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Published on 01 January 1997. Downloaded on 25/10/2014 14:58:38.

Total synthesis of (−)-PA-48153C (pironetin) utilising L-quebrachitol as a chiral building block

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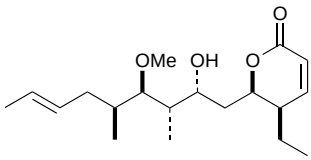
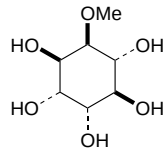
The chiral and stereoselective synthesis of (−)-PA-48153C (pironetin) 1, a novel immunosuppressant, is described; the acyclic portion possessing four contiguous chiral centres in 1 was constructed stereoselectively from L-quebrachitol and the 2-pyranone moiety was prepared from L-malic acid.

PA-48153C (pironetin) **1** is a novel 2-pyranone derivative isolated from the culture broth of *Streptomyces*[1,2] and is reported to show a potent immunosuppressive,[1] cytotoxic[1] and plant growth regulator activities.[2a] Its interesting mode of action, its suppressive effect on the responses of both T and B lymphocytes to mitogens[1] as well as its unique structure[1,2b] has attracted much synthetic interest and three total syntheses of **1** have been reported to date.[3] Recently, reports on the synthesis and the structure–activity relationship study of the analogues of **1** have appeared.[4] Here we report an alternative approach to **1**, which utilises L-quebrachitol **2**, an optically active cyclitol obtained in a large quantity from the serum of the rubber tree[5,6] as a chiral building block.



