Tetrahedron Letters Vol.21, pp2733-2736 0040-4039/80/0708-2733$02.00/0

A HIGHLY EFFICIENT ASYMMETRIC SYNTHESIS OF OPTICALLY ACTIVE α,β-EPOXYALDEHYDES FROM α,β-UNSATURATED ACIDS

Shiro Terashima,* Masaji Hayashi, and Kenji Koga
Faculty of Pharmaceutical Sciences, University of Tokyo,
Hongo, Bunkyo-ku, Tokyo, 113, Japan

Summary: The bromolactones(3) prepared from α,β-unsaturated acids(1) were converted to optically active α,β-epoxyaldehydes(2(R),3(S)-6)(84-98% ee) by successive epoxide formation and reductive cleavage of the proline moiety. The overall process constitutes a highly efficient asymmetric synthesis of 2(R),3(S)-6 from 1.

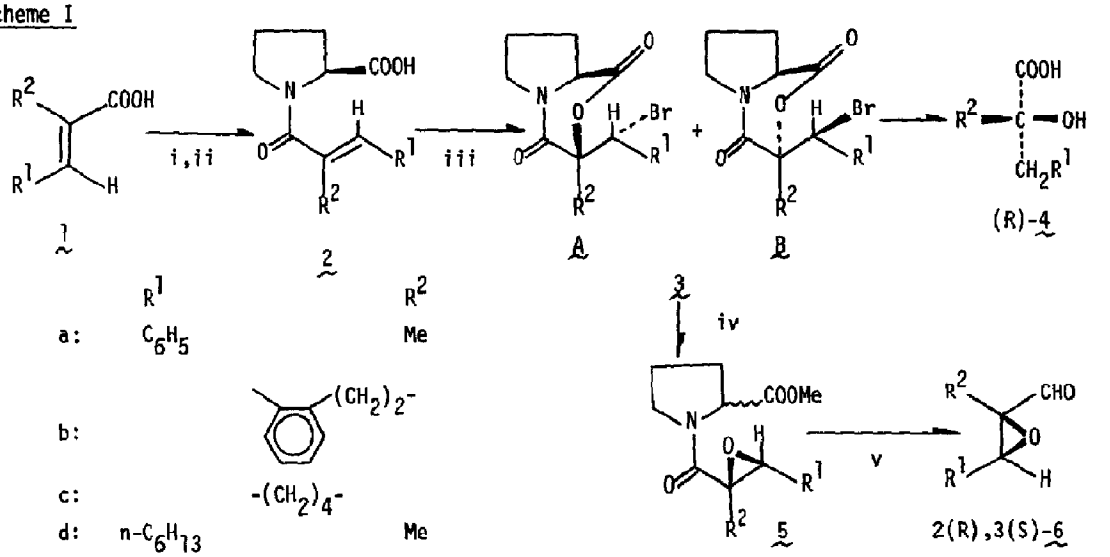
Optically active epoxides attract much attention because of their importance in biochemistry[1] and synthetic organic chemistry.[2] As methods for producing optically active epoxides, various types of asymmetric syntheses including catalytic epoxidations in the presence of optically active transition metal complexes[3] and biological epoxidations with microorganisms,[4] have been developed. Although high optical yields(ca. 100% ee) have been achieved in the preparation of simple unfunctionalized olefins,[3c,4b] practical asymmetric syntheses of highly optically active functionalized epoxides whose absolute configurations can be mechanistically established, have not been exploited.

We have previously described that the bromolactonization of (S)-N-(α,β-unsaturated)acylprolines(2) obtainable from α,β-unsaturated acids(1) proceed stereoselectively to give mixtures of the bromolactones(3A and 3B) in which 3A are highly predominant, and that debromination of 3 followed by acidic hydrolysis produces (R)-α-hydroxy acids((R)-4) of high enantiomeric purity (87-98% ee).[5] This paper reports a novel application of the asymmetric reaction developed for preparing (R)-4, to asymmetric synthesis of highly optically active α,β-epoxyaldehydes(2(R), 3(S)-6) which are considered potentially useful in natural product syntheses.

According to the reported procedure,[5a] preparation of a mixture of 3Aa and 3Ba(3Aa:3Ba 99:1) was effectively carried out from α-methylcinnamic acid(1a) by way of 2a(see Table I). As shown in Scheme I and Table II, treatment of the mixture of 3Aa and 3Ba with sodium methoxide in methanol gave the crude epoxy ester(5a)[6a,7] showing two singlets at 3.72 and 3.80 ppm in its NMR spectrum. This spectral feature clearly disclosed that epimerization of the methyl ester occurred during the epoxide formation. The ratio of two epimers involved in 5a could be roughly determined as 2:1 by the peak integration. Reductive cleavage of the epimerized proline moiety afforded optically active (+)-2-methyl-3-phenyl-2(R),3(S)-epoxypropanal(2(R), 3(S)-6a)[6] after purification by column chromatography(silica gel, Et_2O) and distillation. The structure of 2(R),3(S)-6a was definitely confirmed by spectral comparison with the corresponding racemic α,β-epoxyaldehyde(dl-6a).[9] The optical purity of 2(R),3(S)-6a could be

calculated as 98% since the diastereomeric mixture of 3Aa and 3Ba(99:1) was subjected to the sequential reactions.

