

0040-4039(95)00650-8

First 'Chiron Approach' based convergent synthesis of (-)-Colletol from D-xylose

G V M Sharma^{*}, A V S Raja Rao and V S Murthy Bio-Organic Laboratory Indian Institute of Chemical Technology, Hyderabad 500 007, India

Abstract : A protocol, based on 'chiron approach', for the synthesis of (-)-colletol is described, which involves the coupling of two appropriately protected hydroxy acids that are derived from D-xylose and macrolactoni-sation of seco-acid under Yamaguchi conditions.

(-)-Colletol (1), a 14-membered unsymmetrical (bis)macrolactone, was isolated¹ from the fermentation broth of <u>Colletotrichium capsici</u> and structurally related to fungal metabolites such as colletodiol and colletallol¹. In continuation of our programme on the synthesis² of bio-active macrolides, herein we report the first chiron approach based synthesis of (-)-colletol³ (1) using the chiral templates derived from D-xylose.

A synthetic design for 1 has been basically arrived at based on the antithetic analysis, (Scheme 1) where 1 could be conveniently made by a penultimate macrolactonization of seco acid 2. Acid 2 could readily be made by the esterification of two appropriately protected hydroxy acid segments 3 and 4 which inturn would come from 1,2-O-isopropylidene- α -D-xylose (5).

Scheme-1



Thus, the essential transformations that are to be brought about on 5 to get 3 are a) 3,5-dideoxygenation and b) carbon chain elongation by sequential Wittig reactions, while 8 a) on hydrolysis b) oxidative cleavage and c) Wittig olefination gives 4. Accordingly, the known^{2c} alcohol 6 (prepared in two steps from 5) was transformed (Scheme 2) into the xanthate ester 7 (69%) under Barton-McCombie⁴ conditions and exposed to Bu₃SnH in toluene to afford 8^5 (50%), $[\alpha]_D$ -11.2° (c 1, CHCl₃). Methanolysis (conc. HCl, MeOH, 60°C) of 8 and O-alkylation of the resultant 9 with MPMBr (NaH, THF) furnished 10 (75%). Acid (conc. HCl, 50% aq. AcOH) catalysed hydrolysis of 10 gave the lactol 11, which on subsequent Wittig olefination with methyltriphenylphosphonium iodide (KOBu^t, THF, RT)



a) NaH, CS₂, MeI, THF; b) n-Bu₃SnH, AIBN, Toluene, 110°C, c) conc. HCl, MeOH, 60°C; d) NaH, MPMBr, THF; e) conc. HCl, 50% aq. AcOH; f) CH_3PPh_3I , $KOBU^{t}$, THF, RT; g) Dihydropyran, PTSA, CH_2CI_2 ; h) BH_3 -DMS, H_2O_2 , THF, NaOH, 0°C; i) (COCI)₂, DMSO, Et_3N , CH_2CI_2 , -78°C; j) Ph_3P =CHCO₂Et, benzene, 80°C; k) LiOH, 1:1 THF-H₂O, RT.

afforded 12 (60%), $[\alpha]_D +33.6^\circ$ (c 1, CHCl₃). After the protection of hydroxyl group in 12 with dihydropyran (PTSA, CH₂Cl₂) the resulting 13 was subjected to hydroboration (BH₃-DMS, H₂O₂, NaOH, THF, 0°C) to furnish the alcohol 14 (71%). Oxidation of 14 under Swern conditions [(COCl)₂, DMSO, Et₃N, CH₂Cl₂] gave 15 (85%), which on subsequent reaction with (carbethoxymethylene)triphenylphosphorane (benzene, 80°C) gave 16 (63%). Finally, the ester 16 on hydrolysis (LiOH, aq.THF) afforded the requisite acid 3 (73%).

