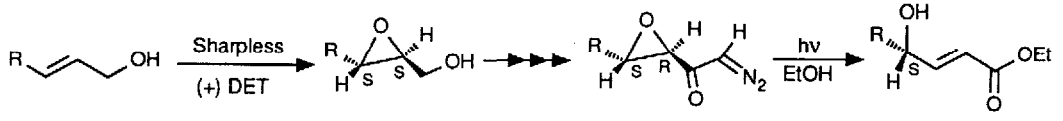
Tetrahedron Letters,Vol.30,No.16,pp 2153-2156,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

AN ENANTIOSELECTIVE TOTAL SYNTHESIS OF THE MACROLIDE PATULOLIDE C

L. Thijs, D.M. Egenberger and B. Zwanenburg*
Department of Organic Chemistry, University of Nijmegen,
Toernooiveld, 6525 ED Nijmegen, The Netherlands

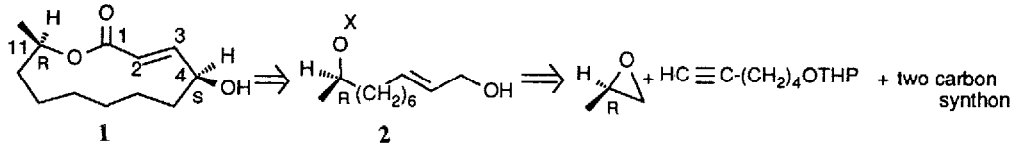
Abstract *A total synthesis of the twelve-membered ring lactone Patulolide C is described. The essentials of this synthesis are: nucleophilic ring opening of R-methyloxirane with a lithium acetylide, a Sharpless epoxidation, strategic use of the photochemical rearrangement of an epoxy diazomethyl ketone to a γ-hydroxy-α,β-unsaturated ester and a macro-lactonization using 2,6-dichlorobenzoyl chloride.*

Some structurally related twelve-membered ring lactones, termed Patulolides, were recently isolated[1,2] from the culture broth of *Penicillium urticae* mutant S11R59. Patulolide[2] C **1** is an interesting target molecule for a total synthesis as it enabled us to demonstrate the synthetic utility of our methodology[3,4,5] for the preparation of 4-hydroxy-alkenoates in an enantiocontrolled fashion. This methodology is based on the photo-induced rearrangement of α,β-epoxy diazomethyl ketones,[6] which can be readily prepared from an appropriate allylic alcohol by a Sharpless epoxidation with subsequent oxidation to an oxiranecarboxylic acid and conversion to the diazo ketones (Scheme 1).



Scheme 1

A retrosynthetic analysis of Patulolide C **1** based on this sequence of events, is depicted in Scheme 2. The stereochemistry at C-4 is in essence controlled by the Sharpless epoxidation, whilst the configuration at C-11 is introduced by an SN_2-opening of R-(+)-methyloxirane. The carbon chain of the allylic alcohol **2** is built up from methyloxirane, 5-hexyn-1-ol[7] and a two-carbon synthon.

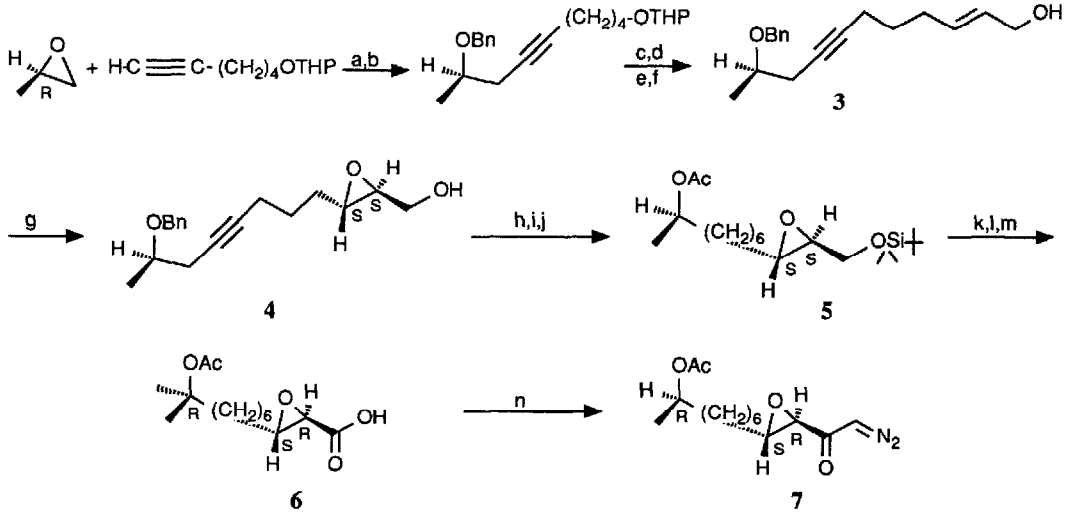


1 **2**

Scheme 2

The actual total synthesis is outlined in the Schemes 3 and 4. Nucleophilic ring opening of R-(+)methyloxirane[8]

