Tetrahedron Letters,Vol.28,No.27,pp 3061-3064,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

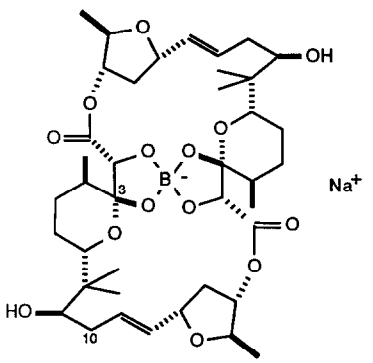
# STEREOSPECIFIC SYNTHESIS OF THE C(3)-C(10) SEGMENT OF APLASMOMYCIN FROM (R)-PULEGONE

James D. White*, Shen-chun Kuo, and Thalathani R. Vedananda

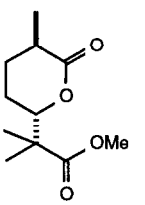
Department of Chemistry, Oregon State University
Corvallis, Oregon 97331-4003

**Summary:** A key subunit of aplasmomycin comprising C3-C10 of the symmetrical macrodiolide structure has been synthesized in optically pure form by two routes from (R)-(+)-pulegone.

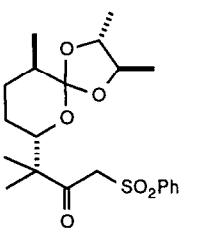
A strategic intermediate in our recent total synthesis of aplasmomycin (**1**)[1] was the δ-lactone **2**, which provided the C(3)-C(10) segment in each half of the macrodiolide. Lactone **2** was prepared in racemic form via condensation of the dianion of tiglic acid with the monoacetal of 2,2-dimethylmalondialdehyde.[2] The mixture of diastereomeric ortholactones obtained upon treatment of **2** with (2R,3R)-(-)-butanediol was condensed with methyl phenyl sulfone and the desired enantiomer **3** was isolated by HPLC.[3]




**1**

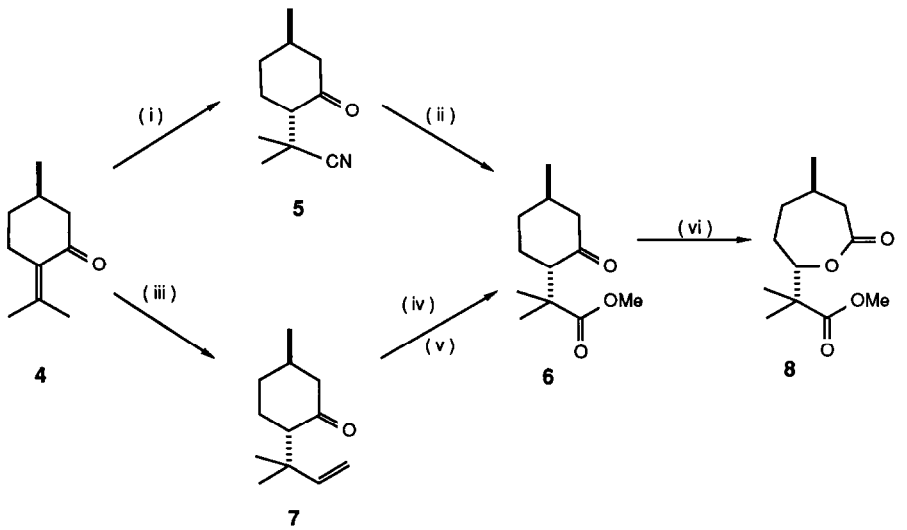



**2**



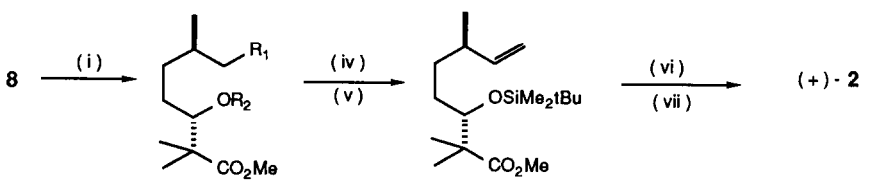

**3**

The lengthy sequence to **3**, together with an optical resolution that required a tedious chromatographic separation, prompted us to seek more chirally efficient pathways to this sulfone. We now describe two routes to (+)-**2** from (R)-(+)- pulegone (**4**) that greatly improve access to this key substance.




(i) NaCN, $NH_4Cl$ (ii) MeOH, $H_2SO_4$ (97% from **4**) (iii) $CH_2$=CHMgBr, CuBr,THF, -20°C (80%) (iv) $RuCl_3$, $NaIO_4$, $CH_3CN$-$CCl_4$-$H_2O$ (1:1:2), 20°C (v) $CH_2N_2$, $Et_2O$ (77% from **7**) (vi) $CF_3CO_3H$ $CH_2Cl_2$, 20°C, 16h (88%)

The preparation of keto ester **6** was accomplished by methanolysis of the hydrocyanation product **5**[4] of pulegone and also by conjugate addition of vinylmagnesium bromide to **4**,[5] followed by oxidative cleavage of the vinyl group of **7** with ruthenium tetraoxide[6] and esterification of the resulting carboxylic acid with diazomethane. Baeyer-Villiger oxidation of **6** afforded ε-lactone **8** with only a trace of the regioisomeric lactone.

