A synthetic approach to the pseudopterosins

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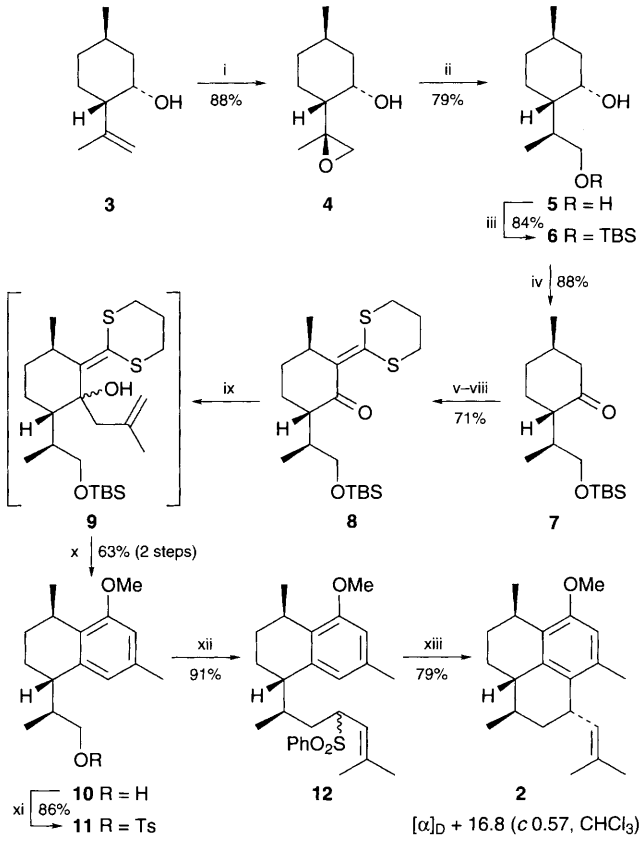
Three Lewis acid catalysed reactions used in a synthesis of the tricyclic core of the marine anti-inflammatory pseudopterosins are reported; the reductive cleavage of an oxirane with inversion, the cyclisation of an α-hydroxy ketenedithioacetal to an arene, and a stereoselective annulation using an allylic sulfone as the electrophile.

Pseudopterosins A–D **1a–d** were the first members of a family of diterpene pentose glycosides isolated from the Caribbean sea whip *Pseudopterogorgia elisabethae*.[1] Their potent anti-inflammatory and analgesic activities were the spur for the total syntheses of the glycoside,[2–4] the aglycone,[5,6] and advanced fragments of pseudopterosins A and E.[7–13] We now report a highly stereoselective synthesis of the tricyclic derivative **2** whose enantiomer had previously been converted to pseudopterosin A **1a**.[6] The absolute configuration of **2** corresponds to the tricyclic core of pseudopterosins K **1e** and L **1f** which have yet to be synthesised.[14]

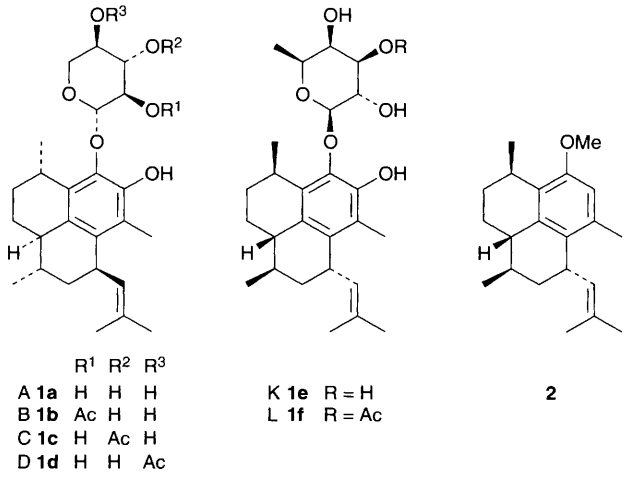
The synthesis began (Scheme 1) with a highly stereoselective hydroxy group directed epoxidation[15] of (1*S*,2*S*,5*R*)-neoisopulegol **3** which is readily available from commercial (1*R*,2*S*,5*R*)-isopulegol.[16] The oxirane **4** was cleaved with clean inversion of configuration by reduction with $NaBH_3CN$ in the presence of $BF_3{\cdot}OEt_2$ to give the diol **5** as a single diastereoisomer in 79% yield.[17] Selective protection of the primary hydroxy group (84%) followed by Swern oxidation returned the ketone **7** which was then converted to the α-oxoketenedithioacetal **8** by a one-pot, four step procedure involving reaction of the lithium enolate derived from **7** with CS_2 followed by a second enolisation and trapping of the intermediate ketene dithiolate with 1,3-dibromopropane (71% overall).