Scheme I



a: R^1 = C_6H_5, R^2 = Me

b: R^1, R^2 = $-(CH_2)_2-C_6H_4-$

c: R^1, R^2 = $-(CH_2)_4-$

d: R^1 = n-C_6H_{13}, R^2 = Me

i) (S)(-)-ethyl prolinate-$(EtO)_2P(O)CN$-Et_3N[5] ii) KOH in aq EtOH[5] iii) NBS(2 eq)-t-BuOH (1 eq) in DMF, rt, 40-48 hr[5] iv) NaOMe(1 eq) in MeOH(for 3a) or MeOH-THF(for 3b,c,d), -78°C, 3-4 hr v) $NaAlH_2(OCH_2CH_2OMe)_2$ in Et_2O, 0°C, 1 hr

Table I Preparation of (S)-N-(α,β-Unsaturated)acylprolines(2) and the Bromolactones(3)

2				3					
Chem. Yields (%)[a]	Mp °C	Optical Rotations $[\alpha]_D^{20}$(c= 1.0-1.1)	Chem. Yields (%)	Ratio of 3A to 3B	Mp of a Mix. of 3A and 3B °C	Optical Rotations of a Mix. of 3A and 3B $[\alpha]_D^{20}$ (c=0.6-1.0)	Mp of 3A °C	Optical Rotations of 3A $[\alpha]_D^{20}$(c= 1.0)
a[5a] 87	115.5-117	-12.6° (MeOH)	95	99:1[b]	oil	-105° (MeOH)	-[d]	-[d]
b[5b] 74	135.5-137	-102° ($CHCl_3$)	88	96:4[b]	162-164	-72.0° ($CHCl_3$)	-[d]	-[d]
c 78	123-124[6]	-54.8° (EtOH)	78	99:1[c]	129-135[6a]	-99.4° (EtOH)	141.5-142.5[6] (from Et_2O)	-112° (EtOH)
d 71	oil[6]	-39.8° (EtOH)	93	92:8[c]	64-71[6a]	-15.3° (EtOH)	77.5-78.5[6] (from hexane)	-19.5° (EtOH)

a) Based on 1. b) The ratio of 3A to 3B had been established by converting the mixture of 3A and 3B to (R)-4.[5] c) The ratio of 3A to 3B was calculated by the optical purity of 2(R), 3(S)-6. d) Isolation of the predominantly formed bromolactone(3A) was not attempted.

In complete the same manner, the crude bromolactone(3b)(3Ab:3Bb 96:4) derived from 3,4-dihydro-2-naphthoic acid(1b)[5b](see Table I), was converted to 2(R),3(S)-6b,[6] 92% optically pure,

Table II Results of the Asymmetric Synthesis of Optically Active α,β-Epoxyaldehydes(2(R),3(S)-6)[a]

	5		2(R),3(S)-6			
	Chem. Yields (%)	Ratio of the Two Epimers[b]	Chem. Yields (%)	Optical Rotations $[\alpha]_D^{20}(CHCl_3)$	Bp or Mp °C	Optical Yields (% ee)
a	90(oil)[6]	2:1	72	+182°(c=2.00)	75-82(0.9 mmHg)[6]	98[c]
b	85(oil)[6]	1:1	85	-189°(c=1.00)[d]	72.5-76[6a),d]	92[c]
c	95(oil)[6a]	2:1	60	+43.6°(c=6.0)	oil[6a]	98[e]
	[96(oil)[6]]		[58]	[+44.7°(c=1.01)]	[oil[6]]	
d	87(oil)[6a]	5:3	68	+96.9°(c=0.80)	oil[6a]	84[e]
	[100(oil)[6]]		[76]	[+115°(c=0.90)]	[oil[6]]	

a) Values in parentheses are those for the results obtained by using pure 3A. b) Determined by NMR spectrum. c) Calculated based on the ratio of 3A to 3B. d) Recrystallization from hexane gave an analytical sample, mp 79-79.5°C, $[\alpha]_D^{20}$-222°(c=1.04, $CHCl_3$). Anal. Calcd. for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.79; H, 5.80. e) Calculated by assuming that 2(R),3(S)-6 prepared from pure 3A was optically pure.

by way of the crude epoxy ester(5b).[6] The α,β-epoxyaldehyde(2(R),3(S)-6b) exhibited the same spectral properties as those of the corresponding racemic compound(dl-6b).[10]

The developed synthetic scheme was further applied to cyclohexene-1-carboxylic acid(1c)[11] and 2-methyl-2(E)-nonenoic acid(1d)[12] in order to explore the generality of the asymmetric synthesis.

