Tetrahedron Letters, Vol.32, No.11, pp 1495-1498, 1991
Printed in Great Britain

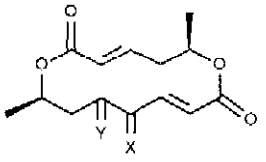
0040 4039/91 $3.00 + .00
Pergamon Press plc

AN ENANTIOSELECTIVE TOTAL SYNTHESIS OF THE MACRODIOLIDE (-)-(*RRR*)-COLLETALLOL

F.J. Dommerholt, L.Thijs and B.Zwanenburg*
Department of Organic Chemistry, University of Nijmegen,
Toernooiveld, 6525 ED Nijmegen, The Netherlands

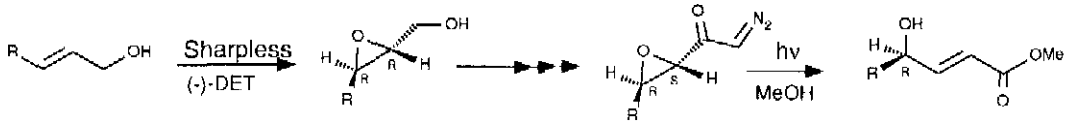
Abstract:
The total synthesis of (-)-colletallol, a naturally occurring macrodiolide, has been completed in 26 steps. An essential step in the sequence is the photo-induced rearrangement of an α,β-epoxy diazomethyl ketone to produce a 4-hydroxy-2-alkenoate.

A series of structurally related macrodiolides, viz. colletallol **1**, colletoketol **2**, colletol **3** and colletodiol **4**, has been isolated from culture filtrates of the plant pathogen *Colletotrichum capsici*[1]. We selected colletal-



	X	Y
1	H, OH	H_2
2	O	H, OH
3	H_2	H, OH
4	H, OH	H, OH

lol **1** as a target molecule for a total synthesis with the aim to demonstrate the utility of our method[2] for the enantiocontrolled preparation of 4-hydroxy-2-alkenoates. This method, which is depicted in scheme 1, invol-

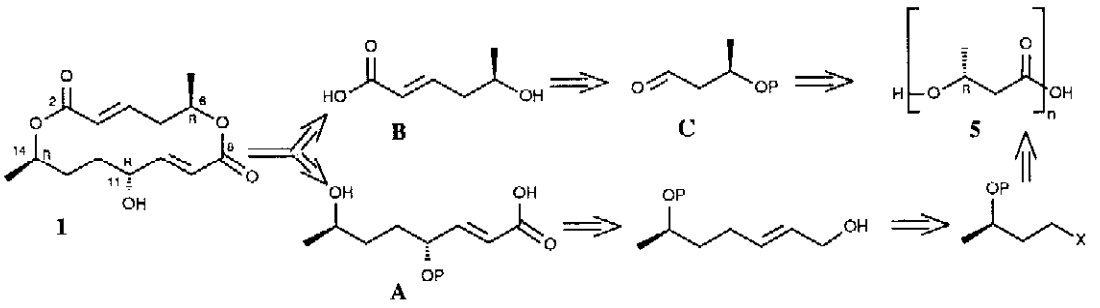


Scheme 1

ves the Sharpless epoxidation of an appropriate allylic alcohol, subsequent oxidation to the homochiral 2,3-epoxy carboxylic acid, conversion into the corresponding epoxy diazomethyl ketone and photo-induced rearrangement thereof in an alcoholic solvent.

