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REGIOSELECTIVE INTRAMOLECULAR ASYMMETRIC CYCLIZATION OF SYMMETRICAL OPEN CHAIN TRIKETONE

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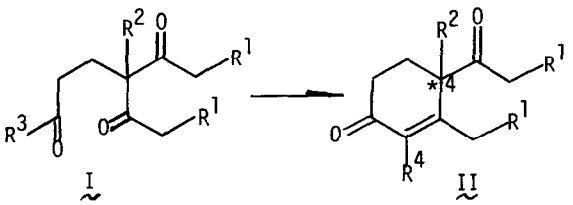
Summary——The title reactions performed with (S)-α-amino acids or their derivatives as chiral sources were found to regioselectively give enantiomeric pairs of optically active 4-acetyl-3,4-dimethyl-2-cyclohexenone((R)(+)- and (S)(-)-4), 16-25% e.e., and those of optically active 6-acetyl-3,6-dimethyl-2-cyclohexenone((R)(+)- and (S)(-)-5), 54-59% e.e., from the open chain triketone(3).

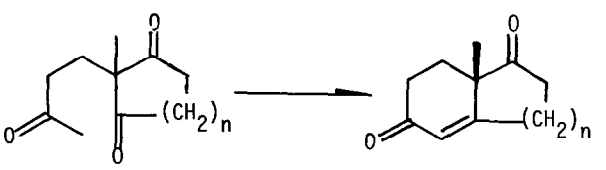
While optically active 2-cyclohexenones involving quarternary asymmetric centers at 4 or 6 position(II or III) are considered quite versatile building blocks for synthesizing various types of optically active natural products including terpenes and alkaloids, simple asymmetric synthesis which can afford II or III by the use of readily available chiral sources, seems quite limited.[1,2]



I II or III

R^1,R^4=H, alkyl, aryl
R^2=alkyl, aryl
R^3=H, R^4CH_2

Recently, Yamada,[3] Wiechert,[4] and Hajos[5,6] have independently succeeded in developing efficient asymmetric syntheses of the steroid CD ring system(Va)[3-5] and the Wieland-Miescher ketone(Vb)[3,4,6] from the symmetrical monocyclic triketone(IVa,b) by employing (S)-α-amino acids[4-6] or their derivatives[3] as chiral sources for intramolecular cyclization. Operational simplicity and high optical yields(at most 95% e.e. for Va[5]) of the reported asymmetric syntheses[3-6] prompted us to examine possible application of the similar intramolecular asymmetric cyclization to the open chain symmetrical triketones(I).



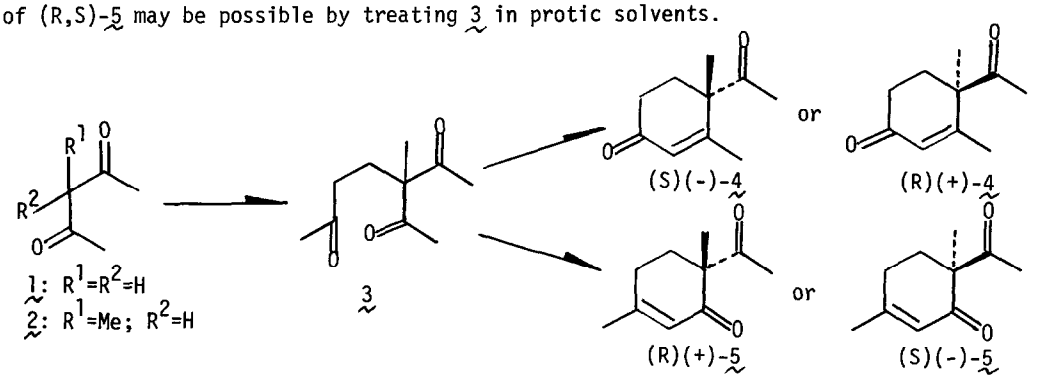
IV V

a: n=1
b: n=2

We have now found that when I are submitted to intramolecular asymmetric cyclization by using (S)-α-amino acids or their derivatives as chiral sources, enantiomeric pairs of II and III can be regioselectively produced, depending upon nature of chiral catalysts and reaction conditions. This report concerns with the preliminary results of our successful regioselective intramolecular asymmetric cyclization carried out by utilizing readily accessible 3-acetyl-3-methyl-2,6-heptadione(3) as a model compound of I.

The requisite symmetrical open chain triketone(3) was prepared from commercially available acetylacetone(1). Thus, Michael addition of 3-methyl-2,4-pentadione(2), bp 166-168°C(760 mmHg)(lit.,[7] bp 170-172°C(760 mmHg)), obtained from 1 according to the reported method(81%),[7] to methyl vinyl ketone(1.2 eq) in methanol in the presence of tris(hydroxymethyl)aminomethane (0.03 eq)(reflux, 7 hr) gave 3, bp 128-130°C(7 mmHg)(lit.,[8] bp 99-102°C(1 mmHg)), in 63% yield.