Results for the preparation of 2c,d from 1c,d and the asymmetric bromolactonization of 2c,d giving the crude bromolactones(3c,d) are summarized in Table I. Being different from the cases for 3a,b in which the ratios of 3Aa,b to 3Ba,b had been established by the previous work,[5] the predominantly formed bromolactones(3Ac and 3Ad) were isolated in pure states by repeated recrystallizations of crude 3c,d. When crude 3c,d were subjected to the reaction conditions for epoxide formation and for reductive removal of the epimerized proline moiety, there could be obtained partially active 2(R),3(S)-6c,d[6a] by way of epimeric mixtures of the epoxy esters(5c,d).[6a] The same sequential treatments of pure 3Ac,d gave optically pure 2(R),3(S)-6c,d[6] (see parentheses in Table II). Comparisons of the optical rotations clearly disclosed that optical yields for 2(R),3(S)-6c,d and formation ratios of the two diastereomeric bromolactones(3Ac,d and 3Bc,d) were 98%, 84%, and 99:1, 92:8, respectively.

Considering operational simplicity and high optical yields(84-98% ee) exemplified above, the exploited asymmetric synthesis might provide the practical preparation method of optically active α,β-epoxyaldehydes which are conceivably quite versatile for synthesis of optically active macrolides and anti-cancer agents. Application of the overall process to synthesis of optically active anthracycline antibiotics, being of current interest due to their promising anti-cancer activity, is under progress in these laboratories.

References and Notes

1) a) K. Shudo and T. Okamoto, J. Syn. Org. Chem. Japan, 32, 670(1974). b) J.D. Connolly and K.H. Overton,"Chemistry of Terpenes and Terpenoids," Ed. by A.A. Newmann, Academic Press, London and New York, 1972, pp 207-287. c) Chem. Eng. News, p 19, June 11(1979).

2) Total syntheses of complex natural products have been accomplished by utilizing chiral epoxides as important synthetic intermediates. a) Methymycin: S. Masamune, et al., J. Am. Chem. Soc., 97, 3512(1975). b) Erythromycin: E.J. Corey, et al., Ibid., 100, 4618, 4620(1978). c) Vernolepin: P.A. Grieco, et al., Ibid., 99, 5773(1977). d) Rhodomycinone: A.S Kende, et al., J.C.S. Chem. Comm., 1977, 140.

3) a) T. Mashiko, S. Terashima, and S. Yamada, Yakugaku Zasshi, 100, 319, 328(1980). b) K. B. Sharpless and T.R. Verhoeven, Aldrichimica Acta, 12, 63(1979)., and references cited therein. c) C. Döbler and E. Höft, Z. Chem., 18, 217(1978).

4) a) S.W. May and R.D. Schwartz, J. Am. Chem. Soc., 96, 4031(1974). b) H. Ohta and H. Tetsukawa, J.C.S. Chem. Comm., 1978, 849.

5) a) S.-s. Jew, S. Terashima, and K. Koga, Tetrahedron, 35, 2337, 2345(1979). b) Idem., Chem. Pharm. Bull.(Tokyo), 27, 2351(1979).

6) a) IR and NMR spectra were in agreement with the assigned structure. b) Satisfactory analytical data and/or mass spectra were obtained for this compound.

7) Similar stereospecific transformations of halolactones to epoxy esters[8] or epoxy acids[2b] have already been reported.

8) a) P.A. Bartlett and J. Myerson, J. Am. Chem. Soc., 100, 3950(1978). b) Idem., J. Org. Chem., 44, 1625(1979).

9) The oily racemic α,β-epoxyaldehyde(dl-6a)[6a] was synthesized from 1a[5a] by successive esterification(EtOH-H_2SO_4, 96%), reduction($LiAlH_4$ in Et_2O, 79%), epoxidation(m-$ClC_6H_4CO_3H$ in CH_2Cl_2, 66%), and oxidation(CrO_3-$(C_5H_5N)_2$, 35%).

10) Preparation of dl-6b,[6a] mp < ca. 30°C, was performed by epoxidation of the ethyl ester of 1b[5b](m-$ClC_6H_4CO_3H$ in CH_2Cl_2, 67%) followed by reduction(i-Bu_2AlH in toluene, 42%).

11) Dihydroxylation(30% H_2O_2-80% HCOOH, 78%) of cycloheptene, followed by cleavage of the diol($NaIO_4$), aldol condensation(aq KOH, 35%(2 steps)), and oxidation(Jones reagent, 65%) gave 1c,[6a] bp 102-105°C(4 mmHg).

12) This compound(1d),[6a] oil, was prepared by olefination of n-heptanal(1-ethoxycarbonylethyl phosphate-NaH in DME, 97%, (E):(Z)=84:16 determined by NMR spectrum) followed by separatio of (E)-isomer and hydrolysis(KOH in aq EtOH, 89%).

(Received in Japan 11 April 1980)