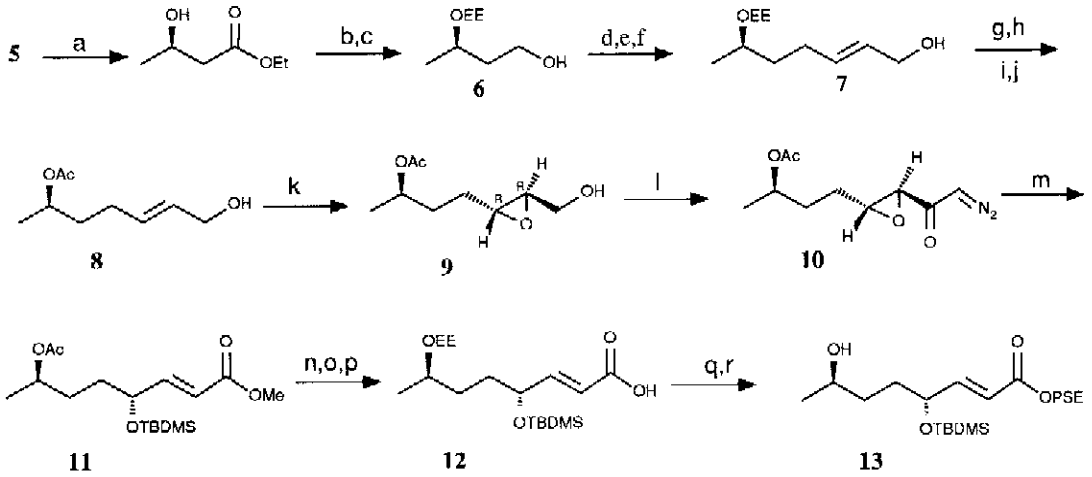
Our retrosynthetic analysis of colletallol is shown in scheme 2. Delactonization leads to the unsaturated hydroxy acids **A** and **B**, of which **A** is accessible through the methodology shown in scheme 1 and **B** by chain elongation of aldehyde **C**. A common starting material for both fragments is poly-(3(*R*)-hydroxy butyric acid) **5**, which will eventually lead to the *R* configuration at C_6 and C_{14} in the target molecule. A problem is that the relative and absolute configuration of the natural dilactone have not been established; furthermore, neither the m.p. nor the optical rotation have been reported. The only useful lead is that the spectral data of (+/-)-(*R*R*R**)-colletallol prepared by Wakamatsu et al.[3], show a close resemblance to those of natural colletallol. Moreover, the related compounds **2** and **4** also have the *R* configuration[4] at C_6 and C_{14}. Therefore, the synthesis of *RRR*-**1** was undertaken.

In the actual synthesis, the choice of protecting functions appeared to be of crucial importance. The synthesis of the C_8-C_{14} fragment **A** is outlined in scheme 3. Poly-(3(*R*)-hydroxy butyric acid **5** was depolyme-



Scheme 2

rized and the β-hydroxy function was protected with an ethoxy ethyl (EE) group. Subsequent reduction to alcohol **6**, conversion into the corresponding iodide, followed by a three-carbon elongation with propargylic alcohol and reduction of the triple bond, produced the allylic alcohol **7** required for the Sharpless epoxidation[5]. It then turned out however, that the EE protecting group is unstable under the conditions of the Sharpless epoxidation. Therefore, the EE group was replaced by an acetyl group as indicated[6]. Asymmetric epoxi-