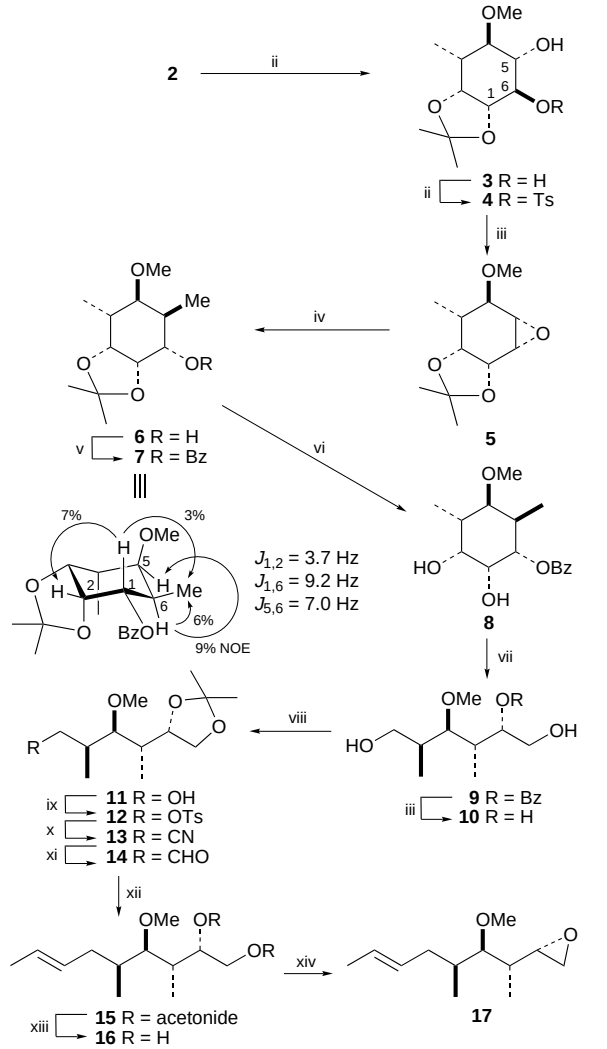
PA-48153C (pironetin) **1**



L-quebrachitol **2**

The known 1D-(1,2,3,5/4,6)-1,2-*O*-isopropylidene-3-methyl-4-*O*-methylcyclohexane-1,2,4,5,6-pentol **3**,[6a] prepared stereoselectively from **2** in five steps, was chosen as the starting material for the preparation of the acyclic moiety in **1**. Reaction of **3** with dibutyltin oxide[7] followed by treatment with *p*-toluenesulfonyl chloride (TsCl) afforded **4** in 82% yield.† Base treatment of **4** provided α-epoxide **5** in 93% yield. Reaction of **5** with trimethylaluminium in CH_2Cl_2–hexane at room temp. caused the *trans*-diaxial opening of the epoxide ring with the methyl group to afford **6**, which was isolated after *O*-benzoylation to provide **7** in 56% yield from **5**. The observed coupling constants and NOE of **7** clearly supported the assigned structure. The *O*-isopropylidene group in **7** was removed to give **8** (96%). The cyclohexane ring in **8** was cleaved by periodate oxidation to provide acyclic diformyl derivative, which, without isolation, was reduced with $NaBH_4$ to afford diol **9** in 90% yield. Removal of the *O*-benzoyl group in **9** and protection of the resulting 1,2-diol moiety gave **11** (89% yield from **9**), which was converted into the nitrile derivative **13** *via* *O*-tosylate **12** (97% for two steps). Reduction of the nitrile function in **13** with DIBAL-H, followed by acidic work-up provide **14**. Wittig olefination of **14** with $Ph_3P{=}CHMe$, followed by photo-induced isomerization, showed low *E*-selectivity and gave an inseparable mixture of **15** and its *Z*-isomer in a ratio of 3:1 (61% yield from **13**). Fortunately, better results were obtained when **14** was reacted with $MeCHI_2$ in the presence of $CrCl_2$ (Takai reaction)[8] to provide **15** as the major product (*E*:*Z* = 11:1, 74% yield from **13**).‡ Acid hydrolysis of the mixture, followed by chromatographic separation afforded geometrically pure **16** in 89% isolated yield. Treatment of **16** under the conditions of Mitsunobu[9] furnished the acyclic moiety, epoxide **17** in 71% yield.

The synthesis of the precursor of the 2-pyranone portion in **1** commenced with known (2*S*,3*S*)-2-ethyl-3,4-isopropylidenedioxypropan-1-ol **18**, obtained from L-malic acid in 6



Scheme 1 Ts = $SO_2C_6H_4$(*p*-Me) *Reagents and conditions*: i, see ref. 6(*a*); ii, Bu_2SnO, MeOH, reflux, then TsCl, DMAP, 1,4-dioxane, room temp.; iii, MeONa, MeOH; iv, Me_3Al (10 equiv.), CH_2Cl_2–hexanes (1:1), room temp.; v, BzCl, pyridine, DMAP, room temp.; vi, 10-camphorsulfonic acid (CSA, 0.2 equiv.), MeOH, room temp.; vii, $NaIO_4$, acetone–H_2O (1:1), 0 °C, then $NaBH_4$, MeOH, 0 °C; viii, acetone, CSA, 0 °C; ix, TsCl, pyridine; x, NaCN, 15-crown-5, DMF 60 °C; xi, DIBAL-H, CH_2Cl_2, −78°C, then 5% aqueous H_2SO_4–CH_2Cl_2, 0 °C, 40 min.; xii, $MeCHI_2$ (2 equiv.), $CrCl_2$ (8 equiv.), THF, room temp., 3 h; xiii, CSA, MeOH, 60 °C; xiv, Ph_3P, diethyl azodicarboxylate, toluene, reflux, 36 h

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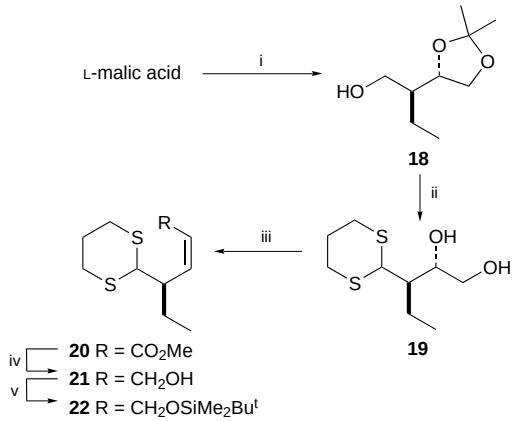
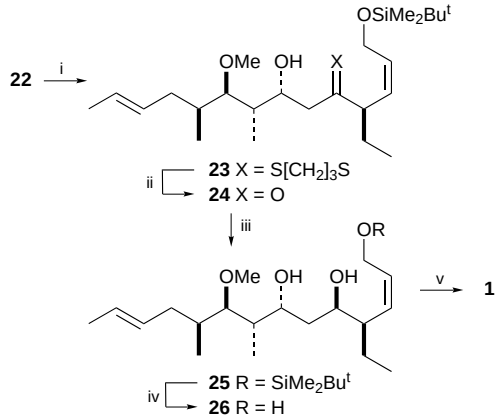
steps.[10] Oxidation of **18** with pyridinium chlorochromate (PCC) on alumina,[11] followed by treatment with propane-1,3-dithiol in the presence of $BF_3{\cdot}OEt_2$ gave diol **19** in 63% yield. Glycol cleavage and subsequent modified Wittig–Horner reaction[12] gave desired *Z*-alkene **20** (63% yield) along with its *E*-isomer (14%). DIBAL-H reduction of **20** followed by protection of the resulting alcohol function provided 2-pyranone precursor **22** in 68% yield from **20**.

