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A NEW ENANTIOSELECTIVE CHEMOENZYMATIC SYNTHESIS OF R-(-)THIAZESIM HYDROCHLORIDE.#

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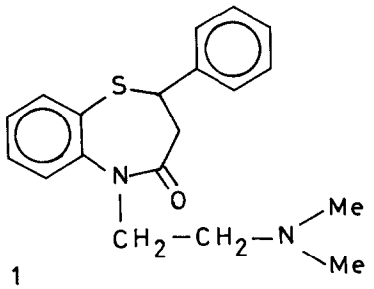
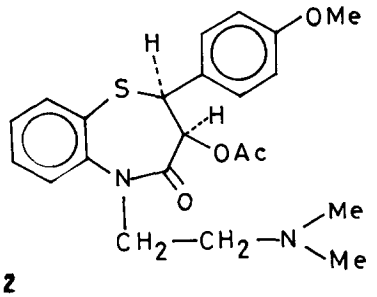
Abstract : A new synthesis of optically active 2-phenyl benzothiazepin-4-(5H)-one i.e. Thiazesim has been described.

In recent years members of the benzothiazepinone class of compounds have received considerable attention. This is mainly due to the diversity they display as far as the biological activity is concerned. In particular, the 2-aryl-1,5-benzothiazepin-4-(5H)-one skeleton constitute the framework of number of biologically active compounds such as anti-depressant, Thiazesim[1] (1), coronary vasodialators like Diltiazem[2,3] (2) and anti-ulcer and anti-secretary agent BTM-1086.[4]



1

Thiazesim

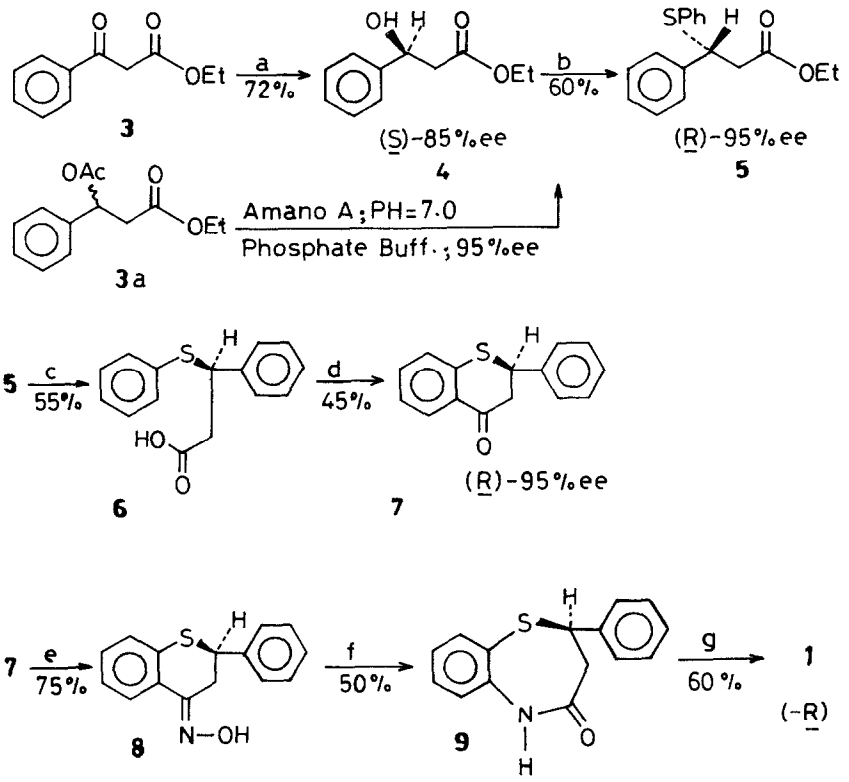


2

Diltiazem

Interest in the synthesis of pure enantiomers has gained new impetus because of the increasing awareness of the importance of optical purity in the context of biological activity. Therefore synthesis of 1 and 2 in optically active form is highly desirable. Although a number of synthetic routes have been reported[1,5] for the construction of 1,5-benzothiazepinones in racemic form, their synthesis in optically active form has so far been relied on classical resolution method[6] except one report.