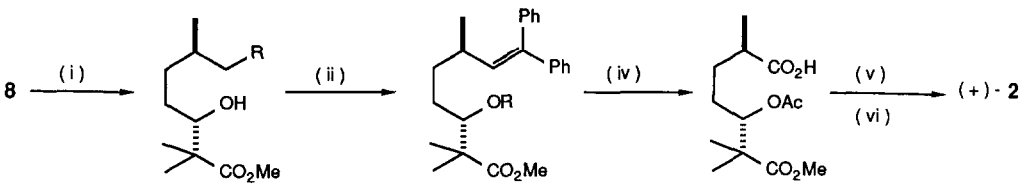



(ii), (iii) **9** $R_1 = CO_2Me$, $R_2 = H$; **10** $R_1 = CO_2Me$, $R_2 = SiMe_2t$-Bu; **11** $R_1 = CH_2OH$, $R_2 = SiMe_2t$-Bu

(i) $K_2CO_3$, MeOH (90%) (ii) t-$BuMe_2SiOSO_2CF_3$, 2,6-lutidine, $CH_2Cl_2$ (98%) (iii) $LiAlH_4$, $Et_2O$, -78°C (85%) (iv) o-$O_2NC_6H_4SeCN$, n-$Bu_3P$, THF (v) $H_2O_2$ (91%) (vi) $RuCl_3$, $NaIO_4$, $CH_3CN$-$CCl_4$-$H_2O$ (1:1:2) (vii) 5% HF, $CH_3CN$ (79% from **12**)

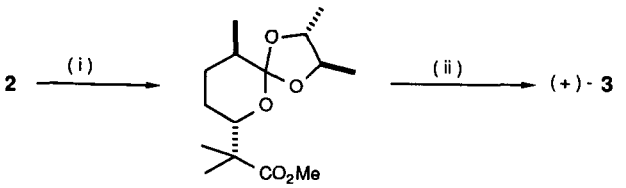
Our initial plan for ring contraction of **8** to the δ-lactone **2** envisioned ozonolytic cleavage of the derived silyl ketene acetal, but all attempts at excising the superfluous carbon by this means met with failure. Instead, two sequences were developed in which an open form of **8** was degraded to its lower homolog which, after final lactonization, yielded **2**. In

the first route, **8** was converted to diester **9** by methanolysis, and the hydroxyl group was protected as its t-butyldimethylsilyl ether **10**. Reduction of the more exposed ester function of **10** with lithium aluminum hydride at low temperature gave **11** with excellent selectivity. This alcohol was then converted to olefin **12** by elimination of the intermediate o-nitrophenylselenoxide.[7] Oxidative cleavage of the olefin with ruthenium(IV)[6] yielded a carboxylic acid which, without purification, was subjected to hydrofluoric acid. This treatment removed the silyl blocking group and effected lactonization to (+)-2, which was identical by comparison of its spectral properties with racemic material prepared previously.[3]




(i) PhMgBr, THF, 0°C, 1h (ii) PPTS, $C_6H_6$, reflux, 4h (55% from **8**) (iii) $Ac_2O$, Py, 4-DMAP, $CH_2Cl_2$, 20°C, 18h (iv) $RuCl_3$, $NaIO_4$, $CH_3CN$-$CCl_4$-$H_2O$ (1:1:2), 20°C, 4h (78% from **15**) (v) $K_2CO_3$, MeOH, reflux, 16h (vi) 1N HCl, $CHCl_3$, 20°C, 48h (87%)

An alternative pathway from **8** to (+)-2 employing a variant of the Barbier-Wieland degradation[8] was found to be even more expeditious. Thus, treatment of **8** with phenylmagnesium bromide gave the diol **13**, together with ketone **14**, and acid catalyzed dehydration of **13** smoothly provided **15**. The latter was acetylated to give **16**, which underwent oxidative cleavage of the olefin[6] to furnish the carboxylic acid **17**. A final methanolysis, followed by acidification, afforded **2**.




**18**

(i) (2R, 3R)-$CH_3CH(OH)CH(OH)CH_3$, p-TsOH (84 %) (ii) $PhSO_2Me$, n-BuLi(2 equiv) (92%)

In order to stereochemically correlate (+)-2 with material prepared previously, it was necessary to convert this compound to ortholactone **18** with (2R,3R)-butanediol. Condensation of **18** with the dianion of methylphenylsulfone produced **3** which was identical by comparison of optical rotation as well as infrared, $^1H$ and $^{13}C$ NMR, and mass spectra, with the same substance obtained by resolution.[3]

**Acknowledgement.** We are indebted to the National Institutes of Health (AI 10964) for support of this work.

**References**

1. White, J.D.; Vedananda, T.R.; Kang, M.-c.; Choudhry, S.C. J. Am. Chem. Soc. **1986**, 108, 8105.
2. Johnson, P.R.; White, J.D. J. Org. Chem. **1984**, 49, 4424.
3. White, J.D.; Avery, M.A.; Choudhry, S.C.; Dhingra, O.P.; Kang, M.-c.; Whittle, A.J. J. Am. Chem. Soc. **1983** 105, 6517.
4. Hann, A.C.O.; Lapworth, A. Proc. Chem. Soc. London **1904**, 20, 54.
5. This reaction gave a mixture of cis and trans isomers which was equilibrated in the presence of KOH-EtOH to a 85:15 ratio favoring the trans isomer 7.
6. Carlsen, P.H.J.; Katsuki, T.; Martin, V.S.; Sharpless, K.B. J. Org. Chem. **1981**, 46, 3936.
7. Grieco, P.A.; Gilman, S.; Nishizawa, M. J. Org. Chem. **1976**, 41, 1485.
8. Shoppee, C.W. Rep. Progr. Chem. **1947**, 44, 184.

(Received in USA 7 April 1987)