Deprotonation of **22** with *tert*-butyllithium in the presence of hexamethylphosphoramide (HMPA),[13] followed by addition of epoxide **17** afforded the coupling product **23** in 56% yield. Deprotection of the dithioacetal function in **23** was achieved by treatment with *N*-chlorosuccinimide (NCS) and $AgNO_3$[14*a*] in the presence of 2,4,6-collidine[14*b*]§ to give **24** quantitatively. Reduction of the ketone carbonyl in **24** with $NaBH(OAc)_3$[15] in MeCN–AcOH afforded *anti*-diol **25** as the major product in 65% isolated yield (*syn* isomer 25% yield). Removal of the *O*-silyl protecting group in **25** afforded triol **26** in 82% yield. The final step was successfully achieved by MnO_2 oxidation of



Scheme 2 *Reagents and conditions*: i, see ref. 10(*a*); ii, PCC, Al_2O_3, CH_2Cl_2, room temp., then 1,3-propanedithiol (1.5 equiv.), $BF_3{\cdot}OEt_2$ (0.3 equiv.), CH_2Cl_2, room temp.; iii, $Pb(OAc)_4$, K_2CO_3, benzene, room temp., then $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, $KN(SiMe_3)_2$, 18-crown-6, THF, −78 °C; iv, DIBAL-H CH_2Cl_2, −78 °C; v, *tert*-butyldimethylsilyl trifluoromethanesulfonate, 2,6-lutidine, CH_2Cl_2, 0 °C



Scheme 3 *Reagents and conditions*: i, Bu^tLi, HMPA, THF, −78 °C, 10 min, then THF solution of **17**, −78 °C, 30 min; ii, NCS (4 equiv.), $AgNO_3$ (4.5 equiv.), 2,4,6-collidine (8 equiv.), MeCN–H_2O (4 : 1), 0 °C, 1 min; iii, $NaBH(OAc)_3$, MeCN–AcOH (2 : 1), 0 °C, 5 h; iv, tetrabutylammonium fluoride, THF, room temp.; v, MnO_2, CH_2Cl_2, room temp., 3 h

26 to furnish **1** in 87% yield. The spectroscopic (^1H and ^{13}C NMR) data for synthetic **1** were identical with those of natural PA-48153C, and the physical properties of **1** [mp, 74–76 °C; $[\alpha]_D^{21}$ − 141 (*c* 0.18, $CHCl_3$); lit.[1,2*b*] mp, 78–79 °C; $[\alpha]_D^{27}$, −143.7[1] (*c* 0.5, $CHCl_3$); −136.6[2*b*] (*c* 1, $CHCl_3$)] showed a good accord with those reported for the natural product.

We thank Dr Kenji Kawada (Shionogi & Co., Ltd., Osaka, Japan) for providing us with natural PA-48153C. We also thank Yokohama Rubber Co. Ltd., (Tokyo, Japan) for the gift of L-quebrachitol. Financial support of the Moritani Scholarship Foundation is gratefully acknowledged.

Footnotes

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† When this reaction was carried out with TsCl and DMAP in pyridine at 50 °C, compound **4** and its positional isomer (5-*O*-tosylate) were obtained in 37 and 22 isolated yield, respectively.

‡ Reaction of **12** (or its corresponding *O*-triflate derivative) with prop-1-enyllithium in the presence of Cu^I salts directly afforded **15**, however, the yield of **15** was low (less than 10%).

§ In the absence of collidine, the formation of cyclic hemi-ketal derivative, which arose from undesired deprotection of *O*-silyl group, was observed.

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Received in Cambridge, UK, 28th February 1997; Com. 7/01404J

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