The second hydroxy ester segment 4 has been essentially made in 4 steps starting from 8, which inturn was prepared from 1,2-O-isopropylidene- α -D-xylose (5). Accordingly, hydrolysis (conc. H₂SO₄, 60% aq. AcOH, 40°C) of 8 (Scheme 3) gave the glycol 17, which on oxidative cleavage (NaIO₄, MeOH) afforded 18 (72%). Wittig olefination of 18 with (p-toluene sulfonyl-ethoxycarbonylmethylene)triphenylphosphorane⁶ (benzene, 80°C) furnished 19 (60%), which finally on exposure to 2% HCl (1:1 aq. dioxane) underwent de-O-formylation to afford 4 (90%) [α] D -5.2° (c 1, CHCl₃).



a) conc. H_2SO_4 , 60% aq. AcOH, 40°C; b) NaIO₄, MeOH; c) $Ph_3P=CHCO_2(CH_2)_2-SO_2Tol$, ben-zene, 80°C; d) 2% HCl, 1:1 dioxane-water.

Having made both the segments 3 and 4 successfully, they were then subjected to esterification (Scheme 4) essentially under Yamaguchi⁷ conditions with 2,4,6-trichlorobenzoyl chloride, (Et₃N, THF) to furnish 20 (70%). Depyranylation (conc. HCl, EtOAc-MeOH, 1:1) of 20 followed by selective removal of PTSE ester group in 21 with DBN (benzene, RT) gave seco-acid 2 (82%), $[\alpha]_D$ +6.6° (c 1.0, CHCl₃). The crucial macrolactonisation of 2 was performed under Yamaguchi conditions in toluene at 95°C under high dilution conditions to furnish 22 (60%) $[\alpha]_D$ +16° (c 0.4, CHCl₃). Finally, 22 on reaction with DDQ (aq. CH₂Cl₂, RT) gave (-)-colletol (1), $[\alpha]_D$ -26.4° (c 0.3, CHCl₃), whose spectral analysis was comparable with the reported³ data.



a) 2,4,6-Trichlorobenzoyl chloride, Et_3N , THF, then DMAP, benzene; b) conc. HCl, 1:1 EtOAc-MeOH; c) DBN, benzene, RT; d) 2,4,6-trichlorobenzoyl chloride, Et_3N , THF, then DMAP, toluene, 95°C; e) DDQ, 18:1 CH₂Cl₂-H₂O.

In conclusion, we have demonstrated the first 'chiron approach' based convergent total synthesis of 1, where both the component chirons 3 and 4 were prepared from a common chiral building block derived from D-xylose.

Acknowledgments : The authors are thankful to Dr A V Rama Rao, Director, for his encouragement. AVSR and VSM are thankful to CSIR, New Delhi, India, for financial support.

References :

- a) MacMillan, J. and Pryce, R.J. Tetrahedron Lett., 1968, 5497; b) MacMillan, J. and Simpson, T.S., J. Chem. Soc., Perkin Trans. I, 1973, 1487.
- a) Rama Rao, A.V.; Bhanu, M.N. and Sharma, G.V.M., Tetrahedron Lett., 1992, 33, 3907; b) Rama Rao, A.V.; Bhanu, M.N. and Sharma, G.V.M., Tetrahedron Lett., 1993, 34, 707; c) Rama Rao, A.V.; Murthy, V.S. and Sharma, G.V.M., Tetrahedron Lett., 1995, 36, 139; d) Rama Rao, A.V.; Murthy, V.S. and Sharma, G.V.M., Tetrahedron Lett., 1995, 36, 143.
- a) Keck, G.E. and Murry, J.A., J. Org. Chem., 1991, 56, 6606; b) Shimizu, I. and Omura, T., Chem. Lett., 1993, 1759.
- 4. Barton, D.H.R. and McCombie, S.W., J. Chem. Soc., Perkin Trans. I, 1975, 1574.
- 5. All new compounds gave satisfactory spectral analysis.
- 6. Colvin, E.W.; Purcell, T.A. and Raphael, R.A., J. Chem. Soc., Perkin Trans. I, 1976, 1718.
- 7. Inagawa, J.; Hirata, K.; Saeki, H.; Katsuki, T. and Yamaguchi, M., Bull. Chem. Soc. Jpn., 1979, 52, 1989.

IICT Communication No. 3517

(Received in UK 23 March 1995; accepted 7 April 1995)