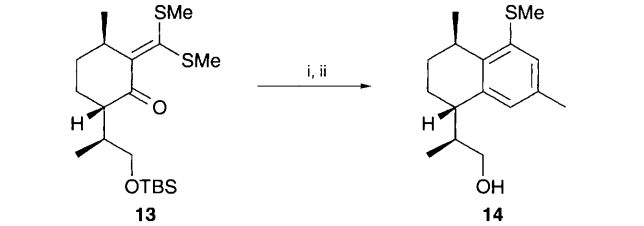
A critical step in the synthesis was the conversion of α-oxoketenedithioacetal **8** to the aromatic ring in intermediate **10**—a reaction which is based on the work of Dieter, Ila and Junjappa.[18,19] Thus, addition of methallylmagnesium chloride to the ketone **8** followed by treatment of the crude alcohol **9** with $BF_3{\cdot}OEt_2$ in MeOH–THF gave methoxyarene **10** in 63% overall yield for the two steps. The structure of the ketenedithioacetal was critical to the success of the reaction since similar treatment of the dithioacetal derivative **13** under identical conditions returned the methylthioarene **14** (Scheme 2) in 84% yield.[20]

To complete the synthesis, the alcohol **10** was converted to its tosylate **11** which was then added to the lithium derivative of



Scheme 1 *Reagents and conditions*: i, $VO(acac)_2$, Bu^tOOH, PhH, room temp.; ii, $NaBH_3CN$, $BF_3{\cdot}OEt_2$, THF; iii, TBSCl, imidazole, DMF, room temp.; iv, Swern oxidation; v, LHMDS, DMPU, THF, −78 °C; vi, CS_2, −78→0 °C; vii, LHMDS, −78 °C; viii, $Br(CH_2)_3Br$, −78 °C→room temp.; ix, methallylmagnesium chloride, THF, 0 °C; x, $BF_3{\cdot}OEt_2$, MeOH–THF, −40 °C→room temp.; xi, TsCl, DMAP, NEt_3, 0 °C→room temp.; xii, $Me_2C{=}CH{-}CH(Li)SO_2Ph$, THF, −78 °C→room temp.; xiii, $EtAlCl_2$, THF, −78 °C→room temp.





Scheme 2 *Reagents and conditions*: i, methallyl magnesium chloride; ii, $BF_3{\cdot}OEt_2$, THF–MeOH, 84%

3-methylbut-2-enyl sulfone to afford the alkylation product **12** as a mixture (*ca.* 1:1) of diastereoisomers in 91% yield. Treatment of the mixture of sulfones **12** with $EtAlCl_2$ in THF at −78 °C returned the tricycle **2** as a mixture of diastereoisomers (10:1) in favour of the desired stereochemistry.[21] The structure and stereochemistry of pure diastereoisomer **2** obtained by simple crystallisation from 2-PrOH (mp 95–96 °C) was confirmed by comparison with NMR spectra kindly provided by Dr Stuart McCombie of the Schering-Plough Research Institute.

In conclusion we have accomplished a concise and efficient synthesis of the enantiomerically pure tricyclic core of the pseudopterosins starting from cheap and readily available starting materials. Since (1*R*,2*R*,5*S*)-neoisopulegol (*ent*-**3**) is available from commercial (*S*)-citronellal, both enantiomeric series of the pseudopterosin aglycones are available by our route. A noteworthy feature of our synthesis is the transformation of α-oxoketenedithioacetal **8** to methoxyarene **10** — a transformation which hitherto has been limited to the production of methylthioarenes as in **13**→**14**.

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References

1 S. A. Look, W. Fenical, G. K. Matsumoto and J. Clardy, *J. Org. Chem.*, 1986, **51**, 5140.
2 C. A. Broka, S. Chan and B. Peterson, *J. Org. Chem.*, 1988, **53**, 1584.
3 E. J. Corey and P. Carpino, *J. Am. Chem. Soc.*, 1989, **111**, 5472.
4 E. J. Corey and P. Carpino, *Tetrahedron Lett.*, 1990, **31**, 3857.
5 S. W. McCombie, B. Cox, S.-I. Lin, A.K. Ganguly and A. T. McPhail, *Tetrahedron Lett.*, 1991, **32**, 2083.
6 S. W. McCombie, B. Cox and A. K. Ganguly, *Tetrahedron Lett.*, 1991, **32**, 2087.
7 A. K. Ganguly, S. W. McCombie, B. Cox, S. Lin and A. T. McPhail, *Pure Appl. Chem.*, 1990, **62**, 1289.
8 A. P. Kozikowski and J. P. Wu, *Synlett*, 1991, 465.
9 S. W. McCombie, C. Ortiz, B. Coz and A. K. Ganguly, *Synlett*, 1993, 541.
10 M. E. Jung and C. S. Siedem, *J. Am. Chem. Soc.*, 1993, **115**, 3822.
11 D. C. Harrowven, S. T. Dennison and P. Howes, *Tetrahedron Lett.*, 1994, **35**, 4243.
12 H. G. Schmalz, A. Majdalani, T. Geller, J. Hollander and J. W. Bats, *Tetrahedron Lett.*, 1995, **36**, 4777.
13 L. Eklund, I. Sarvary and T. Frejd, *J. Chem. Soc., Perkin Trans. 1*, 1996. 303.
14 V. Roussis, Z. Wu, W. Fenical, S. A. Strobel, G. D. Van Duyne and J. Clardy, *J. Org. Chem.*, 1990, **55**, 4916.
15 K. B. Sharpless and R. C. Michaelson, *J. Am. Chem. Soc.*, 1973, **95**, 6136.
16 D. Friedrich and F. Bohlmann, *Tetrahedron*, 1988, **44**, 1369.
17 R. O. Hutchins, I. M. Taffer and W. Burgoyne, *J. Org. Chem.*, 1981, **46**, 5214.
18 R. K. Dieter, *Tetrahedron*, 1986, **42**, 3029.
19 H. Junjappa, H. Ila and C. V. Asokan, *Tetrahedron*, 1990, **46**, 5423.
20 R. K. Dieter and Y. J. Lin, *Tetrahedron Lett.*, 1985, **26**, 39.
21 B. M. Trost and M. Reza Ghadiri, *J. Am. Chem. Soc.*, 1986, **109**, 1098.

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