium cyanide(3.4 eq) in dimethylformamide(60°C, 4 hr) gave (S)(-)-cyanide((S)(-)-16)[5a] as a yellow oil(99%), $[\alpha]_D^{20}$-29.6°(c=0.98, chloroform). The cyanide((S)(-)-16) was hydrolyzed(20% sodium hydroxide(2.0 eq) in ethanol, reflux, 10 hr) to afford (S)(-)-acid((S)(-)-17)[5] (91%), mp 57-59°C, $[\alpha]_D^{20}$-10.1°(c=0.99, chloroform), which, on reaction with methyllithium(2.0 eq) in ether(rt, 4 hr), furnished the desired (S)(-)-6[5a] as an oil(85%), $[\alpha]_D^{25}$-12.1°(c=1.0, chloroform) and $[\alpha]_D^{27}$-14.8°(c=1.4, methanol)(lit.,[8] $[\alpha]_D^{25}$+10.4°(c=1.0, chloroform) for (R)(+)-6; lit.,[7,11] $[\alpha]_D^{27}$-14.1°(c=1.31, methanol)).

Since (R)(+)-6 can be prepared from (R)(+)-4a according to the synthetic scheme exploited here, it has become possible to readily obtain optically pure (R)(+)- and (S)(-)-6 from (S)-2 by way of (S)(-)-1 and the enantiomeric pair of vic-diols((R)(+)- and (S)(-)-4a)).

Considering its operational simplicity and high yield in each synthetic step, the overall process developed here might have wide practical value in the synthesis of optically active epoxyterpenes.

References

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3) a) D.J. Cram and K.R. Kopecky, J. Am. Chem. Soc., 81, 2748(1959). b) S. Terashima, S-s. Jew, and K. Koga, Tetrahedron Letters, 1977, 4507.
4) S.G. Cohen and S.Y. Weinstein, J. Am. Chem. Soc., 86, 5326(1964).
5) a) Infrared(ir) and nuclear magnetic resonance(nmr) spectra were in agreement with the assigned structure. b) Satisfactory analytical data were obtained for this compound.
6) For detailed studies on the preparation of (S)(-)-3 from (S)(-)-1, see S. Terashima, C.C. Tseng, and K.Koga, Chem. Pharm. Bull.(Tokyo), to be published.
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8) M.A. Abdallah and J.N. Shah, J. Chem. Soc. Perkin I, 1975, 888.
9) Discrimination of path a and path b seemed impossible.
10) Spectral(ir and nmr) properties of this sample were identical with those of (R)(+)-15, mp 67°C, $[\alpha]_D^{20}$+17°(c=1.0, chloroform), prepared from (R)-2-hydroxy-γ-butyrolactone in the synthetic approach to optically active epoxysqualene performed by Abdallah, et al.[8] Although they synthesized (R)(+)-6 from (R)(+)-15 by using 2-lithio-2-methyl-1,3-dithiane to extend the carbon chain, we employed the reaction scheme being operationally simpler than that reported.[8]
11) This sample was prepared from (S)-glutamic acid by removing racemic compound at the synthetic intermediate. Without this operation for purification, partially optically pure (S)(-)-6, $[\alpha]_D^{28}$-8.7°(c=0.40, methanol) was obtained from (S)-glutamic acid(S. Yamada, N. Oh-hashi, and K. Achiwa, unpublished results).