We wish to report here the first chemoenzymatic approach (Scheme I) to the enantioselective asymmetric synthesis of (-)-Thiazesim, the simplest



(a) Baker's Yeast; glucose, H_2O; 1 day repeat 1 day (b) $(C_6H_5S)_2$, nBu_3P, Benzene (c) conc.HCl; Acetone; Δ; (d) $(COCl)_2$; CH_2Cl_2; $SnCl_4$
(e) NH_2OH·HCl, NH_4OAc, EtOH (f) PPA, 120°C, 2 hr.
(g) $Cl-CH_2-CH_2-N(CH_3)_2$; KOtBu; DMF.

member of benzothiazepin family. Our approach begins with the commercial available inexpensive ethyl benzoyl acetate 3. Baker's yeast reduction of 3 to yield (S)-ethyl-3-hydroxy-3-phenylproipionate has been reported[7] to give not more than 66% ee (low chemical yield) which is not desirable for further work. Using modified conditions we have been able to obtain 4 in 85% ee. However, we have now found out that lipase (Amano A or Candida Cylindracea) catalyzed hydrolysis of acetate of racemic 4 yields optically active 4 in 95% ee (S or R depending on the enzyme used). These findings will be basis of separate communication. All efforts to react tosylate/ mesylate of 4 with thiophenoxide ion failed to give 5 and gave cinnamate ester by elimination. However, 4 on treatment with diphenyl disulphide and tributyl phosphine[8], which is one of the crucial steps of the reaction sequence gave (R)-ethyl-3-phenylthio-3-phenylpriopionate (5) ($[\alpha]_D$+ 129.5°, $CHCl_3$, C = 1.48) in 60% yield with inversion of configuration. The opticalpurity of 5 was confirmed by H NMR spectrum using chiral shift reagent ($Eu(hfc)_3$). Acidic hydrolysis

of 5 with conc.HCl furnished the corresponding acid 6 ($[\alpha]_D$ +141.97° $CHCl_3$, C = 1.05) m.p. 80°C. The latter was first converted to its acid chloride in-situ followed by cyclization with oxalyl chloride, stannous chloride yielding (R)-2- phenyl benzothiopyran-4-(1H)-one, 7 ($[\alpha]_D$ = -154.48°, $CHCl_3$ C = 1.32), 7 on treatment with hydroxylamine hydrochloride afforded the corresponding oxime 8 ($[\alpha]_D$ -19.10°, $CHCl_3$) m.p. 165°C [9] Beckmann rearrangement ring expansion strategy was employed for the construction of 1,5-benzothiazepin ring system. Although number of reagents have been reported for the Beckmann rearrangement in our hands only polyphosphoric acid (PPA) gave the required product 9 ($[\alpha]_D$ + 469°) m.p. 182°C. Having constructed 1,5-benzothiazepin ring skeleton N-functionalisation was best performed following a method described for alkylation of benzothiazinones[10] using potassium-t-butoxide as a base and DMF as solvent to give (-)-1, with specific rotation comparable to 95% ee.

In conclusion, we have demonstrated a new enantioselective chemoenzymatic approach to 1,5-benzothiazepin, Thiazesim, in optically active form. Application of this strategy for the asymmetric synthesis of 2 will be reported soon.

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9. ^1H NMR comparison of 7 and 8 clearly indicated the desired (anti) orientation of the hydroxyl group.

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11. New compounds were characterised by their IR, ^1H NMR. The data for selected compounds :

    5 : IR (neat) cm^{-1}: 3100-2800 (CH): 1740 (C=O, ester), 1600, 1590 (ar). ^1H NMR ($CDCl_3$) : δ: 1.5 (3H, t, CH): 2.95 (2H, d, J=8Hz, CH): 4.1 (2H, m, OCH): 4.7 (1H, t, CH): 7.2 -7.4 (10H, m, ar).

    7 : ^1H NMR ($CDCl_3$) : δ : 3.28 (2H, d, J=4.8 Hz, CH_2): 4.8 (1H, m, CH): 7.05 7.6 (8H, m, ar): 8.1 (1H, dd, ar).

    8 : ^1H NMR ($CDCl_3$) : δ : 3.25 (2H, m, CH_2): 4.4 (1H, m, CH): 7.05-7.5 (8H, m, ar): 8.1 (1H, m, ar).

    9 : ^1H NMR ($CDCl_3$) : δ : 2.8 (2H, d, J=8.8 Hz, CH_2): 4.7- 5 (1H, m, CH): 7.1- 7.8 (9H, m, ar).