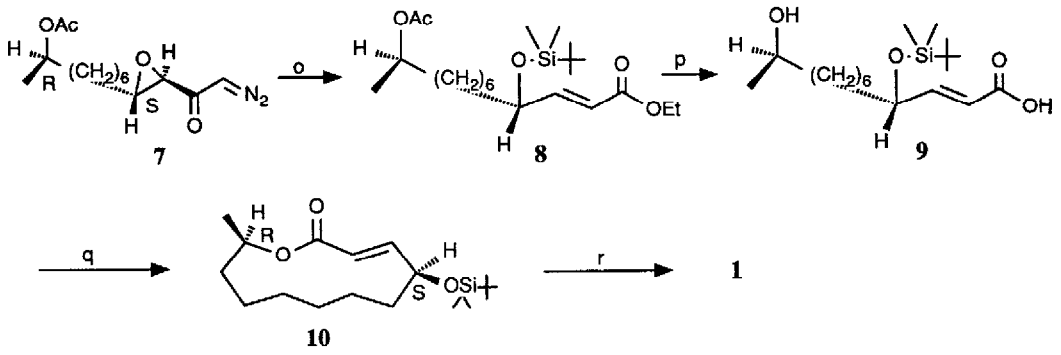
with the lithium acetylide of THP-protected 5-hexyn-1-ol[9], followed by a Wittig-Horner two-carbon chain elongation, and subsequent reduction with Dibal gave the appropriate allylic alcohol **3**[10] which on an enantiospecific Sharpless epoxidation[11] produced the epoxy alcohol **4**. At this stage the triple bond could be conveniently hydrogenated, with concomitant loss of the benzyl protecting group. The oxidation of epoxy alcohol **5** to the corresponding oxiranecarboxylic acid **6** was most effectively performed in two steps: initial conversion to the aldehyde by means of a Collins oxidation[12] (step l) and then further oxidation to the acid **6** using sodium chlorite[13] (step m). The diazo ketone **7**[10] was obtained from acid **6** through the mixed anhydride procedure (step n).



a.	BuLi, HMPA	(80%)	h.	t-BuMe$_2$SiCl, imidazole	(87%)
b.	BnBr, Bu$_4$NJ, NaH	(77%)	i.	H$_2$/Pd(C), Et$_3$N	(94%)
c.	pTosOH, MeOH	(80%)	j.	Ac$_2$O, pyridine, DMAP	(82%)
d.	Swern oxid	(98%)	k.	Bu$_4$NF, THF, 0°	(85%)
e.	(EtO)$_2$P(O)CH$_2$COOEt/ LiCl, EtN(iPr)$_2$	(80%)	l.	CrO$_3$, pyridine, CH$_2$Cl$_2$ (Collins oxid)	(71%)
f.	Dibal, Et$_2$O	(91%)	m.	NaClO$_2$, NaH$_2$PO$_4$.H$_2$O	(96%)
g.	L(+)-Diethyl tartrate, t-BuOOH, Ti(OiPr)$_4$, mol. sieves 4A, CH$_2$Cl$_2$	(80%)	n.	ClCOOiBu, Et$_3$N; CH$_2$N$_2$	(40%)

Scheme 3

The photo-induced rearrangement of diazo compound **7**, in fact the key step in this total synthesis, proceeded smoothly. The seco-lactone **9** was obtained from acetate ester **8** by consecutive removal of the acetate group at C_{11} and the ester function at C_1 by means of a careful treatment with aqueous sodium hydroxide(step p)[14]. The final lactonization of **9** was carried out with 2,6-dichlorobenzoyl chloride in a modified Yamaguchi[15] procedure (step q). It should be noted that the closure of this twelve-membered ring takes place remarkably easily. Removal of the silyl protecting group in **10** then completes the total synthesis[16] of Patulolide C (Scheme 4).



o. EtOH/hν; then t-BuMe$_2$SiCl, imidazole, DMF (48%)
p. NaOH/EtOH, 5h(!), 50° (98%)
q. 2,6-$Cl_2C_6H_3C(O)Cl$, Et_3N DMAP/toluene/100° (67%)
r. Bu_4NF/THF/0°C (70%)

Scheme 4

The spectral features (IR, ^{1}H-NMR, MS) of the synthesized material were identical with those obtained[17] from the authentic natural product. This was not the case however, for the optical rotation. For the natural patulolide C an $[\alpha]_D^{25}$-1.89 [*c* 2, EtOH] has been reported[2], whilst for the compound **1** synthesized above an $[\alpha]_D^{20}$ value of +6.6 [*c* 0.4, EtOH][18] was determined.