With an aim to find out the most critical reaction condition which can influence regioselectivity of the intramolecular aldol reaction, the cyclization of 3 was first examined by changing solvent systems, reaction temperatures, and acid-base catalysts. After several unsuccessful attempts, it was found that when 3 was treated with a mixture of pyrrolidine(0.60 eq) and acetic acid(0.76 eq) in ether at room temperature for 44 hr, (R,S)-4-acetyl-3,4-dimethyl-2-cyclohexenone((R,S)-4),[9,10] bp 114°C(4 mmHg), could be obtained in 81% yield as the sole product. On the other hand, reflux of a mixture of 3, piperidine(2.6 eq), and acetic acid(2.7 eq) in water for 6 days effected highly regioselective cyclization of 3, giving (R,S)-6-acetyl-3,6-dimethyl-2-cyclohexenone((R,S)-5),[9,12,13] bp 101-102°C(5 mmHg)(lit.,[13] bp 120°C (10 mmHg)), in 70% yield. These results clearly show that the intramolecular cyclization of 3 can preferentially give (R,S)-4 under aprotic polar condition, and that the selective formation of (R,S)-5 may be possible by treating 3 in protic solvents.



Based on the above results, the asymmetric intramolecular cyclizations of 3 were next attempted. A part of the preliminary results obtained by treating 3 with (S)-α-amino acids or their readily accessible derivatives in polar aprotic or protic solvents, are shown in the Table. All reactions were performed by stirring a mixture of 3 and a chiral source in an appropriate solvent at the indicated temperature for several days. Addition of a small amount of acid(0.25 eq) was sometimes quite effective for improving the optical yields of the reaction products. Usual extractive isolation followed by purification by a short silica gel column(solvent, ether-hexane) gave pure (R)(+)- and (S)(-)-4 or 5 which showed identical

Table Regioselective Intramolecular Asymmetric Cyclization of 3-Acetyl-3-methyl-2,6-heptadione(3)

Run	Chiral Sources (eq to 3)	Acid Added (eq to chiral source)	Solv.	Temp. (°C)	Time (days)	Reaction Products 4[a] Chem. Yield (%)[c]	$[\alpha]_D^{20}$[d]	Opt. Yield (%)[e]	5[b] Chem. Yield (%)[c]	$[\alpha]_D^{20}$[f]	Opt. Yield (%)[e]
1	(S)-proline(1)	-	DMSO	50	2	47	+27°	16(R)	-[g]		
2	(S)-N-methylphenylalanine[h](1)	-	DMSO	100	4	38	+16°	10(R)	-[g]		
3	(S)-prolinol[i](1)	BF_3-Et_2O (0.25)	DMSO	50	1	48	-42°	25(S)	-[g]		
4	(S)-valine(1)	-	H_2O	ref[j]	3	-[k]			50	+21°	8(R)
5	(S)-tryptophan(1)	-	H_2O	ref[j]	1	-[k]			42	+42°	16(R)
6	(S)-phenylalanine(1)	-	H_2O	ref[j]	1	-[k]			44	+92°	36(R)
7	(S)-histidine(1)	-	H_2O	ref[j]	1	-[k]			48	-21°	8(S)
8	(S)-phenylalanine(1)	$HClO_4$ (0.25)	MeOH-H_2O (100:8)	ref[j]	3	-[k]			32	+133°	52(R)
9	(S)-histidine(1)	$HClO_4$ (0.25)	MeOH-H_2O (100:8)	ref[j]	4	-[k]			24	-112°	44(S)
10	(S)-phenylalanine(1)	TosOH (0.25)	MeOH-H_2O (100:8)	ref[j]	4	-[k]			34	+150°	59(R)
11[n]	(S)-phenylalanine(0.2)	TosOH (0.25)	MeOH-H_2O (100:8)	ref[j]	11	19[l]	-[m]		38[l]	+145°	56(R)
12[n]	(S)-histidine (0.05)	TosOH (0.25)	MeOH-H_2O (100:8)	ref[j]	8	29[l]	-[m]		52[l]	-138°	54(S)