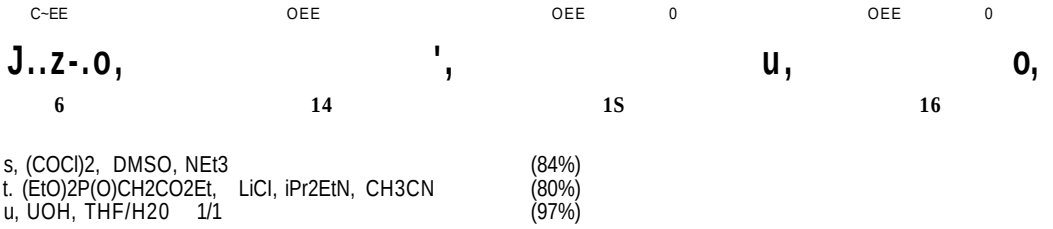
a. H_2SO_4, EtOH, $ClCH_2CH_2Cl$, Δ	(83%)	k. D(-)-DET, tBuOOH, $Ti(OiPr)_4$, mol sieves, CH_2Cl_2	(83%)
b. ethyl vinyl ether, cat. CF_3COOH	(100%)	l. RuO_4, $CH_3CN/CCl_4/H_2O$= 2/2/3; ClCOOiBu, NEt_3; CH_2N_2	(63%)
c. $LiAlH_4$, Et_2O	(98%)	m. hv, MeOH; TBDMSCl, imidazole, DMF	(61%)
d. TosCl, py, $CHCl_3$; NaI, acetone	(84%)	n. NaOMe, MeOH, 0°C	(85%)
e. propargylic alcohol, $LiNH_2$, NH_3(l)	(92%)	o. ethyl vinyl ether, PPTS, CH_2Cl_2	(99%)
f. $LiAlH_4$, Et_2O/THF= 7/8	(99%)	p. LiOH, THF/H_2O= 1/1	(98%)
g. TBDMSCl, imidazole, DMF		q. $HOCH_2CH_2SO_2Ph$, DCC, DMAP, CH_2Cl_2	(68%)
h. $MgBr_2$, Et_2O		r. $MgBr_2$, Et_2O	(99%)
i. Ac_2O, py			
j. HOAc/H_2O/THF= 3/1/1	(78%)		

Scheme 3

dation of allyl alcohol **8** gave epoxy alcohol **9** which was, without isolation of the intermediates, converted

dircctIy into the diazo ketone 10. Irradiation of this diazo ketone in methanol, ff~Ilowed by silylarion, gave compound 11. It was then necessary to decide which ester linkage in dilacmne ! should be eonstnlcted first. Either choice will result in a seco colletallol derivative in which an unsaturated ester needs to be converted into a free carboxylic acid (in order to accomplish the remaining lactonizntion step), without destroying the "lncrone" unit already formed. C.onsequently, the nature of the ester group in either seco-colletallol derivative requires careful consideration. Arbitrarily, we decided to form lactone unit C2-C14 first. For this purpose the neetyl group at Ci4 needed to bereplaced by the base stable EE group, Then the unsaturated ester was saponified wqh LiOH and the carboxylic acid 12 was esterified subsequently with 13-phenylsulfonyl ethanol using dieyclohexylcarbodiimide (DCC) as the coupling reagent7. Subsequent removal of the EE protecting function with MgBr2~'provided alcohol 13 which was used for the coupling reaction with the *CTC 6* fragment **B.**

The prepan14ion of IYagment B is depicted in scheme 4. Alcohol 6, obtained from poly-(3(R)-hydroxy