In order to shed light on this discrepancy an X-ray diffraction analysis of the p-bromobenzoate of **1** (m.p. 136-138 °C, lit.[2]134-135 °C) was carried out. This analysis[20] revealed unambiguously that the absolute configuration at C-4 is S and at C-11 is R, leaving no doubt about the correctness of the stereochemistry of the synthetic Patulolide C and suggesting that the reported rotation[18] for the natural product is not correct.

REFERENCES and NOTES

1. J. Sekiguchi, H. Kuroda, Y. Yamada and H. Okada, Tetrahedron Lett., 26, 2341 (1985).
2. D. Rodphaya, J. Sekiguchi and Y. Yamada, J. Antibiot., 39, 629 (1986).
3. L. Thijs, P.P. Waanders, E.H.M. Stokkingreef and B. Zwanenburg, Recl. Trav. Chim. Pays-Bas, 105, 332 (1986).
4. L. Thijs, E.H.M. Stokkingreef, J.M. Lemmens and B. Zwanenburg, Tetrahedron 41, 2949 (1985).
5. P.P. Waanders, L. Thijs and B. Zwanenburg, Tetrahedron Lett., 28, 2409 (1987).
6. P.M.M. van Haard, L.Thijs and B. Zwanenburg, Tetrahedron Lett., 803 (1975).
7. As an alternative we considered chain elongation of 4-pentyn-1-ol with 2-propyn-1-ol as a three-carbon synthon, however, the yields of this approach were less satisfactory.
8. B. Koppenhoefer, R. Weber and V. Schurig, Synthesis 316 (1982).
9. 5-Hexyn-1-ol was kindly supplied by Professor L. Brandsma, Univ. of Utrecht, The Netherlands.
10. All compounds were checked for purity by GLC and were characterised by spectral means including mass spectroscopy. The acids **6** and **9** were identified by IR and NMR only. Key compound **7** (mp 55-56 °C) $[\alpha]_D^{20}$ + 23 [*c* 0.8, EtOH] showed a correct elemental analysis.

11. Y. Gao, R.M. Hanson, J.M. Klunder, S.Y. Ko, H. Masamune and K.B. Sharpless, J. Am. Chem. Soc., 109, 5765 (1987).
12. J.C. Collins, W.W. Hess and F.J. Frank, Tetrahedron Lett., 3363 (1968).
The Swern oxidation was also attempted for the conversion of the epoxy alcohol to the corresponding aldehyde, however, the resulting product was "polymeric" in nature.
13. B.S. Bal, W.E. Childers and H.W. Pinnick Tetrahedron, 37, 2091 (1981).
14. In this procedure exactly 2 equiv. of sodiumhydroxide were used and the progress of the reaction was monitored by TLC. It took five hours to hydrolyse the ester function at C_1. Under different conditions we observed loss of material and/or disappearance of the double bond.
15. J. Inanaga, K. Hirata, H. Sacki, T. Katsuki and M. Yamaguchi, Bull. Chem. Soc. Jap., 52, 1989 (1979).
In this literature procedure non-commercially available 2,4,6-trichlorobenzoyl chloride is used.
16. For a 10-step synthesis of racemic Patulolide A –this is compound **1** with a ketone instead of a hydroxy function at C-4– see: N.R. Ayyangar, B. Chanda, R.D. Wakharkar and R.A. Kasar, Synth. Commun., 2103 (1988); for a 15-step synthesis, see: A. Makita, Y. Yamada and H. Okada, J. Antibiot., 39, 1257(1986).
17. The IR, ^{1}H- and ^{13}C-NMR spectra were kindly provided by Professor Y. Yamada, Osaka Univ., Japan.
18. The same problem concerning the optical rotation of Patulolide C was recently encountered by Mori and Sakai (ref. 19). These authors report an $[\alpha]_D^{25}$ of + 5.4 (*c* 0.57, EtOH), a value that is very close to ours. This observation substantiates our suggestion that the reported optical rotation for the natural product is erroneous.
19. A diastereomeric mixture of Patulolide C and its C-4 epimer was recently prepared by K. Mori and T. Sakai, Liebigs Ann. Chem. 13 (1988). The epimers were separated by HPLC.
20. G. Beurskens, J.M.M. Smits, P.T. Beurskens, L. Thijs, D.M. Egenberger and B. Zwanenburg, J. Crystallogr. Spectrosc. Res. submitted for publication.

(Received in UK 2 March 1989)