a) The chemical correlation with (S)(-)-2-isopropyl-2-methylglutaric anhydride(M.R. Cox, et al., J. Chem. Soc., 1973, 174) established that optically pure (R)(+)-4 shows $[\alpha]_D^{20}$+168°(C_6H_6).[11] b) The chemical correlation with (S)(-)-3-ethyl-3-methyladipic acid(M.R. Cox, et al., J. Chem. Soc., 1965, 7257) and the measurements of the NMR spectra in the presence of Eu(tfc)$_3$ established that optically pure (R)(+)-5 shows $[\alpha]_D^{20}$+257°(C_6H_6).[11] c) Isolated yield. d) c=1.0-1.2 in C_6H_6. e) Expressed by enantiomeric excess(e.e.). Letters in parentheses mean absolute configurations. f) c=0.74-1.5 in C_6H_6. g) Almost no formation of this compound was ascertained by tlc analysis of the reaction mixture. h) P. Quitt and J. Hellerback, Helv Chim. Acta, 46, 327(1963). i) M. Shibasaki, S. Terashima, and S. Yamada, Chem. Pharm. Bull. (Tokyo), 24, 315(1976). j) Reflux temperature. k) Separation of this compound being formed as a minor reaction product(detected by tlc and/or glc analyses) was not attempted. l) Determined by glc analysis. m) Optical rotation was not recorded. n) 16-19% of 3[l] was recovered.

spectral and chromatographic(tlc and glc) properties with those of (R,S)- 4 or 5, respectively.

From the Table, it is apparent that the reaction of 3 with (S)-proline and (S)-N-methylphenylalanine in DMSO selectively gives (R)(+)-4 being up to 16% e.e.(runs 1,2), and that the use

of (S)-prolinol as a chiral source afforded (S)(-)-4, 25% e.e., in the presence of boron trifluoride-etherate(run 3). When the cyclization of 3 was examined in protic solvents by using (S)-valine, (S)-tryptophan, and (S)-phenylalanine as chiral sources, there could be selectively obtained (R)(+)-5(runs 4-6). The optical yield of (R)(+)-5 was found to reach 52-59% by the addition of perchloric acid($HClO_4$) or p-toluenesulfonic acid(TosOH)(runs 8,10,11). Amazingly, the steric course of the intramolecular cyclization was dramatically inverted by treating 3 with (S)-histidine(run 7) and (S)(-)-5 being 54% e.e., could be obtained when the cyclization of 3 was carried out in the presence of TosOH(run 12). That the regioselective cyclization of 3 giving an enantiomeric pair of (R)(+)- and (S)(-)-5 can be performed by using a catalytic amount of chiral source in the same manner as those for the asymmetric syntheses exploited by Wiechert[4] and Hajos,[5,6] is clearly visualized by experiments in runs 11 and 12.

The precise reaction mechanism which can fully explain the observed results, is still quite obscure. However, the ready formation of an enantiomeric pair of (R)(+)- and (S)(-)-5 by utilizing (S)-phenylalanine and (S)-histidine as chiral sources suggests that not only the carboxyl group of (S)-phenylalanine but also the imidazole group of (S)-histidine might play important roles in determining the steric course of intramolecular cyclization by the possible formation of intramolecular hydrogen bond.[14]

While, in the regioselective formation of an enantiomeric pair of (R)(+)- and (S)(-)-4, improvement of the optical yields should await further experimentations, some practical values may be foreseen for the regioselective asymmetric synthesis of an enantiomeric pair of (R)(+)- and (S)(-)-5 because of its fairly high optical yields.

Being encouraged by the preliminary results cited above, we are currently studying the synthesis of optically active natural products by utilizing this type of the asymmetric synthesis. These results will be reported in due course.

References and Notes

1) D. Valentine, Jr. and J.W. Scott, Synthesis, 1978, 329., and references cited therein.
2) For the asymmetric synthesis of II hitherto reported, see, G. Otani and S. Yamada, Chem. Pharm. Bull.(Tokyo), 21, 2112,2119,2125(1973)., and T. Sone, S. Terashima, and S. Yamada, Ibid., 24, 1273,1288,1293(1976).
3) K. Nagasawa, H. Takahashi, K. Hiroi, and S. Yamada, Yakugaku Zasshi, 95, 33(1975).
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7) A.W. Johnson, E. Markham, and R. Price, Org. Syn. Coll. Vol. V, p. 785.
8) N.K. Kochetkov and B.P. Gottikh, Zhur. Obshchei Khim., 30, 948(1960)(C.A., 55, 1479c(1961)).
9) Infrared, nuclear magnetic resonance, and mass spectra were in good agreement with the assigned structure.
10) The structure of (R,S)-4 was further verified by the successful conversion to (R,S)-5-acetyl-5-methylheptanal.[11]
11) S. Sato, S. Terashima, and K. Koga, unpublished results.
12) Although (R,S)-5 had been prepared by methylation of 6-acetyl-3-methyl-2-cyclohexenone,[13] the structure of this enone was definitely ascertained by the successful conversion of (R)(+)-5 to (S)(+)-3-ethyl-3-methyl-6-oxoheptanal.[11]
13) R.N. Lacey, J. Chem. Soc., 1960, 1625.
14) The complex transition state which involves the intramolecular hydrogen bond with the carboxylate anion, has been proposed for the catalytic asymmetric cyclization of IVa affording highly optically active Va.[5]

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