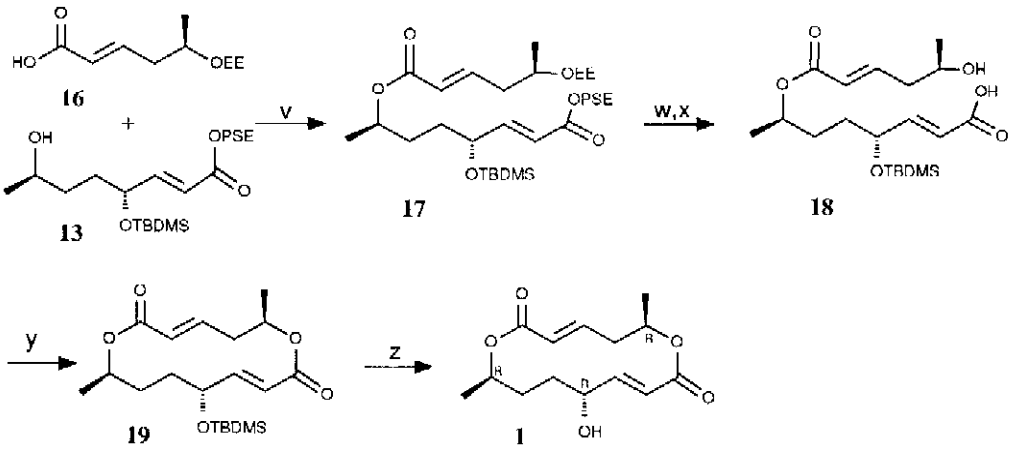


Scheme 4

butyric acid) (see scheme 3), was oxidized m aldehyde 14 and which was then subjected to a Wittig-Homer chain elongation to give ester lg. Subsequent saponification of this ester gave acid 16.

The coupling of acid 16 with the C8-C14 fragment 13 was successfully accomplished using DC(]/DMAP as the condensing agents (scheme 5) The "half htctone" derivative 17 obtained in this manner, was converted into seco-colletallol 18 by successive removal of the EE protecting group with MgBr26 and the PSE group by treatment with I)BU. The latter deprotection step is a base-induced eIimination reacdon and does therefore not affect the already formed "lactone" unit between C2 and C14.

Scco-colletallol 18 was subjcctcd to macrolactonization. Several of the various methods described in the literatures were tried9 but without success. Gratifyingly, the desired ring closure was realized in good yield by the Yamaguchi procedure employing 2,6 dichlorobenzoyl chloride instead of 2,4,6-rriehlorobenzoyl chloride used originally10. Final removal of the silyl protecting group at C11 from 19 gave *(-)-(RRR)-('olletal*-lol, m.p. 108 110 "C and [alp 2° -58" (c 0.7 in CHCI3). The spectral features (tH-NMR, MS and IR) we/x: in full accord with those reported for natnrnl colletallol and synthetic racemic *R*R*R*-eolletallo111.* This observation leads to the conclusion that natural colletallol has either the *RRR* or the *SSS* configuratkm. In view of the sUuctural relationship with collcttx.liol 4 and colletoketol 2, isolated from the same natural source, the *RRR* coafigut-ation is considered to bc the most probabte one.



v. DCC, DMAP, CH_2Cl_2	(97%)
w. $MgBr_2$, Et_2O	(78%)
x. DBU, benzene	(62%)
y. 2,6-$Cl_2C_6H_3C(O)Cl$, Et_3N; DMAP, toluene, Δ	(84%)
z. n-Bu_4NF, THF	(74%)

Scheme 5

References and notes

1. J. MacMillan and T.J. Simpson, J. Chem. Soc. Perkin I, 1487 (1973).
2. L. Thijs, F.J. Dommerholt, F.M.C. Leembuis and B. Zwanenburg, Tetrahedron Lett., 31, 6589 (1990).
3. T. Wakamatsu, S. Yamado, Y. Ozaki and Y. Ban, Tetrahedron Lett., 26, 1989 (1985).
4. P. Schnurrenberger, E. Hungerbühler and D. Seebach, Liebigs Ann. Chem., 733 (1987).
5. Y. Gao, R.M. Hanson, J.M. Klunder, S.Y. Ko, H. Masamune and B. Sharpless, J. Am. Chem. Soc., 109, 5765 (1987).
6. During the removal of the EE protecting function with $MgBr_2$ no epimerization or loss of homo-chirality was observed.
7. It should be emphasized here that selective removal of the methyl ester cannot be accomplished when the connecting ester unit with the C_2-C_6 fragment is already present.
8. K.C. Nicolaou, Tetrahedron, 33, 3041 (1977).
9. This will be described in a forthcoming full paper.
10. J. Inanaga, K. Hirata, H. Saeki, T. Katsuki and M. Yamaguchi, Bull. Chem. Soc. Jap., 52, 1989 (1979).
11. A sample of natural colletallol was not available, but spectra of natural and synthetic racemic *R*R*R**-colletallol were kindly provided by Professor K. Yoshida, Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo, Japan.

(Received in UK 31 December 1990)